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Role of congestion in heart failure: From bench to clinical practice

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Role of congestion in heart failure: From bench to clinical practice

Topic editors

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Editorial: Role of congestion in heart failure: From bench to clinical practice

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Editorial on the Research Topic
Role of congestion in heart failure: From bench to clinical practice

Congestion plays a central role in the pathophysiology of heart failure (HF) and remains a clinical challenge to detect, prevent, and treat it effectively. Residual fluid overload at the time of discharge, which is frequently underdiagnosed, is one of the main risk factors for readmission (Lala et al., 2015; Rivas-Lasarte et al., 2020). To date, congestion is evaluated through clinical history, physical examination, determination of plasma natriuretic peptide, and X-Ray. However, emerging tools such as ultrasound imaging, remote dielectric sensing technology (ReDS), and new biomarkers such CA 12.5 offer an earlier and more accurate diagnosis. In addition, some of the new drugs for the treatment of HF, such as sacubitril-valsartan or type 2 sodium-glucose cotransporter inhibitors (SGLT2i), have a diuretic effect and the weight of this peculiarity on prognosis has yet to be elucidated.

The aim of this Research Topic on the *"Role of Congestion in Heart Failure: From Bench to Clinical Practice"* is to summarize knowledge on the precise mechanisms involved in the development of congestion in HF, new techniques to assess fluid overload, and to discuss current and emerging treatment approaches to relieve congestion and, ultimately, impact prognosis. The eight original articles included cover a range of Research Topic, from cutting-edge research findings in animal models to the novel tools and treatments used in daily clinical practice.

Han et al. reinforce the prognostic impact of congestive HF exerts on survival in nearly 70,000 patients from Singapore undergoing surgery. Making use of several statistical models they indistinctly observe that congestive HF is an independent risk factor for 1-year mortality after surgery, underscoring the need for optimizing clinical decision-making, improving preoperative consultation, and promoting clinical communication.

Three original articles in the Research Topic discuss the role of ultrasound imaging techniques, underlining the emerging prognostic role of lung ultrasound in different clinical

scenarios. Szabó et al. evaluated the prevalence and prognostic value of sonographic pulmonary congestion in 75 consecutive patients with moderate to severe aortic valve stenosis. A third of these patients presented with a high degree of lung congestion and, after a follow-up of 13 months, a number of B-lines ≥30 on ultrasound exam independently predicted a composite outcome including death, hospitalization for HF, and intensification of loop diuretic therapy. Keeping in mind that aortic valve stenosis is, by far, the most common primary valve lesion requiring intervention in Western countries, lung ultrasound offers a promising tool for optimizing the prognostic stratification and timing of valve replacement in a growing population with aortic stenosis. Finally, Maestro-Benedicto et al. analyze the incremental prognostic value of adding the number of B-lines to 4 contemporary HF risk scores applied to a study population from the LUS-HF trial (Rivas-Lasarte et al., 2019). They observed that adding lung ultrasound data evaluated at discharge improved the predictive value of most of the risk scores. Given the fact that lung ultrasound is a relatively simple, fast, and non-invasive test, they recommend incorporating this tool in the risk stratification armamentarium to make medical decisions based on life expectancy and develop appropriate treatment plans.

Two papers investigated new approaches to managing congestion and diuretic resistance. García-Magallón et al. assessed the frequency of HF and the clinical profile of patients with insufficient diuretic response according to the algorithm provided by the 2021 HF European Guidelines (McDonagh et al., 2021). This scheme, based on diuresis and natriuresis, was able to detect up to 29% of patients with diuretic resistance, who had lower systolic blood pressure, worse glomerular filtration rate, higher plasma aldosterone levels, and required more frequent thiazides and inotropes during admission. This is the first study to show the performance of the algorithm for the early assessment of diuretic response in a cohort of patients with acute HF. In addition, Civera et al. evaluated the effect of venous leg compression on short-term changes on intravascular refill, assessed by quantifying inferior vena cava (IVC) diameter in patients with worsening HF requiring parenteral furosemide. They also considered whether early changes in IVC diameter are related to short-term decongestion. Through an exhaustive protocol in 20 patients with congestive HF without signs of intravascular congestion (IVC ≤21 mm) at baseline treated with subcutaneous furosemide, they found that short-term venous leg compression using elastic bandages enhanced the diuretic response. Conversely, it seems to play no role in those with intravascular congestion.

Finally, two exceptional reviews cover the role of congestion in HF from different but complementary viewpoints. Saura et al. discuss several animal models of congestive HF, their advantages, and the limitations of each procedure with respect to the effectiveness of results in terms of clinical application in humans. Rodríguez-Espinosa et al. review the pathophysiological mechanisms involved in cardiorenal syndrome, new tools of biomarkers, or lung, vascular, and renal ultrasound currently being used to detect subclinical fluid overload, and different strategies for treating congestion from a multidisciplinary approach.

This Research Topic aims to increase interest in continuing to advance the pathophysiology, diagnosis, and treatment of congestion, the main feature of most patients with HF.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prognostic Value of Lung Ultrasound in Aortic Stenosis

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Background: Aortic stenosis (AS) is the most common primary valve lesion requiring intervention in Europe and North America. It has a prolonged subclinical period during which, as AS worsens, left ventricular adaptation becomes inadequate and impaired systolic and/or diastolic dysfunction may lead to overt heart failure (HF). The development of HF is an inflexion point in the natural history of AS. Pulmonary congestion is a cardinal feature in HF, and lung ultrasound (LUS) evaluation of B-lines has been proposed as a simple, noninvasive tool to assess pulmonary congestion.

Aim: To assess the presence and the prognostic value of sonographic pulmonary congestion in patients with moderate or severe AS.

Methods: 75 consecutive patients (39 women, mean age 73.85 ± 7.7 years) with moderate or severe AS were enrolled. All patients underwent comprehensive echocardiography and LUS with the 28 scanning-site assessment. Patients were followed-up for 13.4 ± 6 months to establish the prognostic value of LUS. A composite endpoint of death (of any cause), hospitalization for HF and intensification of loop diuretic therapy was considered.

Results: We found a severe degree of B-lines (≥30) in 29.33% of patients. The number of B-lines correlated with the estimated pulmonary artery systolic pressure ($p < 0.001$, r = 0.574) and increased along with NYHA class ($p < 0.05$, rho = 0.383). At multivariable analysis, B-lines ≥30, and mean gradient were the independent predictors of events [B-lines: 2.79 (CI 1.03–7.54), $p = 0.04$; mean gradient: 1.04 (CI 1.01–1.07), $p = 0.004$].

Conclusion: Evaluation of B-lines is a simple, highly feasible method to detect pulmonary congestion in AS. The number of B-lines correlates with the hemodynamic changes caused by AS and with the functional status of patients. A severe degree of sonographic pulmonary congestion is associated with an increased risk of adverse events.

Keywords: aortic stenosis, heart failure, pulmonary congestion, lung ultrasound, prognosis

INTRODUCTION

Aortic stenosis (AS) is the most frequent degenerative valvular heart disease in Western countries; its prevalence continuously increases with ageing (Iung et al., 2003; Nkomo et al., 2006; Vahanian et al., 2021). The development of heart failure (HF) symptoms is a determinant factor in the survival of patients with AS (Frank et al., 1973). The correlation between the severity of AS and the onset of symptoms is poor and depends mostly on the hypertrophic, compensatory response of the left ventricle (LV) to pressure overload (Vahanian et al., 2021). LV hypertrophy is a compensatory mechanism to restore wall stress and maintain cardiac output under increasing pressure overload caused by the stenosis. However, progressive loss of cardiomyocytes and myocardial fibrosis that accompanies LV hypertrophy may eventually lead to LV dysfunction. Increased wall thickness also impairs diastolic function and leads to increased filling pressures to achieve the same diastolic volume (Hess et al., 1984). This augmented diastolic pressure leads to pulmonary congestion (PC) and dyspnoea. In more advanced stages of the disease, the pressure overload cannot be counterbalanced by LV hypertrophy, and reduced left ventricular ejection fraction (LVEF) can develop. Decreased LVEF also contributes to the PC and HF symptoms and is associated with poor outcomes (Carabello and Paulus, 2009; Pibarot and Dumesnil, 2012). PC is a frequent and almost universal pathophysiological phenomenon in patients with heart failure. Lung ultrasound (LUS) evaluation of B-lines has been proposed as a simple, noninvasive, radiation-free and semi-quantitative tool to assess PC (Gargani, 2011; Volpicelli et al., 2012; Pellicori et al., 2019). B-lines have been closely linked to the amount of extravascular lung water and pulmonary capillary wedge pressure in HF patients (Agricola et al., 2005; Gargani et al., 2008; Miglioranza et al., 2013). LUS can identify clinically silent pulmonary oedema (Miglioranza et al., 2013), suggesting that it can be utilized to assess hemodynamics and optimize treatment (Pellicori et al., 2019). Our study aimed to determine the prognostic value of LUS B-lines in predicting adverse events in patients with moderate or severe aortic stenosis.

METHODS

Seventy-five consecutive patients with AS from two sites (University Of Szeged, Hungary, Clinical County Hospital Târgu Mures, Romania) were enrolled. The inclusion criteria were: 1) moderate degenerative AS with mean gradient of 20-40 mmHg and aortic valve area (AVA) 1–1.5 cm^2; 2) or severe degenerative AS with mean gradient >40 mmHg and AVA <1 cm^2; 3) age >18 years; 4) informed consent. We enrolled patients with severe symptomatic AS, only if the patient refused surgery or it was contraindicated.

The exclusion criteria were: 1) low flow-low gradient AS (mean gradient <40 mmHg, AVA <1 cm^2, LVEF<50%); 2) concomitant moderate or severe aortic regurgitation; 3) concomitant moderate or severe mitral regurgitation; 4) severe, decompensated HF, requiring urgent hospitalization (NYHA class IV); 5) severe interstitial lung disease; 6) active pneumonia or acute lung injury; 7) malignancy (except localized skin basal cell carcinoma or localized prostatic cancer); 8) cardiomyopathies—dilated, hypertrophic or infiltrative cardiomyopathy. All patients were evaluated in ambulatory settings in rather stable conditions. None of the patients required hospitalization at the time of TTE and LUS. The patients signed informed consent before inclusion in the study. Data handling and publication respected the Declaration of Helsinki. The registration number of ethical approval is 131/2019/SZTE.

A comprehensive transthoracic echocardiogram (TTE) was performed in both sites, using a Vivid-S70 (GE Vingmed, Horten, Norway) ultrasound machine equipped with the 3S probe (1.5–3.6 MHz). Experienced cardiologists, certified by the European Association of Cardiovascular Imaging (EACVI) for TTE, performed all measurements according to the American Society of Echocardiography and EACVI recommendations (Lang et al., 2015; Baumgartner et al., 2017). Longitudinal myocardial strain was analyzed with GE EchoPAC (version v202) software. LV strain was measured according to EACVI recommendations (Lang et al., 2015). The QRS complex was used as a time reference. LA strain parameters were recorded as per the EACVI consensus document and were post hoc analyzed (Badano et al., 2018). ECG trigger was used as a time reference, using the upslope of the R wave as a surrogate of end-diastole.

Lung Ultrasound

Immediately after TTE, patients underwent B-lines assessment, using the same probe and machine, with the same setting. We screened the anterior and lateral hemithorax, scanning along the parasternal, midclavicular, anterior axillary and mid-axillary lines from the second to the fifth intercostal space on the right hemithorax and from the second to the fourth intercostal space on the left; a total of 28 scanning sites were assessed as previously described (Gargani and Volpicelli, 2014). A B-line was defined as a discrete comet-like vertical hyperechoic reverberation artefact starting from the pleural line, extending to the bottom of the screen and moving synchronously with lung sliding (Volpicelli et al., 2012). The total number of B-lines on the 28 scanned sites (0–10 for each site) was recorded, generating a B-lines score. In each scanning site, the number of B-lines was quantified real-time: when B-lines were distinguishable, they were counted one by one (0–10 for each site); when they were confluent, the percentage of the white screen occupied by B-lines below the pleural line was considered, and then divided by 10 (Volpicelli et al., 2012) (Gargani and Volpicelli, 2014). A total score of B-lines ≥ 30 was considered a cut-off for severe PC (Gargani et al., 2008).

Follow Up Data

Follow-up data were collected every 3 months *via* phone calls to monitor clinical status and adverse outcomes. Outpatient visits were performed six-monthly, and clinical status, adverse events were recorded. We considered a composite endpoint of events. The endpoint was determined by the following events: death (any cause), HF event requiring hospitalization, and ambulatory

TABLE 1 | Clinical characteristics of the study population and comparisons between patients with and without events.

	All Patients (*n* = 75)	Event-free Group (*n* = 47)	HF Event Group (*n* = 28)	*p*
Age (years)	73.85 ± 7.74	72.04 ± 8.1	76.89 ± 6.3	0.008
Gender (female)	39 (52%)	26 (55.3%)	13 (46.4%)	0.456
BMI (kg/m2)	27.11 ± 3.8	26.99 ± 4.19	27.22 ± 3.4	0.812
SBP (mmHg)	127.82 ± 12	126.85 ± 11	129.00 ± 14.7	0.521
DBP (mmHg)	76.66 ± 8	76.71 ± 6	76.71 ± 10.8	0.966
HR (BPM)	70.11 ± 9.4	69.60 ± 9.9	70.43 ± 9.1	0.734
NYHA I	16 (19.2%)	16 (31.4%)	0 (0%)	<0.001
NYHA II	43 (57.3%)	24 (51.0%)	19 (67.8%)	0.185
NYHA III	15 (20%)	6 (12.7%)	9 (32.1%)	0.047
Peripheral oedema	10 (13.3%)	5 (10.6%)	5 (17.8%)	0.374
Syncope	5 (6.67%)	2 (4.2%)	3 (10.7%)	0.302
Rales	12 (16%)	4 (8.5%)	8 (28.5%)	0.048

Data are expressed as mean ± SD, or number and percentage.
BMI, body mass index; SBP, systolic blood pressure; NYHA, new york heart association classification to stages of heart failure.

intensification of loop diuretic therapy. Data collection was based on a standardized clinical questionnaire performed by a researcher blinded to clinical records. If an endpoint event was detected, details were retrieved from medical records.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median and interquartile ranges, as appropriate. Two-sample comparisons were performed using the *t*-test and the Chi-square test for categorical data. A p-value < 0.05 was set for statistical significance. Correlations between parameters were assessed with parametric Pearson or nonparametric Spearman correlation coefficient analysis, as appropriate. The prognostic performance was determined by means of receiver-operating characteristic (ROC) curves. The association of selected variables with the outcome was assessed by Cox's proportional hazard model using univariable and multivariable procedures (Backward LR method). We excluded collinearity using variance inflation factor > 3. The event rates were estimated with Kaplan-Meier curves and compared by the log-rank test. Hazard Ratios were reported. Data were analyzed using IBM SPSS 22 statistical software.

RESULTS

Ninety-seven patients were screened from May 2019 to October 2020: 22 patients were excluded from the initial population (4 patients had concomitant moderate aortic regurgitation, six patients had concomitant moderate or severe mitral regurgitation, four patients had dilated cardiomyopathy with moderate AS, four patients had low-flow, low-gradient AS, three patients had severe chronic obstructive pulmonary disease, and one patient had active lung cancer). Finally, 75 patients (39 women, mean age 73.85 ± 7.7 years) were enrolled in the study. According to the 2021 ESC guideline categorization, the enrolled patient population included 30 patients with high-gradient AS, 22 patients with low-flow, low-gradient AS with a preserved EF, 8 patients with normal-flow, low-gradient AS with preserved EF, and 15 patients with moderate AS. During the 13.4 ± 6 months follow-up, we detected 28 events: 19 patients had hospitalizations due to HF (2 of them underwent urgent AVR), seven of them required ambulatory intensification of loop diuretic therapy. Two patients died (the exact cause of death is unknown). Baseline characteristics of the study population and the comparisons between those with and without events are shown in **Table 1**.

All patients with events were already in NYHA class II-III, but only 66.67% of the event-free group were symptomatic. More patients in the event group had pulmonary rales, whereas the presence of peripheral oedema was not different.

Echocardiographic parameters related to the severity of the valvular disease significantly differed between the two groups (**Table 2**) LVEF was significantly worse in the event group. Parameters describing right ventricular (RV) function also significantly differed: the pulmonary artery systolic pressure (PASP) was higher, and the tricuspid annular plane systolic excursion (TAPSE) was lower in the event group. RV-pulmonary artery (PA) coupling, expressed by TAPSE/PASP ratio, was also significantly different in patients with and without events (**Table 2**).

We found a severe degree of B-lines (≥30) in 29.33% of all patients. LUS also was different, with more B-lines in the event group (p = 0.028) and more patients with a severe degree of B-lines (≥30 B-lines, p = 0.002). The number of B-lines increased significantly along with the worsening NYHA functional classes (**Figure 1**), from 13 ± 12 in NYHA Class I, through 19 ± 15 in Class II, to 43 ± 34 in Class III (p < 0.05, rho = 0.383). Patients with severe AS had significantly more B-lines than patients with moderate AS (14 ± 13 vs. 25 ± 24, p < 0.05).

We also found that the number of B-lines was correlated (**Figures 2A,B**) with LVEF (R = −0.325, p < 0.05) and PASP (R = 0.574, p < 0.001). We did not find a significant correlation between E/e' and B-lines or LAVI and B-lines. Having ≥ 30 B-lines significantly increased the risk of endpoint events [(hazard ratio B-lines CI: 2.79 (1.03–7.54), p < 0.05)]. During multivariable modelling, B-lines and mean aortic gradient were the independent predictors of events.

TABLE 2 | Baseline echocardiographic characteristics of the study population and comparisons between patients with and without events.

	All Patients (*n* = 75)	Event-free Group (*n* = 47)	HF Event Group (*n* = 28)	*p*
Peak Ao Gradient (mmHg)	59.61 ± 22	54.74 ± 19.3	67.79 ± 24	0.012
Mean Ao Gradient (mmHg)	37.60 ± 13.4	34.45 ± 12.6	42.89 ± 13.2	0.008
AVA (cm^2)	0.78 ± 0.2	0.83 ± 0.3	0.71 ± 0.2	0.068
LAVI (ml/m^2)	34.23 ± 19.5	35.34 ± 17.1	44.64 ± 21.5	0.054
LASr (%)	23.55 ± 12.7	24.93 ± 12.9	16.22 ± 9.5	0.173
LA stiffness	0.75 ± 1.1	0.57 ± 0.4	1.01 ± 0.9	0.424
EDV (ml)	114.80 ± 29	115.40 ± 27.5	113.57 ± 32.5	0.806
ESV (ml)	40.97 ± 20.4	36.83 ± 15.8	49.43 ± 26	0.041
EF (Simpson) %	63.32 ± 10.6	67.67 ± 7.4	56.02 ± 11.2	<0.001
IVS (mm)	12.33 ± 1.5	12.11 ± 1.2	12.71 ± 1.9	0.144
PW (mm)	11.97 ± 1.3	11.94 ± 1.2	12.04 ± 1.5	0.762
LV GLS (%)	−17.03 ± 8.5	−17.08 ± 9.8	−16.90 ± 4.3	0.954
PASP (mmHg)	36.59 ± 15.7	31.00 ± 11.5	45.79 ± 17.4	<0.001
E (cm/s)	83.21 ± 31.6	81.46 ± 28.3	85.69 ± 36.1	0.605
A (cm/s)	98.86 ± 27.5	105.44 ± 28.1	88.57 ± 23.7	0.020
E/A	0.87 ± 0.4	0.78 ± 0.2	1.00 ± 0.5	0.093
DCT (ms)	229.29 ± 63.5	238.79 ± 64.2	215.05 ± 60.4	0.177
E' (cm/s)	8.55 ± 3.5	8.72 ± 3.1	8.27 ± 4.2	0.668
E/e' (cm/s)	11.35 ± 6.2	10.83 ± 5.2	12.17 ± 7.6	0.457
RV Basal diameter (mm)	35.55 ± 4.1	34.77 ± 3.3	36.44 ± 4.7	0.125
TAPSE (mm)	23.20 ± 4.9	24.54 ± 4.7	21.25 ± 4.6	0.006
RV-PA coupling	0.74 ± 0.35	0.87 ± 0.33	0.55 ± 0.29	$p < 0.001$
Lung ultrasound				
Total number of B-lines (n)	22 ± 22	18 ± 23	29 ± 18	0.028
≥15 B-lines	38 (50.6%)	17 (36.1%)	21 (75%)	0.001
≥30 B-lines	22 (29.3%)	8 (17.%)	14 (50%)	0.002

Data are expressed as mean±SD, or number and percentage.

Ao Peak Gradient: estimated peak pressure gradient across the aortic valve, Ao mean gradient: estimated mean gradient across the aortic valve, AVA: calculated aortic valve area, LV EF: left ventricular Ejection Fraction, LV GLS: left ventricular Global Longitudinal Strain, IVS: intraventricular septum thickness, PW: posterior wall thickness, LAVI: left atrial volume index, LASR: left atrial reservoir strain, LA, stiffness: left atrial stiffness, E: early mitral inflow peak velocity, A: late mitral peak inflow velocity, DCT: E wave deceleration time, E/E'mean: the relationship between maximal values of passive mitral inflow (E, PW-Doppler) and lateral early diastolic mitral annular velocities (E' TDI) PASP: pulmonary artery systolic pressure, TAPSE: Tricuspid annular plane systolic excursion. RV-PA, coupling is the ratio of TAPSE, and PASP.

Univariate and multivariate predictors of the different endpoints are reported in **Table 3**.

The event-free survival was significantly worse among those who had equal or more than 30 B-lines (Log Rank 8.619, $p = 0.003$) (**Figure 3**).

DISCUSSION

To the best of our knowledge, this is the first study to address the prognostic value of B-lines for the prediction of adverse events in patients with AS. Our results show that the assessment of B-lines in AS adequately reflects patients functional class and the haemodynamic consequences caused by AS. Presence of severe B-lines (≥30) strongly predicts adverse events.

Current guidelines advise valve replacement when an integrative evaluation of pressure gradients, AVA, the extent of valve calcification, and flow indicates severe AS, and there is evidence of LV decompensation evaluated by echocardiographic measurements or appearance of symptoms (Vahanian et al., 2021). The guidelines also pointed out some additional prognostic markers, which also help decide AVR (Vahanian et al., 2021). Exercise stress echocardiography may provide prognostic information in asymptomatic patients (Marechaux et al., 2010); cardiac magnetic resonance enables to assess myocardial fibrosis (Azevedo et al., 2010). Moreover, natriuretic peptides have been shown to predict symptom-free survival and outcome in normal and low-flow severe AS (Bergler-Klein et al., 2004). These predictors especially stress echocardiography and cardiac magnetic resonance, are not always available, and the repeated measurements are not feasible.

LV hypertrophy is a mechanism of accommodation in AS to restore wall stress and maintain cardiac output under increasing pressure afterload caused by the stenotic valve. However, the progressive cardiomyocyte death and consequent fibrosis that accompanies LV hypertrophy may lead to the development of LV systolic and diastolic dysfunction and finally to HF. Historical data have shown that the time from the onset of symptoms to death is about 2 years in patients who develop HF (Frank et al., 1973). Besides the prognostic importance of HF in recent years, the data supports that cardiac damage also holds prognostic significance after AVR (Généreux et al., 2017). Stages of cardiac damage in patients with severe AS have been defined from stage 1 to stage 4. These are: LV dysfunction, left atrial enlargement, pulmonary hypertension, and RV dysfunction. Each stage is associated with an increased mortality risk within one year, ranging from 4% in stage 0 (no damage) up to 25% in stage 4 (Généreux et al., 2017). Our results are

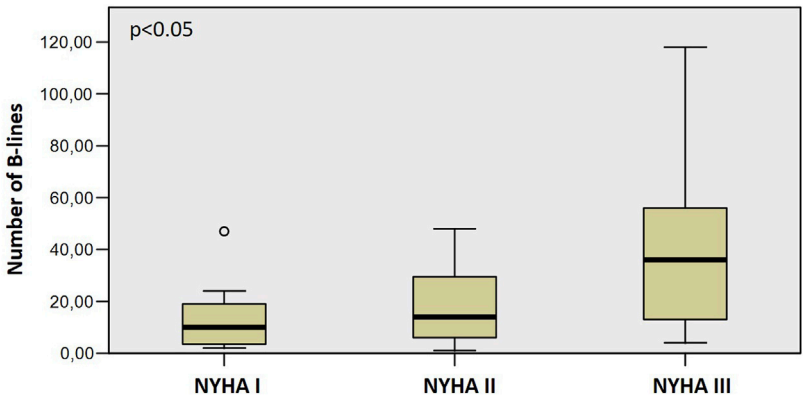

FIGURE 1 | The increasing number of B-lines with worsening NYHA functional class.

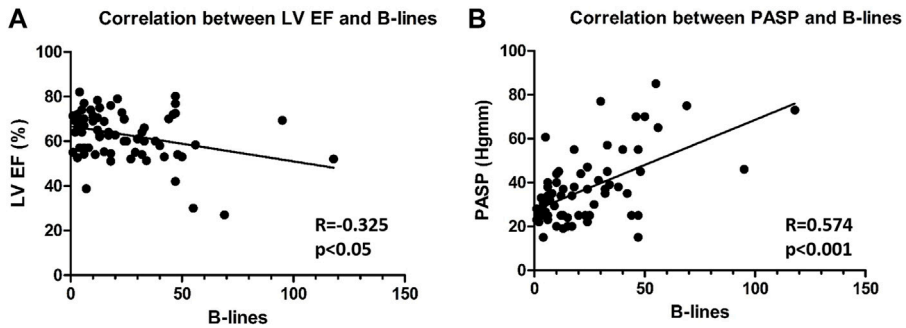

FIGURE 2 | Correlation between B-lines and LVEF **(A)** and PASP **(B)** (LVEF: Left ventricular ejection fraction, PASP: Pulmonary arterial systolic pressure).

TABLE 3 | Cox regression analysis.

	Univariate Analysis		Multivariate Analysis	
	Hr (95% CI)	*p* value	Hr (95% CI)	*p* value
Age	1.06 (1.01–1.11)	0.018	1.03 (0.98–1.08)	0.271
Ao Mean Gradient	1.04 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.004
PASP	1.04 (1.02–1.06)	<0.001	1.01 (0.98–1.04)	0.456
B-lines ≥15	2.609 (1.10–6.19)	0.029	—	—
B-lines ≥30	2.86 (1.36–6.03)	0.006	2.79 (1.03–7.54)	0.043

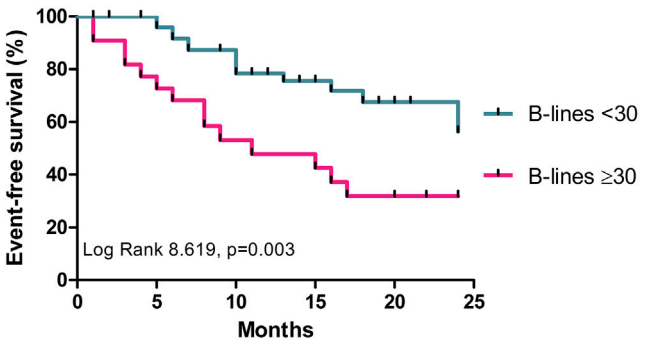

FIGURE 3 | Comparison of HF endpoints among patients with≥30 and <30 B-lines.

consistent with these data, showing that patients with HF events have lower EF, lower TAPSE, higher PASP. However, the worsening LVEF is a late and insensitive marker of myocardial dysfunction (Généreux et al., 2017).

LV systolic and diastolic dysfunction and mitral regurgitation result in PC, which is a common finding in patients with HF. LUS assessment of PC by B-lines has been demonstrated to be an excellent diagnostic tool (Pellicori et al., 2019) (Lichtenstein et al., 1997; Jambrik et al., 2004; Picano et al., 2010; Pivetta et al., 2015). The quick examination time with 100% feasibility allows this method to be easily performed during bedside patient evaluation. Decompensation is clinically silent in most patients and is often not recognized until developing rapid progression that requires urgent hospitalization. LUS can assess lung oedema noninvasively in real-time, even at an early subclinical stage. B-lines are helpful for the differential diagnosis of acute HF syndromes from non-cardiac causes of acute dyspnoea in the emergency setting, with high sensitivity and specificity (Al Deeb et al., 2014) The number B-lines measured by LUS correlated well with NT-proBNP level (Gargani et al., 2008; Miglioranza et al., 2013)

(Volpicelli et al., 2008) and the indexes of diastolic dysfunction (Gargani, 2011). (Gargani et al., 2008). (Frassi et al., 2007a). We did not find a significant correlation between E/e' or LAVI and B-lines. Previous studies have shown this correlation, especially when assessing B-lines during exercise. However, this relation has never been tested in patients with significant aortic stenosis. Reddy and colleagues simultaneously performed stress tests, lung ultrasound, and right heart catheterization in HFpEF. B-lines increase during exercise was associated with lower RV systolic velocity and RV fractional area change, worse RV-PA coupling, higher pulmonary capillary wedge pressure (PCWP), and higher pulmonary artery (PA) pressure. However, baseline E/e' was not higher in patients who increased B-lines during exercise). (Reddy et al., 2019). Simonovic D et al. enrolled HFpEF patients and performed exercise stress echocardiography and B-lines assessment; again, the resting E/e' value was not higher in patients with ≥10 B-lines at exercise (Simonovic et al., 2021). Hubert and colleagues performed direct measurements of LV filling pressure and B-lines assessment on patients with different cardiovascular conditions, undergoing coronary angiography, and found that the total number of B-lines was significantly higher in the elevated LVEDP group (≥20 mmHg). They underline that the diagnostic capacity of B-lines to identify elevated LVEDP is higher than that of classical echocardiographic strategies (Hubert et al., 2019). Volpicelli et al. also assessed B-lines in critically ill patients with simultaneous PCWP monitoring (with only 10 patients with cardiogenic pulmonary edema), confirming that B-lines allow good prediction of pulmonary congestion indicated by EVLW. Whereas B-lines assessment is of limited usefulness for the prediction of hemodynamic congestion indicated by PCWP (Volpicelli et al., 2014). Indeed the added value of B-lines is being a sign of pulmonary congestion, independent of the degree of hemodynamic congestion. Platz et al. also investigated patients with unexplained dyspnea with invasive hemodynamic measurements and LUS: the number of B-lines at rest was correlated to PCWP and mean pulmonary artery pressure (Platz et al., 2019). Reddy et al. showed that stress-induced B-lines elevation was mainly dependent on RV dysfunction and pulmonary hemodynamics (Reddy et al., 2019). We also found a significant correlation between B-lines and RV-PA coupling, expressed by TAPSE/PASP ratio (r −0.443, $p < 0.001$). The meta-analysis by Kobayashi et al. also confirmed that worse RV function and RV–PA coupling were associated with higher B-line counts on admission and at discharge regardless of LVEF (Kobayashi et al., 2021). B-lines also have an exceptional prognostic value, shown in patients with HF (Frassi et al., 2007b; Gargani et al., 2015; Platz et al., 2016; Miglioranza et al., 2017; Gargani et al., 2021). The predictive value is independent and additive over conventional clinical, imaging, and laboratory markers, such as a functional class, signs of congestion, namely crackles over the lungs, LVEF, pulmonary artery systolic pressure, or cardiac natriuretic peptide levels (Frassi et al., 2007b; Bedetti et al., 2010; Gustafsson et al., 2015; Platz et al., 2016). Our results are consistent with these previous findings: patients with AS-related PC have significantly more B-lines, and patients with ≥30 B-lines have significantly more HF-related events and death. According to previous studies, we chose ≥30 B-lines in 28 scanning sites to determine severe congestion (Miglioranza et al., 2017) (Coiro et al., 2015). Residual pulmonary congestion of ≥30 B-lines at discharge in patients with acute heart failure, irrespectively of the HF etiology and EF, is a strong and independent predictor of outcome (Coiro et al., 2015). The determination of B-lines in AS is a promising method because establishing symptomatic status in this population is challenging due to their usually sedentary lifestyle and high prevalence of co-morbidities (Chin et al., 2015), as ageing and concomitant medical problems can cause symptoms similar to AS or conceal them by restricting physical activity. Even though angina and syncope are easily detectable symptoms, HF can be indolent. Therefore, there is a rationale for using additional methods to detect HF early.

Several attempts were made to improve the prognostic stratification of AS patients. CAIMAN-ECHO score is an echocardiography based tool for asymptomatic, moderate or severe AS patients. It takes into account the calcium score of the aortic valve, inappropriate LV mass, and peak gradient across the aortic valve to predict the risk of cardiovascular events (all-cause mortality, AVR, hospitalization for MI and HF) (Cioffi et al., 2013). Monin et al. developed a scoring system for patients with asymptomatic severe AS, including gender, BNP level, and peak aortic jet velocity. It can be used for the prediction of midterm risk of death and AVR (Monin et al., 2009).Kearney et al. followed up AS patients older than 60 years of age (mild to severe valvular disease) for 18 years, and he found that age-adjusted Charlson co-morbidity index and grade of LV dysfunction were risk factors of all-cause mortality while having an AVR acted as a protective factor (Kearney et al., 2012). The predictive role of apical rotation was also assessed in a group of patients with symptomatic and asymptomatic severe AS and preserved EF. It was found that increased apical rotation was linked to worse survival (Holmes et al., 2015). It was also found that raised BNP and troponin I are also markers of adverse prognosis in asymptomatic patients with moderate-to-severe asymptomatic AS (Clavel et al., 2014) (Chin et al., 2014).

The assessment of B-lines has several advantages in patients with moderate and severe AS. The expansion of regular, standard TTE by LUS should improve risk stratification of patients. Cardiac damage, especially LV, mitral valve and LA dysfunction, results in PC and, consequently in HF signs and symptoms. Hence, early detection by LUS holds incremental prognostic and diagnostic possibilities. A more accurate PC assessment might optimize the timing of valve surgery or help tailor HF therapy. It may identify high-risk AS patients whose concomitant heart disease aggravates PC, for example, ischemic LV dysfunction, cardiomyopathies, and mitral valve disease. B-line assessment before surgery (TAVR or open-heart surgery) may influence postoperative events; however, further studies are needed to confirm these hypotheses.

LIMITATIONS

The sample size is relatively small, and our series may not represent the average patient with moderate or severe AS. The detection of B-lines does not necessarily imply their cardiogenic origin; however, we applied strict criteria to exclude patients with potential non-cardiogenic B-lines. We did not collect the baseline levels of NT-proBNP.

CONCLUSION

In a moderate and severe AS, B-lines evaluated by LUS are significantly correlated with NYHA functional class, LV ejection fraction, and pulmonary artery systolic pressure. During the short-term follow-up, a higher number of B-lines was associated with HF-related adverse events and death. Given its accuracy and simplicity, LUS could be considered a reliable tool for assessing PC in patients with AS, and could be incorporated as an extension of the physical examination.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Human Biomedical Research Ethics Committee of the University of Szeged/Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureş. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IS contributed to data collection, analysis and interpretation, manuscript preparation, and gave final approval of the submitted version. LG contributed to the conception and design of the study, data interpretation, and work drafting also gave final approval of the version to be published. BM-I contributed to data analysis, interpretation, work drafting and final approval of the present version. NP-N and AF contributed to the statistical revision of the paper and work drafting and gave final approval of the submitted version. AV contributed to the data interpretation and work drafting and gave final approval of the submitted version. GÃ contributed to the conception and design of the study, data acquisition, analysis and interpretation, and work drafting; gave final approval of the submitted version, taking responsibility for the integrity of the work.

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BRIEF RESEARCH REPORT
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Role of Early Assesment of Diuresis and Natriuresis in Detecting In-Hospital Diuretic Resistance in Acute Heart Failure

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Background and Purpose: European Guidelines recommend early evaluation of diuresis and natriuresis after the first administration of diuretic to identify patients with insufficient diuretic response during acute heart failure. The aim of this work is to evaluate the prevalence and characteristics of patients with insufficient diuretic response according to this new algorithm.

Methods: Prospective observational single centre study of consecutive patients with acute heart failure and congestive signs. Clinical evaluation, echocardiography and blood tests were performed. Diuretic naïve patients received 40 mg of intravenous furosemide. Patients on an oupatient diuretic regimen received 2 times the ambulatory dose. The diuresis volume was assessed 6 h after the first loop diuretic administration, and a spot urinary sample was taken after 2 h. Insufficient diuretic response was defined as natriuresis <70 mEq/L or diuresis volume <600 ml.

Results: From January 2020 to December 2021, 73 patients were included (59% males, median age 76 years). Of these, 21 patients (28.8%, 95%CI 18.4; 39.2) had an insufficient diuretic response. Diuresis volume was <600 ml in 13 patients (18.1%), and 12 patients (16.4%) had urinary sodium <70 mEq/L. These patients had lower systolic blood pressure, worse glomerular filtration rate, and higher aldosterone levels. Ambulatory furosemide dose was also higher. These patients required more frequently thiazides and inotropes during admission.

Conclusion: The diagnostic algorithm based on diuresis and natriuresis was able to detect up to 29% of patients with insufficient diuretic response, who showed some characteristics of more advanced disease.

Keywords: diuretic, acute heart failure, natriuresis, diuretic response, diuretic resistance

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INTRODUCTION

Signs and symptoms of congestion are usually the most common manifestations among patients with acute heart failure (HF) (Adams et al., 2005), and intravenous loop diuretics remain the most widely used therapy to achieve euvolaemia (Fonarow et al., 2004). Diuretic response is defined as the capacity of diuretics to induce natriuresis and diuresis (ter Maaten et al., 2015a).

Identification of patients who may have a poor diuretic response is one of the most important challenges in the field of HF, since a poor diuretic response is associated with a higher risk of rehospitalization and increased mortality (Metra et al., 2012; Neuberg et al., 2002; Valente et al., 2014; ter Maaten et al., 2015b; Testani et al., 2014; Voors et al., 2014). To date, no uniform and standard definition was available to allow the early identification of patients at risk of developing resistance to diuretic treatment during HF hospitalization.

The Position Statement from the Heart Failure Association of the European Society of Cardiology about the use of diuretics in heart failure with congestion (Mullens et al., 2019), and more recently the European Guidelines for the diagnosis and treatment of acute and chronic heart failure (McDonagh et al., 2021), have proposed an algorithm that includes the early assessment of diuresis and natriuresis after the first administration of loop diuretics in patients with acute HF, in order to detect patients with insufficient diuretic response who might benefit from diuretic intensification.

To date, data on the prevalence of early diuretic resistance according to these parameters have not yet been described.

The aim of this work is to evaluate the prevalence and features of acute HF patients who present an insufficient diuretic response according to this algorithm.

METHODS

From January 2020 to December 2021, we conducted a prospective, observational and single centre study on a sample of consecutive patients aged ≥18 years whose primary admission diagnosis was acute HF and were admitted to the cardiology department. The diagnosis of acute HF was based on the current ESCF HF guidelines. In addition, NTproBNP >300 pg/dl and the presence of at least two of the following congestion criteria were required: jugular venous pressure >10 cm, lower limb edema, ascites, or pleural effusion determined by chest x-ray or pulmonary ultrasound.

Patients in cardiogenic shock and/or on dialysis were excluded. Patients in whom urine output or natriuresis could not be recorded or were missed were also excluded.

Study Procedures and Statistical Analysis

Complete clinical evaluation, echocardiogram and laboratory tests were performed. Diuretic naïve patients received 40 mg of intravenous furosemide. Patients on an outpatient diuretic regimen received 2 times the home dose. The diuresis volume was assessed 6 h after the first loop diuretic administration, and a spot urinary sample was taken after 2 h. Urinary sodium was measured using a Siemens Dimension EXL chemistry analyzer. Insufficient diuretic response was defined as natriuresis <70 mEq/L or diuresis volume <600 ml.

Values of continuous variables are given as the median and interquartile range (IQR). Categorical variables are described in absolute and relative frequencies. The associations between clinical characteristics and diuretic response were analyzed by univariate analysis using the Chi square test for categorical variables and the Mann-Whitney U test for contiuous variables. A p-value <0.05 was considered significant. All analyses were performed using STATA v.13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX) and R software (R Foundation for Statistical Computing, version 3.6.0).

The present study conforms to the principles of the Declaration of Helsinki. Approval from the local ethics committee/internal review board was obtained at the participating centers and patients signed an informed consent.

RESULTS

From January 2020 to December 2021, 694 patients were admitted for acute HF. Nearly 50% of these patients did not meet the inclusion criteria as they presented predominant pulmonary congestion. About 30% could not be included as the treating physician didn't follow the ESC protocol, in part due to Covid-19 pandemic.

A final sample of 73 patients were included (59% males, median age 76 years [IQR: 70–85]). Four initially included patients were not finally analysed as urinary output was not correctly collected. Of the remaining sample (73/78), 21 patients (28.8%) met the definition of early insufficient diuretic response.

The diuresis volume was <600 ml in 13 patients (18.1%), and 12 patients (16.4%) had urinary sodium <70 mEq/L. Only 4 patients (5.5%) had both low urinary sodium and decreased urine output.

Compared with patients with an adequate diuretic response, these patients had lower systolic blood pressure (133 mmHg [IQR: 116–148] vs. 148 [IQR: 124–175], p = 0.043), worse glomerular filtration rate (49 ml/min/1.73 m^2 [IQR: 28–63] vs. 69 [44–86], p = 0.044), and showed greater neurohormonal activation (aldosterone levels: 19 ng/dl [IQR: 11–40] vs. 10 [IQR: 7–14], p = 0.005). This group of patients presented a higher percentage of previous admission due to HF (42.9 vs. 17.6%, p = 0.025), and their basal furosemide dose was also higher (80 mg [IQR: 5–88] vs. 40 [IQR: 0–60], p = 0.032) **Table 1**.

During admission, patients with poor diuretic response required more frequently inotropes (19 vs. 0%, p = 0.001), and thiazides (52.4 vs. 23.1%, p = 0.015).

DISCUSSION

To date, this is the first study to show the performance of the algorithm proposed by the HF European guidelines for the early assessment of diuretic response in a cohort of patients with acute HF.

This algorithm based on diuresis volume and natriuresis was able to detect up to 29% of patients with insufficient diuretic response who might benefit from enhanced diuretic treatment.

TABLE 1 | Legend. Patient characteristics per diuretic response (*n* = 73).

Patient characteristics per diuretic response	All patients *n* = 73	Poor DR *n* = 21 (28.8%)	Good DR *n* = 52 (71.2%)	*p*-value
Age (years)[a]	76 (70–85)	76 (50–87)	78 (70–85)	0.845
Male *n* (%)	43 (58.9)	12 (57.1)	31 (59.6)	0.846
Diabetes mellitus 2, *n* (%)	29 (39.7)	12 (57.1)	17 (32.7)	0.137
Arterial hypertension, *n* (%)	62 (84.9)	18 (85.7)	44 (84.6)	0.905
Chronic kidney disease, *n* (%)	17 (23.3)	6 (28.6)	11 (21.1)	0.575
Atrial Fibrillation, *n* (%)	43 (58.9)	14 (66.7)	29 (56.9)	0.441
Previous hospitalization for heart failure, *n* (%)	18 (24.7)	9 (42.9)	9 (17.6)	**0.025**
De novo HF, *n* (%)	26 (35.6)	5 (23.8)	21 (40.4)	0.280
Heart failure evolution (days)[a]	293 (0–1965)	436 (0–3,030)	232 (0–1,647)	0.250
Basal treatment				
Furosemide, *n* (%)	48 (66)	15 (71)	33 (64)	0.594
Ambulatory furosemide dose[a] (mg)	40 (0–80)	80 (5–88)	40 (0–60)	**0.032**
MRA, n (%)	8 (11)	2 (10)	6 (12)	0.583
Thiazides, *n* (%)	6 (8)	3 (14)	3 (6)	0.345
Acetazolamide,*n* (%)	2 (2.7)	1 (4.8)	0 (0)	0.080
SLGT2i, *n* (%)	3 (4)	1 (5)	2 (4)	0.645
RAASi, *n* (%)	41 (56)	10 (48)	31 (60)	0.427
Betablockers, *n* (%)	33 (45)	11 (52)	22 (42)	0.450
Admission				
Charlson score[a]	2 (1–3)	2 (2–4)	2 (1-3)	0.212
LVEF (%)[a]	55 (38–60)	55 (31–59)	55 (40-60)	0.225
Type of HF, *n* (%)	—	—	—	0.235
HFrEF	24 (33.8)	7 (33.3)	17 (32.7)	—
HFmrEF	9 (12.3)	2 (9.5)	7 (13.5)	—
HFpEF	40 (54.7)	12 (57.1)	28 (53.8)	—
TAPSE (mm)[a]	17 (14-21)	16 (14–21)	17 (14–21)	0.680
Tricuspid regurgitation III-IV, *n* (%)	10 (13.7)	2 (9.5)	8 (15.4)	0.714
sPAP (mmHg)[a]	45 (35–55)	50 (40–55)	45 (35–55)	0.491
Systolic blood pressure (mmHg)[a]	141 (123–166)	133 (116–148)	148 (124–175)	**0.043**
Diastolic blood pressure (mmHg)[a]	76 (69–86)	75 (65–83)	76 (69–90)	0.227
Everest score[a]	11 (9–12)	11 (9–13)	11 (8–12)	0.186
Inferior cava vein (mm)[a]	22 (19–24)	23 (20–26)	22 (19–24)	0.499
Length of stay (days)[a]	8 (6–12)	10 (7–15)	8 (5–11)	0.124
Chlorthalidone during admission, *n* (%)	23.0 (31.5)	11.0 (52.4)	12.0 (23.1)	**0.015**
Inotropes during admission, *n* (%)	4.0 (5.5)	4 (19)	0	**0.001**
Blood tests				
Glomerular filtration ml/min/1.73 m^2[a]	57.2 (41.9–84.5)	49.3 (28.0–63.2)	69.4 (44.1–86.2)	**0.044**
Urea (mg/dl)[a]	56.0 (41.0–77.5)	74.0 (50.5–80.5)	51 (40–75)	**0.044**
Creatinine (mg/dl)[a]	1.0 (0.8–1.5)	1.3 (0.9–2.1)	1.0 (0.7–1.4)	**0.032**
Sodium (mmol/L)[a]	141 (138–143)	141 (135–143)	141.00 (138.25–143)	0.419
Potassium (mmol/L)[a]	4.3 (4.0–4.9)	4.2 (4.0–4.7)	4.5 (4.0–5.0)	0.294
Chloride (mmol/L)[a]	105 (103–107)	104 (101–106)	105 (103–107)	0.074
Uric acid (g/dl)[a]	8.2 (7.0–9.1)	8.2 (7.0–10.1)	8.2 (6.4–9.1)	0.749
NT-proBNP (pg/ml)[a]	5,691 (2,447–9731)	7583 (3,421–11944)	5,039 (1976–9368)	0.165
Ca 125 (U/ml)[a]	62 (20–128)	57 (9–159)	62 (24–127)	0.606
Albumin (g/dl)[a]	3.9 (3.7–4.1)	3.8 (3.5–4.1)	3.9 (3.7–4.1)	0.213
Cholesterol(mg/dl)[a]	137 (120–161)	129 (114–153)	139 (122–163)	0.434
Aldosterone (ng/dl)[a]	11.5 (7.3–18.0)	19.1 (10.7–40.3)	9.7 (6.8–14.2)	**0.005**
Hemoglobin (g/dl)[a]	12.8 (11.3–14.5)	12.8 (10.9–14.0)	12.8 (11.7–14.6)	0.394

DR, diuretic response; MRA, mineralocorticoids receptor antagonists; SLGT2i, Sodium–glucose cotransporter 2 inhibitors; RAASi, Renin-angiotensin-aldosterone system inhibitors; LVEF, left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; NTproBNP, N-terminal pro-brain natriuretic peptide; CA125, cancer antigen 125. Bold type: statistically significant values.

[a]*Continous variables are expressed by medians and interquartile range.*

These patients showed some characteristics traditionally described in patients with diuretic resistance in other settings.

Natriuresis and Diuresis in Acute Heart Failure

Sodium and fluid retention is a hallmark of HF. As effective diuretic response is produced by natriuresis, urinary sodium has emerged as a useful parameter to predict natriuretic response in patients with HF soon after diuretic administration (Verbrugge et al., 2014), which can be measured from a urinary spot sample with good accuracy (Testani et al., 2016). In this line, several studies have reported the usefulness of natriuresis after the first dose of diuretic to predict long-term adverse events (Singh et al., 2014; Honda et al., 2018; Luk et al., 2018; Biegus et al., 2019; Hodson et al., 2019), and two studies have also suggested its usefulness in detecting the development of worsening HF during hospitalization (Collins et al., 2019; Cobo -Marcos et al., 2020).

Although a high diuresis volume following a first intravenous loop diuretic administration is usually associated with good diuretic response and a high urinary sodium (Testani et al., 2016; Singh et al., 2014), some data indicate that in patients with low to medium volume output, spot urinary sodium content offers independent prognostic information (Brinkley et al., 2018). Indeed, in our cohort only 4 patients (5.5%) had both low urinary sodium and a decreased urine output.

Therefore, a spot urine sodium content of <50–70 mEq/L after 2 h, and/or an hourly urine output <100–150 ml during the first 6 h, provide additional information and could identify patients with an insufficient diuretic response.

Characteristics of Patients With Insufficient Diuretic Response

The present study confirms findings from previous studies, that a poor response is associated with some features of more advanced disease (Metra et al., 2012; Neuberg et al., 2002; Valente et al., 2014; ter Maaten et al., 2015b; Testani et al., 2014; Voors et al., 2014; ter Maaten et al., 2015a). In our cohort 43% of the patients had a previous HF hospitalization, and the outpatient diuretic dose was high. Besides, compared with patients with an adequate diuretic response, these patients had lower systolic blood pressure at admission, worse glomerular filtration rate, and showed greater neurohormonal activation. It should be noted that variables such as age, left ventricular ejection fraction or natriuretic peptides are not usually associated with the diuretic response in different studies (Metra et al., 2012; Neuberg et al., 2002; Valente et al., 2014; ter Maaten et al., 2015b; Testani et al., 2014; Voors et al., 2014; ter Maaten et al., 2015a). Furthermore, in our cohort no other clinical (Charlson index, Everest score) or echocardiogram features (TAPSE, inferior cava vein) were different between both populations. These data highlight the role of this algorithm in the evaluation of diuretic response in this setting.

Finally, although this study didn't assess long term events, we showed that patients with a worse diuretic response required diuretic association and inotropes more frequently during admission.

Feasibility of the ESC Algorithm

At this time, two other studies are evaluating the performance of this diagnostic strategy, the ENACT-HF trial (Rationale and Design of the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure Study) (Dauw et al., 2021), and the PUSH-HF trial (Natriuresis-guided therapy in acute heart failure: rationale and design of the Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart) (Maaten et al., 2022).

It should be noted that this novel algorithm involves a more proactive approach and closer monitoring of the diuretic response.

This requires specific training and coordinated and continuos collaboration between the professionals involved in the management of HF patients, especially with emergency department staff, in order to extend the implementation of this diuretic protocol.

Limitations

Our cohort consisted of 73 patients from one academic institution so the findings may not be generalizable to the wider acute HF population.

In addition, there is a low percentage of patients included (11%) in terms of overall acute HF admissions. Patients with predominantly pulmonary congestion without other congestion signs were not included. Some patients didn't follow the protocol by decision of the responsible staff. Recruitment was also affected by the COVID-19 pandemic.

CONCLUSION

The diagnostic algorithm based on diuresis and natriuresis provided complementary information and was capable of early detection of up to 29% of patients with acute HF from this cohort who presented an insufficient diuretic response.

This finding may help to stratify patients who may benefit from more intense treatment for decongestion during hospital admission.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Comité de Ética e Investigación con Medicamentos (CEIm) del Hospital Puerta de Hierro Majadahonda. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MC-M, FD, PG-P and JS contributed to conception and design of the study. AiM, MM, AS, and CG, contributed to

the patient inclusion. DD, PM, FT, RG, AnM, and DE contributed to the data inclusion on the database. AG organized the laboratory tests. MC-M organized the database. BG-M performed the statistical analysis. BG-M and EH wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Pulmonary Congestion Assessed by Lung Ultrasound and Cardiovascular Outcomes in Patients With ST-Elevation Myocardial Infarction

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Background: Lung ultrasound (LUS) shows a higher sensitivity when compared with physical examination for the detection of pulmonary congestion. The objective of our study was to evaluate the association of pulmonary congestion assessed by LUS after reperfusion therapy with cardiovascular outcomes in patients with ST-segment Elevation acute Myocardial Infarction (STEMI) who received reperfusion therapy.

Methods: A prospective observational study including patients with STEMI from the PHASE-Mx study. LUS was performed in four thoracic sites (two sites in each hemithorax). We categorized participants according to the presence of pulmonary congestion. The primary endpoint of the study was the composite of death for any cause, new episode or worsening of heart failure, recurrent myocardial infarction and cardiogenic shock at 30 days of follow-up.

Results: A total of 226 patients were included, of whom 49 (21.6%) patients were classified within the "LUS-congestion" group and 177 (78.3%) within the "non-LUS-congestion" group. Compared with patients in the "non-LUS-congestion" group, patients in the "LUS-congestion" group were older and had higher levels of blood urea nitrogen and NT-proBNP. Pulmonary congestion assessed by LUS was significantly associated with a higher risk of the primary composite endpoint (HR: 3.8, 95% CI 1.91–7.53, $p = 0.001$). Differences in the primary endpoint were mainly driven by an increased risk of heart failure (HR 3.91; 95%CI 1.62–9.41, $p = 0.002$) and cardiogenic shock (HR 3.37; 95%CI 1.30–8.74, $p = 0.012$).

Conclusion: The presence of pulmonary congestion assessed by LUS is associated with increased adverse cardiovascular events, particularly heart failure and cardiogenic shock.

Abbreviations: LUS, Lung ultrasound; KKC, Killip-Kimball class; STEMI, ST-segment elevation myocardial infarction; HF, heart failure; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; GRACE, Global Registry on Adverse Cardiovascular Events.

The application of LUS should be integrated as part of the initial risk stratification in patients with STEMI as it conveys important prognostic information.

Keywords: STEMI, lung ultrasound, pulmonary congestion, acute heart failure, heart failure

INTRODUCTION

Pulmonary congestion is a powerful prognostic factor for the detection of adverse cardiovascular events, including death, in patients with STEMI (Killip and Kimball, 1967). In addition, the presence of pulmonary congestion increases the discriminatory capacity of scoring classifications such as Thrombolysis in Myocardial Infarction (TIMI) and Global Registry on Adverse Cardiovascular Events (GRACE) (Bedetti et al., 2010).

Lung ultrasound is a non-invasive, risk-free tool that has demonstrated to be superior when compared with physical examination for the detection of pulmonary congestion due to a higher sensitivity (Gopar -Nieto et al., 2019). However, the association between the degree of pulmonary congestion detected by LUS and cardiovascular outcomes in patients with STEMI has not been completely elucidated.

The objective of our study was to evaluate the association of pulmonary congestion assessed by LUS with cardiovascular outcomes in patients with STEMI.

MATERIALS AND METHODS

Study Population and Design

The study population derives from PHASE-Mx Study "PHArmacoinvasive Strategy vs. primary PCI in STEMI: a prospective registry in a largE geographical area" (www.clinicaltrials.gov NCT03974581); the description, design, scope and detailed results of PHASE-MX study have been published elsewhere (Baeza -Herrera et al., 2020; Araiza-Garaygordobil et al., 2021a). Briefly, this prospective observational study was conducted from March 2018 to March 2020 and included adults older than 18 years-old diagnosed with STEMI, who received reperfusion treatment in the first 12 h since symptoms onset. Patients with previous diagnosis heart failure (HF), pulmonary diseases, >12 h from symptom onset to treatment, unknown ischemic time, those who did not receive acute reperfusion, with in- hospital STEMI from other causes, or with a discharge diagnosis other than STEMI were excluded. Lung ultrasound was performed during the first 24 h from symptom onset and after reperfusion therapy. The protocol received local research and ethics committee approval (PT-19-109) and complies with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to study inclusion.

Lung Ultrasound Technique

LUS was performed using a portable device equipped with a 3.8 MHz phased array transducer (VScan® Dual Probe; GE Healthcare, Chicago, IL, United States) during the first 24 h of hospitalization and after reperfusion therapy. LUS was recorded in four thoracic sites, two sites in each hemithorax (4-point method) (**Figure 1**) with the transducer in axial orientation and at 18 cm imaging depth with the patient in semi-recumbent position, following expert panel recommendations (Platz et al., 2019). The number of B-lines reported was the higher sum of B-lines visualized in each site during a 3-s clip.

Definition of Pulmonary Congestion

For analytical purposes, participants who had at least one bilateral quadrant with ≥3 B-lines were considered within the "LUS-congestion" group; the rest of the participants were considered within the "non-LUS-congestion" group.

Outcomes

The patients were followed-up by a pre-specified visit. As the follow-up was short, no losses were recorded. The primary endpoint was the composite of death for any causes, new episode or worsening of HF, recurrent myocardial infarction (MI) and cardiogenic shock at 30 days of follow-up. HF was defined as the onset or worsening of symptoms such as dyspnea, edema, orthopnea or initiation/increase of intravenous diuretics dose. Recurrent MI was defined according to the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials (Hicks et al., 2018). Cardiogenic shock was defined as systolic blood pressure lower than 90 mm Hg or use of vasopressors with signs of poor peripheral perfusion, secondary to low cardiac output (assessed by echocardiography) at any time during hospitalization.

Sample Size Estimation

Based on an interim analysis after the enrollment of the first 60 patients, considering an estimated incidence of the primary endpoint to be around 10% at 30 days follow-up, an expected absolute difference of the occurrence of the primary endpoint between groups of 15%, and accounting for a power (1-β) of 80% and an alpha level of 0.05%, a sample size of 194 patients was calculated. Accounting for 10% potential losses during follow-up, a final sample of 214 patients was estimated.

Statistical Analysis

Categorical variables were expressed as relative and absolute frequencies. Continuous variables were expressed as means (standard deviation) or medians (interquartile range). Covariates were compared between congestion groups using Student's t test, Mann-Whitney's U test and Chi square test, as appropriate. Time to occurrence of the primary outcome was evaluated with Kaplan-Meier curves, log-rank test and Cox proportional hazards models. We used a multivariate model adjusted for age, sex and NT-proBNP, and it was tested with the variables that showed significance after univariate analysis. Inter and intra-observer agreement in LUS interpretation was

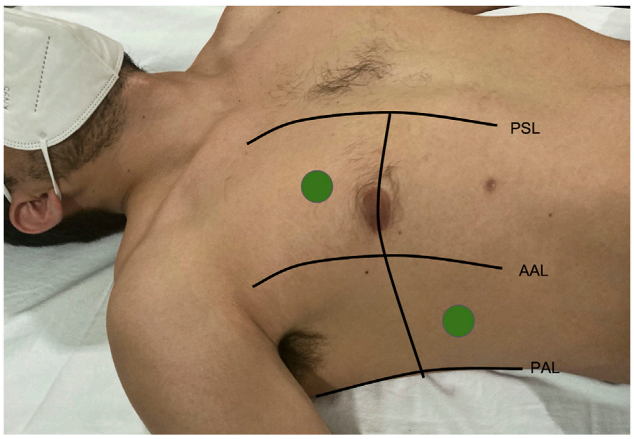

FIGURE 1 | Schematic lung ultrasound technique.

evaluated with intraclass correlation coefficients and is included in the Supplementary Appendix S1. A two-sided level of 0.05 was considered significant. Stata 14 (STATA corp) was used for all analyses, and results were reported following STROBE diagram and checklist (Von Elm et al., 2007).

RESULTS

From the total population included in the PHASE-Mx study, LUS was performed only in 329 of which 103 were excluded due to the following specific causes: 91 patients due to failed thrombolysis, six patients due to first contact time greater that 12 h, three patients due to previous heart failure, and three patients due to previous revascularization surgery. Therefore, the final analytic sample consisted of 226 patients. Baseline laboratory characteristics were taken at hospital admission, while lung ultrasound was performed at any time after revascularization and within 24 h from the symptom onset. There were 49 (21.6%) patients classified within the "LUS-congestion" group and 177 (78.3%) within the "non-LUS-congestion" group (**Figure 2**). Baseline characteristics of the study population stratified by presence or absence of LUS congestion are summarized in **Table 1**. Compared with patients in the "non-LUS-congestion" group, patients in the "LUS-congestion" group were older (61.51 vs. 57.23 years, p = 0.015) and had higher levels of blood urea nitrogen (21.22 vs. 17.75 mg/dl, p = 0.023) and NT-proBNP (3,488.01 vs.1377.04 pg/ml, $p < 0.001$).

Patients in the LUS-congestion group had higher TIMI, GRACE and CRUSADE scores compared to patients in the non-LUS-congestion group. The total ischemic time was not different between patients with and without pulmonary congestion (median time: 316 vs. 282 min, respectively, p = 0.169). A higher proportion of patients with LUS congestion (55.3%) were classified as Killip-Kimball class (KKC) >I compared with patients in the non-LUS- congestion group (30.4%) ($p < 0.001$).

Outcomes

Overall, 14.60% (n = 33) of patients presented the primary outcome after 30 days of follow-up. Pulmonary congestion assessed by LUS was significantly associated with a higher risk of the primary composite endpoint (HR: 3.8, 95%CI 1.91–7.53, p = 0.001) (**Figure 3**). Differences in the primary endpoint were mainly driven by an increased risk of heart failure (HR 3.91; 95% CI 1.62–9.41, p = 0.002) and cardiogenic shock (HR 3.37; 95%CI

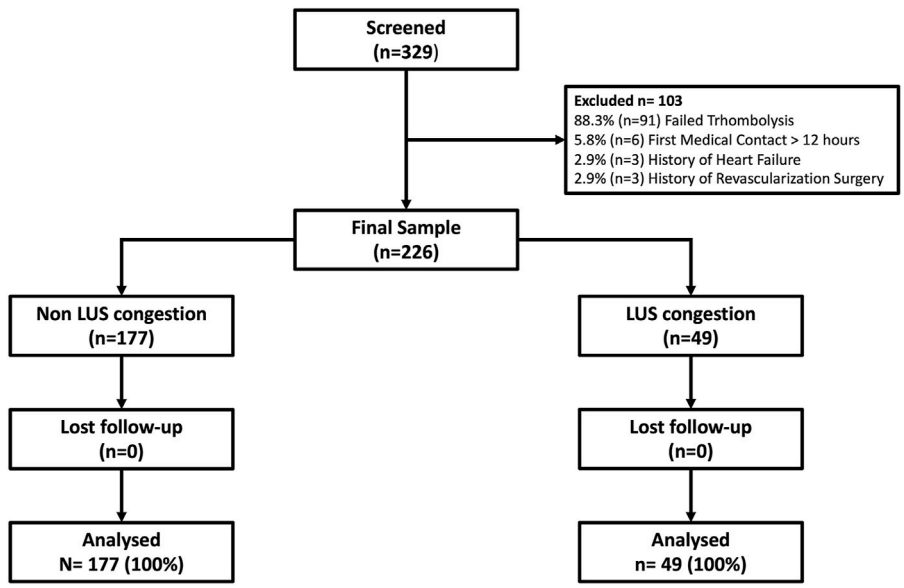

FIGURE 2 | Flowchart of the sampling process.

TABLE 1 | General characteristics of the population according to pulmonary congestion evaluated by LUS.

	Overall	No LUS congestion *n* = 177	LUS congestion *n* = 49	*p* Value
Demographic characteristics				
Male, (%)	202 (89.3)	162 (93.64%)	40 (85.11%)	0.058
Age, (IQR)	59.9 (50–65)	57.23 (49–64)	61.51 (56–66)	0.015
Diabetes, (%)	66 (29.33)	53 (30.11%)	13 (26.53%)	0.0626
Hypertension, (%)	100 (55.25%)	74 (41.81%)	26 (53.06%)	0.160
Dyslipidemia, (%)	39 (17.26%)	33 (18.64%)	6 (12.24%)	0.294
Current smokers, (%)	109 (48.23)	87 (49.15%)	22 (44.90%)	0.598
Ever smokers, (%)	31 (13.72%)	24 (13.56%)	7 (14.29%)	0.896
Obesity, (%)	48 (21.24%)	40 (22.60%)	8 (16.33%)	0.342
Previous PCI, (%)	12 (5.31%)	11 (6.21%)	1 (2.04%)	0.222
Previous CABG, (%)	2 (0.88%)	1 (0.56%)	1 (2.04%)	-
Admission characteristics				
Heart Rate (IQR)	77.63 (67.89)	76.70 (65–89)	81.02 (70–89)	0.111
Respiratory Rate (IQR)	18.33 (16–19)	18.10 (16–18)	19.14 (16–20)	0.422
Systolic Blood Pressure (IQR)	131.30 (114–146)	131.02 (115–145)	132.30 (111–149)	0.751
Diastolic Blood Pressure (IQR)	81.65 (70–90)	81.61 (70.90)	81.77 (70–92)	0.952
Glucose (normal range 70–105 mg/dl) (IQR)	191.54 (124–225)	186.72 (124–216)	208.93 (124–273)	0.172
Creatinine (normal range 0.5–0.9 mg/dl) (IQR)	1.23 (0–1)	1.23 (0–1)	1.22 (0–1)	0.972
BUN (normal range 6–20 mg/dl) (IQR)	17 (14–21)	16 (14–20)	19 (15–25)	0.006
LVEF (SD)	44.68 (11.95)	45.39 (11.7)	42.57 (12.3)	0.154
Troponin (normal range 3–14 pg/ml) (IQR)	24.83 (0–50)	23.92 (0–39)	28.10 (0–59)	0.408
NT-ProBNP (normal range 15–450 ng/ml) (IQR)	541.5 (125–2209)	384 (113–1371)	1701 (407–4025)	0.001
TIT (min) (IQR)	270 (171–382)	261 (155–367)	280 (190–420)	0.169
Reperfusion method				
Thrombolysis, (%)	92 (40.71)	77 (43.50)	15 (30.61)	0.104
DNT (IQR)	79.93 (25–90)	81.96 (58–99.2)	73.92 (23–112.5)	0.262
PCI, (%)	134 (59.29)	100 (56.50)	34 (69.39)	0.104
DBT (IQR)	90.03 (59–99)	85.96 (58–99.2)	100.2 (60–102.2)	0.262
Prognostic scales				
Killip-Kimball Class				<0.001
Class I	139 (61.5%)	118 (66.6%)	21 (42.8%)	
Class II	76 (33.62%)	56 (31.6)	20 (40.8%)	
Class III	4 (1.76%)	2 (1.12%)	2 (9.8%)	
Class IV	7 (3.09%)	1 (0.56%)	6 (12.2%)	
TIMI (IQR)	3.42 (3.12–3.73)	3.25 (2.93–3.5)	4.08 (3.25–4.91)	0.028
GRACE (IQR)	121.05 (166.21–125.91)	117.28 (112–122.41)	135.02 (123.7o–146.96)	0.003
CRUSADE (IQR)	27.65 (25.4–29.8)	25.92 (23.85–27.99)	33.73 (27.14–40.32)	0.003
Angiographic characteristics				
Culprit artery				0.465
LMCA, (%)	9 (4.57)	6 (3.90)	3 (6.98)	
LADA, (%)	80 (38.96)	60 (38.96)	20 (46.51)	
Circumflex artery, (%)	21 (10.66)	16 (10.39)	5 (11.63)	
RCA, (%)	87 (44.16)	72 (46.75)	15 (34.88)	
No reflow phenomenon, (%)	29 (20.71%)	21 (20%)	8 (22.86%)	0.718

IQR, interquartile range; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BUN, blood urea nitrogen; LVEF, left ventricular ejection fraction; SD, standard deviation; NT-ProBNP, N-terminal pro-B type natriuretic peptide; TIT, total ischemic time; DNT, door needle time; DBT, door balloon time; TIMI, thrombolysis in myocardial infarction; GRACE, global registry on acute coronary events; CRUSADE, Can Rapid risk of major bleeding of Unstable angina patients suppress Adverse outcomes with Early implementation of the ACC/AHA, guidelines; LMCA, left main coronary artery; LADA, left anterior descending artery; RCA, right coronary artery.

1.30–8.74, $p = 0.012$). (**Figure 4**). No significant differences were noted in the rates of reinfarction and cardiovascular mortality **Table 2** shows the proportion of events according to the presence or absence of LUS- congestion.

After multivariable analysis, the association of LUS-congestion and the occurrence of the primary endpoint remained statistically significant and exceeded the effect of other clinically relevant variables such as age, diabetes, TIMI and GRACE scores and

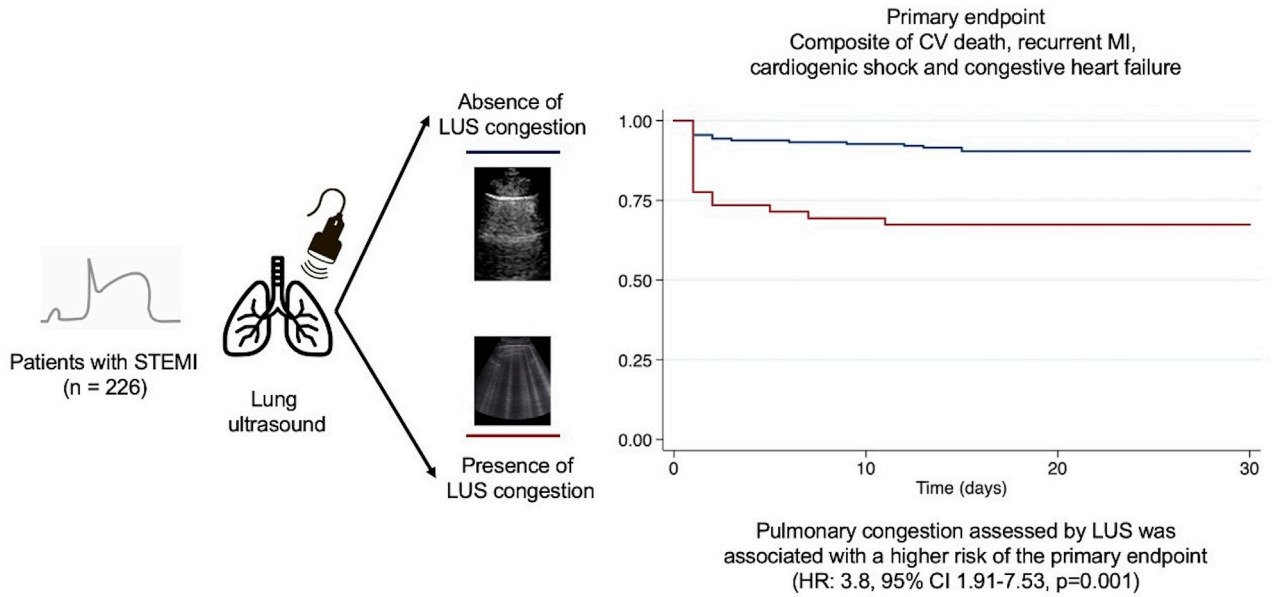

FIGURE 3 | Central figure. Kaplan Meier estimates for the primary endpoint in patients with STEMI and pulmonary congestion assessed by lung ultrasound.

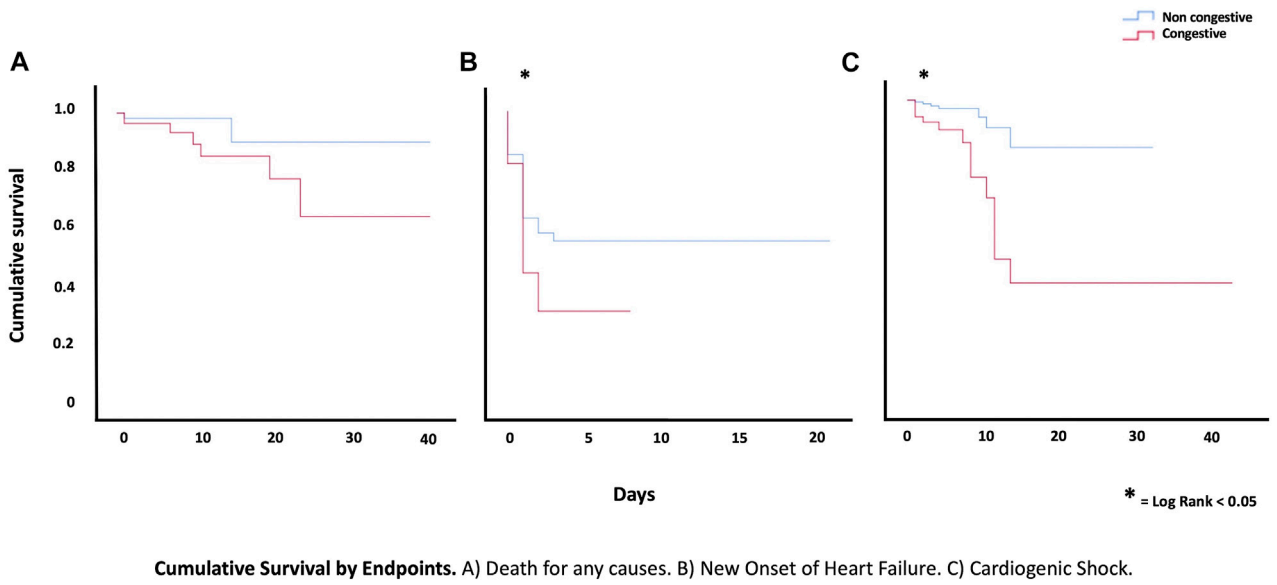

FIGURE 4 | Cumulative Survival by Endpoints. **(A)** Death for any causes. **(B)** New Onset of Heart Failure **(C)** Cardiogenic Shock.

NT-proBNP (**Table 3**). Finally, the sensitivity, specificity and area under the ROC curve to predict the composite primary outcome were 60, 77.2 and 73%, respectively. The incremental prognostic value of LUS-congestion (when compared with KKC) as assessed by integrated discrimination improvement (IDI) was 6.0% (95%CI 4.3–8.7, $p < 0.001$).

DISCUSSION

In the present study, pulmonary congestion assessed by LUS in patients with STEMI was associated with a higher frequency of adverse cardiovascular events, particularly acute HF and cardiogenic shock.

TABLE 2 | Outcomes in patients with ST-segment elevation myocardial infarction and pulmonary congestion assessed by LUS.

	Overall	Without congestion N = 177	Congestion *n* = 49	*p*
Primary Outcome, n (%)	34 (15%)	17 (9.6%)	17 (34.69%)	0.001
Heart Failure, n (%)	20 (8.85%)	10 (5.65%)	10 (20.41%)	0.001
Reinfarction*, n (%)	2 (0.56%)	1 (0.56)	1 (2.04)	0.387*
Death for any causes, n (%)	11 (4.8)	6 (3.39%)	5 (10.2%)	0.063*
Cardiogenic shock, n (%)	17 (7.52%)	9 (5.08%)	8 (16.33%)	0.008

**Fisher's exact test. IQR, interquartile range (Q1–Q3); LUS, lung ultrasound.*

TABLE 3 | Predictors of the primary outcome in Cox regression analysis.

	Univariate		Multivariate	
	HR CI 95%	*p*	HR CI 95%	*p*
Age >60 years	3.80 (1.91–7.53)	0.001	1.82 (0.79–4.19)	0.159
Diabetes Mellitus	3.05 (1.53–6.05)	0.001	2.62 (1.28–5.33)	0.008
TIMI >4 points	5.32 (2.30–12.32)	0.001	2.63 (1.03–6.69)	0.042
GRACE score >140	2.86 (1.44–5.66)	0.003	1.53 (0.73–3.23)	0.255
Pulmonary Congestion (LUS)	3.80 (1.91–7.53)	0.001	3.17 (1.52–6.62)	0.002
NT-ProBNP	3.86 (1.79–8.32)	0.001	1.61 (0.68–3.80)	0.277

GRACE, global registry on acute coronary events; HR, hazard ratio; LUS, lung ultrasound; TIMI, thrombolysis in myocardial infarction.

The interest in the use of LUS as a non-invasive tool for semi-quantification of pulmonary congestion has grown in recent years (Platz et al., 2017; Picano et al., 2018). LUS has demonstrated to be superior in the detection of pulmonary congestion in patients with HF, showing a higher sensitivity when compared with physical examination or chest X-ray (Pivetta et al., 2019; Araiza-Garaygordobil et al., 2021b). Furthermore, studies including patients with chronic or acute decompensated HF have demonstrated that LUS derived B- lines have an important prognostic role for the detection of HF-derived events, such as rehospitalizations or cardiovascular mortality (Miglioranza et al., 2017; Rivas-Lasarte et al., 2019; Araiza-Garaygordobil et al., 2020). This prognostic role exceeds that of other commonly used congestion evaluation parameters such as clinical examination or concentrations of natriuretic peptides (Miglioranza et al., 2013).

Acute HF after MI is a potentially serious complication that increases mortality. Detection of signs of HF after MI allows the identification of a subgroup of patients with worse prognosis. Reduced left ventricular ejection fraction, increased concentrations of natriuretic peptides, increased pulmonary capillary wedge pressure (using a pulmonary flotation catheter), and physical examination showing signs of HF (lung crackles, presence of a third heart sound, jugular vein distention or peripheral oedema) have all been associated with increased hospital mortality after MI (Platz et al., 2017; Öhman et al., 2018; Ye et al., 2019). LUS may complement the findings of the aforementioned techniques with additional advantages such as low cost, bedside availability and no associated risks. Recently, a prospective observational study (Araujo et al., 2020) documented the prognostic ability of admission LUS in 215 patients with STEMI. The investigators reported an area under the ROC curve of 0.89 for in-hospital mortality and a 0.18 net reclassification improvement over the KKC. It is worth mentioning that absence of pulmonary congestion detected by LUS implied a negative predictive value for in-hospital mortality of 98.1%. Likewise, our study shows consistent results, with an increased risk of adverse outcomes seen in those patients showing LUS congestion.

There are some limitations in our study. One of the most important limitations is that our study may be influenced by selection bias. As our Institute is a reference center, it is possible that some patients, who were unable to be transferred because of instability or who could have died before reaching our center, were not registered in our study. This would explain a relatively low frequency of some risk factors of adverse events, manifested by the low frequency of stage III or IV of the KKC, and lower TIMI score values. There is a small difference, with no statistical significance, in the pulmonary congestion group, as more received primary PCI. This could be related to the administration of contrast; unfortunately, we do not have the amount of contrast administered in each study. Although there is a difference mortality, it is not statistically significant, which may be determined by the relatively small sample size.

Lung ultrasound was performed after reperfusion therapy, and although the type of reperfusion strategy is balanced between both groups, we believe it may be one of the factors that influenced the limitation to predict mortality. To date, we do not know the influence of timely reperfusion on the presence and variation of the number of B-lines in STEMI patients. Nonetheless, a statistically significant association between the presence of B-lines in STEMI and major adverse endpoints during hospital stay was found, which strengthens the importance of pulmonary congestion among patients with STEMI, even after adequate reperfusion therapy was received.

LUS is a readily available, risk-free diagnostic tool that predicts adverse cardiovascular events in patients with STEMI. The application of this technique should be integrated as part of the initial risk stratification protocol for all patients with suspected STEMI as it conveys important prognostic information.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article is available under reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Ética e Investigación del Instituto Nacional de Cardiología—Ignacio Chávez. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LB conceived and designed the research, drafted the original manuscript. DA designed the research and is the responsible of the work. RG, AC, and PM performed statistical analysis and interpretation of data. FS drafted de manuscript. DA, FS, DS, and JB made critical revision of the manuscript for critical intellectual content. VS. acquired the data and reviewed and edited the manuscript. HG and AA approved the publication of the content.

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The Association Between Congestive Heart Failure and One-Year Mortality After Surgery in Singaporean Adults: A Secondary Retrospective Cohort Study Using Propensity-Score Matching, Propensity Adjustment, and Propensity-Based Weighting

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Background: Although congestive heart failure (CHF) is considered a risk factor for postoperative mortality, reliable quantification of the relationship between CHF and postoperative mortality risk is limited. We aimed to investigate the association between CHF and 1-year mortality after surgery in a large cohort of the Singaporean population.

Methods: In this retrospective cohort study, the study population included 69,032 adult patients who underwent surgery at Singapore General Hospital between 1 January 2012 and 31 October 2016. The target independent and dependent variables were CHF and 1-year mortality after surgery, respectively. Propensity score was estimated using a non-parsimonious multivariable logistic regression model. Multivariable adjustment, propensity score matching, propensity score adjustment, and propensity score-based weighting Cox proportional-hazards regression were performed to investigate the association between CHF and 1-year mortality after surgery.

Results: The multivariate-adjusted hazard ratio (HR) in the original cohort was 1.39 (95% confidence interval (CI): 1.20–1.61, $P < 0.001$). In additional propensity score adjustment, the HR between CHF and 1-year mortality after surgery was 1.34 (95% CI: 1.15–1.56, $P < 0.001$). In the propensity score-matched cohort, the multivariate-adjusted Cox proportional hazard regression model analysis showed participants with CHF had a 54% increased risk of 1-year mortality after surgery (HR 1.54, 95% CI: 1.19–1.98, $P < 0.001$). The multivariate-adjusted HR of the inverse probability of

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treatment-weighted and standardised mortality ratio-weighted cohorts was 1.34 (95% CI: 1.10–1.62, $P = 0.004$) and 1.24 (95% CI: 1.17–1.32, $P < 0.001$), respectively.

Conclusion: CHF is an independent risk factor for 1-year mortality after surgery in patients undergoing surgery. Depending on the statistical method, patients with CHF had a 24–54% increased risk of 1-year all-cause mortality after surgery. This provides a reference for optimising clinical decision-making, improving preoperative consultation, and promoting clinical communication.

Keywords: heart failure, standardised mortality ratio-weighted, propensity-score matching, inverse-probability-of-treatment-weighted, mortality

INTRODUCTION

Congestive heart failure (CHF) is the leading cause of morbidity and mortality worldwide (1). Its prevalence is more than 22 million cases worldwide, with the incidence of 2 million new cases per year (2). The 5-year mortality rate is 62% for women and 75% for men after CHF (3). With advancements in medical care, an increasing number of patients with CHF may select surgery to treat certain diseases. Therefore, it is imperative to improve our understanding of the impact of HF on postoperative outcomes. Although CHF has been recognised as a risk factor for postoperative mortality and has been incorporated into several risk indicators (4–8), few studies have examined the relationship between CHF and postoperative mortality. The hazard ratio (HR)/odds ratio (OR) produced by previous studies on the relationship between CHF and the prognosis of surgical patients varied widely (9–11).

Previous studies have mainly applied traditional parsimonious regression models based on analytical adjustments to control for confounders. However, such models may still result in a bias owing to unmeasured or residual confounding of the model and overfitting (12, 13). Research methods based on propensity score (PS) are considered the core alternative for controlling the confounding of observational research. Both large and small sample theories show that adjustment for the scalar PS is sufficient to remove bias due to all observed covariates (14, 15). Several adjustment methods incorporating the estimated PS have been proposed, including matching, regression adjustment, and weighting (13, 15–18).

Therefore, based on the current status of research on the impact of CHF on the prognosis of surgical patients, no studies have applied PS-based methods to investigate this relationship. We used a large sample of patients discharged from a general hospital in Singapore to study the differential impact of CHF on surgical outcomes using various statistical models.

Abbreviations: CHF, congestive heart failure; IPTW, inverse probability of treatment-weighted; SMR, standardised mortality ratio; HF, heart failure; PSM, propensity score matching; RCT, randomised controlled trials; CVA, previous cerebrovascular accidents; IHD, ischaemic heart disease; DMI, diabetes mellitus on insulin; ASA-PS, American Society of Anaesthesiologists Physical Status; RDW, red cell distribution width; HR, hazard ratios; SD, standardised differences; CAD, coronary artery disease.

MATERIALS AND METHODS

Data Source and Participants

This was a post-mortem analysis of a large vertical cohort established by Yilin Eileen Sim's team in Singapore. The analysed data were stored in the Dryad database[1] by Yilin et al. The author of the original study waived all copyrights and related ownership of these data. Therefore, we can use these data for secondary analysis without infringing on the rights of the author. The data were obtained from a published paper: Sim et al. (19).

These clinical records were obtained from the hospital's clinical information system [Sunrise Clinical Manager (SCM); Allscripts, IL,United States]. The mortality and follow-up data of the original study were paired with their national electronic health records. The variables included in the database file were as follows: sex, age, race, history of previous cerebrovascular accidents (CVA), history of ischaemic heart disease (IHD), history of diabetes mellitus on insulin (DMI), history of CHF, creatinine category, priority of surgery, surgical risk classification, American Society of Anaesthesiologists Physical Status (ASA-PS), red cell distribution width (RDW) category, stage of chronic kidney disease (CKD), degree of anaemia, type of anaesthesia (general or regional anaesthesia), follow-up days, and survival status (19, 20). The original study was approved by the Institutional Review Board (SingHealth CIRB 2014/651/D), which waived the requirement for individual informed consent (19). As reported elsewhere, the current study is a secondary analysis of the original study and did not receive ethical approval (21).

Study Sample

Consistent with the original study, patients who underwent surgery at Singapore General Hospital from 1 January 2012 to 31 October 2016 and were aged ≥18 years were included. The original research exclusion criteria were as follows: (1) patients who underwent transplantation and burn surgeries, (2) patients who had no surgery, and (3) patients who underwent minor surgeries (19). The final dataset consisted of 97,443 participants. In the present study, we excluded participants with missing CHF information (n = 28,411). **Figure 1** depicts the participant selection process. Finally, our study included a total of 69,032 participants for secondary analysis.

[1] www.Datadryad.org

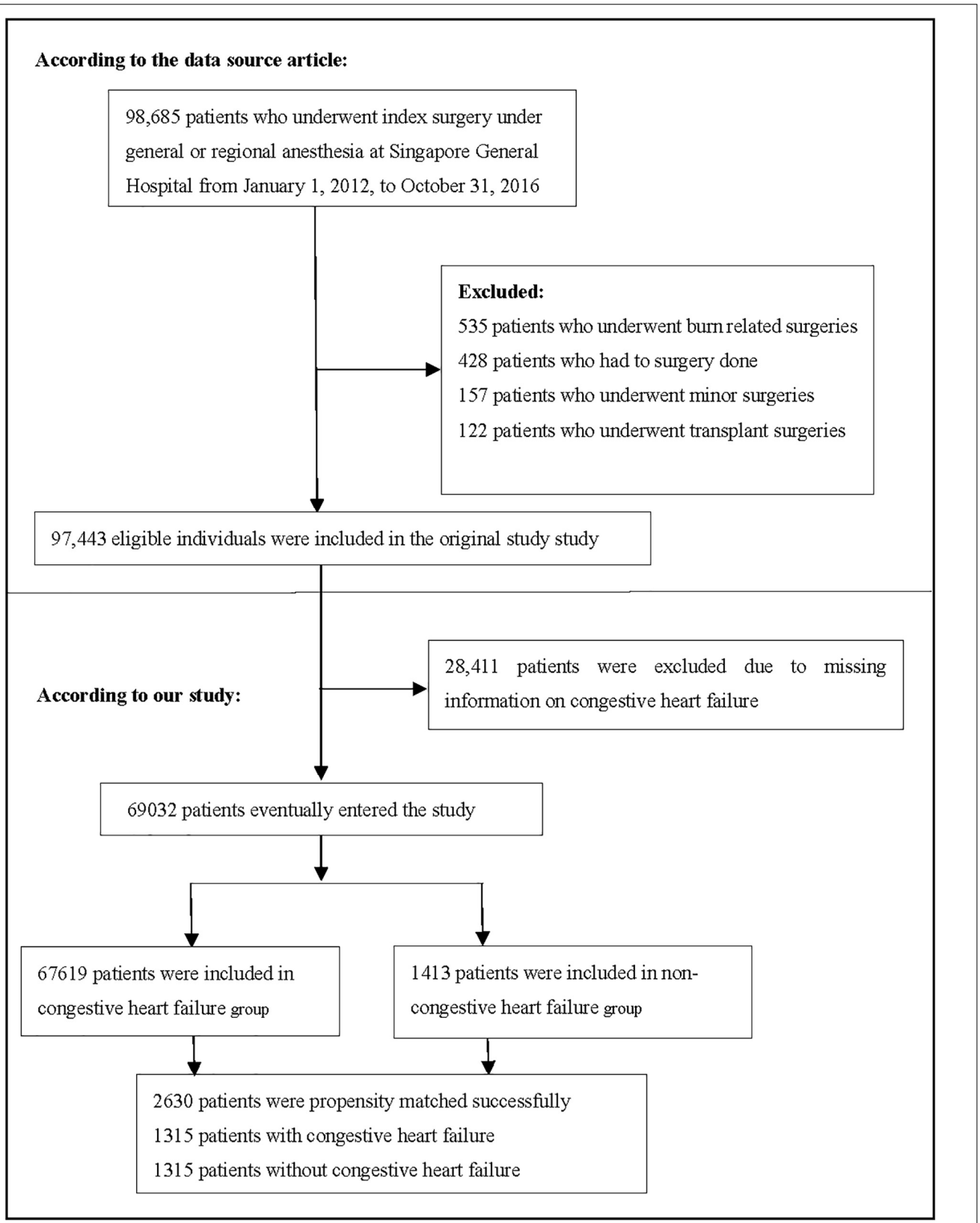

FIGURE 1 | Flowchart of study participants. It showed the process of screening participants.

Variable Definitions

Laboratory examinations were performed within 90 days of surgery. These included serum creatinine level, serum haemoglobin, and RDW. Anaemia was defined by the World Health Organization gender-based classification of anaemia severity (19, 22). The severity of anaemia is characterised as follows: mild anaemia (haemoglobin concentration: male 11–12.9 g/dL, female 11–11.9 g/dL); moderate anaemia (haemoglobin concentration: 8.0–10.9 g/dL), and severe anaemia (haemoglobin concentration: 8.0 g/dL). RDW was reported as a coefficient of variation (percentage) of red blood cell volume; levels above 15.7% were defined as high RDW, and the normal reference range for RDW was 10.9–15.7%. The target independent variable was the presence or absence of CHF history obtained at baseline. The dependent variable was 1-year mortality event during follow-up. Of the study patients, 88.7% were followed up for 1 year and mean duration of follow-up was 258 days (19).

Missing Data Processing

Missing data in observational studies are a frequently encountered problem that cannot be fully avoided. Missing data accounted for 2.71% of all variables in the dataset analysed in this study (**Supplementary Table 1**). To reduce the deviation caused by missing covariates, which cannot reflect the statistical efficiency of the target sample in the modelling process, missing data in this study adopted multiple imputations (23, 24). In the present study, the analysis steps in the original and imputed datasets were calculated and compared. Similar core results were obtained using the original and imputed datasets; thus, we report the results for the imputed dataset (**Supplementary Table 2**).

Statistical Analysis

Participants were stratified by CHF, continuous variables are expressed as median (quartile) (skewed distribution) or mean ± standard deviation (normal distribution), and categorical variables are expressed as a frequency or percentage. Two-sample *t*-tests were performed for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables and ordered categorical variables, and chi-square tests for categorical variables.

The study goal was to use different methods to control for confounding factors and evaluate the impact of CHF on the 1-year postoperative mortality of patients who underwent surgery. Specifically, we applied five methods: the original cohort multivariate-adjusted Cox proportional-hazards regression model and four PS methods. The four PS methods included PS matching multivariate-adjusted Cox proportional-hazards regression model; PS adjustment Cox proportional-hazards regression model; inverse probability of treatment-weighted (IPTW) model, and standardised mortality ratio (SMR)-weighted multivariate-adjusted Cox proportional-hazards regression model. (1) PS was estimated using a non-parsimonious multivariable logistic regression model wherein CHF was used as the independent variable, and all baseline characteristics listed in **Table 1** were covariates (25). The variables used for matching included age, sex, race, CVA, IHD, DMI, stage of CKD, degree of anaemia, priority of surgery and surgical risk classification, ASA-PS, RDW category, type of anaesthesia, matching using a 1:1 matching protocol, no replacement (greedy matching algorithm), and calliper width of 0.0005. Standardised differences (SDs) were estimated for all baseline covariates before and after matching to assess pre-matched and post-matched balance. SD of <20.0% for a given covariate indicate a relatively small imbalance (26–28). We used a multivariate-adjusted Cox proportional hazard regression model to evaluate the association between CHF and 1-year mortality after surgery in the PS-matched cohort. (2) PS adjustment: a multivariable Cox proportional-hazards model with the same strata and covariates, with additional adjustment for PS. The analysis included all patients (29–31). (3) The IPTW estimator estimates the treatment effect in a population whose risk factor distribution is equal to that found in all study subjects. IPTW was calculated as the inverse of the PS of patients with combined CHF and the inverse of (1 - PS) for non-CHF patients. The IPTW model was applied to generate a weighted cohort (15, 31, 32). IPTW multivariate-adjusted Cox proportional-hazards regression model has the same strata and covariates with inverse probability weighting according to PS. The analysis included all patients (31). (4) The SMR-weighted estimator estimates the treatment effect in a population whose distribution of risk factors is equal to that found in the treated study subjects only. SMR-weighted analyses used 1 as the value of the CHF group and the probability of propensity PS/(1 - PS) for the non-CHF group as weights and estimated the standardised effect measure for the CHF group (exposed group) as the standard population (15, 18). SMR-weighted multivariate-adjusted Cox proportional-hazards regression model, with the same strata and covariates with inverse probability weighting according to PS. All patients were included in the analysis. Cumulative mortality was used to describe mortality (15, 33). When added to the model, the covariates that changed the hazard ratios by at least 10% were considered confounders and were adjusted for in the multivariate analysis (34). In addition, Kaplan–Meier analysis and log-rank tests were performed to compare 1-year mortality after surgery.

We performed a series of sensitivity analyses to test the robustness of the results; first, because of the extreme difference in the mortality OR among the low- and high-propensity strata. Mortality was lower in patients with low PS. Therefore, we excluded participants with a PS of <0.05 and performed a sensitivity analysis using five models. Second, bias may arise because substantial CHF information was missing. We applied multiple imputations to estimate missing CHF values (n = 28,411). The imputation model included age, sex, race, CHF, CVA, IHD, DMI, stage of CKD, degree of anaemia, priority of surgery and surgical risk classification, ASA-PS, RDW category, and type of anaesthesia. Multiple statistical models were used to analyse the association between CHF and postoperative mortality in patients to verify the reliability of our analysis after excluding participants with missing CHF information. In addition, we explored the possibility of unmeasurable confounding between CHF and 1-year mortality after surgery by calculating E-values (35).

TABLE 1 | Baseline characteristics before and after propensity score matching.

	Before matching			After matching		
	CHF	**Non-CHF**	**SD (100%)**	**CHF**	**Non-CHF**	**SD (100%)**
Participants	1,413	67,619		1,315	1,315	
Age(years)			80.5			115.3
18–<30	7 (0.495%)	7,281 (10.768%)		6 (0.456%)	1 (0.076%)	
30–49	127 (8.988%)	19,047 (28.168%)		121 (9.202%)	645 (49.049%)	
50–69	737 (52.159%)	29,532 (43.674%)		686 (52.167%)	578 (43.954%)	
≥70	542 (38.358%)	11,759 (17.390%)		502 (38.175%)	91 (6.920%)	
Sex			28.3			1.4
Female	537 (38.004%)	35,139 (51.966%)		508 (38.631%)	517 (39.316%)	
Male	876 (61.996%)	32,480 (48.034%)		807 (61.369%)	798 (60.684%)	
Race			26.8			25.0
Chinese	975 (69.002%)	48,641 (71.934%)		923 (70.190%)	796 (60.532%)	
Malay	227 (16.065%)	6,641 (9.821%)		210 (15.970%)	219 (16.654%)	
Indian	147 (10.403%)	5,869 (8.680%)		126 (9.582%)	188 (14.297%)	
Others	64 (4.529%)	6,468 (9.565%)		56 (4.259%)	112 (8.517%)	
ASA-PS			220.5			20.0
1	4 (0.283%)	16,216 (23.981%)		4 (0.304%)	2 (0.152%)	
2	103 (7.289%)	38,212 (56.511%)		103 (7.833%)	68 (5.171%)	
3	1023 (72.399%)	12,122 (17.927%)		1010 (76.806%)	970 (73.764%)	
4	279 (19.745%)	1,046 (1.547%)		198 (15.057%)	268 (20.380%)	
5	4 (0.283%)	23 (0.034%)		0 (0.000%)	7 (0.532%)	
CVA			38.5			3.2
No	1237 (87.544%)	65,918 (97.484%)		1165 (88.593%)	1178 (89.582%)	
Yes	176 (12.456%)	1,701 (2.516%)		150 (11.407%)	137 (10.418%)	
IHD			150.8			7.3
No	461 (32.626%)	61,604 (91.105%)		461 (35.057%)	507 (38.555%)	
Yes	952 (67.374%)	6,015 (8.895%)		854 (64.943%)	808 (61.445%)	
DMI			46.5			11.3
No	1179 (83.439%)	65,540 (96.925%)		1117 (84.943%)	1061 (80.684%)	
Yes	234 (16.561%)	2,079 (3.075%)		198 (15.057%)	254 (19.316%)	
Creatinine category			56.1			8.8
Normal	1132 (80.113%)	65,752 (97.239%)		1077 (81.901%)	1031 (78.403%)	
High	281 (19.887%)	1,867 (2.761%)		238 (18.099%)	284 (21.597%)	
Anemia			69.8			8.9
Normal	582 (41.189%)	49,564 (73.299%)		571 (43.422%)	546 (41.521%)	
Mild	380 (26.893%)	10,087 (14.917%)		356 (27.072%)	336 (25.551%)	
Moderate	432 (30.573%)	7,710 (11.402%)		370 (28.137%)	404 (30.722%)	
Severe	19 (1.345%)	258 (0.382%)		18 (1.369%)	29 (2.205%)	
Stage of CKD			100.7			29.5
1	326 (23.071%)	41,181 (60.902%)		316 (24.030%)	383 (29.125%)	
2	442 (31.281%)	19,798 (29.279%)		424 (32.243%)	325 (24.715%)	
3	358 (25.336%)	4,316 (6.383%)		329 (25.019%)	242 (18.403%)	
4–5	287 (20.311%)	2,324 (3.437%)		246 (18.707%)	365 (27.757%)	
Anaesthesia			18.3			14.5
General	1114 (78.839%)	58,019 (85.803%)		1032 (78.479%)	1106 (84.106%)	
Regional	299 (21.161%)	9,600 (14.197%)		283 (21.521%)	209 (15.894%)	
Priority of surgery			8.1			3.2
Elective	1123 (79.476%)	55,884 (82.645%)		1050 (79.848%)	1033 (78.555%)	
Emergency	290 (20.524%)	11,735 (17.355%)		265 (20.152%)	282 (21.445%)	
Surgery risk			31.0			1.4
Low	556 (39.349%)	33,912 (50.152%)		521 (39.620%)	518 (39.392%)	
Moderate	663 (46.921%)	29,841 (44.131%)		626 (47.605%)	623 (47.376%)	
High	194 (13.730%)	3,866 (5.717%)		168 (12.776%)	174 (13.232%)	
RDW category			38.2			14.0
≤15.7%	1084 (76.716%)	61,247 (90.577%)		1034 (78.631%)	955 (72.624%)	
>15.7%	329 (23.284%)	6,372 (9.423%)		281 (21.369%)	360 (27.376%)	

Values were n (%) or mean ± SD.

SD, standardised differences; CVA, history of previous cerebrovascular accidents; IHD, history of ischemic heart disease; DMI, history of diabetes mellitus on insulin; CHF, congestive heart failure; ASA-PS, American society of anaesthesiologists physical Status; CKD, chronic kidney disease; RDW, red cell distribution width.

Differences in age and CKD stage remained between the CHF and non-CHF groups after PS matching. This may be associated with increased mortality in surgical patients (36). This may lead to overestimation of the relationship between CHF and 1-year mortality after surgery. Therefore, we stratified the participants according to CKD (stages 1–2 vs. 3–5) (37, 38). Pre-specified subgroup analyses were performed based on these two characteristics. The subgroups were based on age and CKD stage. Each stratification adjusted for all factors except the stratification factor itself. Only the corresponding matched pairs in the same subgroup were selected to maintain the balance of baseline characteristics between the CHF and non-CHF groups in subgroup analyses.

All results are reported according to the STROBE statement (39). All analyses were performed using the statistical software packages R[2] (The R Foundation) and Empower-Stats[3] (X&Y Solutions, Inc., Boston, MA, United States). All tests were two-tailed, and *P*-values of <0.05 were regarded as statistically significant.

[2]http://www.R-project.org

[3]http://www.empowerstats.com

RESULTS

A total of 69,032 participants (48.32% men and 51.68% women) were included in the analysis. Among them, 1,413 (2.05%) had CHF and 67,619 (97.95%) did not have CHF. The number of participants aged 18–29, 30–49, 50–69, and ≥70 was 7,288 (10.562%), 19,174 (27.78%), 30,269 (43.85%) and 12,301 (17.82%), respectively. PS was estimated using a non-parsimonious multivariable logistic regression model, and CHF was used as the independent variable. The variables used for matching included age, sex, race, CVA, IHD, DMI, stage of CKD, degree of anaemia, priority of surgery and surgical risk classification, ASA-PS, RDW category, type of anaesthesia, matching using a 1:1 matching protocol, no replacement (greedy matching algorithm), and calliper width of 0.0005. Before PS matching, there were differences in almost all baseline characteristics between the CHF and non-CHF groups (**Table 1**). After one-to-one matching using PS analysis, 1,315 patients with CHF were successfully matched with 1,315 non-CHF participants. After matching, except race and age, the SD for almost all variables were $<20.0\%$, indicating that the PSs were well matched. In other words, there was only a small difference in

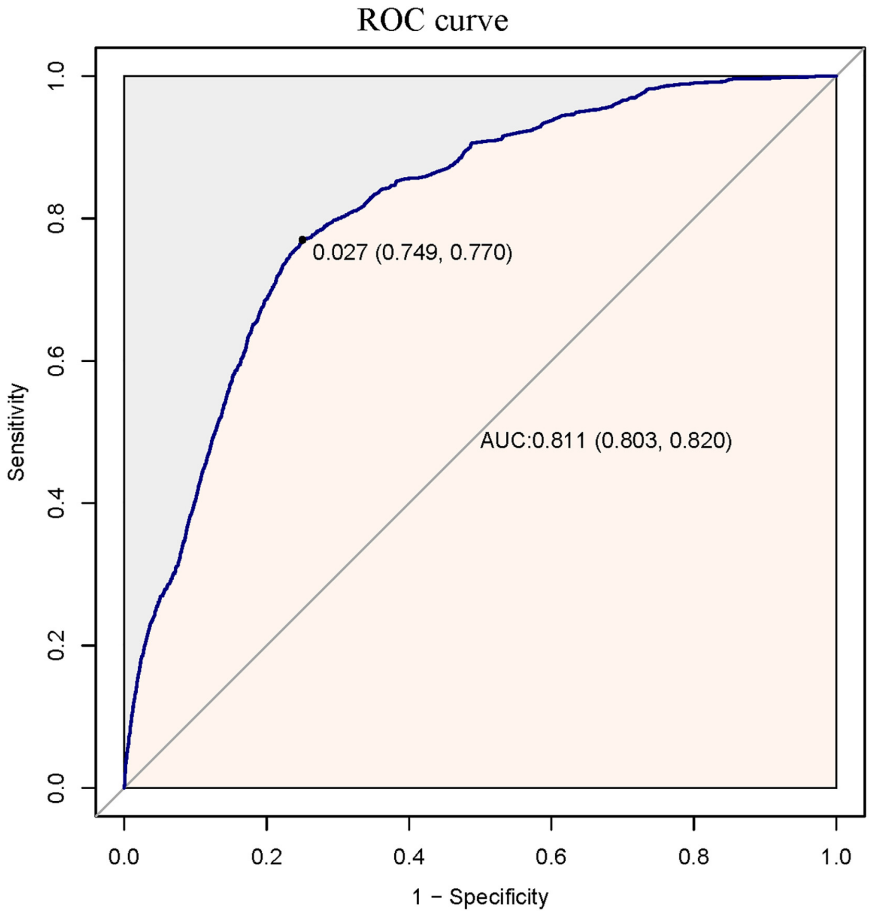

FIGURE 2 | The ROC curve of propensity score to predict one-year mortality after surgery. It showed that the logistic model used to estimate the propensity score yielded a c-statistic of 0.811.

baseline characteristics between the CHF and non-CHF groups (**Table 1**). The logistic model used to estimate PS yielded a c-statistic of 0.811 (**Figure 2**).

Supplementary Figure 1 showed that in the original cohort, the mean PS was 0.017 ± 0.049 for the CHF group and 0.163 ± 0.159 for the non-CHF group ($P < 0.01$). However, the mean PS in the matched population was 0.166 ± 0.125 for both groups ($P = 0.995$). (**Supplementary Figure 2**). The probability density functions of the PS for the CHF and non-CHF groups are summarised in **Figure 3**. As expected, the distribution of PS for the non-CHF group shifted toward 0 and for the CHF group shifted somewhat toward 1. The figure also illustrates that the overlap of PS for the CHF and non-CHF groups is limited to a narrow range (**Figure 3A** and **Supplementary Figure 3A**). The probability density functions of PS for the CHF and non-CHF groups after matching are summarised in **Figure 3B**. As expected, the distribution of PS for the CHF and non-CHF groups remained basically the same (**Supplementary Figure 3B**).

Propensity Stratum-Specific Effects

For 1-year mortality after surgery, the gradients across levels of PS for the CHF and non-CHF groups were strong and unexpectedly different. **Supplementary Table 3** summarises the proportions of patient mortality during the follow-up period in the CHF and non-CHF groups according to PS percentiles. We noted some important considerations. First, the PS of very few patients in the CHF group was below the 70th percentile of the overall PS. Second, the mortality rate of both groups increased as PS increased. The associated empirical OR for 1-year mortality after surgery increased from 0.821 in the 70th–80th percentiles of PS to 1.247 in the 99th percentile (**Supplementary Table 3**).

One-Year Mortality After Surgery

Supplementary Table 4 showed the 1-year mortality after surgery of the CHF and non-CHF groups before and after PS matching. Before PS matching, 2,307 participants died during the follow-up period. The corresponding mortality rates in the CHF and non-CHF groups were 15.9% (95% confidence interval (CI): 14.0–17.8) and 3.1% (95% CI: 2.9–3.2), respectively. After PS matching, the difference in mortality between the two groups changed significantly; the corresponding mortality rates in the CHF and non-CHF groups were 14.8% (95% CI: 12.8–16.7) and 10.0% (95% CI: 8.4–11.7). Kaplan–Meier analysis showed that the CHF group had a higher 1-year mortality after surgery than the non-CHF group in the original cohort ($P < 0.001$). After

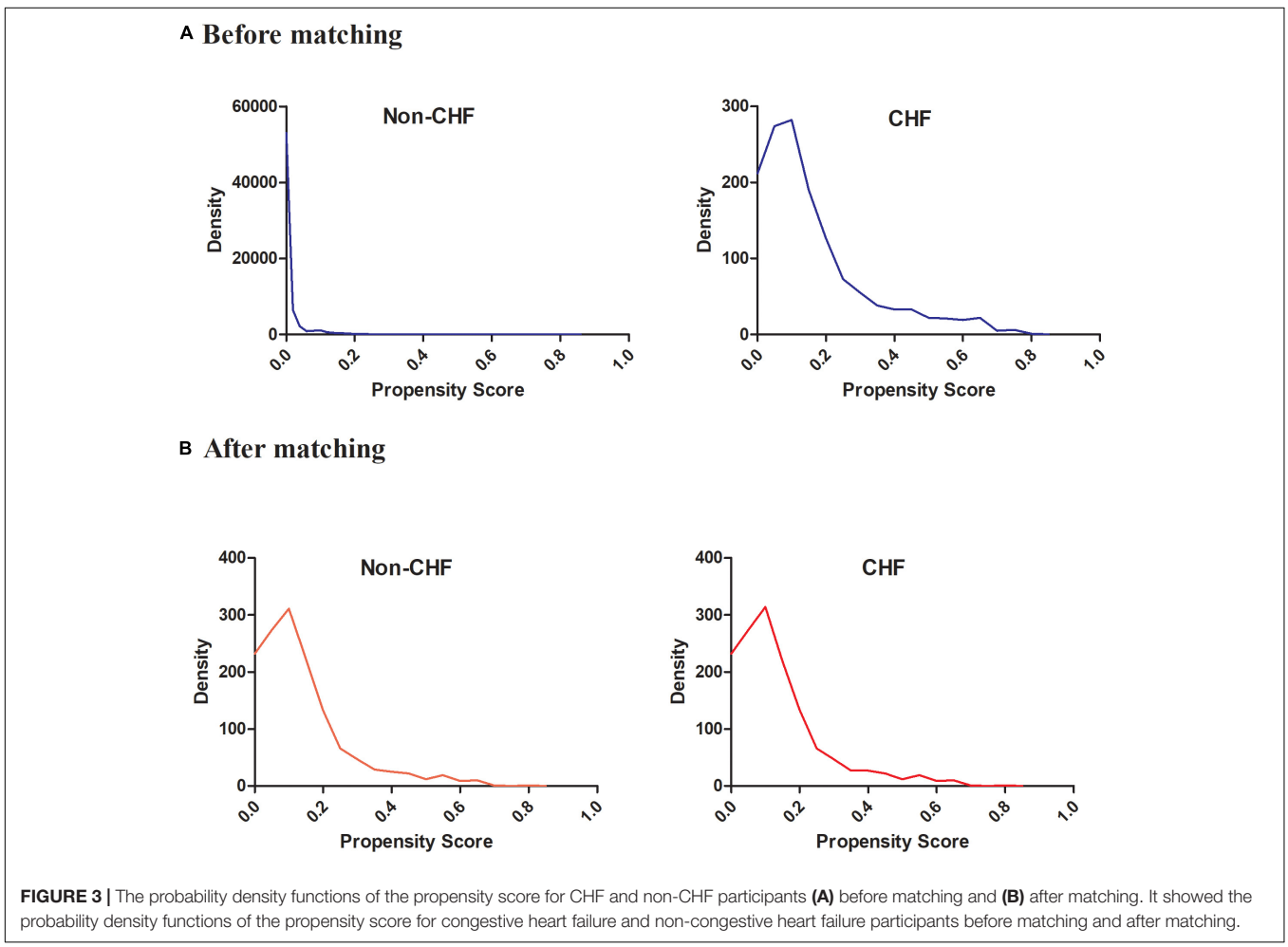

FIGURE 3 | The probability density functions of the propensity score for CHF and non-CHF participants **(A)** before matching and **(B)** after matching. It showed the probability density functions of the propensity score for congestive heart failure and non-congestive heart failure participants before matching and after matching.

PS matching, the difference in mortality between the two groups significantly reduced (**Figure 4**).

Analysis Results Through Different Confounding Control Methods

We used the Cox proportional-hazards regression model to assess the association between CHF and 1-year mortality after surgery in the original, PS matching, and weighted cohorts. In the original cohort, CHF was significantly associated with 1-year mortality after surgery (HR, 5.65; 95% CI: 4.92–6.48, $P < 0.001$). In other words, compared with participants without CHF, those with CHF had a 4.65-fold increased risk of 1-year mortality after surgery. After multivariate adjustment (adjusted for sex, age, race, CVA, IHD, DMI, priority of surgery, surgical risk classification, ASA-PS, stage of CKD, degree of anaemia, and type of anaesthesia), the association still existed (HR: 1.39, 95% CI: 1.20–1.61, $P < 0.001$). In PS adjustment (adjusted variables include PSs and the same strata and covariates), the HR between CHF and 1-year mortality after surgery was 1.34 (95% CI: 1.15–1.56, $P < 0.001$). Second, in the PS-matched cohort, the multivariate-adjusted Cox proportional hazard regression model analysis showed that the HR between CHF and 1-year mortality after surgery was 1.54 (95% CI: 1.19–1.98, $P < 0.001$). The adjusted variables were the same as those used in the original cohort. Finally, in the weighted cohort, after multivariate adjustment, the SMR-weighted analysis yielded an HR of 1.34 (95% CI: 1.10–1.62, $P < 0.001$) and the result of the IPTW multivariate-adjusted Cox proportional-hazards regression model analysis showed that the HR between CHF and 1-year mortality after surgery was 1.24 (95% CI: 1.17–1.32, $P < 0.001$). It should be emphasised that in the original cohort multivariate adjustment, PS matching multivariate adjustment, IPTW, and SMR-weighted multivariate adjustment, the adjusted variables were the same, including sex, age, race, CVA, IHD, DMI, priority of surgery, surgical risk classification, ASA-PS, stage of CKD, degree of anaemia, and type of anaesthesia. In PS adjustment, the adjusted variables included other model-adjusted variables and PS (**Table 2**).

Sensitivity Analysis

We considered a significant difference in the associated empirical OR for 1-year mortality after surgery between the participants with low and high PSs (**Supplementary Table 3**). We further analysed patients with PS of ≥0.05. The crude HR for the restricted population was 1.81 (95% CI: 1.55–2.12, $P < 0.001$); the HRs for the five different methods were similar. The multivariate-adjusted HR in the original cohort was 1.59 (95% CI: 1.35–1.89, $P < 0.001$); PS adjustment revealed that the HR between CHF and 1-year mortality after surgery was 1.54 (95% CI: 1.30–1.85, $P < 0.001$). In the PS-matched cohort, after multivariate adjustment, HR was 1.55 (95% CI: 1.19–2.02, $P < 0.001$); the multivariate-adjusted HR of the IPTW and SMR-weighted cohorts was 1.49 (95% CI: 1.36–1.67, $P < 0.001$) and 1.45 (95% CI: 1.18–1.78, $P < 0.001$), respectively (**Supplementary Table 5**).

In addition, bias may arise due to the excessive missing CHF information. We applied multiple imputations to estimate missing CHF values (n = 28,411). After imputation, there were 2,101 participants in the CHF group and 95,342 in the non-CHF group. We applied five statistical models to the analysis, which yielded similar results (**Supplementary Table 6**). The HRs of the original cohort-adjusted model, PS adjustment model, PS matching adjusted, IPTW model, and SMR-weighted model were 1.24, 1.26, 1.31, 1.16, and 1.31, respectively. Therefore, excluding

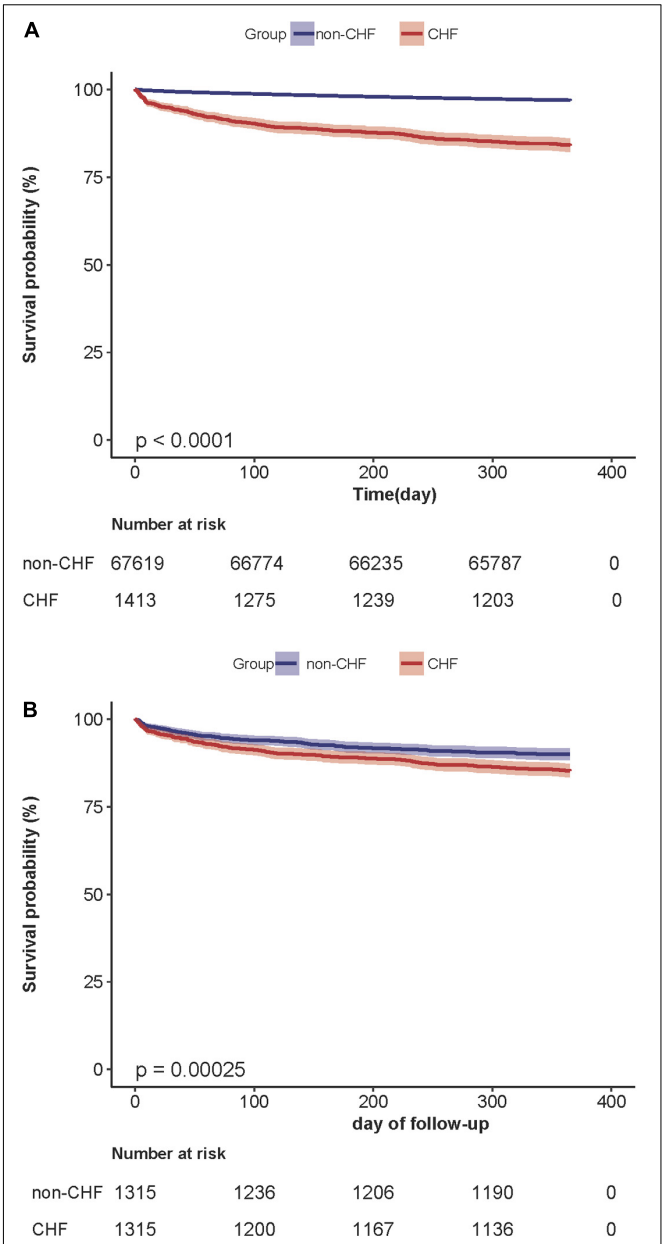

FIGURE 4 | (A) Kaplan–Meier survival curve based on congestive heart failure in the original cohort. Kaplan–Meier analysis of one-year mortality after surgery based on congestive heart failure(CHF) and non-congestive heart failure (non-CHF) in the original cohort(log-rank, $P < 0.0001$). **(B)** Kaplan– Meier survival curve based on congestive heart failure in the propensity-score matching cohort. Kaplan–Meier analysis of one-year mortality after surgery based on congestive heart failure (CHF) and non-congestive heart failure (non-CHF) in the propensity-score matching cohort (log-rank, $P = 0.0002$).

TABLE 2 | Associations between CHF and one-year postoperative mortality of surgical patients in the crude analysis, multivariable analysis, and four propensity-score methods analyses.

Cox proportional-hazards regression model	Adjusted variables	No.	HR	95%CI	*P*-value
Crude		69,032	5.65	4.92, 6.48	<0.001
Multivariable-adjusted model	Multivariable†	69,032	1.39	1.20, 1.61	<0.001
Propensity score adjustment	Propensity score + Multivariable†	69,032	1.34	1.15, 1.56	<0.001
Propensity score matching	Multivariable†	2,630	1.54	1.20, 1.98	<0.001
IPTW	Multivariable†	69,032	1.24	1.17, 1.32	<0.001
SMR–weighted	Multivariate†	69,032	1.34	1.10, 1.62	0.004

HR, hazard ratio; CI, confidence interval; IPTW, inverse-probability-of-treatment weighted; SMR, standardised mortality ratio.
Multivariable†: Adjusted for gender, age, race, history of previous cerebrovascular accidents, history of ischemic heart disease, diabetes mellitus on insulin, priority of surgery, surgical risk classification, American society of anaesthesiologists physical status, stage of CKD, degree of anaemia, type of Anesthesia.

participants with missing CHF information did not affect the core findings of this study and suggests that our results are robust.

Furthermore, we generated an E-value to assess the sensitivity to unmeasured confounding factors. The E-value (2.13) was lower than the relative risk (3.34) of unmeasured confounders and 1-year mortality after surgery, suggesting that unmeasured or unknown confounders had little effect on the relationship between CHF and 1-year mortality after surgery. Our primary findings were robust.

Subgroup Analysis

We performed subgroup analysis to examine the impact of potential confounders that may influence the association between CHF and 1-year mortality after surgery. Age and CKD stage were used as stratified variables to assess the trend of effect size. We observed interactions among the subgroups according to our specification. We found that age and CKD stage did not affect the relationship between 1-year mortality after surgery (all P-values for interaction < 0.05), respectively (**Supplementary Table 7**).

DISCUSSION

This one-to-one PS-matched cohort study showed that CHF was associated with a higher risk of mortality 1 year after surgery. After PS matching, CHF had a significant association with 1-year mortality after surgery, and the risk of mortality increased by 54% in the population with CHF (HR = 1.54, 95% CI: 1.1–1.98, $P < 0.001$). In PS adjustment, the HR between CHF and 1-year mortality after surgery was 1.34 (95% CI: 1.15–1.58, $P < 0.001$). We applied a Cox proportional-hazards model based on PS-based weighting to further verify the association between CHF and 1-year mortality after surgery. In the IPTW and SMR-weighted cohorts, compared with participants without CHF, those with CHF had a 24% and 34% increase in the risk of mortality 1 year after surgery, respectively.

We found that different methods of controlling confounding factors resulted in different HRs. The results of the PS matching multivariate-adjusted Cox proportional-hazards regression model were slightly higher, whereas the original cohort multivariate-adjusted, PS-adjusted, and SMR-weighted multivariate-adjusted Cox proportional-hazards regression models had similar hazard ratios. In comparison, the results of the IPTW multivariate-adjusted Cox proportional-hazards regression model were lower (**Table 2**). The number of participants without CHF was many times greater than the number of those with CHF. PS matching usually results in a successful match for almost all patients with CHF; many unmatched patients without CHF were excluded from the analysis. As a result, the distribution of covariates in the (successfully) matched subpopulation would be close to that in the treated study population. Most patients in the CHF group were in the propensity strata with a high risk of associated mortality, and the SMR-weighted method estimated the average effect of CHF in a population whose distribution of risk factors was equal to that found in the CHF group. Thus, it was not surprising that the SMR-weighted estimate was closer to the PS-matched estimate.

In contrast, the IPTW model estimated the average CHF effect for the entire study population. Given that 90% of the study population was in the propensity strata associated with low empirical odds ratios, the results of the IPTW multivariate-adjusted Cox proportional-hazards regression model were lower. The IPTW estimate increased to 1.49 when the patients in these three strata were excluded by restricting the analysis to the subpopulation of the CHF and non-CHF groups whose PS was $\geq$0.05. Indeed, once we restricted the analysis to subjects with PS of $\geq$0.05, all adjustment methods provided approximate results, with HR fluctuating around 1.50. The results of all these methods showed that the four PS methods could control for confounding factors well.

CHF is an established risk factor for poor prognosis after surgery across a wide range of specialties. A study conducted in Sweden showed that the crude and adjusted HRs for 30-day mortality after elective surgery in patients with CHF were 5.36 and 1.79, respectively (9). An analysis of 21,560,996 surgical hospitalisations revealed that the adjusted OR for in-hospital perioperative mortality in patients was 2.15 (11). Another study found similar results; compared with patients without CHF, patients with CHF had a 96% increased risk of 30-day mortality (10). Our study complements the existing literature supporting the hypothesis that CHF increases the risk of postoperative mortality in patients undergoing surgery. However, the estimated HR for the relationship between CHF and postoperative mortality was lower than that reported in previous studies.

We analysed these inconsistent findings, which may be justified by the following possible explanations: (1) The research population was different, including age, sex and race. As the original data failed to define the surgical category, our study population included all cardiac and non-cardiac surgery patients. Other studies have generally analysed these two populations separately. (2) Sample sizes in these studies varied widely. (3) The studies were adjusted for different covariates. (4) Previous studies mainly used variable adjustments to control confounding factors; this traditional parsimonious regression model could result in a bias because of unmeasured or residual confounding or overfitting of the model (40). We used PS methods to control for confounding factors and verify the association between CHF and 1-year mortality after surgery. (5) The outcome variables were different. Previous studies have focused on in-hospital or 30-day mortality rates. However, the dependent variable in our study was 1-year mortality after surgery.

Although the exact mechanism underlying the increased risk of postoperative death associated with CHF is unclear, the incidence of complications in this population may provide clues. A study found that, compared with patients without CHF, the incidence of crude complications in patients with CHF doubled (41). There is convincing evidence that this may be because patients with CHF have poor recovery, and even minor postoperative complications can significantly affect postoperative mortality (42).

Our study has two other strengths: (1) Our sample size was relatively larger than that of previous similar studies. (2) To the best of our knowledge, few cohort studies have used PS matching to explore the relationship between CHF and 1-year mortality after surgery. Research methods based on PSs are considered a core alternative for controlling the confounding effects of observational research.

The potential limitations of this study are as follows. First, the population included in this study was Singaporean and the race was mainly Chinese. Therefore, the universality of these results in other races requires further verification. Second, this study is a secondary analysis based on published data, so variables not included in the dataset cannot be adjusted. However, we used the E-value to evaluate the unmeasured confounding factors and found that our study was stable and reliable. Third, this study was based on a secondary analysis of published data and lacked some relevant information, such as recent surgical observations (perioperative and 30-day mortality), minor surgeries, and types of transplants. Fourth, PS methods balance the known confounding variables as much as possible. However, it could not ensure that all measured baseline characteristics were matched, and the influence of unknown variables was considered. However, we reduced the calliper width to 0.0005 to minimise the interference of some variables in the results. Fifth, differences in CKD stage and age remained between the CHF and non-CHF groups after PS matching. However, multivariate adjustment and subgroup analyses were performed. These analyses suggest that our results are robust. In addition, this observational study provides inferences about the association between CHF and 1-year mortality after surgery but cannot establish a causal relationship. Therefore, our findings need to be further validated by future prospective studies.

CONCLUSION

CHF is an independent risk factor for 1-year mortality after surgery in patients undergoing surgery. This study quantified the relationship between CHF and surgical patient outcomes by applying various statistical models and presented a range of HR (1.24–1.54). This provides a reference for optimising clinical decision-making, improving preoperative consultation, and promoting clinical communication.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (Singhealth CIRB 2014/651/D). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YH, HH, and YL conceived the research, drafted the manuscript, and performed the statistical analysis. DL and LW revised the manuscript and designed this study. All authors have read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.858068/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Multimodal Strategies for the Diagnosis and Management of Refractory Congestion. An Integrated Cardiorenal Approach

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Refractory congestion is common in acute and chronic heart failure, and it significantly impacts functional class, renal function, hospital admissions, and survival. In this paper, the pathophysiological mechanisms involved in cardiorenal syndrome and the interplay between heart failure and chronic kidney disease are reviewed. Although the physical exam remains key in identifying congestion, new tools such as biomarkers or lung, vascular, and renal ultrasound are currently being used to detect subclinical forms and can potentially impact its management. Thus, an integrated multimodal diagnostic algorithm is proposed. There are several strategies for treating congestion, although data on their efficacy are scarce and have not been validated. Herein, we review the optimal use and monitorization of different diuretic types, administration route, dose titration using urinary volume and natriuresis, and a sequential diuretic scheme to achieve a multitargeted nephron blockade, common adverse events, and how to manage them. In addition, we discuss alternative strategies such as subcutaneous furosemide, hypertonic saline, and albumin infusions and the available evidence of their role in congestion management. We also discuss the use of extracorporeal therapies, such as ultrafiltration, peritoneal dialysis, or conventional hemodialysis, in patients with normal or impaired renal function. This review results from a multidisciplinary view involving both nephrologists and cardiologists.

Keywords: heart failure, refractory congestion, diuretic resistance, peritoneal dialysis, extracorporeal ultrafiltration

1. INTRODUCTION

The clinical course of patients with heart failure (HF) is characterized by frequent exacerbations that require urgent medical attention. It has been demonstrated that congestion, not low cardiac output, is the main reason for these acute episodes, which are associated with increased morbidity and mortality and impose a considerable economic burden on health care systems (Chioncel et al., 2017; Mullens et al., 2019).

Early detection of congestion is paramount since it allows intensification of treatment before signs and symptoms worsen, which, in turn, may prevent the need for urgent medical care (Abraham et al., 2011). Furthermore, poorly controlled congestion has also been associated with atrial and ventricular remodeling, recurrent hospital admissions, and increased mortality (Melenovsky et al., 2015; Pellicori et al., 2019). This is particularly relevant considering that up to 50% of patients

admitted with acute HF (AHF) are discharged with residual congestion, which, if present, is associated with rehospitalizations and death within 6 months from discharge (Ambrosy et al., 2013).

Traditionally, clinicians have relied on the physical exam to detect congestion; however, clinical signs and symptoms are late manifestations and are neither sensitive nor specific to HF (Girerd et al., 2018). Recently, biomarkers–such as natriuretic peptides–, and imaging modalities–particularly ultrasound–have emerged as valuable aids in the early detection of congestion (Boorsma et al., 2020; Pellicori et al., 2021).

Given the central role of congestion in HF exacerbations, an adequate understanding and knowledge of diverse decongestive strategies is a must for anyone involved in the care of HF patients. Chronic kidney disease (CKD) is present in up to 51–65% of HF patients (Ahmed and Campbell, 2008) and is associated with worse outcomes, more complex management, and demands for increased monitoring (House et al., 2019). In that sense, a 2019 American Heart Association statement and the 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure highlight the role of integrated cardiorenal management in improving quality of life and outcomes in HF (Rangaswami et al., 2019; McDonagh et al., 2021). A multidisciplinary approach is mandatory since both entities are closely related in pathophysiological and clinical terms.

This review covers the main mechanisms that lead to congestion in HF patients, the different diagnostic modalities to detect it, and the available treatment strategies from an integrated cardionephrology approach.

2. HEART AND KIDNEY. A DEPENDENT RELATIONSHIP

The association between the kidney and the heart has been reported since the early 19th century when Robert Bright depicted significant cardiac structural changes in patients with advanced kidney disease (Bright, 1836). Since then, a shared etiological pathway and interdependent relationship have been described to a point where they may be referred to as the *cardiorenal vascular system* and not as each organ system separately.

As the heart pumps, blood is delivered throughout the human body. Kidneys are essential in this interaction because, depending on the pressure at which blood is provided, they will produce several hormones aiming to adjust urine output and regulate blood pressure. These hormones will act not only on blood vessels but also on cardiac muscle tissue. For instance, a low stroke volume or heart rate can lead to low cardiac output, reducing the renal blood flow and, thus, the amount of filtered plasma. Kidneys sense the reduced blood flow received and, in turn, activate the renin-angiotensin-aldosterone system (RAAS), increasing glomerular hydrostatic pressure, sodium tubular avidity, and water retention while inducing cardiac remodeling and worsening systemic hypertension. These mechanisms are required for survival in the short term; however, they lead to structural heart damage, chronic kidney disease, and volume overload when perpetuated. The latter is of current interest as it has been settled as the primary pathophysiological mechanism of that new entity described as *congestive nephropathy*. This phenomenon develops when severe volume overload significantly increases the venous system pressure, which is transmitted to the efferent arteriole, reducing the differential glomerular pressures required to generate a sufficient net glomerular ultrafiltration pressure, resulting in oliguria, increased cardiac afterload, and congestion (Jentzer et al., 2020).

Moreover, Boorsma et al. (2022) proposed another novel term, *renal tamponade,* to describe severe cases of congestive nephropathy where the rigid renal capsule, kidney surrounding fat tissue, and the peritoneal cavity exert cumulative pressure on the retroperitoneal space, limiting the space available for renal expansion. Animal models of HF showed that renal decapsulation effectively reduced kidney pressure-related injury. This might be a new vision with potential forthcoming therapeutic implications in HF by alleviating intrarenal congestion.

3. CLASSIFICATION

The National Heart, Lung, and Blood Institute Working Group has defined the cardiorenal vascular interplay as Cardiorenal syndrome (CRS) and proposed a classification based on the volume retention by the kidneys (Cardio-Renal Connections in Heart Failure and Cardiovascular Disease, 2004); however, since this definition places the heart at its center and the kidneys as the culprit, other organizations have proposed additional definitions with a broader clinical spectrum. For instance, the Acute Dialysis Quality Initiative in 2008 split the CRS into five types to easily characterize its clinical presentation for diagnostic and therapeutic purposes (Ronco et al., 2010). Type 1 or acute cardiorenal syndrome refers to AHF leading to acute kidney injury (AKI); type 2 or chronic cardiorenal syndrome, to chronic HF leading to progressive and permanent CKD; type 3 or acute renocardiac syndrome, to AKI causing AHF; type 4 or chronic renocardiac syndrome, to CKD leading to chronic HF and CKD progression; and, finally, type 5 is known as secondary CRS, and it is described as a systemic insult resulting in heart and kidney failure (e.g., sepsis, cirrhosis, or amyloidosis) (Ronco et al., 2010). Another classification proposed by Hatamizadeh et al. (2013) states that, besides cardiac pump failure, multiple body systems can lead to volume retention by the kidney and contribute to CRS. This group proposed seven categories: hemodynamic (heart failure), uremia and kidney failure, atherosclerosis, endothelial dysfunction, neurohumoral, anemia and iron disorders, mineral disorders (FGF23, phosphorus, or vitamin D disorders), and inflammatory pathways leading to malnutrition.

The classification of CRS is rather complex, mainly because, in many cases, it is almost impossible to identify where the process started (**Figure 1**). Moreover, given the importance of blood pressure and vessels in this relationship, the kidneys and the heart share vascular risk factors for disease development and progression. For instance, diabetes mellitus, hypertension,

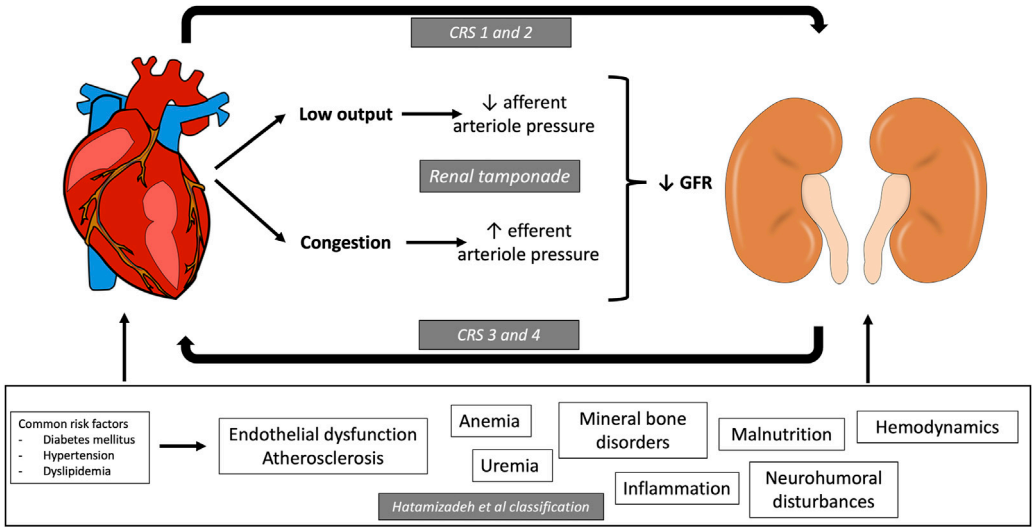


FIGURE 1 | Cardiorenal pathophysiology. Interrelation between heart and kidney in the development of the different types of cardiorenal syndrome (CRS). Type 1 and type 2 CRS are described as acute (Chioncel et al., 2017) or chronic (Mullens et al., 2019) heart failure resulting in acute kidney injury (AKI) or chronic kidney disease (CKD). Type 3 and 4 CRS are known as acute and chronic renocardiac syndrome and are described as AKI (Abraham et al., 2011) or CKD (Melenovsky et al., 2015), resulting in heart failure. Type 5 is known as secondary CRS, and it is described as a systemic process resulting in heart and kidney failure. The classification by Hatamizadeh et al. proposes seven disease categories that contribute to CRS: hemodynamic (heart failure), uremia and kidney failure, atherosclerosis, endothelial dysfunction, neurohumoral, anemia and iron disorders, mineral disorders (FGF23, phosphorus or vitamin D disorders), and inflammatory pathways leading to malnutrition.

dyslipidemia, atherosclerosis, endothelial inflammation, mineral bone disorders, and anemia have been associated with both cardiovascular and renal diseases (Zannad and Rossignol, 2018). Therefore, regardless of the chosen classification, it is fundamental for nephrologists and cardiologists to understand the underlying maladaptive mechanisms that lead to the decompensation of both organ systems so a proper pathophysiological and holistic management can be offered to this complex group of patients.

4. CONGESTION

Congestion in HF is defined as the combination of signs and symptoms of extracellular fluid accumulation that result in increased cardiac filling pressure (Martens et al., 2015). Congestion and volume overload are usually misused interchangeably; however, these terms are not precisely equal. For instance, up to half of the patients with AHF barely gained weight during the weeks preceding their hospital admissions. This is because sympathetic tone decompensation in HF leads to vasoconstriction of splanchnic circulation, resulting in blood redistribution and not volume gain. This redistribution increases hydrostatic pressure and the effective circulating volume, which produce signs and symptoms of congestion (Chaudhry et al., 2007; Verbrugge et al., 2013). Volume overload, on the contrary, is due to increased neurohumoral activation that increases renal sodium and water avidity, which results in global water gain (Nijst et al., 2015). Both mechanisms increase venous return, cardiac preload, and cardiac filling pressures. Moreover, advanced HF is related to cachexia, where low plasma proteins reduce oncotic pressure and decrease plasma refilling from the interstitium. Thus, the gain in body weight could be an inaccurate measure in some cases of HF decompensation. The difference between absolute volume overload and volume redistribution may have important implications for the therapeutic approach.

Refractory congestion is defined as the persistence of symptoms that limit daily life [at least, functional class III or IV of the New York Heart Association (NYHA)] despite optimal treatment, including chronic diuretics (Nohria et al., 2002); and described as the failure to decongest or achieve euvolemia despite adequate and escalating doses of diuretics (ter Maaten et al., 2015). While the expected diuretic and natriuretic responses to 40 mg of furosemide are thought to be around 3–4 L per day and 200–300 mmol/L, respectively, up to 40% of hospitalized patients with HF fail to do so (Valente et al., 2014), and in the context of a cardiorenal syndrome, these doses will hardly achieve these diuretic outputs.

Several mechanisms have been classically described as causes of an impaired diuretic response. Among these, we have: 1) a reduced delivery of diuretic to the kidney's proximal tubule due to reduced cardiac output, which constitutes the cause of the increasingly high diuretic doses required in HF; 2) compensatory sodium reabsorption either after the diuretic effect wears off or at other nephron segments, something that has been described in healthy adults but seems not to occur in patients with AHF (Cox et al., 2021); and 3) congestive nephropathy, where the increased sympathetic tone causes a chronic redistribution of blood into the central circulation,

leading to a rise in intraabdominal pressure, which in turn increases renal venous pressure, decreases renal blood flow, glomerular filtration, and, therefore, urine output (Husain Syed et al., 2021).

In any case, once congestion begins, volume overload will progressively worsen HF signs and symptoms by adding more workload to the heart and increasing renal vein pressures, thus initiating a vicious cycle where diuretic resistance leads to prolonged lengths of stay and increased mortality (O'Connor et al., 2011). Therefore, it is crucial to identify these patients rapidly, as they could benefit from more aggressive and individualized treatment.

5. DIAGNOSTIC TOOLS IN CONGESTION

Congestion must be evaluated clinically in patients at risk. Although clinical history and physical exam are the first steps in congestion assessment, other tools can help us identify subclinical congestion, quantify its severity, and provide treatment monitoring and follow-up measures (Adamson et al., 2014).

5.1. Anamnesis and Physical Exam

On anamnesis, we need to identify dyspnea, orthopnea, bendopnea, and paroxysmal nocturnal dyspnea. Also, inquiring about the abdominal or ankle perimeters is critical (McDonagh et al., 2021). Less frequent symptoms are nocturnal cough, loss of appetite, bloated feeling, confusion, depression, dizziness, and syncope.

Physical signs of congestion are based on detecting increased filling pressures or extravascular fluid overload. The more specific signs are elevated jugular venous pressure, hepatojugular reflux, third heart sound, and laterally displaced apical impulse (McGee, 1998; McDonagh et al., 2021). One of the most useful physical findings is the jugular venous pulse, which detects systemic congestion and elevated left-sided filling pressures (McDonagh et al., 2021).

However, clinical signs of congestion do not have a high sensitivity and are usually evident in advanced states. In some series of patients with chronic HF, physical signs of congestion were absent in up to 42% of patients with the Pulmonary Capillary Wedge Pressure (PCWP) > 22 mmHg (Stevenson and Perloff, 1989).

5.2. Biomarkers

A clinically helpful biomarker should possess the following characteristics: it should be quickly determined, affordable, and provide additional information not attainable from the clinical interrogatory or physical examination alone. There is no current definitive biomarker that fulfills all these requisites; however, in this section, we will discuss the ones available or under development.

Clinical guidelines suggest measuring natriuretic peptides in all patients with AHF. These have a high negative predictive value for HF and congestion as causes of dyspnea (Ponikowski et al., 2016), with thresholds for ruling out AHF of Brain Natriuretic Peptide (BNP) < 100 pg/ml and N-terminal prohormone of BNP (NT-proBNP) < 300 ng/ml, which may vary according to sex, ejection fraction, and the presence of atrial fibrillation. They are elevated due to increased ventricular filling pressures, often defined as hemodynamic or *intravascular congestion*, while not necessarily tissular congestion (e.g., edema, crackles) (de la Espriella et al., 2022a). The possible reliance of natriuretic peptides on renal clearance has motivated some discussion about their clinical utility in patients with a severely reduced estimated glomerular filtration rate (eGFR) (de la Espriella et al., 2022b). One of the differences between both natriuretic peptides relies on their elimination and half-life. BNP is degraded by enzymatic processes and has a short lifespan in circulation of approximately 20 min. On the other hand, NT-proBNP is eliminated renally and has a longer half-life of around 120 min, hence its higher blood values. With this reasoning, BNP used to be the recommended natriuretic peptide to be measured in the setting of renal dysfunction. However, it has been demonstrated that both are equally unreliable markers in patients with AKI or unstable worsening renal function (WRF) (Koratala and Kazory, 2017). They could probably have a role in showing improvement trends at low eGFRs as long as they remain stable. However, the recommended cut-off in patients with an eGFR <60 ml/min/1.73 m^2 to keep a sensibility close to 90% and a specificity of 72% is a remarkably high value of 1,200 ng/ml (Anwaruddin et al., 2006). To date, there is no evidence that natriuretic peptides have a significant correlation with congestion in patients on dialysis treatment; therefore, their use is not recommended in this population (Koratala and Kazory, 2017). Given all these caveats, there is an important limit to the information and usefulness of NT-proBNP in the setting of renal dysfunction, and, although normal values can help discard congestion or HF, high values are dependent on the patients' eGFRs and, therefore, they are suboptimal biomarkers in cardiorenal syndrome.

Antigen carbohydrate 125 (CA125), a glycoprotein synthesized by celomic epithelium in pleura, pericardium, or peritoneum, is well-known as a biomarker for some malignancies, such as ovarian cancer. Recently, it has been identified as a reliable biomarker for congestion (Núñez et al., 2014). Among the favorable characteristics associated with this rediscovered biomarker are its low price, long half-life (up to a week), and that it is unaffected by renal dysfunction (Núñez et al., 2020a; de la Espriella et al., 2022a). The pathophysiology of CA125 elevation in congestion is not well-established. Nevertheless, it has been hypothesized that it is due to the activation of mesothelial cells due to hydrostatic pressure increase, mechanical stress, and inflammatory cytokines (Huang et al., 2012). Recent evidence demonstrated a good positive and improved correlation with NT-proBNP, with other *tissular congestion* markers, such as pleural effusion, ascites, elevated jugular venous pressure, hepatomegaly, and leg edema (Núñez et al., 2020a; de la Espriella et al., 2022a). The cut-off of 35 U/ml has been used to guide treatment and has been associated with improved eGFR compared to those treated by clinical guidance alone at 72 h post-admission (Núñez et al., 2020b). Currently, two clinical trials evaluated a therapeutic strategy guided by CA125

concentration, contrasting it with classic management guided by signs and symptoms with promising results (Núñez et al., 2016; Núñez et al., 2020b).

It is essential to highlight the role of plasma creatinine in clinical practice, as an increase of this parameter could reflect parenchymal damage in the kidney or hemodynamic changes (e.g., hyperfiltration correction). Thus, if decongestion is being achieved and there is clinical improvement, modest rises in serum creatinine are expected and should not result in treatment suspension or dose reduction, as this phenomenon is not associated with renal damage (McCallum et al., 2021). On the other hand, a lack of clinical improvement or adequate diuresis is associated with ominous outcomes, and nephrology should be consulted (Emmens et al., 2022).

Hemoconcentration has been seen after diuretic treatment, but studies revealed a weak association, making it a poor marker for decongestive therapy (Darawsha et al., 2016). Soluble CD146 (Gayat et al., 2015) and adrenomedullin (Kremer et al., 2018) are other novel biomarkers that can offer additional information for cardiac congestion, but their use is currently restricted to research (Ambrosy et al., 2013).

5.3. Imaging

5.3.1 Chest X-Ray

Chest X-ray has been an essential tool in the diagnosis of congestion. It can show signs of vascular redistribution towards the upper lobes, upper pulmonary veins' distention, hilar structures' enlargement, or septal lines in the lower lung (Kerley A and B lines). Moreover, pleural fluid accumulation in right HF leads to the thickening of interlobar fissures or pleural effusion. Another radiologic finding frequently detected in congestion is cardiomegaly. If congestion increases up to alveolar edema, chest X-rays show bilateral opacities with central distribution and no air bronchogram. These radiologic signs can precede clinical symptoms' onset and may be visible for days after successful decongestion (Cardinale et al., 2014).

5.3.2 Multi-Organ Ultrasound

Although the findings mentioned above in chest X-rays are common, up to 20% of patients with clinical congestion have a normal chest X-ray (Collins et al., 2006). Lung ultrasound has recently emerged as a more reliable tool in ruling out interstitial edema or pleural effusion. The echogenicity of the lung is related to the amount of water in the interstitial space. Thus, lung ultrasound detects B-lines originating from fluid in the interstitium and alveoli (Al Deeb et al., 2014). At least three B-lines in two fields bilaterally have a sensitivity of 94%–97% and specificity of 96%–97% to detect congestion in AHF (Pivetta et al., 2019). Lung-ultrasound-guided diuretic treatment of pulmonary congestion has proven to reduce the number of decompensations and improve the functional capacity of patients with HF (Rivas - Lasarte et al., 2019). Moreover, diagnosis of pleural effusion with lung ultrasound is also an easily acquired skill that may not only be useful for diagnosis but also as guidance for diagnostic or therapeutic thoracentesis. Thus, as a non-invasive, safe, and easy-to-use technique, lung ultrasound may have an important role in congestion diagnosis and management.

Echocardiography, used as a bedside tool, can estimate right- and left-sided filling pressures. Assessment of inferior vena cava (IVC) and its collapsibility and width estimates right atrial pressure (RAP) and left ventricular filling pressures (Berthelot et al., 2020). Thus, an IVC diameter lower than 1.5 cm and collapsibility >50% is a good estimate for RAP <5 mmHg. On the other hand, a diameter >2.5 cm and no collapsibility estimate a RAP >20 mmHg (Pellicori et al., 2021).

When the IVC is enlarged, one should assess the hepatic veins. These veins are thin-walled and communicate with the IVC. Although the right and middle veins are the most readily observed, any of the three hepatic veins (right, middle, or left) can be measured. When applying the pulsed Doppler on the hepatic vein of healthy subjects, the tracing observed should show a small retrograde A wave and two antegrade waves: first, the larger wave called S wave corresponding to systole and then a smaller one called D wave corresponding to diastole (panel A, **Figure 2**) (Beaubien-Souligny et al., 2020). In volume overload, RAP will increase, causing the S wave's magnitude to progressively decrease, first becoming smaller than the D wave (panel B, **Figure 2**) and later becoming retrograde (panel C, **Figure 2**). However, volume overload and other causes of increased RAP will generate this phenomenon (e.g., tricuspid regurgitation) (Argaiz et al., 2021).

Unlike the hepatic veins, the walls of the portal vein are thick. When applying pulsed Doppler over the portal vein of healthy subjects, a continuous flow should be observed (panel A, **Figure 2**). In a state of volume overload, the pressure in the vein increases, causing the flow to become pulsatile (panel B, **Figure 2**) and then biphasic in cases of severe congestion (panel C, **Figure 2**) (Argaiz et al., 2021; de la Espriella et al., 2022a). The portal vein study is of great value in cases where the IVC or hepatic veins cannot be evaluated due to confounding factors (e.g., tricuspid insufficiency and mechanical ventilation). A case in which its study will not be valuable is in patients with liver cirrhosis or other severe hepatic interstitial pathology.

Cardiac Doppler imaging and tissue Doppler can assess left-sided filling pressures (Mullens et al., 2009). When filling pressures increase, diastolic mitral inflow velocities change with an increase in early velocities (high E-wave with short deceleration time and low A-wave; E/A ratio >2). Oppositely, tissue Doppler velocities decrease with a low e' (59). Thus, ratio E/e' > 15 indicates a restriction in diastole and elevated left-sided filling pressures. These assumptions have some limitations in daily practice. Diastolic mitral inflow velocities cannot be correctly assessed in patients with atrial fibrillation, a frequent pathology in patients with AHF. Moreover, e'-wave has limitations in patients with prosthetic mitral valves or significant mitral annulus diseases such as degenerative calcification.

Recommendations for the evaluation of left ventricular diastolic function by echocardiography were updated in 2016 by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) (Nagueh et al., 2016). Despite the large number of parameters that can be evaluated with echocardiography, both in HF with preserved (HFpEF) and reduced ejection fraction (HFrEF) a

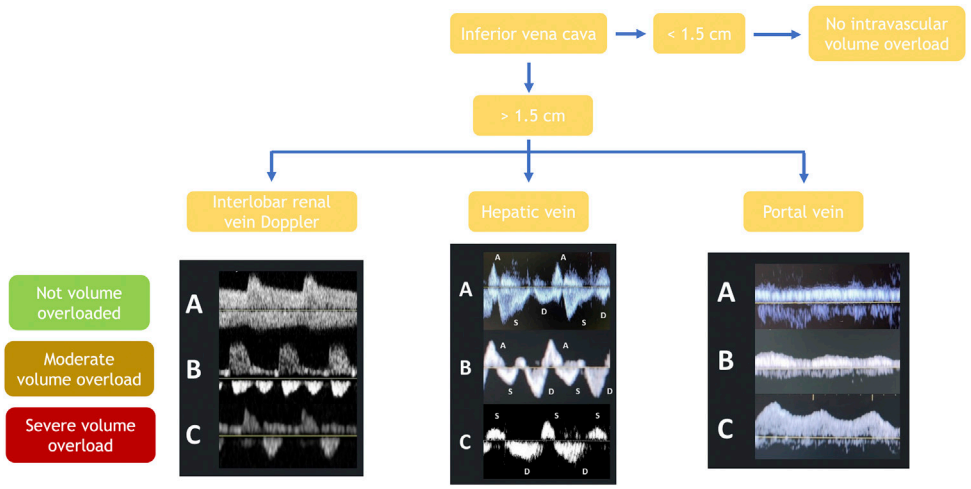


FIGURE 2 | Abdominal ultrasound-guided diagnosis of volume status and its severity by assessing the inferior vena cava's diameter, followed by Doppler evaluation of portal, hepatic and renal interlobar vein waves.

simplified scheme is proposed including: E/e' ratio >14, left atrium volume >34 ml/m^2, tricuspid regurgitation velocity >2.8 m/s and e' septal velocity <7 cm/s or e' lateral velocity <10 cm/s. Patients with at least two previous conditions are likely to have diastolic dysfunction with chronic exposition to high left-side filling pressures.

Ultrasound evaluation of renal blood flow in HF has become another valuable tool for congestion diagnosis and management (Nijst et al., 2017). The objective of renal venous ultrasound is to observe the interlobar or arcuate arteries and veins located in the renal cortex. As they pass together, they can be distinguished as blue and red pulsatile flows with the color Doppler. In euvolemic subjects, a continuous wave should be observed below the arterial pulsatile wave (panel A, **Figure 2**). In cases of volume overload, this continuous wave will become biphasic (panel B, **Figure 2**), and in cases of severe congestion, it becomes monophasic (panel C, **Figure 2**) (Nijst et al., 2017). As the renal blood flow is part of the systemic circulation, it may be altered by other causes of increased RAP and volume overload (e.g., tricuspid regurgitation or high intrabdominal or intraparenchymal renal pressure in ascites or obstructive uropathy) (Argaiz et al., 2021).

Two indexes have been developed to quantify venous renal flow modifications secondary to elevated central venous pressures. The first, the venous impedance index (VII), quantifies the velocity changes in renal venous flow during the cardiac cycle (if congestion increases, the index approaches 1). The second one, the venous discontinuity index (VDI), quantifies the time without blood flow in interlobar veins (high when a single flow phase in diastole is observed) (Pellicori et al., 2021).

The role of this technique in congestion management has hardly been studied. One study evaluated the effect of volume loading and diuretics on renal venous flow pattern observing that intravascular expansion resulted in significant blunting of venous flow before a substantial increase in cardiac filling pressures could be demonstrated (*via* IVC diameter). Moreover, impaired renal venous flow was correlated with less diuretic efficiency, and patients with a lower VII had a better diuretic response (Nijst et al., 2017). Thus, this parameter might be an early marker of congestion development and become helpful in treating congestion prematurely.

There is a lack of evidence in the renal-ultrasound-guided diuretic treatment of congestion; a future field for further investigations and its usefulness in individuals with advanced CKD is unknown.

Internal jugular vein (IJV) ultrasound has been related to the classical jugular vein distention (JVD) sign and is a volume or pressure overload marker. Clinical evaluation might be subjective and challenging in some patients, but ultrasonography allows for identifying and quantifying this phenomenon. It should be performed with the head and neck elevated 45° and carefully to avoid IJV compression. If it is difficult to visualize, asking the patient to cough or perform a Valsalva will allow to identify it. The JVD ratio is the difference between IVJ at rest and during Valsalva. When congestion worsens, IJV diameter at rest increases. Thus, a JVD ratio <4 is abnormal, and if congestion is severe, it can decrease to <2 (Pellicori et al., 2021). A low JVD ratio is related to severe symptoms and elevated natriuretic peptides (Pellicori et al., 2014) and predicts increased HF hospitalizations or deaths (Pellicori et al., 2015).

5.3.3 Others

Bioelectrical impedance analysis (BIA) measures the impedance of the body to an alternating electric current of known characteristics, this being the result of two variables: Resistance (R) and Reactance (Xc). The BIA measures the resistance of the whole body resembling a homogeneous cylinder. Though there are several commercially available devices with different characteristics (bioimpedance spectroscopy (BIS), single-frequency BIA, multifrequency-BIA (MF-BIA), bioelectrical impedance vector analysis (BIVA)), to determine the amount of intra- and extracellular water indirectly and thus estimate the degree of overhydration of congestive patients. Its results are not

reliable if the patient has metal objects such as prostheses or major amputations (although in the case of BIS, results can be adjusted), and it is contraindicated if the patient has a pacemaker or self-implantable defibrillator in the case of MF-BIA, BIVA, BIS or segmental BIA (Moissl et al., 2013). Moreover, it must be considered that some devices can detect the third-space volume while others do not.

5.4. Invasive Measurements

Right heart catheterization (RHC) has long been considered the gold standard to diagnose the presence of increased intracavitary filling pressures, including RAP and PCWP and for the measurement of pulmonary vascular resistances (Bootsma et al., 2022). These measures play a pivotal role in diagnosing HFpEF (Pieske et al., 2019). RHC is also mandatory for diagnosing pulmonary hypertension (Simonneau et al., 2019) and for the workup of patients considered for heart transplantation or implantation of a left ventricular assist device (Mehra et al., 2016; Guglin et al., 2020).

RHC use in AHF decreased considerably after the publication of the ESCAPE trial, which did not show a benefit of RHC-guided therapy for patients admitted for decompensated heart failure compared with usual care; this trial, however, did not include patients in cardiogenic shock (Hill et al., 2005). Interestingly, RHC appears to be gaining ground, particularly in the setting of cardiogenic shock, where hemodynamic profiling of patients has been associated with lower in-hospital mortality in observational studies (Garan et al., 2020), and as part of a team-based approach, where decisions to institute mechanical circulatory support based on RHC data may improve outcomes in this patient population (Tehrani et al., 2019). There are some caveats in the use of right heart catheterization. It is invasive and not available in everyday clinics and only provides information on the specific moment when it is performed.

Nevertheless, wireless pulmonary artery hemodynamic monitoring has shown promising results in HF patients with previous HF hospitalizations to detect subclinical congestion, leading to anticipated decongestive therapies that significantly decrease HF hospitalizations, regardless of left ventricular ejection fraction (Givertz et al., 2017; Shavelle et al., 2020). The use of this device is on the rise, having recently received expanded FDA approval for HF patients with NYHA II functional class and elevated natriuretic peptides (NP). The indication was supported by the results of the GUIDE HF trial, where after adjustment for COVID-19 impact on the trial results, patients in NYHA class II and elevated NP had a reduction in the composite primary endpoint of reduced mortality and HF events (defined as HF hospitalizations and urgent visits when their therapy was guided by hemodynamic monitoring (Lindenfeld et al., 2021).

6. MANAGEMENT

The key to managing cardiorenal syndrome should always be to solve the root issue: heart failure or kidney disease. However, most times, the root problem does not have a solution, or if it has one, it is not instantaneous. In such cases, physicians must manage congestion, which derives from either organ's dysfunction. Herein, we discuss pharmacological and extracorporeal therapies that have alleviated congestion, reduced readmissions, and sometimes mortality. A multimodality diagnostic and treatment algorithm is proposed in **Figure 3**.

6.1. Diuretics

Most patients who present with an acute cardiorenal syndrome are volume overloaded. The only way to remove the excess fluid pharmacologically is by blocking sodium and water reabsorption at the kidney tubules with diuretics (**Table 1**). When the kidneys cannot increase urine output and achieve decongestion, we find ourselves with a case of diuretic resistance (Wilcox et al., 2020).

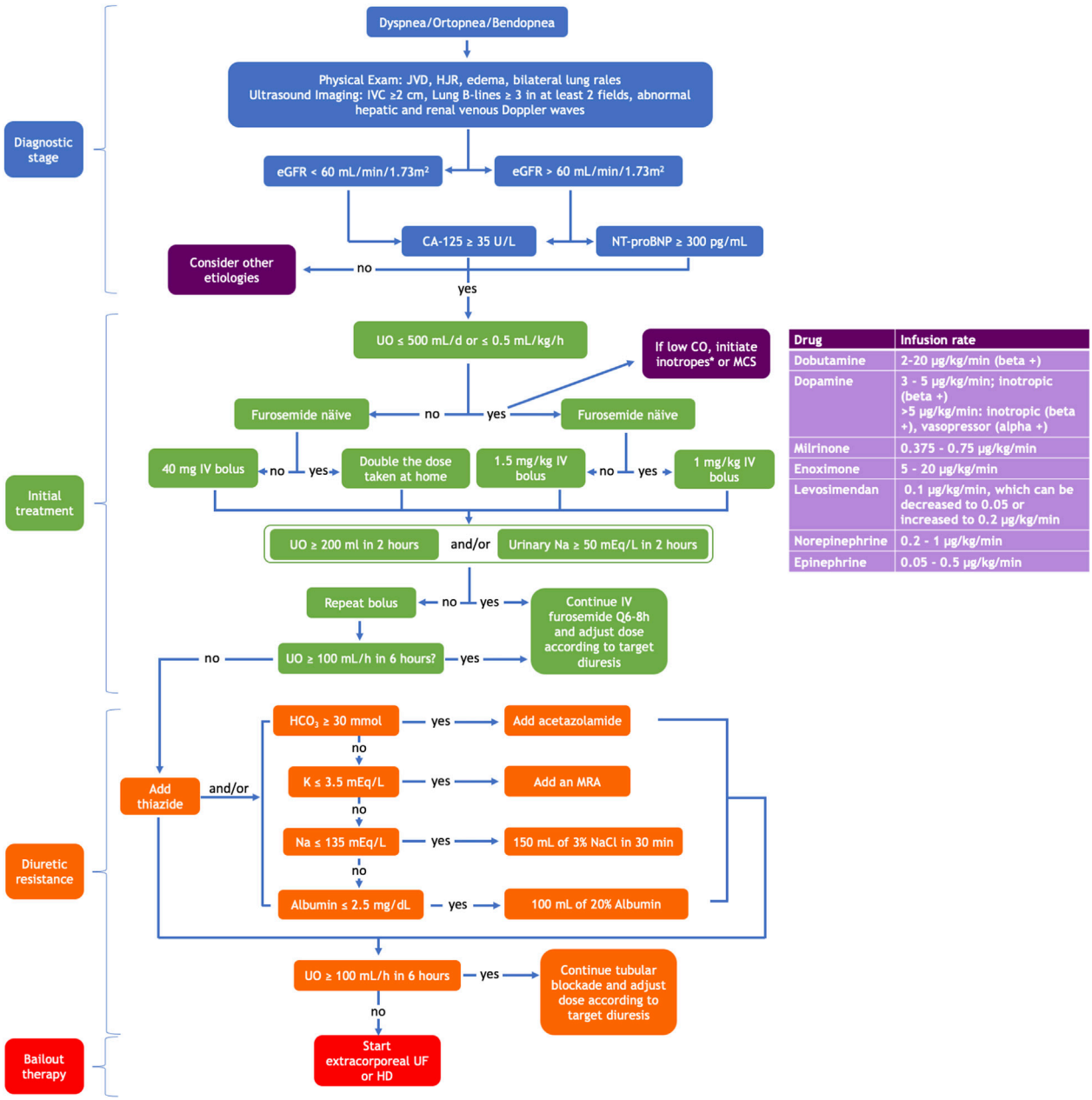
6.1.1 Loop Diuretics

In a healthy individual, kidneys filter 180 L of plasma a day. Most water reabsorption occurs thanks to the sodium-potassium-chloride cotransporters (NKCC) in the loop of Henle, which reabsorb sodium in high quantities, increasing the solute concentration at the kidney's medulla (Novak and Ellison, 2022). This osmotically potent medulla will allow most of the filtered water to be reabsorbed by the aquaporins in the collecting duct. This countercurrent effect disappears when the loop's channels are blocked, increasing urine output significantly. These drugs' most notable side effects are hypokalemia, hypomagnesemia, hypochloremia (with the consequent metabolic alkalosis), and volume depletion.

6.1.1.1 Which One Should be Used?

Furosemide is the most used and cheap loop diuretic; unfortunately, its oral bioavailability is highly variable, ranging from 10 to 100%. More modern loop diuretics like bumetanide and torsemide have a higher and more consistent oral bioavailability between 80 and 100%. However, torsemide is of particular interest as it has a longer half-life than furosemide and bumetanide (3.5 vs. 1.5 h), and its effect can last up to 16 h. Moreover, torsemide has proven to significantly reduce HF symptoms by improving the NYHA functional class, increasing cardiovascular survival, and non-significantly reducing heart failure-related hospital admissions (Abraham et al., 2020). Moreover, there is evidence that torsemide can produce aldosterone inhibition (Tsutamoto et al., 2004), potentially impacting cardiac remodeling (Yamato et al., 2003). There are two ongoing clinical trials, TORNADO (The Impact of Torsemide on hemodynamic and Neurohormonal Stress, and cardiac remodeling in Heart Failure) (NCT01942109) and TRANSFORM-HF (Torsemide comparison with furosemide for management of Heart Failure) (NCT03296813), that put this hypothesis to the test.

Furthermore, furosemide's bioavailability can be affected by many factors, such as other medications, delayed gastric emptying, reduced systemic perfusion, or gut edema. Acute congestion can produce the last two. Hence, the most efficient way to deliver enough loop diuretics in circulation in acute



Drug	Infusion rate
Dobutamine	2-20 μg/kg/min (beta +)
Dopamine	3 - 5 μg/kg/min; inotropic (beta +) >5 μg/kg/min: inotropic (beta +), vasopressor (alpha +)
Milrinone	0.375 - 0.75 μg/kg/min
Enoximone	5 - 20 μg/kg/min
Levosimendan	0.1 μg/kg/min, which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	0.2 - 1 μg/kg/min
Epinephrine	0.05 - 0.5 μg/kg/min

FIGURE 3 | A multimodal approach using clinical assessment, biomarkers, and imaging tools to diagnose heart failure and kidney disease congestion and its stepwise therapeutic algorithm. CO, cardiac output; eGFR, estimated glomerular filtration rate; HCO_3, bicarbonate; HD, hemodialysis; HJR, hepatojugular reflux; IV, intravenous; IVC, inferior vena cava; JVD, jugular vein distention; K, potassium; MCS, mechanical circulatory support; MRA, mineral receptor antagonist; Na, sodium; NaCl, sodium chloride; UF, ultrafiltration; UO, urinary output; *Adapted from the ESC Guidelines for the diagnosis and treatment of chronic heart failure 2021.

congestion is intravenously. There is no clear data on which is the proper initial furosemide dose in cases of AHF (Mullens et al., 2019). Recently, Rao et al. (2021) have proposed the implementation of a natriuretic response prediction equation (NRPE) to guide loop diuretic treatment in HF patients by assessing urinary sodium output, calculated according to the equation described in the article, 2 h after receiving a loop diuretic and increasing the dose if urinary sodium output is suboptimal (<50 mmol).

Similarly, a post-hoc analysis of the ROSE-AHF trial associated urinary sodium at the first void <60 mmol with longer hospital stays and lower weight loss. Nevertheless, the clinical application of this "suboptimal urinary sodium excretion" needs to be better defined, as some measure it in the first 6 h, others in the first hour, and others in the first void. Likewise, the urinary sodium threshold is not well defined either, though it is usually 50—60 mmol (Tersalvi et al., 2021). However, it is known that high diuretic doses improve dyspnea, reduce weight, and

increase net fluid loss without worsening long-term renal outcomes (Felker et al., 2011; Brisco et al., 2016).

The suggested initial furosemide dose in the ESC position paper on diuretic use in HF (Mullens et al., 2019) recommends starting with 40 mg of furosemide or an equivalent if the patient is diuretic naïve, or if not, then 1 to 2 times the dose they were taking at home. However, we suggest that there should be a distinction if the patient is oliguric or anuric. If this is the case, we recommend initiating the furosemide stress test, which has been validated in the oliguric AKI setting (Chawla et al., 2013). It consists of administering a 1 mg/kg (~60 mg) bolus if the patient is diuretic naïve or a 1.5 mg/kg (~100 mg) bolus if the patient is on chronic diuretic therapy. With either method, if the diuretic response in 2 h is equal to or greater than 150–200 ml, the next dose should be adjusted and administered in the following 6–8 h, according to the initial diuretic response observed. Contrarily, if the urine output in the next 2 h is less than 150–200 ml, then a new bolus of the same dose should be immediately administered. If diuresis continues to be less than 150–200 ml in 2 h, then the patient is considered non-responsive to intravenous furosemide and could benefit from a sequential diuretic blockade approach (Gill et al., 2021).

In patients who do respond to intravenous loop diuretics, there are conflicting data on whether it is better to administer the drug in a continuous infusion or bolus (Cox et al., 2020). The DOSE trial (Felker et al., 2011) found no difference in symptoms between patients who received bolus vs. continuous infusion; however, patients in the continuous group did not receive an initial bolus, which could have delayed the time until the drug reached threshold levels, potentially affecting the results.

6.1.1.2 Subcutaneous Diuretic Infusion

Furosemide has been reformulated for subcutaneous administration to allow an "intravenous-like" diuretics delivery in out-hospital patients.

Nevertheless scarce, there is evidence that subcutaneously administered furosemide for AHF treatment (Gilotra et al., 2018; Birch et al., 2021). This route allows patients to (Pitt et al., 1999; Zannad et al., 2011) be treated at home and can reduce HF hospitalizations, safely as no WRF, ototoxicity, or skin irritation has been reported as a consequence of this treatment (Ojeifo et al., 2016; Sica et al., 2018). Despite the potential advantages seen with this therapy, it has not been incorporated into management guidelines. More evidence should come in this area in the following years.

6.1.2 Thiazide and Thiazide-Like Diuretics

Thiazide diuretics act on the sodium-chloride cotransporter (NCC) located in the distal convoluted tubule. The most used thiazide diuretics are hydrochlorothiazide, metolazone, and chlortalidone. There is also available an intravenous thiazide, chlorothiazide. These agents are primarily utilized in the clinical setting as an antihypertensive medication rather than diuretics *per se*. However, in combination with a loop diuretic, they can significantly increase natriuresis and improve congestion by acting as a sequential diuretic (Cox et al., 2022). It should be noted that chlorthalidone and metolazone are slowly absorbed, and their first dose should be given around 8 h before administering a loop diuretic (Mullens et al., 2019).

Though these drugs were thought not to be effective in patients with an eGFR below 30 ml/min/1.73 m^2, there is compelling evidence of their effectiveness in advanced CKD. For instance, chlortalidone has been proven to increase diuresis and improve blood pressure control in advanced CKD while significantly reducing albuminuria, rendering a nephroprotective effect (Agarwal et al., 2021). Currently, there is an ongoing study (NCT03574857) comparing metolazone and chlorothiazide in diuretic resistance in the context of AHF. These drugs' most important side effects are hypokalemia, hyponatremia, hypochloremia, and hyperuricemia (Novak and Ellison, 2022).

6.1.3 Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRA) act by inhibiting the action of aldosterone in the principal cells of the connecting and collecting tubule, reducing the number of epithelial sodium channels (ENaC). They have a weak diuretic effect, though their efficacy is significantly augmented in cases of hyperaldosteronism related to HF or cirrhosis. Three main agents belong to this class, spironolactone, eplerenone, and, in the immediate future, finerenone.

They have a more delayed onset of action than the rest of the mentioned diuretics, requiring 2 or 3 days until any effect can be seen. Blocking sodium reabsorption creates a lumen-positive electrical gradient that impedes potassium and hydrogen secretion, thus potentially leading to hyperkalemia and acidosis. Therefore, they should be used cautiously in patients with CKD stage 3b or greater. However, they are quite useful in the setting of HF as part of the sequential tubular blockade, given that this side effect balances the risk of hypokalemia and metabolic alkalosis produced by the concomitant use of loop and thiazide diuretics.

Moreover, this drug class is of particular interest given that they serve as diuretics and are also cardioprotective. The RALES (Pitt et al., 1999) and EMPHASIS-HF (Zannad et al., 2011) studies have proven that both eplerenone and spironolactone reduce cardiovascular events in patients with HFrEF. In the TOPCAT trial (Pitt et al., 2014), spironolactone did not benefit patients with HFpEF, though there are doubts about adherence to the medication in the eastern European individuals included in this study (de Denus et al., 2017). Furthermore, finerenone has reduced the number of cardiovascular and kidney events in patients with diabetic kidney disease (Bakris et al., 2020; Pitt et al., 2021; Agarwal et al., 2022), though their diuretic potency has not been assessed yet.

6.1.4 Epithelial Sodium Channel (ENaC) Blockers

Amiloride and Triamterene act similarly to MRA though instead of indirectly blocking ENaC channel expression by blocking aldosterone, they directly inhibit ENaC function. Amiloride is currently recommended over triamterene as it is better tolerated, and it can be administered once a day instead of twice daily. It does not have triamterene's side effect of crystalluria, leading to cast formation and triamterene stones (Sica and Gehr, 1989). Given that these agents do not block aldosterone, they do not

have the added cardioprotective benefit, so MRAs are recommended above this class.

6.1.5 Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, works in the proximal convoluted tubule by blocking the sodium–hydrogen exchanger 3 (NHE3), inhibiting bicarbonate and sodium reabsorption, causing metabolic acidosis. Its diuretic effect may be minimal due to the multiple distal compensation mechanisms; however, like in the case of MRA, this side effect is desirable to balance the metabolic alkalosis produced by the urinary chloride losses caused by both loop and thiazide diuretics (Verbrugge et al., 2019). In fact, it has an intense diuretic effect when combined with other diuretic classes, although tachyphylaxis has been described after 72 h of use, as alkalosis is corrected.

In addition, acetazolamide has been associated with renal vasodilation due to the increased sodium that reaches the *macula densa*, similar to the effect seen with SGLT2 inhibitors, which could be nephroprotective. Moreover, it can also improve apnea-hypopnea symptoms associated with central sleep apnea, a common disorder found in HF patients (Gill et al., 2021).

An ongoing multicenter clinical trial (NCT03505788) will evaluate if the addition of intravenous acetazolamide 500 mg once daily to loop diuretics adds clinical benefit in acutely decompensated HF patients.

6.1.6 Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i)

SGLT2i also act at the proximal convoluted tubule by blocking the sodium-glucose cotransporter 2. This way, they reduce glucose reabsorption by 30%–50% (Narasimhan et al., 2021) and increase natriuresis reducing volume overload and improving tension control by reducing preload (Lytvyn et al., 2017). The current members of this family are empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin. There is compelling evidence that these agents reduce cardiovascular events in both diabetic (Zinman et al., 2015; Neal et al., 2017) and non-diabetic patients with HF with reduced (McMurray et al., 2019; Packer et al., 2020) and preserved ejection fraction (Anker et al., 2021) in the chronic and acute settings.

In addition to these beneficial cardiac effects, they have also proven to slow CKD progression in both diabetic (Perkovic et al., 2019) and non-diabetic patients (Heerspink et al., 2020). The natriuretic, cardiovascular, and renal beneficial effects of this drug family make them particularly attractive for patients with CRS. Moreover, the recently published EMPULSE study determined the safety and usefulness of empagliflozin in managing acute decompensated HF (Voors et al., 2022). The only agents that have proven beneficial in renal and cardiovascular outcomes in the absence of type 2 diabetes are dapagliflozin and empagliflozin (McMurray et al., 2019; Heerspink et al., 2020; Packer et al., 2020; Butler et al., 2022). For its part, empagliflozin seems beneficial independent of the left ventricular ejection fraction (Packer et al., 2020; Butler et al., 2022). Therefore, they should be introduced during the HF admission and maintained at discharge if tolerated well. As with RAAS inhibitors, a drop in eGFR <30% is expected and should not lead to its withdrawal.

6.1.7 Vasopressin Receptor 2 Antagonists

Vaptans act by inhibiting vasopressin receptor type 2 at the collecting duct, the nephron's last site of water reabsorption (Greenberg and Verbalis, 2006), making them an attractive target in volume overloaded HF patients. These agents are widely used to treat hyponatremia, autosomal dominant polycystic kidney disease (Torres et al., 2018), and inappropriate antidiuretic hormone secretion syndrome (Burst et al., 2017). Despite achieving a faster improvement in weight loss and edema, no mortality or readmission benefit was seen with tolvaptan in AHF in the EVEREST trial (Konstam et al., 2007). This negative result was confirmed by two additional trials (Felker et al., 2017; Konstam et al., 2017). The absence of long-term beneficial effects could mean that natriuresis is more important in AHF than mere free-water excretion (Narasimhan et al., 2021). Nevertheless, these agents could help manage refractory congestion in the presence of hyponatremia in selected patients.

6.1.8 Diuretic Resistance

6.1.8.1 Why Does Diuretic Resistance Occur?–Do Not be Afraid of High Doses

Like all other diuretics except for MRA, loop diuretics circulate in the blood bound to albumin and are, therefore, not filtered by the kidney. They can then act on the NKCC channel placed in the loop's lumen only after being secreted by a transporter in the proximal tubule in competition with other molecules such as urea. This means that in cases of acute tubular necrosis or reduced nephron mass, there are fewer transporters available to secrete these diuretics into the lumen, which is why in cases of AKI or CKD, higher diuretic doses are required to allow for enough drug to make its way to the channel we want to block.

The reduced systemic perfusion and renal blood flow in AHF mislead the kidneys into wanting to reabsorb as much volume as possible, increasing the number of transporters in the proximal and distal tubule. When the loop NKCC transporter is blocked, the concentration of sodium and chloride that reaches the distal tubule in the presence of an increased number of transporters enhances the amount of water reabsorbed at this level (Narasimhan et al., 2021). This is the basis for the sequential or segmental diuretic therapy approach (Narasimhan et al., 2021; Cox et al., 2022).

For many years, compensatory post-diuretic sodium reabsorption (CPSR) was thought to be the main reason for intravenous loop diuretic resistance. CPSR was described in healthy individuals as a decrease in renal sodium secretion after the loop diuretic level drops to concentrations lower than its threshold (Kelly et al., 1983). This phenomenon was not only recently disproven to participate in the development of diuretic resistance in AHF, but that those patients who have a greater diuretic and natriuretic response to furosemide present a larger post-diuretic spontaneous diuresis (Cox et al., 2021).

6.2. Sequential Diuretic Tubular Blockade

The renal tubule consists of four main segments, the proximal convoluted tubule, the loop of Henle, the distal tubule, and the collecting duct. The main concept of this approach is that when the loop diuretic effect is insufficient to achieve decongestion, we must block the rest of the tubular transporters.

6.2.1 Proposed Sequential Diuretic Tubular Blockade

There is evidence that a multi-diuretic drug sequential blockade regimen benefits roughly 60% of patients with diuretic resistance (Cox et al., 2022). Our proposed approach in the acute setting is explained in **Figure 3**. In the outpatient setting, on top of the indicated therapy according to the patients' ejection fraction, we suggest they could benefit from an oral loop diuretic (preferably torsemide). If insufficient, oral metolazone or chlortalidone may be considered (it could be administered every other day, given its long half-life). Finally, if these diuretics are insufficient or the patient becomes alkalotic (bicarbonate >30 mmol/L) or hypokalemic (potassium <3.5 mmol/L), oral acetazolamide and MRAs could be added. We do not recommend adding amiloride or tolvaptan due to the lack of long-term cardiovascular benefits.

6.3. Additional Treatment to Diuretic Therapy

6.3.1 Inotropic Agents

Inotropic agents can be of use in cases of hypoperfusion due to low cardiac output syndromes that lead to low renal blood flow, sodium retention, and less diuretic delivery to the proximal tubule. In general terms, current guidelines restrict the use of inotropes for the treatment of HF patients who are hypotensive or hypoperfused since they have been otherwise associated with a worse long-term prognosis (Nagao et al., 2022). Inotropes aim to increase cardiac output by enhancing cardiac contractility, and they are considered the third pharmacological pillar in decompensated HF treatment after diuretics and vasodilators (Farmakis et al., 2019). Currently, three classes of inotropes are recommended for decompensated HF: beta-adrenergic agonist (dobutamine, epinephrine, and norepinephrine), phosphodiesterase III inhibitor (milrinone), and calcium sensitizers (levosimendan) (Farmakis et al., 2019). Selecting the proper agent in each situation can be challenging.

Dobutamine, a beta-adrenergic inotrope, has a renal sympathetic activity that increases renal blood flow and the glomerular filtration rate but impairs oxygenation of the medulla, increasing the oxygen demand in the kidney tissue (Al-Hesayen and Parker, 2008). Milrinone, a phosphodiesterase III inhibitor, induces vasodilation, enhancing trans-renal perfusion pressure and increasing renal blood flow and renal oxygen delivery without significant glomerular filtration rate changes. In the end, for any beneficial renal effect to occur, the mean arterial pressure needs to be maintained to ensure proper renal perfusion pressure. This can be achieved with the administration of vasopressors such as norepinephrine (Zima et al., 2020), though trial results have only found limited beneficial results with these agents (Cuffe et al., 2002).

Levosimendan has been used to facilitate the weaning of continuous inotropes, augment diuresis in cardiorenal syndrome, and as cardiogenic shock therapy in selected patients (Yeung et al., 2021). Various lines of clinical investigation have produced indications of a net beneficial impact of levosimendan on renal dysfunction (Mebazaa et al., 2007). Apart from improving left ventricular performance, levosimendan effects include pre-glomerular vasodilation, increased artery diameter, and renal blood flow (Yilmaz et al., 2013). Compared to dobutamine in the LIDO trial (Follath et al., 2002), levosimendan was associated with an increase in the glomerular filtration rate.

In the past, dopamine was thought to increase renal blood flow and urinary sodium excretion; nevertheless, the addition of low-dose dopamine (2 mcg/kg/min) to diuretic treatment in patients with AHF and renal dysfunction has not shown significant effects on urine volume or renal function, and it is no longer used for this purpose (Ungar et al., 2004).

Therefore, in the setting of a low cardiac output-induced cardiorenal syndrome, we propose that levosimendan may be the first inotrope treatment option (Farmakis et al., 2019).

6.3.2 Intravenous Albumin

Albumin has been broadly prescribed for critically ill patients, although it has no known mortality benefit. It increases intravascular oncotic pressure and produces fluid mobilization from the interstitium to the intravascular space, which is thought to improve diuresis. The hypothesis that co-administration of furosemide and albumin can achieve a better diuresis response than diuretics alone has been debated. In theory, given that furosemide travels albumin-bound in the circulation, good renal perfusion and albumin are required for furosemide to arrive and be secreted at the tubular lumen of the proximal tubule. Hence hypoalbuminemia could decrease furosemide diuretic efficacy. Different trials showed inconsistencies in published results on this topic. A retrospective analysis (Doungngern et al., 2012) in intensive care unit patients with continuous furosemide infusion therapy did not show significant differences in mean urine output in patients with albumin co-administration. On the other hand, a randomized controlled crossover study (Phakdeekitcharoen and Boonyawat, 2012) in stable hypoalbuminemic CKD patients demonstrated superior short-term efficacy of albumin co-administration over furosemide alone in enhancing water diuresis and natriuresis. It is important to highlight the population and methods differences of these previous studies that might explain the results differences. A recent meta-analysis revealed that albumin co-administration increased urine output by 31.45 mL/h and urine sodium excretion by 1.76 mEq/h compared to furosemide alone (Lee et al., 2021). This effect was better in patients with low baseline serum albumin levels (<2.5 g/L) and high albumin infusion dose (>30 g) and within 12 h after administration. Diuretic and natriuretic effects were better in patients with mildly impaired renal function. Nevertheless, further clinical trials are needed to examine outcomes due to limited enrolled participants. In view of this data, we suggest the co-administration of albumin and furosemide only in cases of diuretic resistance and moderate-severe hypoalbuminemia (2–2.5 mg/dL).

6.3.3 Hypertonic Saline Infusion

The combination of hypertonic saline infusion, ranging from 1.4% if serum sodium greater than 136 and 4.6% if lesser than 125, with high-dosed furosemide has been proposed to mitigate renal dysfunction and promote natriuresis (Paterna et al., 2011). A meta-analysis demonstrated that in patients with advanced HF, concomitant hypertonic saline administration improved weight loss, preserved renal function, and decreased length of hospitalization, mortality, and HF rehospitalization (Gandhi et al., 2014). Similarly, real-world analysis in patients with refractory AHF (Griffin et al., 2020) showed that the administration of 150 mL of 3% sodium chloride in 30 min improved urine output, weight loss, serum sodium, chloride, and creatinine concentrations. Diuretic efficiency, defined as the change in urine output after doubling the diuretic dose, also improved. The mechanism involved is not fully understood, though it is believed that not only sodium but chloride plays a crucial role in salt-sensitive renal responses and acts on the family of WNK kinases which regulate the transporters where loop and thiazide diuretics act (Griffin et al., 2020). An ongoing clinical trial will measure the effects of chloride supplementation in cases of AHF (Mechanism and Effects of Manipulating Chloride Homeostasis in Stable Heart Failure; NCT03440970).

Despite the wide heterogeneity between different analyses, and the lack of an adequately powered, multi-center, randomized, blinded trial, we believe that hyponatremic and hypochloremic patients with diuretic resistance may benefit from the co-administration of hypertonic saline infusion and intravenous diuretics.

6.3.4 Neprilysin Inhibitors

Natriuretic peptides such as atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) are cardiac hormones. ANP exerts diuretic, natriuretic, and vasodilatory effects that help maintain water-salt balance and regulate blood pressures by reducing preglomerular vascular resistance stimulating diuresis and natriuresis (Tersalvi et al., 2020). Pleiotropic effects on cardiac homeostasis have also been described as pro-angiogenetic, anti-inflammatory, and anti-atherosclerotic (Forte et al., 2019). However, their biological function is impaired in HF patients due to neprilysin-mediated degradation. Treatment with sacubitril/valsartan, first-line therapy in HFrEF, reduces the degradation of natriuretic peptides by inhibiting neprilysin and inhibits the renin-angiotensin-aldosterone system. This combination reduces cardiovascular mortality (McMurray et al., 2014) and adverse myocardial remodeling and slows down WRF (Damman et al., 2018). Additionally, treatment with sacubitril/valsartan has been associated with a higher reduction of congestive clinical signs and less diuretic intensification (Selvaraj et al., 2019). Hence sacubitril/valsartan could be considered an interesting therapeutic tool in the outpatient setting to maintain euvolemia and avoid congestion in patients with HFrEF without deleterious effects on renal function (Witteles et al., 2007; Owan et al., 2008; Dandamudi and Chen, 2012).

6.4. Ultrafiltration

6.4.1 Peritoneal Dialysis

Peritoneal dialysis (PD) is mainly known as a renal replacement therapy technique. However, it has also been used as a tool for volume removal for more than 50 years. It consists of the infusion of osmotically active solutions in the peritoneal cavity, where these solutions ultrafiltrate both free-water and sodium through the peritoneal membrane (Teitelbaum, 2021). The most frequently utilized solutions rely on glucose to induce the osmotic gradient necessary for ultrafiltration. However, glucose-based solutions require longer dwell times in the peritoneal cavity to efficiently remove plasma sodium, increasing glucose absorption by the patient and injuring the peritoneal membrane with glucose end-products (Zemel et al., 1994). In this sense, icodextrin (a glucose polymer) allows for higher sodium removal and longer dwell times without the harmful side effects of glucose-based solutions, thus improving sodium balance and patients' metabolic profile. There is evidence that, in patients with HF and CKD, PD improves the quality of life, reduces hospital readmissions, helps preserve renal function (Courivaud et al., 2014), maintains patient autonomy as it can be performed at home, and is also beneficial in patients with right-sided HF, pulmonary hypertension, and ascites (Lu et al., 2015). In addition, some reports show that left ventricular ejection fraction can slightly improve after initiating PD (Morales et al., 2021). Recovery of ventricular and renal function may be explained by the better management of congestion and the prescription of the standard of care pharmacological treatments that are often withdrawn from patients with CKD due to the risk of hyperkalemia. Moreover, PD has also been associated with removing inflammatory cytokines such as interleukin-1, -6, and TNF-α, which could induce cardiac and renal fibrosis (Zemel et al., 1994).

In summary, despite the lack of clinical trials evaluating PD effect on mortality and other hard cardiovascular outcomes, we recommend it as a valuable option in autonomous patients with CKD and frequent readmissions due to AHF. This therapy allows them more independence, renal function preservation, and improved quality of life with fewer HF hospital readmissions (Lu et al., 2015).

6.4.2 Extracorporeal Ultrafiltration

Given the side effects and limitations of diuretic treatments, there has been growing interest in a non-pharmacological management approach to congestion. There is conflicting evidence on whether ultrafiltration (UF) brings any benefit on top of a proper diuretic regimen. The CARESS-HF trial by Bart et al. (2012) tried to answer this question by recruiting patients with AHF and then assigning them to diuretic therapy targeting a urine output of 3–5 L per day or venovenous fixed UF at a rate of 200 mL/h with the Aquadex System 100. There was no difference in weight loss between groups, though there was a rise in serum creatinine, bleeding events, risk of initiating renal replacement therapy, and catheter-related complications in the UF group (Bart et al., 2012).

However, there are reports showing that UF slightly reduces rehospitalizations within 30 days of an acute decompensated HF episode and helps achieve greater weight reduction if an individualized rather than a fixed UF rate is used. For instance, in the CUORE trial (Marenzi et al., 2014), the UF rate was adjusted according to each participant's clinical needs without exceeding 75% removal of the weight gained. This study

TABLE 1 | Most frequently used diuretics. Type, site of action, dose, absorption, onset, and duration of action.

Diuretic type	Frequently used	Site of action	Oral absorption	Route of administration	Dose	Onset	Peak of action	Duration
Loop diuretics	Furosemide	Ascending loop of Henle	10—100%	Oral	20 mg QD—200 mg TID	30—60 min	1—2 h	6—8 h
				IV	20 mg QD—2g QD	5—10 min	0.5 h	2 h
	Bumetanide		80—100%	Oral	0.5 mg QD—5 mg TID	0.5—1 h	1—2 h	4—6 h
				IV		2—3 min	15—30 min	2—3 h
	Torsemide		80–100%	Oral	10 mg QD—100 mg TID	1 h	1—2 h	6—8 h
Thiazide and thiazide-like diuretics	Hydrochlorothiazide	Early distal tubule	65—75%	Oral	25 mg QD—50 mg QID	2 h	4 h	6—12 h
	Chlorthalidone		-	Oral	25 mg QOD—50 mg BID	2.6 h	2—6 h	24—72 h
	Metolazone		65%	Oral	2.5–20 mg QD	1 h	-	24 h
Mineralocorticoid receptor antagonists (MRA)	Spironolactone	Late distal tubule	90%	Oral	12.5 mg QD—50 mg BID	-	2.6—4.3 h	48—72 h
	Eplerenone		69%	Oral	25—50 mg QD	-	1.5—2 h	-
Epithelial sodium channel (ENaC) blockers	Amiloride	Late distal tubule	30—90%	Oral	5 mg QD—BID	2 h	6—10 h	24 h
Carbonic anhydrase inhibitors	Acetazolamide	Proximal tubule	Dose dependent	Oral	250 mg QD—500 mg TID	1—2 h	8—18 h	8—24 h
				IV	500 mg QD—TID	2—10 min	15 min	4—5 h
Sodium-glucose co-transporter 2 inhibitors (SGLT2i)	Dapagliflozin	Proximal tubule	78%	Oral	10 mg QD	-	2 h	72 h
	Empagliflozin		-	Oral	10 mg QD	-	1.5 h	72 h
Vasopressin antagonists	Tolvaptan	Collecting duct	56%	Oral	15—60 mg QD	2—4 h	4—8 h	Dose dependent

IV, intravenous; QD, once a day; BID, twice a day; TID, three times a day; QOD, every other day; QID, four times a day; h, hours; min: minutes

found that despite weight reduction being similar in both groups, patients who received UF had fewer hospital admissions up to 6 months after being discharged from the hospital. The AVOID-HF (Costanzo et al., 2016) and UNLOAD trials (Costanzo et al., 2007) have also reported fewer hospital HF readmissions after using UF devices. To date, there is no data on whether UF has any mortality benefit over intravenous diuretic therapy; however, the ongoing PURE-HF trial (NCT03161158) is reassessing this dilemma by evaluating cardiovascular mortality and HF events at 90 days after discharge in patients managed with tailored UF in addition to low-dose diuretics vs. intravenous diuretics alone.

In summary, isolated UF is useful, particularly in patients who have trouble achieving sufficient decongestion with diuretic therapy, though one should not forget the implications of such a therapy. There could be bloodstream catheter-associated infections and potential bleeding complications derived from the anticoagulation required to perform this technique.

7 DISCUSSION AND FUTURE DIRECTIONS

The interplay between the heart and the kidney has been a matter of concern for a long time. Still, it has gained interest recently, leading to the constitution of cardiorenal units with a multidisciplinary approach. Recent advances have highlighted the need for the pre-clinical and multiparameter diagnosis of congestion, with the integrated use of biomarkers and bedside ultrasound. Multiple treatment strategies have been studied: diuretics in different doses or combinations have been the cornerstone of congestion treatment, but newer drugs and less conventional pharmacological and non-pharmacological approaches are becoming available to clinical practice. The lack of strong scientific evidence for many of these strategies contrasts with the clinical need to implement them for the increasingly diagnosed refractory congestion.

There is an urgent need for collaborative research in the field of heart and kidney failure, especially in the setting of congestion. Better diagnostic techniques to identify a pre-clinical state may lead to anticipated and effective treatment. A multidisciplinary approach, led by cardiology and nephrology, will eventually answer the needs of this increasing patient population.

AUTHOR CONTRIBUTIONS

JB and MF contributed to the conception and design of this revision. DR-E, JG-B, and JD wrote the first draft of the manuscript. All authors wrote sections of the manuscript, contributed to its revision, and read and approved the final version.

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Venous Leg Compression for Tissue Decongestion in Patients With Worsening Congestive Heart Failure

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Aims: Venous leg compression (VLC) with elastic bandages has been proposed as a potentially useful strategy for decreasing tissue congestion. We aimed to evaluate the effect of VLC on short-term changes on intravascular refill, assessed by inferior vena cava (IVC) diameter in patients with worsening heart failure (WHF) requiring parenteral furosemide. Additionally, we sought to evaluate whether early changes in IVC were related to short-term decongestion.

Methods: This is a prospective study in which we included 20 consecutive ambulatory patients with WHF treated with subcutaneous furosemide and VLC for at least 72 h. The endpoints were (a) short-term changes in IVC, (b) the association between decongestion and 3-h IVC changes following VLC. Changes in continuous endpoints and their longitudinal trajectories were estimated with linear mixed regression models. All analyses were adjusted for multiple comparisons.

Results: Following administration of subcutaneous furosemide and VLC, we found a significant increase in 3-h IVC diameter (ΔIVC = 1.6 mm, CI 95%: 0.7–2.5; $p < 0.001$), with a greater increase in those with baseline IVC≤21 mm (2.4 vs. 0.8 mm; $p < 0.001$). 3-h intravascular refill (increase in IVC≥2 mm) was associated with greater decongestion (natriuresis, weight, peripheral edemas, and dyspnea) in those with baseline IVC≤21 mm but not when IVC>21 mm ($p < 0.05$ for all comparisons).

Conclusions: In this cohort of patients with congestive WHF treated with subcutaneous furosemide and VLC, we found a greater increase in short-term IVC in those with IVC ≤21 mm at baseline. In this subset of patients, a 3-h increase in IVC≥2 mm was associated with greater short-term decongestion.

Keywords: worsening heart failure, congestion, diuretic efficiency, inferior vena cava, venous leg compression

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INTRODUCTION

Fluid overload explains most of the symptoms and signs of patients with worsening heart failure (WHF) (1, 2). Diuretics constitute the mainstay armamentarium in these patients, although the evidence endorsing the optimal diuretic strategy (intensity and sequence of the diuretic prescription) is scarce (3, 4). Optimal decongestion should imply tissue and vascular decongestion. However, at least in the short-term, most used interventions, such as parenteral diuretics, have a predominant effect by reducing intravascular congestion (3, 4). Several strategies have been postulated to mobilize extravascular volumes, such as infusion of loop diuretics and hypertonic solutions (sodium or albumin), without consistent evidence about their utility (5, 6). Venous leg compression (VLC) by using elastic bandages has been proposed as another potentially useful strategy for decreasing tissue congestion. However, its efficacy and safety in heart failure (HF) patients require a profound evaluation (7).

In this work, we sought to evaluate the association between VLC and short-term changes in intravascular refill and whether these changes are related to decongestion parameters in patients with WHF that require parenteral furosemide administration.

MATERIALS AND METHODS

Study Design and Eligibility Criteria

This is a one-arm open-label prospective study in which we included 20 consecutive ambulatory patients with WHF treated with subcutaneous furosemide and VLC for at least 72 h between January 1st, 2020, and June 1st, 2021, at an outpatient HF-Clinic in Spain (Hospital Clinic Universitari, Valencia-Spain). All patients received a subcutaneous furosemide infusion for the treatment of WHF. Patients were eligible if they presented with WHF with peripheral edema (at least grade 1+) that required parenteral ambulatory administration of furosemide. All patients had an established diagnosis of HF according to ESC guidelines (8). Exclusion criteria consisted of (a) acute decompensated HF requiring hospital admission (acute pulmonary edema, evidence of hypoxemia, defined as an oxygen saturation <90% in pulse oximetry or oxygen partial pressure <80 mmHg in arterial blood gas analysis), (b) cardiogenic shock, (c) symptomatic hypotension or any systolic blood pressure (SBP) <90 mmHg, and d) index event triggered by an uncontrolled arrhythmia (advanced heart block without a pacemaker, sustained ventricular tachycardia, therapeutic defibrillator shock, or atrial fibrillation/flutter with sustained ventricular response >150 bpm), infection/sepsis, or severe anemia (hemoglobin <7 g/dL), and patient that require hospitalization at clinician judgment. Patients on renal replacement therapy or ultrafiltration were also excluded. This study complied with the Declaration of Helsinki and was approved by the local institutional review committees. All patients signed an informed consent form.

Procedures

Subcutaneous Administration of Furosemide

Subcutaneous furosemide was administered by using a single-use, continuous infusion pump system (DOSI-FUSER®, Leventon, S.A.U, Barcelona, Spain) and a standard commercial subcutaneous infusion set. The infusion pump system consists of an elastomeric balloon inside a rigid container, an infusion line with the capillary device, and a Luer-lock connector that attaches to the standard subcutaneous infusion set. After the balloon is inflated, the medication flows through the capillary device due to the pressure from the elastomeric balloon, which determines the flow rate. We used an infusion pump containing a 250 mL balloon reservoir with a nominal continuous flow rate of 2.1 mL/h over 72 h.

Subcutaneous furosemide dose was calculated based on the subject's outpatient oral dose using a 1:1.25 conversion (80 mg of oral furosemide = 100 mg of subcutaneous furosemide). Therefore, for administering a daily dose of 100 mg of subcutaneous furosemide, a 2 mg/mL drug concentration was required (dilution: 500 mg of non-formulated furosemide in 250 mL of 0.9% sodium chloride). Specialized HF nurses filled the infusion system following the manufacturer's instructions, placed the subcutaneous catheter, and thoroughly explained general guidelines and troubleshooting to study participants.

Venous Leg Compression

Compression of the lower limbs was performed with a multi-component layer compression bandage system at a pressure of 20 mmHg (UrgoK2 LITE®) consisting of two dynamic components: an inelastic and elastic bandage. When combined, the two layers constitute one compression bandaging system that provides both a dynamic static stiffness profile and tolerable resting pressures. The first layer, KTech®, is an inelastic bandage (approximately 75% extensibility), consisting of viscose and polyester wadding with a knitted layer made of polyamide and elastane. When in contact with the skin, the KTech® layer distributes the pressure uniformly over the surface of the leg and provides compression, along with protection and absorbency when needed (9). Ktech® provides a high working pressure with a low resting pressure, which in combination with the action of the calf muscle creates a massage effect, assisting venous return and reducing edema levels. The second layer, KPress®, is an elastic cohesive bandage of approximately 160% extensibility, made from synthetic components, such as acrylic, polyamide, and elastane. This outer bandage provides the additional compression necessary to achieve the required therapeutic pressure and, more critically, maintains the recommended resting pressures necessary to maintain improved blood flow (9). These pressures are consistently maintained over time (during 7 days) (10). Each bandage layer displays an oval indicator (the PresSure® system, also known as the etalonnage) that expands into a circle when stretched correctly. Proper application is further enhanced by guides for appropriate overlap of layering. There are two different sizes of UrgoK2 LITE® according to the ankle perimeter (18–25 or 25–32 cm). For each patient, the ankle perimeter was measured, and the right size was selected.

Assessment of Inferior Vena Cava Diameter

The inferior vena cava (IVC) diameter was visualized by echography (11), with patients in the supine position, using subcostal 4 chamber view (midline, inferior to the xiphoid, angling to the right). The maximum IVC diameter during the respiratory cycle was measured approximately 3 cm before the merger with the right atrium. An IVC maximum diameter of >21 mm was defined as dilated IVC. IVC diameter was evaluated at baseline and 3, 24, 48, and 72 h after applying the compression bandage. A change in IVC at 3-h >2 mm was considered significant.

Clinical Monitoring and Biomarkers Assessment

All patients were physically visited on the day of presentation, at 24, 48, and 72-h. At these encounters, we registered the New York Heart Association (NYHA) class, pedal edema, weight, and vital signs. The pedal edema was assessed by 1+ to 4+ grade (grade 1+: slight pitting 2 mm depth, grade 2+: somewhat deeper pit 4 mm, grade 3+: noticeably deep pit 6 mm, and grade 4+: very deep pit 8 mm), and by measuring the diameter of lower limbs 10 cm above the external malleolus. The mean diameter between both limbs was registered.

We also assessed dyspnea visual analog scale (VAS) and standard plasma laboratory data [estimated glomerular filtration rate (eGFR), plasma electrolytes (sodium and potassium), and amino-terminal pro-brain natriuretic peptide (NT-proBNP)] at presentation and 72-h. The dyspnea VAS scale of 0 corresponds to the patient's subjective feeling of "I can breathe normally," and a dyspnea VAS score of 10 corresponds to "I can't breathe at all." Spot urinary sodium was assessed each 24-h after treatment intervention, at 24, 48, and 72 h.

Endpoints

The endpoints were: a) changes in short-term IVC following administration of subcutaneous furosemide and VLC, and b) the relationship between 3-h changes in IVC and parameters of decongestion (natriuresis, pedal edema, weight, dyspnea VAS, and NT-proBNP). In addition, safety endpoints included changes in eGFR, SBP, electrolytes, and the proportion of patients that symptomatically did not tolerate the 72-h leg venous compression.

Statistical Analysis

Continuous baseline variables were expressed as median [interquartile interval (IQI)]. Discrete variables were presented as numbers (percentages). Changes in continuous endpoints and their longitudinal trajectories were estimated with linear mixed regression models (LMRMs). Continuous exposures with a non-parametric distribution were log-transformed [NT-proBNP (lnNT-proBNP)]. Multivariate estimates were adjusted for age, sex, baseline eGFR, left ventricular ejection fraction (LVEF), and the baseline endpoint value regardless of their *p*-value. The LMRMs are presented as least square means (LSM) with their respective 95% confidence intervals. *P*-values were adjusted for multiple comparisons (Sidak procedure). A 2-sided *p*-value of < 0.05 was set as a criterion for statistical significance. All analyses were performed in Stata 15.1 (Stata Statistical Software, Release 15 [2017]; StataCorp LP, College Station, TX, USA).

RESULTS

The median age was 80 years (73–85), 8 (40%) patients were female, 15 (75%) showed a prior history of NYHA III, and all of them were previously admitted for acute HF, all of them were on treatment with oral loop diuretics [median furosemide equivalent doses 80 mg/day (40–120)] and showed peripheral edema at presentation (90% with grades 3+ to 4+). The median (p25–p75%) SBP, heart rate, eGFR, NT-proBNP and carbohydrate antigen (CA125) at presentation were 127 mmHg (110–139), 74 bpm (64–82), 44 ml/min/1.73 m^2 (33–61), 2,738 pg/ml (1,290–8,585), and 34 U/mL (15–125), respectively. The median (p25–p75%) of LVEF and tricuspid annular plane systolic excursion (TAPSE) were 52% (36–60) and 17.5 mm (14–19), respectively. A total of 12 (60%) patients had LVEF ≥50%. The median (p25–p75%) of IVC diameter was 22.5 mm (15–27). Half of the patients displayed IVC diameter ≤21 mm. Patients were treated with homogenous doses of subcutaneous furosemide [median 100 mg/day (min: 80, and max: 120)].

Baseline characteristics across IVC status (≤21 vs. >21 mm) are summarized in **Table 1**. Patients with IVC ≤21 mm showed lower NYHA class, NT-proBNP, and jugular engorgement (**Table 1**). There were no differences in the severity of peripheral edema or other clinical parameters of congestion.

Changes in IVC Following Venous Leg Compression

Following administration of subcutaneous furosemide and VLC, we found a significant increase in 3-h IVC diameter (ΔIVC = 1.6 mm, 95% CI: 0.7 to 2.5; $p < 0.001$). A total of 9 patients (45%) displayed a 3-h increase in IVC ≥2 mm. Afterward, a stepwise decrease of IVC diameter was noticed at 24, 48, and 72-h (**Figure 1**). However, the effect of VLC on the short-term trajectory of IVC diameter was heterogeneous across IVC status at baseline (*p*-value for interaction <0.001). In patients in which IVC was below or equal to the median (≤21 mm), we found a greater increase in 3-h IVC diameter (ΔIVC = 2.4 mm, 95%CI: 1.0 to 3.8; $p < 0.001$). In those with IVC >21 mm, IVC did not significantly increase at 3-h (ΔIVC = 0.8 mm, 95% CI:−0.6–2.2; $p = 0.611$), as is shown in **Figure 2**. The number of patients that increased IVC at least 2 mm at 3-h was higher in those with baseline IVC ≤21 mm [7 (70%) vs. 2 (20%), $p = 0.025$]. At later time-points (24, 48, and 72-h), and compared to baseline values, we found a greater decrease in IVC diameters in those with dilated IVC (>21 mm), but a neutral effect in those with IVC ≤21 mm (**Figure 2**).

Decongestion Following Leg Compression

In the whole sample, and compared to baseline values, we found a significant increase in natriuresis, weight reduction, and decreased peripheral edema during the first

TABLE 1 | Baseline characteristics.

	Total population (*N* = 20)	IVC at baseline ≤21 mm (*N* = 10)	IVC at baseline >21 mm (*N* = 10)	*p*-value
Demographics and medical history				
Age, years	80.0 (72.5–84.5)	82.0 (68.0–85.0)	78.0 (74.0–83.0)	0.705
Male, *n* (%)	12 (60.0)	5 (50.0)	7 (70.0)	0.650
Hypertension, *n* (%)	17 (85.0)	9 (90.0)	8 (80.0)	1.000
NYHA class, *n* (%) II	5 (25.0)	5 (50.0)	0	
III	15 (75.0)	5 (50.0)	10 (100.0)	
Diabetes mellitus, *n* (%)	13 (65.0)	7 (70.0)	6 (60.0)	1.000
Weight, Kg	83.0 (77.4–89.5)	80.2 (77.3–89.0)	85.4 (77.5–89.9)	0.597
COPD, *n* (%)	3 (15.0)	1 (10.0)	2 (20.0)	1.000
Renal failure, *n* (%)	14 (70.0)	8 (80.0)	6 (60.0)	0.628
Atrial fibrillation, *n* (%)	15 (75.0)	6 (60.0)	9 (90.0)	0.303
Vital signs and physical examination				
SBP, mmHg	127 (110–138)	123 (102–137)	129 (112–140)	0.406
DBP, mmHg	70.5 (62.5 –75.5)	69.5 (65–73)	71 (60–78)	0.597
Heart rate, bpm	73.5 (64–2)	68.5 (62–75)	81 (70–86)	0.059
Peripheral edema, *n* (%)				
1+ (slight)	2 (10.0)	1 (10.0)	1 (10.0)	
2+ (moderate)	0	0	0	
3+ (marked) 12 (60.0)	6 (60.0)	6 (60.0)		
4+ (serious)	3 (15.0)	1 (10.0)	3 (30.0)	
Pleural effusion, *n* (%)	3 (15.0)	1 (10.0)	2 (20.0)	1.00
Jugular engorgement, *n* (%)	15 (75.0)	5 (50.0)	10 (100.0)	0.033
Lower limb perimeter, cm	27.5 (25.5 – 29.5)	26.8 (25.0 – 29.0)	28.0 (26.0 – 29.5)	0.438
Echocardiography				
LVEF, %	51.5 (36–60)	55 (37–60)	48 (35–60)	0.678
PASP, mmHg	44.5 (35–50)	39.5 (35–45)	50 (35–52)	0.109
TAPSE, mm	17.5 (14–19)	17 (15–19)	18 (14–21)	1.000
Inferior vena cava, mm	22.5 (14.5–27)	14.5 (14–20)	27 (25–28)	< 0.001
Laboratory tests				
Serum sodium, mmol/L	139.5 (137–142.5)	140.5 (139–143)	138 (137–142)	0.212
Serum potassium, mmol/L	4.4 (4.1–4.6)	4.5 (4.3–4.7)	4.3 (4.0–4.5)	0.102
eGFR, mL/min/1.73 m2	31.3 (23.0–40.7)	23.0 (15.1–48.8)	37.3 (25.3–40.7)	0.513
Hematocrit, %	35 (31–43)	37 (31–43)	35 (33–41)	0.775
Urine creatinine mmol/L	68 (43–94)	73 (65–94)	39.5 (27–95.5)	0.131
Urine sodium, mmol/L	64 (49–86)	64 (56–83)	64 (33–87)	0.935
Urine potassium mmol/L	35.5 (28–45)	35 (31–42)	37 (23–51)	0.894
NT-proBNP, pg/mL	2738 (1290–8585)	1950 (880–4246)	8585 (2588–11765)	0.018
CA125, U/mL	33.5 (15–125)	32 (15–379)	34 (14.5–87)	0.790
Pharmacological heart failure therapy at baseline				
Loop diuretics (oral), *n* (%)	20 (100)	10 (100)	10 (100)	1.000
FED, mg	80 (40–80)	70 (40–80)	80 (80–120)	0.186
Furosemide sc dose, mg	100 (90–120)	100 (80–100)	110 (100–120)	0.054
Chlorthalidone, *n* (%)	13 (65.0)	4 (40.0)	9 (90.0)	0.057
Acetazolamide, *n* (%)	1 (5.0%)	0	1 (10.0)	1.000

(Continued)

TABLE 1 | Continued

	Total population (*N* = 20)	IVC at baseline ≤21 mm (*N* = 10)	IVC at baseline >21 mm (*N* = 10)	*p*-value
MRA, n (%)	12 (60.0)	4 (40.0)	8 (80.0)	0.170
Sacubitril-valsartan, *n* (%)	6 (30.0)	3 (30.0)	3 (30.0)	1.000
ACEI/ARB, *n* (%)	7 (35.0)	4 (40.0)	3 (30.0)	1.000
iSGLT-2, *n* (%)	9 (45.0)	5 (50.0)	4 (40.0)	0.656
Betablockers, *n* (%)	18 (90.0)	9 (90.0)	9 (90.0)	1.000

ACEI, angiotensin converting enzyme-inhibitors; ARB, angiotensin receptor blockers; CA125, carbohydrate antigen 125; COPD, chronic obstructive coronary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FED, furosemide equivalent dose; iSGLT-2, sodium-glucose co-transporter-2 inhibitors; LVEF, left ventricle ejection fraction; MRA, mineralcorticoid receptor antagonists; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PASP,: pulmonary arterial systolic pressure; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.
Continuous variables are expressed as median (p25–p75%).

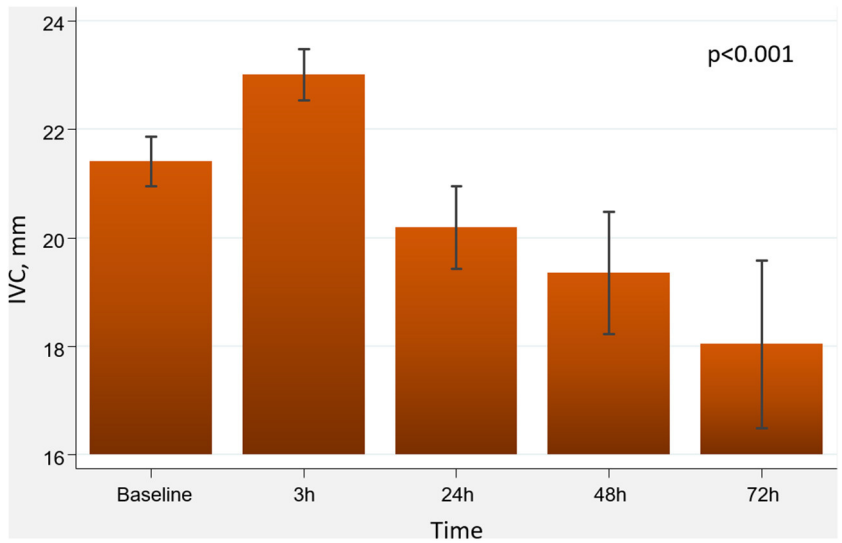

FIGURE 1 | Changes in IVC diameter following administration of subcutaneous furosemide and venous leg compression. IVC, inferior vena cava.

72 h (**Supplementary Figure 1**). Likewise, dyspnea VAS significantly decreased at 72-h (ΔVAS = −3.4, 95% CI: −4.1–−2.6; $p < 0.001$). We did not find significant changes in 72-h NT-proBNP (ΔLnNT-proBNP = −0.05, 95% CI: −0.23–0.34; $p = 0.718$). Renal function decreased at 72-h (ΔGFR = −4.2, 95% CI: −7.7–−0.7; $p = 0.019$). We also found a significant SBP and heart rate reduction at 24-h with posterior recovery (**Supplementary Figure 1**).

Short-term Increase in Intravascular Volume and Decongestion/Safety: The Role of Baseline IVC Diameter

Overall, a short-term increase in IVC ≥2 mm was differentially associated with diuretic efficacy across baseline IVC diameter. An increase in IVC ≥2 mm was associated with a greater decongestion in those with baseline IVC ≤21 mm compared to those with dilated IVC (**Figures 3**, **4**). All patients tolerated 72-h venous leg compression.

Urinary Sodium

A 3-hour increase in IVC ≥2 mm was associated with a greater natriuresis in those with IVC ≤21 mm but not in those with IVC >21 mm, in which most of the comparisons were neutral (p-value for interaction=0.012) (**Figure 3A**).

Weight

An increase in IVC ≥2 mm at 3-h was associated with a greater weight reduction when IVC ≤21 mm compared to those with IVC >21 mm (p-for interaction <0.001). In this latter group, intravascular refill was associated with higher weight (**Figure 3B**).

Peripheral Edema

The increase in IVC was borderline differentially associated with the resolution of edemas (*p*-value for interaction = 0.061). Intravascular refill led to a significant decrease in leg diameter in those with IVC ≤21 mm. Conversely, higher leg diameters were found in those with an increase in IVC ≥2 mm and baseline IVC >21 mm (**Figure 3C**).

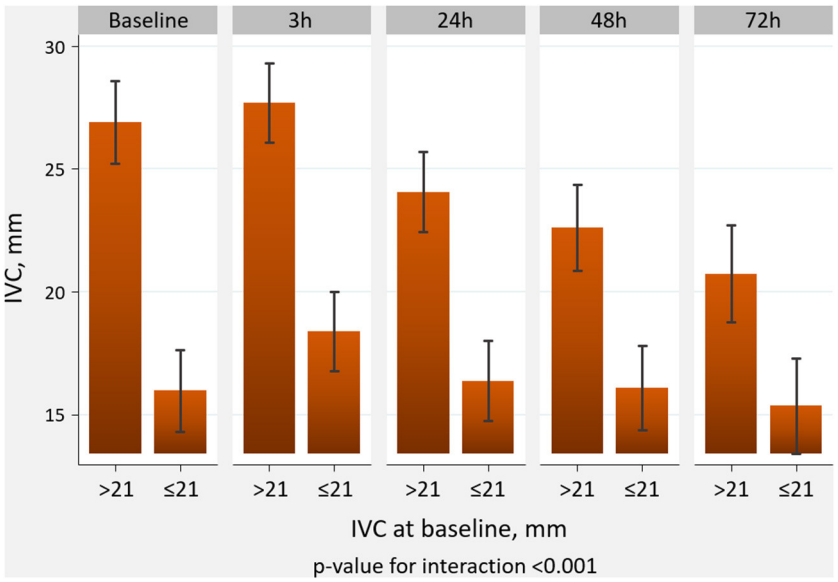

FIGURE 2 | Effect of venous compression on the trajectory of IVC diameter across IVC status at baseline. IVC, inferior vena cava.

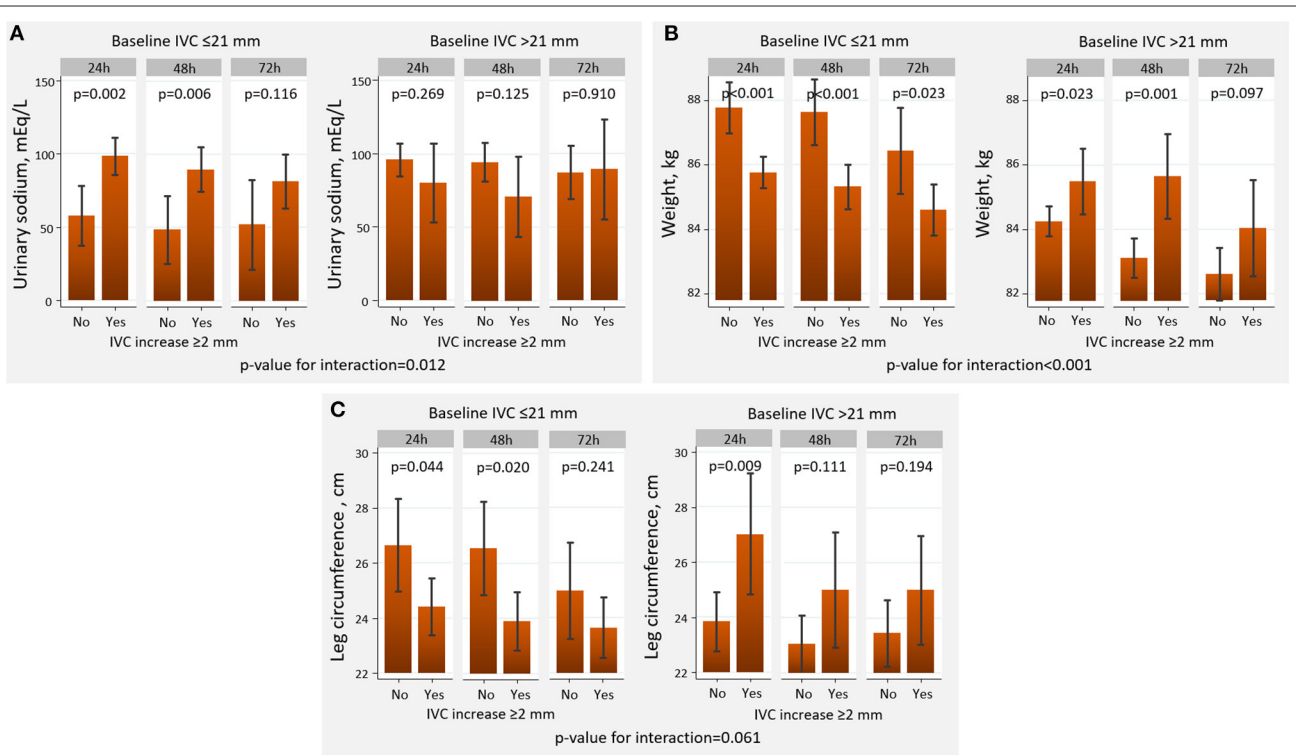

FIGURE 3 | Changes in decongestion parameters across baseline IVC diameter and the presence of IVC increase at 3-h. **(A)** Urinary sodium. **(B)** Weight. **(C)** Leg circumference. IVC, inferior vena cava.

Dyspnea VAS

IVC increase ≥2 mm at 3-h was associated with resolution of dyspnea in those with IVC ≤21 mm at 72-h, but not in those with IVC >21 mm (p-value for interaction=0.020). In this latter group, IVC increase ≥2 mm was associated with greater dyspnea at 72 h (**Figure 4A**).

NT-ProBNP

The relationship between an increase in IVC and 72-h NT-proBNP did not significantly differ across IVC status at baseline (p-value for interaction=0.131). However, we found higher LnNT-proBNP values in those with increased 3-h IVC and plethoric IVC at baseline (**Figure 4B**).

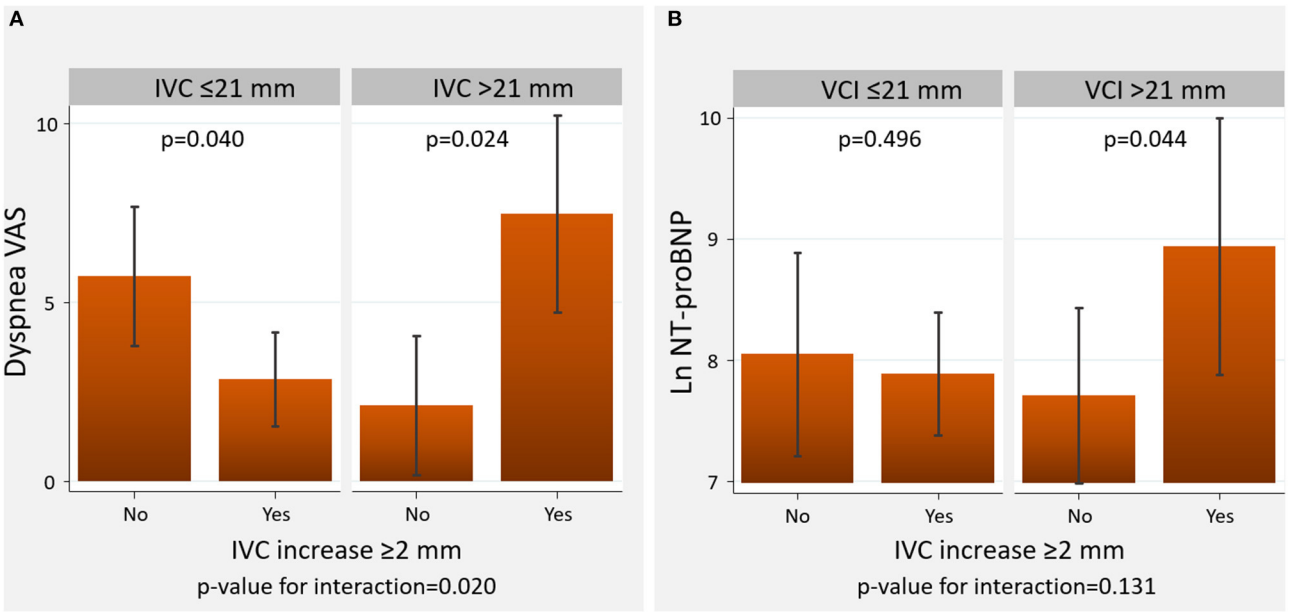

FIGURE 4 | Changes in VAS and the logarithm of NT-proBNP across baseline IVC diameter and the presence of IVC increase at 3-h. **(A)** Visual analog scale. **(B)** Amino-terminal pro-brain natriuretic peptide. NT-proBNP, amino-terminal pro-brain natriuretic peptide, IVC, inferior vena cava; VAS, visual analog scale.

Estimated Glomerular Filtration Rate

IVC 3-hour increase ≥2 mm was not differentially related to 72-h eGFR across baseline IVC (p-value for interaction = 0.835), as is presented in **Figure 5A**.

Systolic Blood Pressure

Short-term IVC increase ≥2 mm was not associated with a differential effect across baseline IVC (p-value for interaction = 0.776) (**Figure 5B**).

Summary of the main findings is presented in a central illustration.

DISCUSSION

We found that short-term VLC using elastic bandages may be useful for enhancing diuretic response in patients with congestive WHF treated with subcutaneous furosemide and absence of intravascular congestion (IVC ≤21 mm) at baseline. Conversely, it seems to have no role in those with intravascular congestion (**Figure 6**).

Diuretic Response: The Role of Extravascular Congestion and Intravascular Refill

Parenteral loop diuretic agents are the mainstay of the treatment of patients with congestive WHF (3, 4, 8). Despite their ubiquitous use in daily clinical practice, the evidence base for the appropriate use of these agents remains largely empirical (3, 4, 8). Clinical trials are scarce, and most of them have resulted in non-conclusive results (3, 4, 8, 12, 13). Although congestion explains most symptoms and signs in decompensated patients, the severity and body distribution are largely heterogeneous (1, 2, 14, 15). Clinical proxies of congestion have also shown a limited ability for profiling the congestive phenotype in WHF (16), a fact that may easily explain the disappointing findings in several randomized clinical trials. Thus, there is consensus about the need to improve the assessment of HF congestion by using a multiparametric approach, including imaging, biomarkers, and clinical parameters (15, 16).

Most of the volume overload, especially at more advanced phases of the disease, corresponded to tissue and not circulatory congestion (17). Patients with predominant tissue congestion identified a subset of patients with lower diuretic efficiency and at higher risk of diuretic resistance (3, 4). Traditional depletive strategies mainly play a role in controlling intravascular congestion (3, 4), while effective treatment strategies for targeting tissue/extravascular congestion remain a clinical challenge (3, 4). To manage tissue congestion, different approaches aiming to facilitate the intravascular volume recruitment (transferring water from extravascular to an intravascular compartment) by increasing plasmatic osmolarity are used without robust evidence. These strategies included the infusion of loop diuretic together with a saline hypertonic solution or albumin (5, 6, 18, 19). Another approach consists of using pharmacological agents such as SGLT2i or tolvaptan that increase urine-free water elimination (4, 20).

This study postulates that VLC in patients with WHF, evident tissue congestion, and absence of intravascular congestion, might be a widely available therapeutic alternative for short-term intravascular compartment expansion. Interestingly, we found that intravascular expansion following VLC was greater in those with normal-low intravascular volume, and, in this subset of patients, it was positively associated with a greater decongestion. On the contrary, this maneuver appears futile or even not recommended in cases with circulatory volume overload.

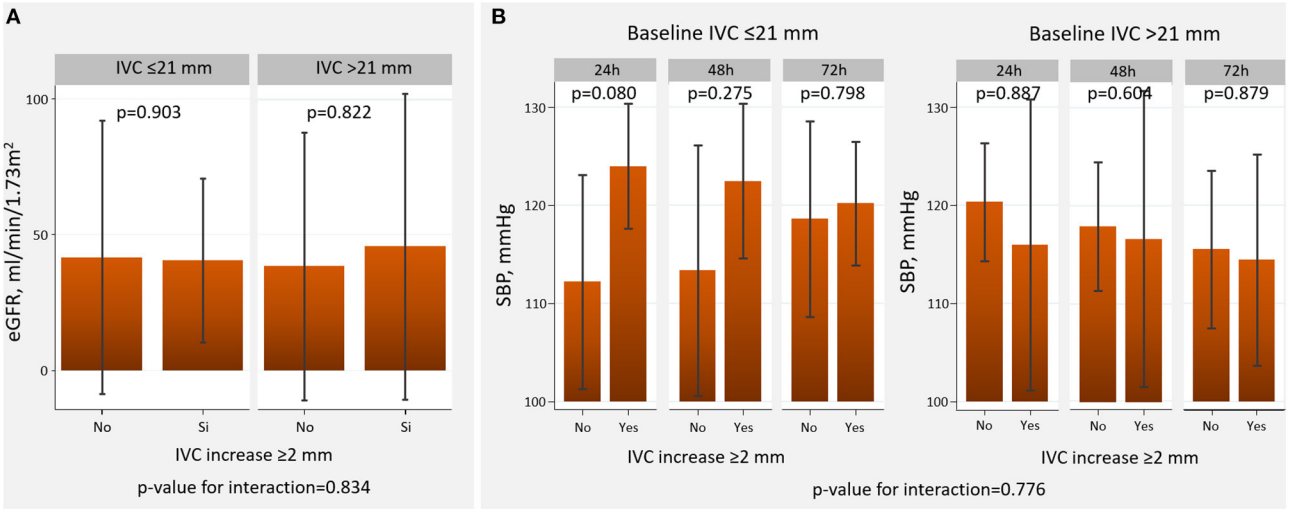

FIGURE 5 | Changes in eGFR and SBP across baseline IVC diameter and the presence of IVC increase at 3-h. **(A)** Estimated glomerular filtration rate. **(B)** Systolic blood pressure. eGFR, estimated glomerular filtration rate; IVC, inferior vena cava; SBP, systolic blood pressure.

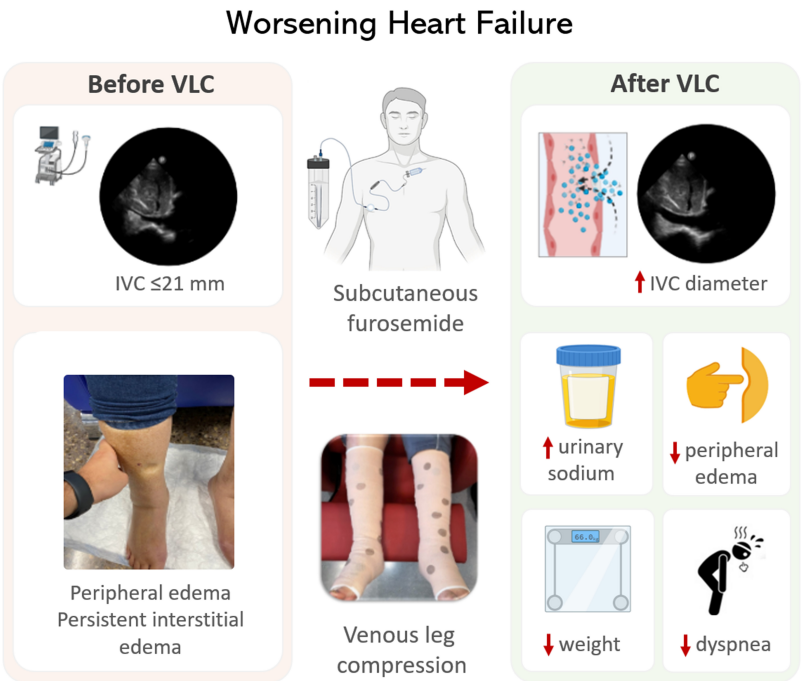

FIGURE 6 | Central illustration. The use of venous leg compression in congestive heart failure. IVC, inferior vena cava.

Previous Studies

To date, studies of VLC mainly focused on the treatment of chronic lower limb edema and ulcer, and few studies have been performed in congestive HF (7). Moreover, VLC in patients with severe and WHF appears as a contraindication in the guidelines dedicated to leg ulcer treatment (21), as a sudden movement of a large amount of blood from lower limbs veins could lead to a rapid increase in preload and afterload, precipitating pulmonary edema (7, 22). However, a contemporary report has suggested this strategy as safe in patients with venous ulcers and HF (23).

Among available studies in patients with HF, different populations have been analyzed. Dereppe et al. performed an invasive measurement of venous pressures using a Swan-Ganz catheter in 11 patients with HF (5 with chronic HF and 6 with acute myocardial infarction). After VLC, a significant increase in right auricular, pulmonary artery, and pulmonary wedge

pressures was observed, and the values returned to baseline 30 min after finishing compression (24). Brain et al. also reported, in 15 patients with moderate to severe HF, that pneumatic VLC was associated with an increase in both mean right atrial pressure and pulmonary pressure, which did not translate into significant changes in left-sided heart function (25). However, Wilputte et al. observed, in 5 patients with HF and NYHA class III and IV that simultaneous bandage VLC and muscle contraction induced a significant increase in the right arterial pressure and a transient deterioration of the right and left ventricular function (26).

More recently, the effects of VLC with elastic bandages compared to hypertonic albumin on diuretic efficiency were evaluated in a large retrospective cohort of patients (N = 1147) with volume overload and diuretic resistance during the de-escalation phase of sepsis resuscitation (27). The use of elastic bandages was associated with superior diuretic efficiency than hypertonic albumin solution, despite lower baseline serum albumin levels in those receiving elastic bandages (27). Unfortunately, none of the prior works evaluated the effect of VLC across the intravascular status.

Clinical Feasibility

In case of safety and efficacy confirmation, VLC by using elastic bandages is a widely available, simple, well-tolerated, and cheap intervention that may be easily translated into daily clinical practice.

Further Studies

These findings underscore (a) the heterogeneous pathophysiology of congestion in WHF, (b) the complexity of managing congestion in HF, and (c) the need for moving toward a more precise medicine when tackling congestion in HF. Larger and more controlled studies are required to confirm current findings and unravel whether VLC may have a clinical role in managing patients with congestive HF with predominant tissue but not intravascular congestion.

Limitations

First, it is a one-arm small pilot study with the absence of a control group. Further controlled studies are required comparing the effect of VLC plus parenteral administration of furosemide vs. parenteral administration of furosemide only. Second, the patients evaluated were older, with predominant preserved ejection fraction and features of advanced HF. Thus, current findings cannot be extrapolated to milder forms of the disease and those with predominantly left ventricular systolic dysfunction. Third, this study has the inherent limitations of the small number of participants. As such, we cannot discard that the neutral finding on some exposures may be due to low statistical power (Type II error). Fourth, the patients here included were those with ambulatory WHF. Leg compression's feasibility, efficacy, and safety should also be tested in hospitalized patients. Finally, the diuretic strategy used here was the subcutaneous administration of furosemide. Further studies should confirm current findings using intravenous administration of loop diuretics and better define the causal contribution of VLC in intravascular refilling.

CONCLUSIONS

VLC treatment is safe in patients with congestive WHF. Treatment with VLC and subcutaneous furosemide was associated with a greater 72-h decongestion when IVC at baseline is within normal values. Conversely, it appears not to have a role in increasing diuretic response in those with WHF and dilated IVC at presentation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Investigación del Instituto de investigación del Hospital Clínico Universitario de Valencia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JC and GM: conceptualization, data curation, investigation, methodology, project administration, validation, visualization, writing–original draft, and writing–review and editing. RE, ES, and AB-G: data curation, investigation, methodology, validation, visualization, and writing–review and editing. CS, AMo, AC, and AMa: data curation, visualization, and writing–review and editing. EN: formal analysis, investigation, methodology, resources, software, supervision, validation, and writing–review and editing. JN: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.847450/full#supplementary-material

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Preclinical models of congestive heart failure, advantages, and limitations for application in clinical practice

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Congestive heart failure (CHF) has increased over the years, in part because of recent progress in the management of chronic diseases, thus contributing to the maintenance of an increasingly aging population. CHF represents an unresolved health problem and therefore the establishment of animal models that recapitulates the complexity of CHF will become a critical element to be addressed, representing a serious challenge given the complexity of the pathogenesis of CHF itself, which is further compounded by methodological biases that depend on the animal species in use. Animal models of CHF have been developed in many different species, with different surgical procedures, all with promising results but, for the moment, unable to fully recapitulate the human disease. Large animal models often provide a more promising reality, with all the difficulties that their use entails, and which limit their performance to fewer laboratories, the costly of animal housing, animal handling, specialized facilities, skilled methodological training, and reproducibility as another important limiting factor when considering a valid animal model versus potentially better performing alternatives. In this review we will discuss the different animal models of CHF, their advantages and, above all, the limitations of each procedure with respect to effectiveness of results in terms of clinical application.

KEYWORDS

congestive heart failure, large animal models, rodent models, myocardial ischemia, myocardial infarction, hypertension, atherosclerosis, embolization

Introduction

Heart failure (HF) is one of the most challenging public health concerns and affects a significant portion of the population. (Benjamin et al., 2019). CHF is the manifestation in which the left ventricle fails to provide sufficient blood to meet the minimum metabolic demand. In this scenario, congestion is the consequence of neurohormonal and sympathetic nervous system activation to compensate a reduced cardiac output (CO),

increasing cardiac filling pressures through chronically elevated left-sided filling pressures, and connected to the right ventricle, resulting in systemic congestion. It can be defined as a set of situations that make the heart dysfunctional including prevention of adequate tissue perfusion. In an attempt to increase blood flow, the sympathetic stimulation induces vasoconstriction of the splanchnic capacitance vessels and vasodilation of the hepatic veins, the main mechanism to increase cardiac filling pressures. This process is associated to venous congestion disorders, that include a significant increase in both central venous pressure (CVP) and intra-abdominal pressure (IAP).

Clinical manifestations of congestion comprise the development of dyspnea, orthopnea, the appearance of abnormal pulmonary sounds, edema and jugular ingurgitation as a mechanism to compensate for a reduced CO. In many cases, the increase in left filling pressure is responded by the pulmonary system, which eventually shunts to the right ventricle, finally resulting in a systemic congestive problem.

The term congestive heart failure (CHF) unifies both the failing heart and congestive behavior, a combination difficult to explore in the clinic at the molecular level. Classical assessment of left-sided filling pressures includes measurement of left ventricle end-diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP). Elevated LVEDP is the main indicator of left ventricular diastolic dysfunction (Mielniczuk et al., 2007), while PCWP measures left atrial pressure, through insertion of a balloon-tipped catheter (Swan-Ganz catheter) to occlude a branch of the pulmonary artery (Aalders and Kok, 2019). In both cases cardiac catherization is required, and hence, assessing these two parameters are limited to humans and big animal models of CHF. To overcome these limitations, non-invasive assessment of filling pressures are useful alternatives. In this regard, echocardiographic quantification of left ventricle filling pressure is based on E/e′ measurement: the ratio between early diastolic velocity on transmitral Doppler (E) and the early diastolic velocity of mitral valve annulus from tissue Doppler (e′). However, this ratio is still under debate as predictor of left ventricle filling pressure (Sharifov and Himanshu Gupta, 2017). On the other hand, a non-invasive echocardiographic assessment of left atrial (LA) strain is used to evaluate heart failure with preserved ejection fraction to predict disease severity and risk of severe outcome (Reddy et al., 2019). CHF is also assessed by lung ultrasound, and in particular ultrasound lung comets, as to visualize extravascular lung water, is a useful method to estimate pulmonary congestion in heart failure patients (Li et al., 2018). Despite all the invasive and non-invasive ways to assess CHF, a set of molecular fingerprints that can shed light on the early diagnosis and progression of disease is still poorly understood, which implies the need to develop reliable animal models that may help to a better understanding and effective approach to this pathology.

Ideally, a valid experimental model should be reproducible, having to fulfill, if not all, a significant number of the features of disease. Furthermore, translation of the experimental results to the clinic must represent a top priority, and hence, although there is a wide variety of small preclinical models of HF, the use of animals with a cardiovascular system closer to humans, such as swine or sheep models, are preferably used for the generation of valid results. In view of the above, the following are models used with varying degrees of reproducibility (Table 1), thanks to which we can now gain a deeper understanding of this complication.

Myocardial ischemia

Myocardial ischemia often leads to adverse ventricular remodeling and CHF as a multifactorial process in which neurohormonal response, activation of cell death signaling pathways, and persistent degradation of myocardial extracellular matrix play a major role.

The development of ischemic-induced CHF models, including recapitulation of the patient's underlying condition, is a challenge of great complexity. Etiologically, CHF involves a set of significant events over the life time and is further aggravated by patient´s comorbidities and polymedication (Pound and Ritskes-Hoitinga, 2018). Furthermore, ischemia-induced CHF is biased by factors like the age, sex, ethnic conditions, and even geographic location (Virani et al., 2021). Besides, current models of myocardial ischemia in the absence of subsequent reperfusion are not representative of human disease. Therefore, many animal models have failed, since almost no the aforementioned factors are addressed, and in general models use young, healthy animals, of the same sex and from the same pool (Pound and Ritskes-Hoitinga, 2018).

Several preclinical models have been developed by external occlusion of one or more coronary arteries, which is not representative of the pathophysiology of disease, since intracoronary plaque formation is the leading culprit of disease (Lee et al., 2017). In addition, Although rodents offer substantial advantages over other species: low cost, large sample sizes and relative ease of genetic manipulation, nevertheless, the differences in coronary architecture, cardiac anatomy, and hemodynamics imply the choice of other species as better candidates for the study of CHF, in which the large animal models have provided significant advances for the clinical practice.

Acute myocardial infarction

Porcine models of AMI are widely used for reasons ranging from similar collateral circulation (Hill et al., 2009) and architecture (Dixon and Spinale, 2009) to humans, making possible to predict, and control infarct size and disease severity.

As with rodent models (Cuadrado et al., 2016), the procedure can be induced by exposing the heart and externally occluding the coronary artery(s) of interest with gradually inflating pressure

TABLE 1 Preclinical models of CHF.

Preclinical model	Procedure	Advantages	Limitations	Species	References
Myocardial Infarction	External oclusion of cornary artery	Economic cost Sample sizes	Different anatomy and hemodinamics External oclussion of the artery High variability High mortality rates CVP minimally affected	Rodents	Cuadrado et al. (2016)
	Open chest internal oclusion of coronary artery	Similar collateral Similar anatomy and hemodinamics	Economic cost Sample sizes Open chest requirement Inflammation related side effects in response to surgery Risk of V-FIB	Pigs	Heusch et al. (2011), Heusch and Rassaf, (2016)
	Close chest PCI angioplasty balloon inflation	Similar collateral Similar anatomy and hemodinamics	skilled trained personnel in percutaneous catheterization Economic costs Sample sizes Risk of V-FIB	Pigs	Heusch et al. (2011); Ishikawa et al. (2014); Hernandez et al. (2021)
Microembolization	Injection of microshperes into the LAD and/or LCX	Severe ventricular dysfunction Increase of PCWP LV dilatation Reduction of LV wall thickness	Does not recapitulate human condition Risk of embolic infarction at the LCX	Dog	Franciosa et al. (1980), Ikeda et al. (2001)
	Coronary slow flow model by receiving repeated low-dose LAD microsphere injection	LV remodeling at 4 weeks of procedure	Does not recapitulate human condition Economic costs Sample sizes	Pig	Hu et al. (2014)
	Ischemia/reperfusion plus autologous injection of platelet thrombi	Severe reduction of LVEF and CO Diastolic ventricular failure Increased PCWP	Does not recapitulate human condition Economic costs Sample sizes Risk of V-FIB	Pig	Sassi et al. (2019)
Pacing-Induced Tachycardia	Accelerated chronified atrial and ventricular rhythms with HR between 200–400 bpm	Biventricular dilatation Ventricular dysfunction Neurohormonal stimulation Severe reduction of LVEF and CO Cesation restores hemodynamic values	Absence of mechanistic information about the underlying mechanisms that lead CHF	Dog, Pig	Riegger and Liebau (1982); Moe et al. (1989); Ohno et al. (1994)
Atrial Fibrilation	Applying cycles of atrial pacing	Atrial fibrilation Dogs recapitulate pathogenesis of disease In rodents, GWAS/ CRISPR are used to find new targets of disease	Lack of manifestations of CHF excepting dogs	Dog, Goat, Pig Mouse	Power et al. (1998); Yarbrough and Spinale (2003); Dosdall et al. (2013) Zhang et al. (2019)
Aortic Banding	Surgical banding of the ascending aorta	Procedure mirrors aortic stenosis Neurohormonal activation LV dysfunction Depressed LVEF and CO Mithocondrial, Endothelial, microvascular dysfunction HF with preserved LVEF Correlation with cerebrovascular dysfunction in pigs	Elevated mortality high variabiliy intra and inter species	Dog, Sheep, Pig	Dellsperger and Marcus (1990); Moorjani et al. (2003); Wang et al. (2006); Moorjani et al. (2007); Ishikawa et al. (2015); Chaanine et al. (2017); Fleenor et al. (2018); Merino et al. (2018); Hayward et al. (2019); Olver et al. (2019); Baranowski et al. (2021)

(Continued on following page)

TABLE 1 (*Continued*) Preclinical models of CHF.

Preclinical model	Procedure	Advantages	Limitations	Species	References
Pulmonary Banding	Surgical bainding of the central or in combination with the left pulmonary artery	Right ventricule dysfunction Chronic pressuer overload Development of HF Neurohormonal activation	Variability intra and inter species Absence of peripheral edema Absence of pulmonary vascular remodeling	Dog, Pig	Pereda et al. (2014); Wehman et al. (2017); Nguyen-Truong et al. (2020); Ukita et al. (2021a); Ukita et al. (2021b)
Hypertension	Surgical by embolization of renal arteries in combination of streptozotozine and western diet	HF with preserved LVEF Microvascular dysfunction Integration of cormobidites	Few sample sizes, and studies	Pig	van de Wouw et al. (2021), Sharp et al. (2021)
Toxicity	Pharmacological be treatment with deoxycosterone and western diat Doxorubicin Norepinephrine	Dilated cardiomyopathy in dog and sheep Left ventricular dilatation	Variability intra species Partially recovery after 1 week in dogs	Dog, Seep, Rabbit, Rodent	Movahed et al. (1994); Toyoda et al. (1998); Chekanov (1999); Aguero et al. (2016); Hong et al. (2016); Weil et al. (2018); Galán-Arriola et al. (2019); Yip et al. (2020); Yeh et al. (2021)

rings, which ultimately precipitates the development of an AMI and collateral circulation. Other models comprise AMI in dogs, although extensive collateral flow justifies porcine models (Maxwell et al., 1987; Sabe et al., 2016).

Preclinical open-chest models have provided a substantial amount of information to characterize HF in depth, yet they do not recapitulate the pathogenesis of disease, since intracoronary atherothrombotic lesions are the most frequent cause leading to tissue necrosis, and the inflammatory response related to open-chest surgery, consequently limit the clinical translation.

Currently, percutaneous catheterization by angioplasty balloon inflation and reperfusion, closely resembles interventional catheterization, and is by far the most commonly preclinical model of AMI (Heusch et al., 2011; Hernandez et al., 2021). The left anterior descending coronary artery (LAD) is occluded in most models given the larger size of MI and induces more severe systolic dysfunction. The left circumflex coronary artery (LCX) can also be occluded to induce mitral regurgitation, but LAD occlusion causes more severe left ventricle (LV) remodeling than LCX occlusion (Ishikawa et al., 2014). Limitations include the need of a surgical room, and skilled trained personnel in percutaneous catheterization. In addition, pharmacological support to avoid arrhythmogenic behavior, and sometimes ventricular fibrillation (V-FIB) cardioversion procedures are mandatory in many cases. However, the procedure also offers to perform cardiac preconditioning, the event that occurs when patients undergo coronary occlusion and reperfusion in short and repeated times, prior to a longer temporary occlusion, a mechanism previously described of myocardial cardioprotection (Heusch and Rassaf, 2016), and reduced arrhythmogenic behavior (Ramirez-Carracedo et al., 2020). In addition, if percutaneous occlusion of the coronary artery last no longer than 60 min part of ischemic tissue remains contractile (myocardial salvage), allowing to perform studies of cardiac protection (Santos-Gallego et al., 2016). However, in case of HF studies, at least 2 hours of coronary occlusion are mandatory (Santos-Gallego et al., 2019). These models of HF also allow for investigation of myocardial metabolism either by PET or with direct trans cardiac gradient of metabolites by simultaneous sampling of coronary artery and coronary sinus (Christensen et al., 2017; Santos-Gallego et al., 2019).

Microembolization

Angioplasty balloon inflation is a noninvasive procedure that partially recapitulates the occlusion that defines acute anginous behavior. However, in most situations, the patient suffers a progressive coronary artery occlusion over time that eventually leads to AMI, in which cardiac remodeling and thus CHF, has already begun and progress ahead of infarction. A canine microembolization procedure initially emerged by injecting microspheres into the LAD and/or LCX artery, over time (Franciosa et al., 1980), while injection of 5 separate dosages every 2 weeks in sheep resulted in severe ventricular dysfunction (left ventricle ejection fraction, LVEF <25%), together with a marked increase in PCWP and dilatation of the left ventricle, accompanied by a significant reduction in left ventricular wall thickness, indicative of CHF (Ikeda et al., 2001). As an important concern, the thrombus generated by using microspheres does not fully resemble human

condition, and microembolization of the LAD, can often result in embolic infarction in the LCX.

Patients with slow-flow after percutaneous coronary intervention have a worse prognosis after revascularization. However, the studies were limited to ischemia/reperfusion, which partially reflects this condition, since no- or slow-flow is induced by microembolization. To this regard, an angiographic coronary slow flow model was created in pigs receiving repeated low-dose LAD microsphere injection up to a total of about 300,000 microspheres, in which left ventricle remodeling was visible even 4 weeks after post-procedure (Hu et al., 2014). More recently, the combination of coronary ischemia/reperfusion together with microembolization from autologous injection of platelet thrombi in pigs, provided a new model of CHF, with significant decreases LVEF and CO after 1 week of embolization, together with the appearance of diastolic ventricular failure and increased PCWP (Sassi et al., 2019).

Tachyarrhythmias

Dilated cardiomyopathy (DCM) is often associated with CHF in response to sustained arrhythmogenic complications over time, like atrial fibrillation (AF), which increase up to three fold the risk of HF (January et al., 2014). In this regard, models should recapitulate ventricular wall dilatation and thinning, along with a progressive decline in cardiac function, and neurohormonal activation.

Pacemaker-induced tachycardia pacing-induced tachycardia

Over the years, different models of PIT have been developed in dogs, sheep and pigs that eventually lead to reduced ejection fraction. Accelerated chronified rhythms, both atrial and ventricular, with heart rates ranging between 200 and 400 bpm, can generate eccentric bi-ventricular dilatation, inducing ventricular dysfunction and neurohormonal stimulation, accompanied by a significant reduction in LVEF and CO (Riegger and Liebau, 1982). Interestingly, cessation of pacemaker activation returns hemodynamic values to physiological levels. However, the procedure does not shed light on the underlying mechanisms leading to CHF, as heart failure in patients precedes arrhythmogenic behavior (Ohno et al., 1994).

Atrial fibrillation

As mentioned above, AF may also lead to CHF. In response to a significant reduction of stroke volume, AF patients develop adverse cardiac remodeling, neurohormonal activation and, at the end, heart failure. AF is also a very complex arrhythmogenic disease in regard to its etiology, which limits the development of reliable AF-induced CHF models. The advantages of using pigs lie in the similarity of cardiac architecture, coronary architecture and electrophysiology with humans. However, the substantial risk of developing episodes of V-FIB should be considered before using this species. Indeed, animal models consisting on applying several cycles of atrial pacing in sheep (Moe et al., 1989), dogs, goats and pigs (Yarbrough and Spinale, 2003; Dosdall et al., 2013) have tried to reproduce AF-dependent CHF, but only dogs partially recapitulated the pathogenesis of disease.

Rodent models have recently become a significant advance in the study of AF, thanks to the burst of genetic data through GWAS (Genome-wide association study). In combination with CRISPR/Cas9, many difficult-to-detect non-coding targets implicated in this pathology have been found in mice, which may shed light about the molecular mechanism of disease (Zhang et al., 2019). However, the association with CHF in rodent models is still poorly understood.

Pressure overload

CHF is also related to chronic pressure overload. Continually having to overcome elevated afterload values eventually reverts to adverse remodeling, where patients develop left ventricular hypertrophy to maintain adequate perfusion, along with increased myocardial stiffness leading to increased ventricular filling pressures and pulmonary congestion. For this reason, patients transiently undergo to an interesting phenotype similar to heart failure with preserved LVEF (Braunwald, 2018; Silva and Emter, 2020). As seen below, large animal models of PO have been developed with CHF symptoms that include pulmonary congestion or dyspnea.

Transverse aortic constriction (aortic banding)

Aortic constriction models aim to recreate by surgical techniques the phenomenon of aortic stenosis through vessel constriction. This procedure mirrors aortic stenosis for up to 4 weeks depending on stenosis diameter (Merino et al., 2018), which locally triggers neurohumoral activation along with increased myocardial afterload, resulting in increased left ventricular pressure gradient, left ventricular hypertrophy, and myocardial stiffness.

Initially developed in dogs (Dellsperger and Marcus, 1990), aortic constriction in sheep lead to HF, with depressed LVEF, whereas in swine models left ventricular stiffness is the first manifestation (Ishikawa et al., 2015), in which PO is generated by aortic constriction for months (Moorjani et al., 2003; Wang et al., 2006; Moorjani et al., 2007; Fleenor et al., 2018). In these models, the neurohumoral response plays a key role, conditioning adverse remodeling through activation extracellular matrix proteolytic

enzymes, together with mitochondrial, endothelial, and microvascular dysfunction (Hayward et al., 2019). However, although constriction devices apply gradual increases in afterload, it takes years for patients to reach the same level of complication, and mortality rates are lower compared to animals. Notably, in almost all species tested, a common feature is the HF with preserved LVEF, which, considering the enormous importance of this pathology yet to be fully explored, makes these models of current relevance and interest (Chaanine et al., 2017; Olver et al., 2019).

Aortic constriction in combination with a high fat diet, have pointed the evidence between the association of HF with cerebrovascular failure, neuroinflammation and amyloidosis with preserved LVEF. At the molecular level and considering limitations that include a lack of nutritional control groups and histopathological data, a transcriptomic pattern can be obtained in animals subjected to aortic constriction typical of frontotemporal dementia and Alzheimer's disease, implying the clear relationship between HF with preserved LVEF with cognitive impairment (Baranowski et al., 2021).

Hypertension in combination with other factors

It is increasingly common to identify HF with preserved LVEF, although its etiology, progression and therapeutic targets are largely unknown. In this regard, systemic PO models have been developed in combination with streptozotocin-treated diabetic pigs undergoing renal artery embolization and fed a hypercholesterolemic diet to create a clear model of HF with preserved LVEF and microvascular dysfunction (van de Wouw et al., 2021). More recently, a new model of HF with preserved LVEF has been developed, integrating most of the comorbidities of this pathology, exhibiting sensitivity to obesity, metabolic syndrome, and vascular disease, through a combination of hypercholesterolemic diet and treatment with deoxycorticosterone as a hypertensive agent. As commented by the authors, the main limitation is that conclusions are based on a very small sample size (Sharp et al., 2021), and therefore, more testing is required for further validation of the model.

Pulmonary artery constriction (pulmonary banding)

Constriction of the pulmonary artery have been used in different animal species to develop a chronic pressure overload model that ends in right HF, a good approach for the study of CHF, since increases right ventricular and central venous pressures.

Although rodent studies are commonly used, the clinical interest in CHF made possible to generate different experimental models in large animals, including two recent studies in which the central pulmonary artery is constricted in sheep (Nguyen-Truong et al., 2020) or simultaneously combined with ligation of the left pulmonary artery (Ukita et al., 2021a). More recently, the use of porcine models of pulmonary hypertension by pulmonary vein constriction (Pereda et al., 2014; Ukita et al., 2021b), has evidenced its validity for studying HF in pathologies related to regenerative cardiology (Wehman et al., 2017). These models can also be used to evaluate the efficacy of therapeutic interventions such as the effect of intratracheal delivery of SERCA2a to ameliorate chronic post-capillary pulmonary hypertension by using a porcine model of chronic post-capillary PH by partial pulmonary vein banding (Aguero et al., 2016).

As we have described throughout this review, a series of surgical approaches have helped us to better understand the etiology and progression of CHF, providing new molecular targets and novel therapeutic approaches to increase the life quality of patients. In addition, it should also pay attention to pharmacology, as a useful strategy in specific aspects not to improve, but to induce HF models, as we will discuss below.

Toxicity models

Among the different substances affecting cardiac performance, the role of doxorubicin as a chemotherapeutic agent is of particular interest, since it is noteworthy that it often leads to the development of dilated cardiomyopathy in a significant number of cases. The search for new molecular targets against the impact of doxorubicin is subject of intense research, having initially developed preclinical models in dogs (Movahed et al., 1994; Toyoda et al., 1998), sheep (Chekanov, 1999) and more recently in pigs (Galán-Arriola et al., 2019). However, the bulk of research is currently being conducted in rodent (Yip et al., 2020; Yeh et al., 2021) and rabbit models (Hong et al., 2016), with the aforementioned limitations derived from the use of small animal models. The relationship between neurohormonal overproduction of catecholamines and heart failure led to development of models of high norepinephrine exposure in pigs (Weil et al., 2018). Although increasingly out of use, dogs exposed to catecholamines have been developed signs of CHF. Prolonged norepinephrine infusion should be investigated for translation to the clinic, as the model may not be directly comparable, as claimed by the authors, because the norepinephrine infusion was relatively brief (Movahed et al., 1994).

Conclusions

Congestive heart failure is a highly complex pathology from its onset at the subclinical level, in symptomatology and prognosis. Therefore, it is key to tackle CHF from different perspectives in order to find new molecular targets that enable a significant improvement

against this pathology. In this regard, preclinical models of CHF, particularly large animal models, play a central role in providing new tools for early diagnosis and treatment. Although economic costs, handling, personnel skills, and the necessary equipment are often limiting factors, large animal models offer important advantages in terms of better clinical translation: they offer greater structural and functional similarity, and in general many models recapitulate the associated comorbidities. Their use also adds valuable information about safety of existing treatments, even adding economic value in terms of patient outcome.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Corrigendum: Preclinical models of congestive heart failure, advantages and limitations for application in clinical practice

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The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Incremental prognostic value of lung ultrasound on contemporary heart failure risk scores

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Introduction: Over the last decades, several scores have been developed to aid clinicians in assessing prognosis in patients with heart failure (HF) based on clinical data, medications and, ultimately, biomarkers. Lung ultrasound (LUS) has emerged as a promising prognostic tool for patients when assessed at discharge after a HF hospitalization. We hypothesized that contemporary HF risk scores can be improved upon by the inclusion of the number of B-lines detected by LUS at discharge to predict death, urgent visit, or HF readmission at 6- month follow-up.

Methods: We evaluated the discrimination improvement of adding the number of B-lines to 4 contemporary HF risk scores (Get with the Guidelines -GWTG-, MAGGIC, Redin-SCORE, and BCN Bio-HF) by comparing the change in the area under the receiver operating curve (AUC), the net reclassification index (NRI), and the integrated discrimination improvement (IDI). The population of the study was constituted by the 123 patients enrolled in the LUS-HF trial, adjusting the analyses by the intervention.

Results: The AUC of the GWTG score increased from 0.682 to 0.789 ($p = 0.02$), resulting in a NRI of 0.608 and an IDI of 0.136 ($p < 0.05$). Similar results were observed when adding the number of B-lines to the MAGGIC score, with an AUC that increased from 0.705 to 0.787 ($p < 0.05$). This increase translated into a NRI of 0.608 and an IDI of 0.038 ($p < 0.05$). Regarding Redin-SCORE at 1-month and 1-year, the AUC increased from 0.714 to 0.773 and from 0.681 to 0.757, although it did not reach statistical significance ($p = 0.08$ and $p = 0.06$ respectively). Both IDI and NRI were significantly improved (0.093 and 0.509 in the 1-month score, $p < 0.05$; 0.056 and 0.111 in the 1-year score, $p < 0.05$). Lastly, the AUC for the BCN Bio-HF score increased from 0.733 to 0.772, which was statistically non-significant, with a NRI value of 0.363 ($p = 0.06$) and an IDI of 0.092 ($p < 0.05$).

Conclusion: Adding the results of LUS evaluated at discharge improved the predictive value of most of the contemporary HF risk scores. As it is a simple, fast, and non-invasive test it may be recommended to assess prognosis at discharge in HF patients.

KEYWORDS

congestion, heart failure, lung ultrasound, scores, biomarkers, prognosis

1 Introduction

Risk prediction in heart failure (HF) remains essential to identify those patients who may benefit from a closer management. Since the turn of the century, several scores have been proposed and externally validated (Levy et al., 2006; Peterson et al., 2010; Pocock et al., 2013; Lupón et al., 2014; Álvarez-García et al., 2015). Most can be easily calculated using demographics, laboratory, and medication data, and are available through free-access websites. Nevertheless, no predictive scale has been found uncontrovertibly better than the rest (Codina et al., 2021), illustrating the complexity of risk prediction in HF.

As HF treatment has dramatically evolved during the last decades, existing prognostic scores, have been continuously updated adding emerging data from both newer therapeutic and diagnostic tools (Sinha et al., 2021). Particularly, lung ultrasound (LUS) has emerged in the last years as a simple and non-invasive instrument for detecting pulmonary congestion in patients with HF. Its prognostic value has been assessed in different clinical scenarios (Coiro et al., 2015; Coiro et al., 2015; Gargani et al., 2015; Platz et al., 2016; Scali et al., 2017; Coiro et al., 2020; Rivas-Lasarte et al., 2020; Domingo et al., 2021; Gargani et al., 2021; Kobayashi et al., 2021; Mazzola et al., 2021; Pugliese et al., 2021; Pugliese et al., 2021), showing that the presence of B-lines detected by LUS is associated with an increased risk of worse outcomes.

Thus, we hypothesized that contemporary risk scores can be improved by incorporating the number of B-lines detected by LUS at HF discharge to predict death or hospital readmission at 6- month follow-up.

2 Material and methods

2.1 Study design

This is a sub-analysis including 123 patients enrolled in the LUS-HF trial, whose study design and primary results have been previously reported (Rivas-Lasarte et al., 2019). In brief, the LUS-HF was a single-center, single-blind, randomized clinical trial evaluating tailored LUS-guided diuretic treatment of pulmonary congestion in patients with HF. Patients were required to be aged ≥18 years and to have been hospitalized for HF defined by shortness of breath, pulmonary congestion on X-ray, and elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) values in the first 24 h of admission (cut-off values: 450 ng/L in patients aged <50 years; >900 ng/L in patients aged 50–75 years; >1800 ng/L in patients aged >75 years). Exclusion criteria included inability to attend follow-up visits, life expectancy of <6 months, haemodialysis, and the presence of severe lung disease preventing LUS interpretation. Eligible patients were randomized at discharge to either the non-LUS-guided group (control group) or the LUS-guided group (LUS group). Visits were scheduled in the HF clinic at 14, 30, 90, and 180 days after discharge. LUS was performed in both groups, but the result was only available to the treating physician in the LUS-guided arm.

The primary endpoint was a composite of urgent visit, hospitalization for worsening HF, and death at 6 months. Urgent visits for worsening HF were defined as visits to the emergency department or un-scheduled visits to the HF unit as a result of signs and/or symptoms of worsening HF that required intravenous diuretic treatment or diuretic increase with a hospital stay of <24 h. Hospitalization for worsening HF was defined as a stay in hospital for >24 h mainly as a result of signs and/or symptoms of worsening HF. The reported events were reviewed by an independent panel of investigators.

The protocol was approved by the ethics committee and the study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to study participation.

2.2 Lung ultrasound protocol

According to current expert recommendations (Platz et al., 2019), LUS was recorded using a pocket ultrasound device (VScan, General Electrics) with a cardiac phased array transducer at four sites in each hemithorax (mid clavicular, mid axillar superior and inferior in each side) with the transducer perpendicular to the ribs and at a 16 cm imaging depth being the patient in the semi-recumbent position. The number of B-lines reported was the sum of the B-lines visualized in each thoracic site.

TABLE 1 Baseline characteristics of the study population.

	Total (N = 123 patients)
Age, years	69 ± 12
Female sex	34 (28%)
BMI, kg/m2	26.8 ± 5.4
Cardiovascular risk factors	
Hypertension	89 (72%)
Dyslipidaemia	84 (68%)
Diabetes	50 (41%)
Smokers	25 (20%)
Comorbidities	
COPD	31 (25%)
Renal insufficiency*	46 (37%)
Stroke	19 (15%)
Anaemia**	25 (20%)
Charlson index	2.7 ± 1.6
Previous cardiac history	
Previous HF	68 (55%)
Ischemic HF aetiology	54 (44%)
Atrial fibrillation	68 (55%)
Median LVEF (%)	36 (30–49)
HFrEF	68 (55%)
HFmrEF	25 (21%)
HFpEF	28 (23%)
Characteristics at discharge	
Systolic blood pressure, mmHg	130 ± 24
Heart rate, b.p.m	68 ± 11
eGFR, mL/kg/min/1.73m2	63 ± 24
NT-proBNP, ng/L	1723 (884–3,776)
Peripheral oedema	21 (17%)
Pulmonary rales	23 (19%)
Treatment at discharge	
Loop diuretics	94 (76%)
Thiazide diuretics	4 (3%)
ACE inhibitors/ARB	75 (61%)
Sacubitril/valsartan	5 (4%)
Beta-blocker	104 (85%)
Mineralocorticoid receptor antagonist	36 (29%)
Implantable cardioverter-defibrillator	18 (15%)
Cardiac resynchronization therapy	7 (6%)
LUS data at discharge	
Number of B-lines	4 (2-7)
Pleural effusion	11 (9%)
Outcomes at 6 months	
Composite endpoint	39 (32%)
Heart failure admission	27 (22%)
Urgent visits for worsening HF	16 (13%)
Death	5 (4%)

*Renal insufficiency refers to eGFR <60 ml/min/1.73 m2.
**Anaemia refers to haemoglobin levels of <13 g/dl in men and <12 g/dl in women. Data are expressed as number (%), mean ± standard deviation, or median (interquartile range), as appropriate.

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LUS, lung ultrasound; LVEF, left ventricular ejection fraction.

For this post-hoc analysis, the number of B-lines detected by LUS at discharge was analysed.

2.3 Contemporary HF risk scores

We selected 4 contemporary scores: Get with the Guidelines, MAGGIC, Redin-SCORE and BCN Bio-HF.

2.3.1 The get with the guidelines–heart failure score (GWTG- HF) (Peterson et al., 2010)

The GWTG-HF score incorporates 9 variables (age, systolic blood pressure (BP), body mass index (BMI), total cholesterol, high-density lipoprotein cholesterol, QRS duration, smoking status, use of antihypertensive medication, use of diabetes medication) to predict the risk of in-hospital mortality for patients hospitalized with HF.

2.3.2 The meta-analysis global group in chronic heart failure score (MAGGIC) (Pocock et al., 2013)

The MAGGIC score was derived from a metanalysis of 30 studies to predict mortality rates in patients with HF, and includes 13 predictors: age, lower ejection fraction (EF), New York Heart Association (NYHA) class, serum creatinine, diabetes, not prescribed beta-blocker, lower systolic BP, lower BMI, time since diagnosis, current smoker, chronic obstructive pulmonary disease, male gender, and not prescribed angiotensin converter enzyme inhibitors (ACEi) or angiotensin-receptor blockers.

2.3.3 The Redin-SCORE (Álvarez-García et al., 2015)

The Redin-SCORE is a risk score developed to predict short-term (1 month) and long-term (1 year) risk of HF in ambulatory patients. Predictors of 1-month readmission were the presence of elevated natriuretic peptides, left ventricular (LV) HF signs, and estimated glomerular filtration rate (eGFR) < 60 ml/min/m2. Predictors of 1-year readmission were elevated natriuretic peptides, anaemia, left atrial size >26 mm/m2, heart rate >70 beats per minute (bpm), LV HF signs, and eGFR <60 ml/min/m2.

2.3.4 The BCN Bio-HF score (Lupón et al., 2014)

The first version of the BCN Bio-HF included clinical variables, medications, conventional laboratory analytes

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TABLE 2 Incremental prognostic value of B-lines to predict 6-month outcomes in the LUS-HF trial.

	AUC	*p* Value	AIC	BIC	H-L *p* value	IDI	NRI
GWTG score	0.682 (0.587–0.778)		148	153	0.3		
GWTG score + number of B-lines	0.798 (0.704–0.783)	0.018	131	136	0.2	0.136 ($p < 0.001$)	0.608 ($p = 0.002$)
MAGGIC score	0.705 (0.614–0.797)		146	152	0.5		
MAGGIC score + number of B-lines	0.787 (0.706–0.869)	0.045	131	137	0.3	0.119 ($p < 0.001$)	0.608 ($p = 0.002$)
BCN Bio-HF	0.733 (0.639–0.827)		145	150	0.2		
BCN Bio-HF + number of B-lines	0.772 (0.685–0.859)	0.340	133	139	0.4	0.092 ($p = 0.003$)	0.363 ($p = 0.060$)
Redin-SCORE 1-month	0.714 (0.621–0.808)		141	147	0.3		
Redin-SCORE 1-month + number of B-lines	0.773 (0.621–0.864)	0.08	130	135	0.2	0.093 ($p = 0.003$)	0.509 ($p = 0.009$)
Redin-SCORE 1-year	0.681 (0.579–0.783)		146	152	0.6		
Redin-SCORE 1-year + number of B-lines	0.757 (0.663–0.851)	0.056	133	137	0.9	0.056 ($p = 0.004$)	0.111 ($p < 0.001$)

AUC, area under the curve; AIC, akaike criteria; BIC, bayesian criteria; H-L, Hosmer-Lemeshow; IDI, integrated discrimination improvement index; NRI, net reclassification improvement index.

(sodium, estimated glomerular filtration rate), and NT-proBNP, high-sensitivity troponin T (hs-TnT), and interleukin-1 receptor-like-1 (known as ST2). It was updated in 2018 by incorporating the use of angiotensin receptor neprylisin inhibitor (ARNI), cardiac resynchronization therapy (CRT), and implantable cardioverter defibrillator (ICD).

2.4 Statistical analysis

Continuous variables are expressed as mean (standard deviation) or as median (interquartile range) whenever appropriate. Differences in continuous variables were tested by the analysis of variance (ANOVA), Student's t-test, or Wilcoxon signed rank test for independent samples. Categorical variables were presented as frequency and percentage. Differences in the categorical variables were assessed by the $\chi 2$ test or by Fisher's exact test.

Discrimination, calibration and reclassification methods are recommended when evaluating candidate variables in prognostic studies (Januzzi et al., 2014). Thus, we first assessed the discriminative ability of each selected HF score to predict the occurrence of the primary endpoint at 6 months in the study population by calculating the area under the receiver operating curve (AUC). Thereafter, we analysed the incremental prognostic value of the number of B-lines at discharge on top of each score by comparing the AUC with and without LUS data and calculated the integrated discrimination improvement (IDI), and net reclassification improvement (NRI). Finally, we also performed decision curve analysis (DCA) to visualize the net benefit for clinical decisions. Data were analysed using STATA SE Version 15.0 (StataCorp LLC, College Station, TX, United States). A two-sided $p < 0.05$ was considered significant.

3 Results

3.1 Characteristics of the study population and number of B-lines at discharge

Clinical characteristics of the LUS-HF population and LUS data at discharge are shown in Table 1. Briefly, median age of the patients was 70 years, most patients were male (72%), had a reduced LVEF (55%), and a high prevalence of comorbidities. Median number of B-lines at discharge was 4 (Levy et al., 2006; Pocock et al., 2013; Lupón et al., 2014; Álvarez-García et al., 2015; Codina et al., 2021; Sinha et al., 2021) and 41 patients (33%) had ≥5 B-lines.

3.2 Incremental prognostic value of LUS over contemporary heart failure risk scores

Table 2 summarizes the discrimination, calibration, IDI, and NRI parameters by the 4 HF scores for the primary outcome alone and in combination with the number of B-lines. Overall, the addition of the number of B-lines at discharge improved the AUC of each risk score (Figure 1). However, the incorporation of the number of B-lines only reached statistically significance for the GWTG and MAGGIC scores, but not for the Redin-SCORE at 1-month and 1-year, nor the BCN Bio-HF.

Regarding reclassification indexes, both NRI and IDI after adding the number of B-lines showed a significant improvement with all scores, except for NRI in BCN Bio-HF

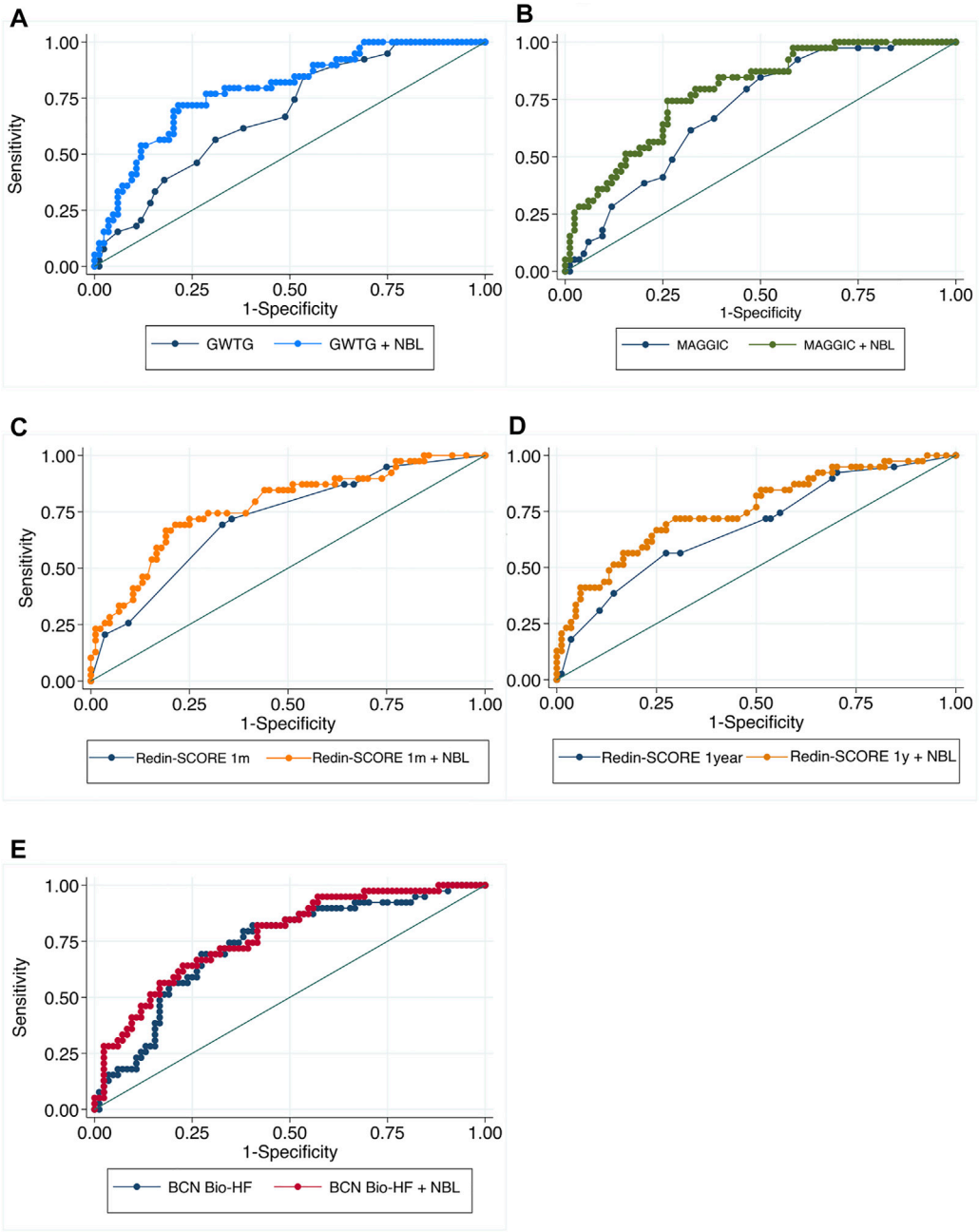

FIGURE 1
Comparison between the Receiver Operating Characteristic curves (ROC) for the composite endpoint at 6-month follow-up: score alone versus score + number of B-lines. ROC curves compare sensitivity versus specificity across a range of values for the ability of the score to predict the composite endpoint. Each patient is given a score with the intention that the test will be useful in predicting event occurrence and the different points on the curve correspond to the different cutpoints used to determine whether the test results are positive. Adding B-lines to GWTG, MAGGIC and REDIN-Score 1 year scores **(A,B,D)** makes the true positive rate higher and the false positive rate lower at all cutpoints compared with the score alone. Regarding BCN Bio-HF and REDIN-Score 1 m **(C,E)** adding B-lines improves both sensitivity and specificity in almost all cutpoints.

score. As Figure 2 shows, the calibration curves indicating good concordance. Finally, Figure 3 displays the DCA, showing that the net benefit of adding LUS data was higher than that of the score alone for any threshold probabilities, except for the GWTG score, which applied only for an event probability under 70%.

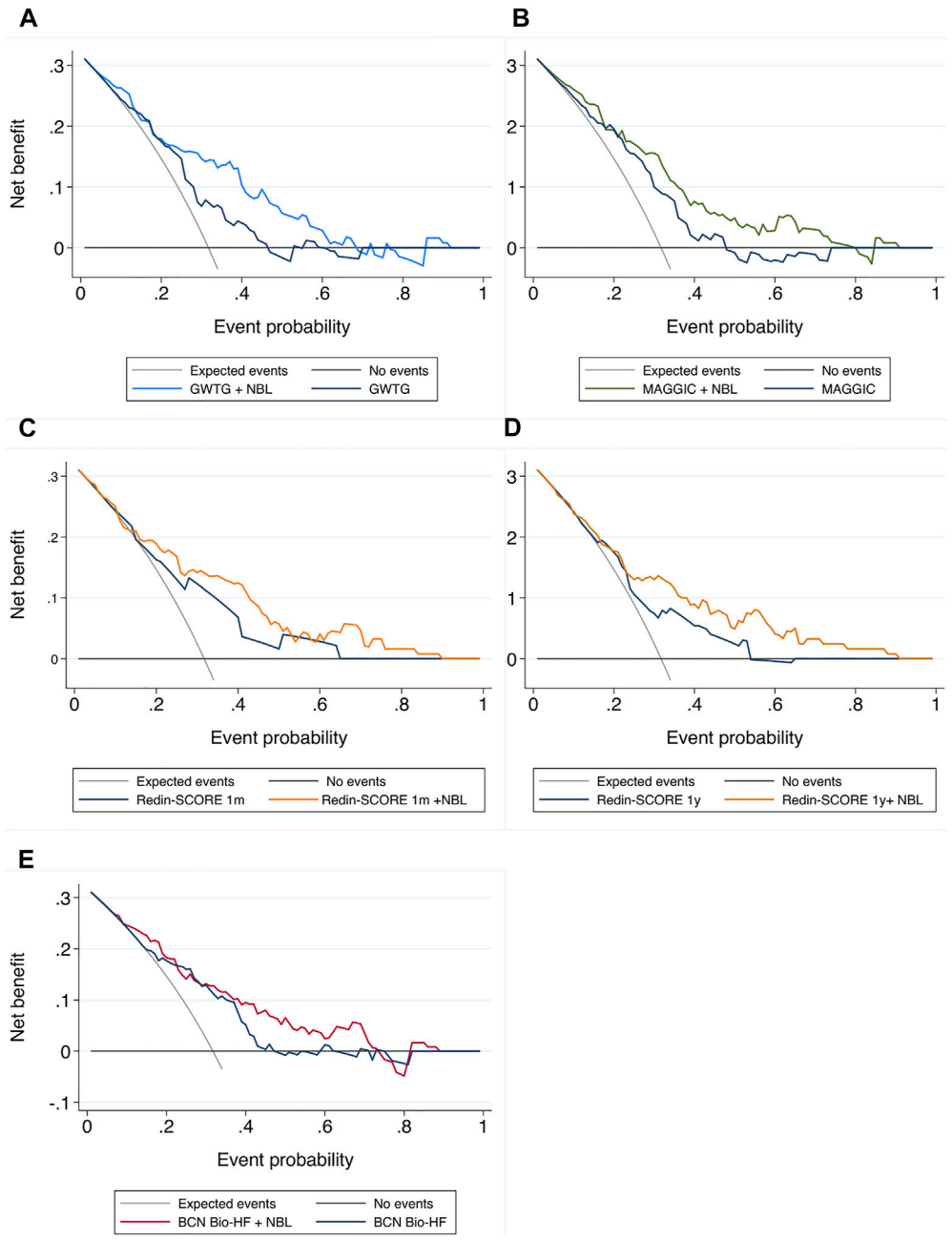

FIGURE 2
Calibration plots. X-axis: predicted outcome; Y-axis: observed outcome. NBL: number of B lines **(A)** GWTG: Get With the Guidelines score; **(B)** MAGGIC score; **(C)** Redin-SCORE 1 month; **(D)** Redin-SCORE 1 year; **(E)** BCN Bio-HF score.

4 Discussion

4.1 Main findings

Our work shows that the predictive value of contemporary HF risk scores can be improved by integrating LUS.

4.2 Prognostic value of LUS over HF risk scores

Prior research (Bettencourt et al., 2004; Khanam et al., 2018; Lupón et al., 2018) has already focused in analysing the prognostic value of new clinical variables to allow better

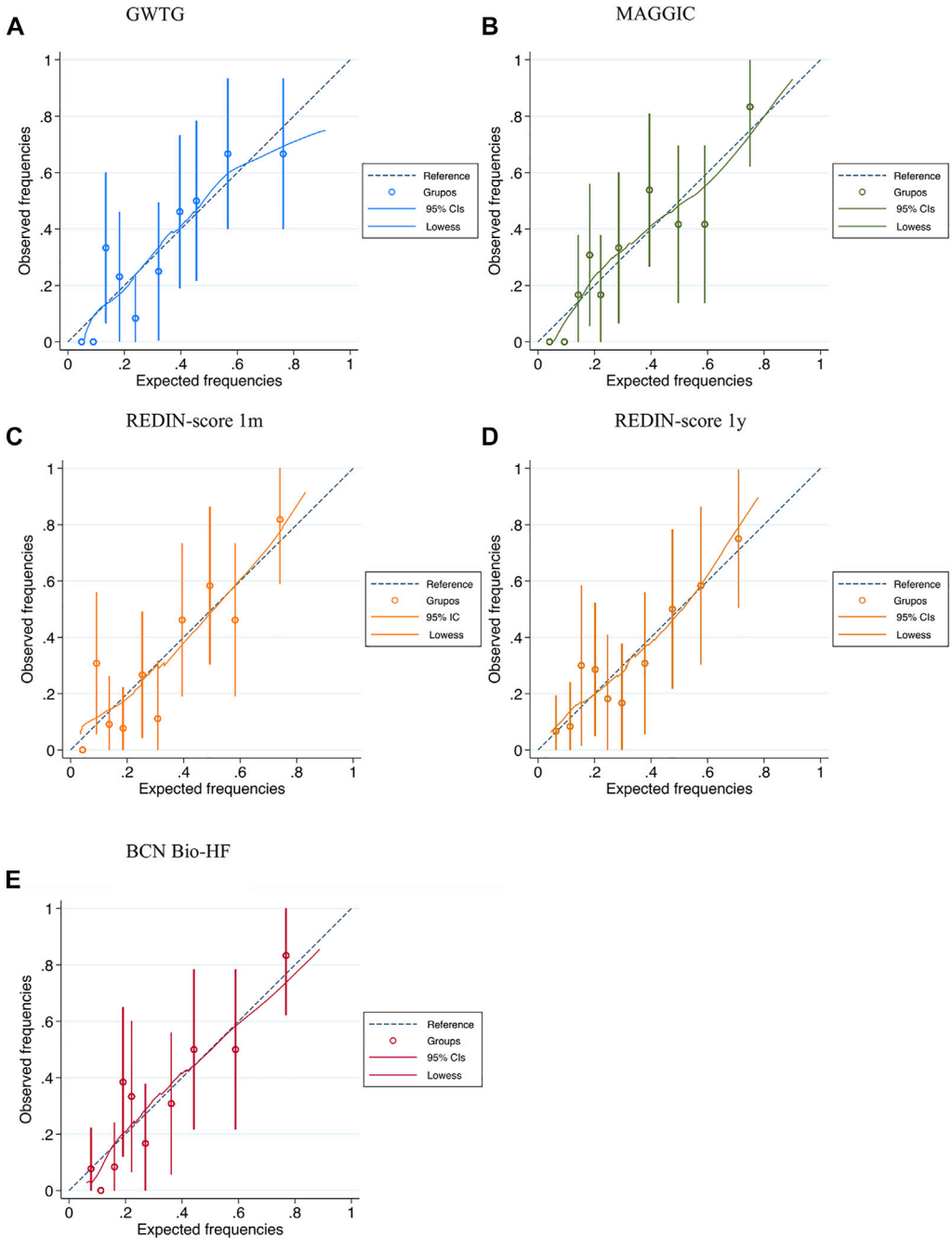

FIGURE 3
Decision curve analysis for predicting the primary composite endpoint. Decision curve analysis illustrates the performance of the model in a range of threshold probabilities, which may of interest to the clinician making the decision. X axis represents the probability threshold for the composite endpoint according to the score. The y axis represents the net benefit ([true positives - w x false positives]/total number of patients): positive values indicate an improvement in the classification of patients, and w is a correction factor for the probability threshold. The upper limit is 0.32 because the incidence of readmission for HF in LUS-HF was 32%. The diagonal black line assumes that all expected patients were readmitted, 32% at 6 months. The coloured lines represent the result of applying the different scores. Adding B-lines provided a net benefit due to better classification of the patients for probabilities below 70% in GWTG and BCN Bio-HF scores **(A,E)**. When B-lines were incorporated to MAGGIC score **(B)**, a net benefit was obtained due to better classification of the patients for probabilities between 0 and 80%. Regarding REDIN-score 1 year and 1m, a net benefit was obtained in all probability spectrum when using LUS data **(C,D)**.

prediction, such as the incorporation of ARNI or the effect of adding natriuretic peptides. The BCN Bio-HF score was one of the pioneers developing an updated version integrating those variables that allowed a better risk prediction.

LUS has emerged in the last decade as a simple, fast, and non-invasive test for lung congestion quantification. Several studies have shown that it might be a better tool for detecting subclinical pulmonary congestion than clinical assessment (Platz et al., 2016; Pellicori et al., 2019) and it has become widely available in an increasing number of centres, with the generalization of echographic equipments including pocket devices.

As NT-proBNP, it has also been reported that the presence of B-lines in HF patients is an independent prognostic factor (Coiro et al., 2015; Gargani et al., 2015; Gustafsson et al., 2015; Aras and Teerlink, 2016; Platz et al., 2016; Rivas-Lasarte et al., 2020; Domingo et al., 2021) although no study to date has analysed its prognostic value when added to the most used contemporary risk scores. To the best of our knowledge, this is the first study analysing if risk scores can be improved upon by the inclusion of B-lines detected by LUS at discharge and we found that the predictive yielding improved in a different degree according to the presence or absence of hemodynamic or biochemic markers of left ventricular function in their respective models.

Moreover, the number of B-lines is not only a prognostic marker but has shown to be also a therapeutic target in HF patients improving their prognosis when monitored during follow-up, mainly due to a reduction of HF decompensations (Rivas-Lasarte et al., 2019). As it is a dynamic marker that evolves with therapeutic measures, we hypothesize that its changes may also be of interest in predicting prognosis, although this remains to be elucidated in further studies.

4.3 Clinical implications

Risk stratification remains essential in HF to make medical decisions based on life expectancy and develop appropriate treatment plans, but the accuracy of available prognostic risk scores in patients with HF is still limited. Our study contributes on this important issue by integrating in existing contemporary HF risk scores LUS and allowing for a significant improvement in their predictive value in the majority of cases.

Some variables included in the pre-existing predictive HF models are not frequently obtained in the clinical care of HF, but LUS can be performed quickly and easily at bedside, and has already become an add-on to lung auscultation for the evaluation of pulmonary congestion.

As a semi-quantitative measure of pulmonary congestion, LUS adds new and valuable information to the scores. Due to its dynamic behaviour, it can be used as a monitoring tool allowing reassessment of patient's status whenever clinical situation changes, and also as a therapeutic target. Several studies had proved a LUS-guided therapy reduces acute decompensation events in the follow-up (Rivas-Lasarte et al., 2019; Araiza-Garaygordobil et al., 2020; Marini et al., 2020; Mhanna et al., 2021; Rastogi et al., 2022), which explains its rapid and wide implementation in the HF field.

4.4 Study limitations

Our study has some limitations. First, we tested prognostic scores which were specifically designed for ambulatory HF patients in a sample that was comprised by HF patients discharged from hospital. Second, LUS-HF was designed for a 6-month follow-up which may have determined an underestimation of the number of events, since some scores were originally designed to predict longer time points. Also, this is a retrospective (not pre-specified) analysis of the LUS-HF. Finally, our analysis accounts for a composite endpoint consisting in HF hospitalizations, urgent visits for worsening heart failure and all-cause mortality so it may not be generalized to prognostic risk scores specifically designed for other outcomes.

We consider our study as hypothesis generating and acknowledge the need of testing the hypothesis in other HF larger cohorts, especially multicentric and with a longer follow-up.

5 Conclusion

Adding the results of LUS evaluated at discharge improved the predictive value of most of the contemporary HF risk scores. As it is a simple, fast, and non-invasive test it may be recommended to assess prognosis at discharge in HF patients.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Hospital Sant Pau. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization and methodology: MR-L, JA-G, JC, ER, and AS Investigation conduction: MR-L, JA-G, ES, AM-B, JF-M,

VB, SM, and LL-L Writing original draft: AM-B, MR-L, JA-G, and AS Writing: review and editing: all the authors.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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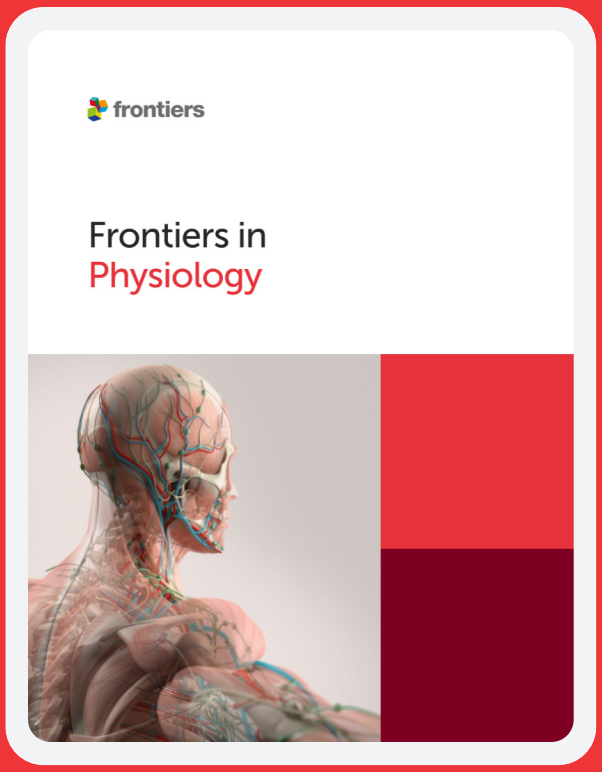

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