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Usefulness of Antigen Carbohydrate 125 and N-Terminal Pro-B-Type Natriuretic Peptide for Assessing Congestion in Chronic Heart Failure: Insights from the CARDIOREN Registry

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Keywords
Carbohydrate antigen-125 · Chronic heart failure · Congestion · Fluid overload · Natriuretic peptides · Ultrasound

Abstract
Introduction: A comprehensive assessment of congestion, including circulating biomarkers, is recommended in patients with acute heart failure. The circulating biomarkers natriuretic peptides (NPs) and carbohydrate antigen-125 (CA125) could

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be useful for congestion assessment in ambulatory chronic heart failure (CHF), but there is only limited information about their applicability in this context. Therefore, this study aimed to examine the association of plasma CA125 and NP levels with clinical and ultrasound congestion parameters in CHF. ***Methods:*** This is a cross-sectional substudy of the Cardioren Spanish Registry, which enrolled 1,107 patients with CHF from 13 tertiary hospitals in Spain between October 2021 and February 2022. Through ambulatory visits, we performed a comprehensive assessment of congestion-related parameters, including clinical variables (orthopnea, peripheral edema, and jugular engorgement, represented by the composite congestion score [CCS]), echocardiography variables (lung B-lines and inferior vena cava [IVC] diameter), and circulating biomarkers (CA125 and NPs). The association of the NP and CA125 levels with the clinical and echocardiographic congestion parameters was examined by multiple linear and logistic regression analyses. ***Results:*** This substudy included 802 patients for whom all the biomarker parameters were available {median age, 74 (interquartile range [IQR], 63–81) years; 65% male}. The proportion of patients with left ventricular ejection fraction ≥50% and estimated glomerular filtration rate <60 was 34% and 58%, respectively. The median CCS was 0 (IQR: 0–1), with 45% of the sample exhibiting a median CCS of ≥1. The jugular engorgement, peripheral edema, and orthopnea rates were 32%, 21%, and 21%, respectively. A total of 35% of patients who underwent ultrasound examination showed lung B-lines, and the median IVC diameter was 16 mm. The median CA125 and NTproBNP levels were 14 U/mL (IQR: 9–28) and 1,382 pg/mL (IQR: 563–3,219), respectively. Multivariate analysis showed that higher CA125 levels were independently associated with higher odds of peripheral edema ($p = 0.023$) and lung B-lines ($p < 0.001$). Further, NTproBNP was positively associated with jugular engorgement ($p < 0.001$), orthopnea ($p = 0.034$), and enlarged IVC diameter ($p = 0.031$). ***Conclusions:*** Clinical signs of congestion are frequent in CHF. In the ambulatory setting, NTproBNP was associated with parameters linked to intravascular congestion such as orthopnea, jugular engorgement, and IVC diameter, whereas CA125 was associated with extravascular volume overload parameters (peripheral edema and lung B-lines).

Introduction

Patients with chronic heart failure (CHF) frequently present with symptoms attributed to fluid overload (FO), also referred to as congestion, which is associated with increased morbidity and mortality [1, 2]. Congestion remains a primary component of the pathophysiology and presentation of patients with heart failure (HF), with subclinical and residual congestion considered as markers of worse prognosis [3]. The diagnosis and quantification of congestion are a clinical challenge because FO may be underestimated with traditional clinical assessment based on signs and symptoms. There is growing interest in tools (imaging and biomarkers) that can help clinicians better identify and quantify FO along the entire spectrum of patients with HF and, thereby, improve diagnostic accuracy, risk stratification, and the management of CHF [4–7]. With regard to potential biomarkers for assessing FO, there is some evidence, although limited, that carbohydrate antigen-125 (CA125) (a glycoprotein synthesized by mesothelial cells that is classically associated with ovarian cancer) and natriuretic peptides (NPs) may be valuable in ambulatory CHF cases [7].

CA125 is synthesized by serous epithelial cells in response to FO and/or inflammatory stimuli [6]. Accordingly, there is cumulative evidence that supports the value of the glycoprotein CA125 for FO assessment, especially tissue congestion, in patients with acute heart failure (AHF) [8–12]. Furthermore, it may also have prognostic value and may be useful for guiding the intensity of diuretic treatment [13–20]. With regard to NPs, they are released in response to volume and/or pressure overload stress in cardiomyocytes [21–28]. NPs are currently the most widely used biomarkers for diagnosis and prognostic stratification in HF, but their usefulness as congestion parameters is limited.

Based on the previous studies discussed above, we postulated that the assessment of CA125 as a proxy of tissue congestion and NPs as a proxy of intravascular congestion might help clinicians to diagnose and better profile the congestion phenotype in CHF. Accordingly, the aim of this study was to evaluate the association of CA125 and NP levels with the clinical/echocardiographic parameters of congestion in a cohort of patients with CHF.

Methods

Study Design and Population

This work is a substudy of the Spanish Cardioren Registry, which a prospective multicenter registry that included 1,107 consecutive patients with CHF who attended 13 HF clinics in Spain between October 2021 and February 2022 [29].

The main objective of this registry was to evaluate the prevalence and clinical profile of kidney disease in patients with CHF. HF was diagnosed according to the current European guidelines, including patients with the presence of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs

(e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) with a structural and/or functional heart abnormality and that justify it [30]. The only exclusion criterion was refusal to participate. Data were collected on patient demographics, medical history, medical, and device therapy at baseline, vital signs, and physical examination. Data on medical treatment were obtained directly from the patient's history and were verified with the electronic prescription data. This study protocol was reviewed and approved by the Puerta de Hierro Hospital Committee (Approval No. H.U.P.H.: PI 232/20) and by the Ethics Committees of the participating centers and was conducted in compliance with the Declaration of Helsinki. Written informed consent to participate in the study has been obtained from all adult participants and all underaged participants' parent/legal guardian/next of kin. Strobe statement is available in the online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541324).

Clinical Congestion Assessment

Clinical congestion was assessed by the composite congestion score (CCS) [31], which is the sum of the scores for orthopnea (0: none, 1: seldom, 2: frequent, 3: continuous), peripheral edema (0: absent, 1: slight, 2: moderate, 3: marked), and jugular engorgement (cm H_2O) (0: ≤6, 1: 6–9, 2: 10–15, 3: ≥15). Jugular assessment was conducted with the patient's head elevated at an angle of 30°–40°. This evaluation was conducted bedside by the attending physician in the HF unit of each center.

Laboratory Analysis

Blood tests included measurements of NPs and CA125. Both parameters were assessed at baseline (within a 48-h window from inclusion) and analyzed at the local laboratory of each center. The estimated glomerular filtration rate (eGFR) was calculated based on creatinine levels using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Blood cell counts and electrolytes were also evaluated.

Ultrasound Parameters

Information about IVC diameter and the presence of lung B-lines was obtained in 79% of the patients. US images were obtained and assessed by the attending HF physician of each center. Both parameters were evaluated with the patient in the supine decubitus position. The IVC diameter was measured in the subcostal position about 2 cm from the right atrium, and the IVC was considered to be dilated if the diameter was greater than 20 mm [32, 33]. The presence of lung B-lines was assessed with the eight-zone method, that is, four zones on each hemithorax. Lung B-lines were considered pathological if two or more lung fields presented with ≥3 B-lines bilaterally [34].

Statistical Analysis

Continuous variables are presented as median (interquartile range [IQR]) or mean (SD). Categorical variables are expressed as percentages. For categorical variables, the χ^2 test was used to compare across CCS categories (CCS = 0 vs. CCS ≥1). For continuous variables, the *t* test was used for variables with normal distributions, and the Wilcoxon test was used for variables with non-normal distributions.

Multivariate linear and logistic regressions analyses were used to evaluate the variables associated with CCS, CCS ≥1, each of the CCS components (edema, orthopnea, and jugular engorgement), and echocardiographic parameters (lung B-lines and IVC >20 mm). The contribution of the covariates to the variability of CCS and IVC in the linear regression analyses was evaluated by R^2. The association between the exposures (NTproBNP and CA125) with the risk of CCS and IVC (as continuous) was explored by multivariate linear regression analyses and estimates reported as Beta-coefficients. For the associations between the exposures and peripheral edema (yes vs. no), jugular engorgement (yes vs. no), orthopnea (yes vs. no), and lung-B-comets (yes vs. no) were assessed by logistic regression. In the multivariable models, all the variables listed in Table 1 are tested. We simultaneously tested the linearity assumption for all continuous variables, and the variables were transformed using fractional polynomials when appropriate. Next, we derived a reduced and parsimonious model using backward stepwise selection on prior knowledge/biological plausibility, independent of the *p* value. The covariates included in the final models were the New York Heart Association (NYHA) functional class, eGFR, the presence of diabetes mellitus, atrial fibrillation, systolic blood pressure, furosemide dose, hematocrit, and the exposure variables CA125 and NTproBNP. We set a two-sided *p* value of <0.05 as the threshold for statistical significance. The covariates included in the model were the same as those evaluated in the first model. STATA 16.1 (Stata Statistical Software, Release 15, 2017; StataCorp LP, USA) was used for the analyses.

Results

Baseline Characteristics

This substudy included 802 patients who had complete data about biomarkers and other key clinical and laboratory parameters (Fig. 1). The characteristics

Table 1. Baseline characteristics stratified by the presence of clinical congestion

	Total (N = 802)	No clinical congestion (score 0), N = 438 (55%)	Clinical congestion (score ≥1), N = 364 (45%)	p value
Demographics and medical history				
Age, years	74 [63, 81]	71 [60, 79]	77 [67, 83]	<0.001
Sex (male), *n* (%)	523 (65.2)	295 (67.4)	228 (62.6)	0.163
Current smoker, *n* (%)	66 (8.2)	41 (9.4)	25 (6.9)	0.046
Former smoker, *n* (%)	346 (43.1)	201 (45.9)	145 (40.0)	0.046
Hypertension, *n* (%)	551 (68.7)	275 (62.8)	276 (75.8)	<0.001
Dyslipidemia, *n* (%)	501 (62.5)	275 (62.8)	226 (62.1)	0.839
Diabetes, *n* (%)	324 (40.0)	183 (41.8)	141 (38.8)	0.667
Ischemic etiology, *n* (%)	317 (39.5)	178 (40.6)	139 (38.2)	0.479
Atrial fibrillation, *n* (%)	415 (51.7)	189 (43.2)	226 (62.1)	<0.001
Valvular heart disease, *n* (%)	129 (21.1)	72 (16.4)	97 (26.6)	<0.001
Kidney disease, *n* (%)	432 (53.9)	197 (44.9)	235 (64.6)	<0.001
COPD, *n* (%)	139 (17.0)	65 (14.8)	74 (20.3)	0.041
Ictus, *n* (%)	118 (14.7)	57 (13.1)	61 (16.7)	0.306
Cancer, *n* (%)	53 (6.6)	30 (6.8)	23 (6.3)	0.649
Dementia, *n* (%)	21 (2.6)	10 (2.3)	11 (3)	0.514
Charlson comorbidity index	5 [4, 7]	5 [4, 7]	6 [5, 8]	<0.001
Vital signs and baseline assessment				
Systolic blood pressure, mm Hg	120 [108, 137]	120 [110, 137]	120 [105, 137]	0.822
Diastolic blood pressure, mm Hg	70 [62, 77]	70 [62, 75]	70 [61, 79]	0.338
Heart rate, bpm	69 [60, 76]	68 [60, 75]	70 [61, 78]	0.019
Body mass index, kg/m^2	27 [24, 31]	27 [25, 31]	27 [24, 31]	0.691
NYHA functional class classification, *n* (%)				<0.001
I, *n* (%)	116 (14.5)	99 (22.6)	17 (4.7)	
II, *n* (%)	535 (66.7)	310 (70.8)	225 (61.8)	
III, *n* (%)	149 (18.6)	29 (6.6)	120 (33.0)	
IV, *n* (%)	2 (0.2)	0 (0.0)	2 (0.5)	
Orthopnea, *n* (%)	166 (20.7)	–	166 (45.6)	
Seldom	115 (14.3)		115 (31.6)	
Frequent	45 (5.6)		45 (12.4)	
Continuous	6 (0.7)		6 (1.6)	
Jugular engorgement, *n* (%)	255 (31.8)	–	255 (70.1)	
6–9	174 (21.7)		174 (47.8)	
10–15	57 (7.1)		57 (15.7)	
≥15	24 (3.0)		24 (6.6)	
Peripheral edema, *n* (%)	170 (21.2)	–	170 (47.8)	
Slight	135 (16.8)		135 (37.1)	
Moderate	27 (3.4)		27 (7.4)	
Marked	8 (1.0)		8 (2.2)	
Clinical congestion score	0 [0, 1]	0 [0, 0]	2 [1, 3]	<0.001
Echocardiography				
LVEF, %	40 [30, 55]	39 [30, 51]	42 [30, 58]	0.047
LVEF >50%, *n* (%)	271 (33.8)	129 (29.5)	142 (39.0)	0.017
TAPSE, mm	19 [16, 21]	20 [17, 22]	18 [15, 20]	<0.001
sPAP, mm Hg	40 [31, 52]	37 [30, 48]	45 [34, 55]	<0.001
LA volume, mL	78 [56, 107]	74 [51, 102]	83 [58, 110]	0.010
IVC, mm[a]	16 [14, 20]	15 [13, 17]	19 [15, 23]	<0.001
Inferior vein cava dilatation, *n* (%)[a]	148 (23.1)	27 (8.0)	121 (39.7)	<0.001
Lung B-lines, *n* (%)[b]	221 (34.7)	54 (16.1)	167 (55.5)	<0.001

Table 1 (continued)

	Total (N = 802)	No clinical congestion (score 0), N = 438 (55%)	Clinical congestion (score ≥1), N = 364 (45%)	p value
Laboratory data				
Sodium, mEq/L	140 [139–142]	141 [139, 142]	140 [138, 142]	0.054
Potassium, mEq/L	4.6 [4.2–4.9]	4.6 [4.3, 4.9]	4.5 [4.1, 4.8]	<0.001
Urea, mg/dL	60 [43–83]	54 [40, 75]	66 [49, 95]	<0.001
Creatinine, mg/dL	1.2 [0.9, 1.6]	1.1 [0.9, 1.5]	1.3 [1.0, 1.8]	<0.001
eGFR, mL/min/1.73 m^2	53.2 [36.1, 76.8]	60.4 [39.2, 83.4]	46.4 [31.7, 65.4]	<0.001
Kidney failure stage, n (%) (KDIGO classification)				<0.001
I	110 (13.7)	86 (19.6)	24 (6.6)	
II	224 (27.9)	135 (30.8)	89 (24.5)	
IIIa	149 (18.5)	74 (16.9)	75 (20.6)	
IIIb	187 (23.3)	88 (20.1)	99 (27.2)	
IV	119 (14.8)	51 (11.6)	68 (18.7)	
V	13 (1.6)	4 (0.9)	9 (2.5)	
Albuminuria[c], n (%)				0.002
<30 mg/g	427 (53.2)	251 (57.3)	176 (48.4)	
30–300 mg/g	207 (25.8)	104 (23.7)	103 (28.3)	
>300 mg/g	51 (6.4)	22 (5.0)	29 (28.0)	
UACR, mg/g	20.7 [6.5, 55.5]	16.0 [5.6, 45.0]	22.0 [8.1, 80.3]	0.002
Glycosylated hemoglobin, %	5.9 [5.5, 6.5]	6.0 [5.6, 6.5]	5.9 [5.5, 6.4]	0.217
NTproBNP, pg/mL	1,382 [563, 3,219]	907 [365, 2,040]	2,199 [938, 4,927]	<0.001
CA125, U/mL	14 [9, 28]	12 [8, 20]	18 [11, 41]	<0.001
Hemoglobin, g/dL	13.7 [12.3, 15.1]	14.0 [12.7, 15.5]	13.3 [11.9, 14.6]	<0.001
Hematocrit, %	42.0 [38.0, 46.0]	43.3 [39.0, 47.0]	40.5 [36.7, 45.0]	<0.001
Treatment				
Furosemide, n (%)	569 (70.9)	264 (60.3)	305 (83.8)	<0.001
Furosemide dose, mg	40 [0, 80]	20 [0, 40]	60 [20, 80]	<0.001
Thiazide, n (%)	109 (13.7)	32 (7.3)	77 (21.3)	<0.001
MRA, n (%)	485 (60.5)	283 (64.6)	202 (55.5)	0.009
ACEi/ARB/ARNI, n (%)	627 (78.2)	367 (83.8)	260 (71.4)	<0.001
SGLT2i, n (%)	501 (61.2)	293 (65.5)	208 (55.2)	0.026
Beta-blockers, n (%)	657 (81.9)	371 (84.7)	286 (78.6)	0.025
Statins, n (%)	542 (67.6)	303 (69.2)	239 (65.7)	0.289

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CA125, cancer antigen-125; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LA volume, left atrial volume; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SLGT2i, sodium-glucose cotransporter inhibitors; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; NTproBNP, N-terminal pro-brain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion. Data are expressed as n (%), or median [IQR]. [a]Data available in 636 patients. [b]Data available in 641 patients. [c]Data available in 685 patients.

of the patients according to the presence of clinical congestion are shown in Table 1. The median age of the study sample was 74 years (IQR, 63–81 years), and 65% of the patients were men. Kidney failure was present in 58% of patients, defined as a glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2. At the time of the visit, 16% of patients had an estimated GFR (eGFR) below 30 mL/min/1.73 m. Two-thirds (66%) of the patients were classified as having stable function based on NYHA class II and the number of patients with preserved left ventricular ejection fraction (≥50%) was 271 (34%). The median NTproBNP and CA125 values were 1,382 pg/mL (IQR: 563–3,219) and 14 U/mL (IQR, 9–28), respectively. The number of patients with orthopnea, jugular engorgement, and peripheral edema was 166 (21%), 255 (32%), and 170 (21%), respectively. The median CCS was 0 (IQR, 0–1), with 45% of the sample having a score of ≥1. The median IVC diameter

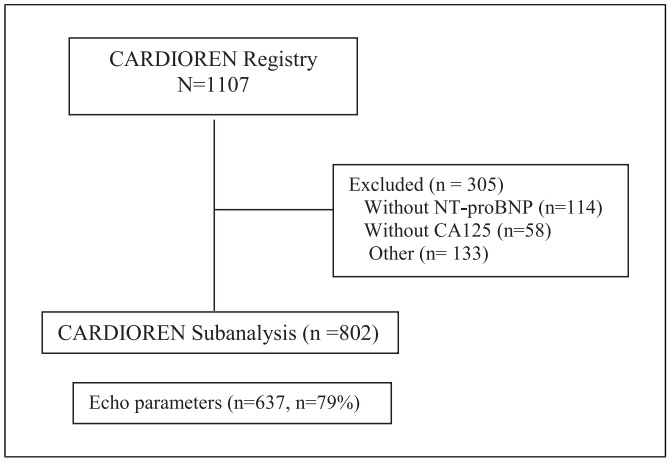


Fig. 1. Flow diagram of patients included in CARDIOREN substudy.

was 16 mm (IQR, 14–20), and 35% of the sample presented with pathological lung B-lines.

Patients with at least one sign of congestion (corresponding to a CCS of ≥1) tended to be older and have a higher prevalence of valvular heart disease. They showed worse function based on their NYHA class and a higher burden of comorbidities such as hypertension, atrial fibrillation, anemia, kidney dysfunction, and chronic obstructive pulmonary disease. Further, their left ventricular ejection fraction was higher, and they showed lower tricuspid annular plane systolic excursion and increased systolic pulmonary artery pressure. Accordingly, these patients were more frequently treated with a more intensive diuretic regimen but a lower prescription of mineralocorticoid receptor antagonists, β-blockers, renin angiotensin aldosterone system inhibitors, and sodium-glucose cotransporter inhibitors.

CA125 and NTproBNP as Markers for Assessing Clinical Congestion

Composite Congestion Score

Multivariate analysis showed that CA125 and NTproBNP were significant, positive, and linearly associated with CCS (Fig. 2a). The contribution of CA125 to the variability of the model (R2) was higher than that of NTproBNP. Indeed, after NYHA class (R2: 59%, $p < 0.001$) and furosemide dose equivalents (R2: 16%, $p < 0.001$), CA125 was the third most significant variable in terms of R2 (R2: 5%, $p < 0.001$). In comparison, the magnitude of the contribution of NTproBNP was lower (R2: 1%, $p < 0.001$). The list of all the covariates independently associated with CCS and their corresponding R2 values are shown in Figure 3.

Orthopnea

Patients experiencing orthopnea exhibited increased plasma levels of NTproBNP and CA125 (Table 2). The multivariate logistic regression model showed that NTproBNP ($p = 0.034$), but not CA125 ($p = 0.614$), was positively associated with higher odds of presenting with orthopnea (Fig. 2d).

Jugular Engorgement

Patients with jugular engorgement displayed higher values of NTproBNP and CA125 (Table 2). After multivariate adjustment, NTproBNP ($p < 0.001$) was found to be significantly and positively associated with the presence of jugular engorgement, whereas CA125 showed only borderline association ($p = 0.053$) (Fig. 2b).

Peripheral Edema

Raw data showed that the NTproBNP and CA125 levels were higher in patients with peripheral edema (Table 2). After multivariate adjustment, only CA125 showed a positive and linear association with the risk of peripheral edema ($p = 0.023$) (Fig. 2c).

Association of CA125 and NTproBNP Levels with Imaging Markers of Congestion

Lung B-Lines

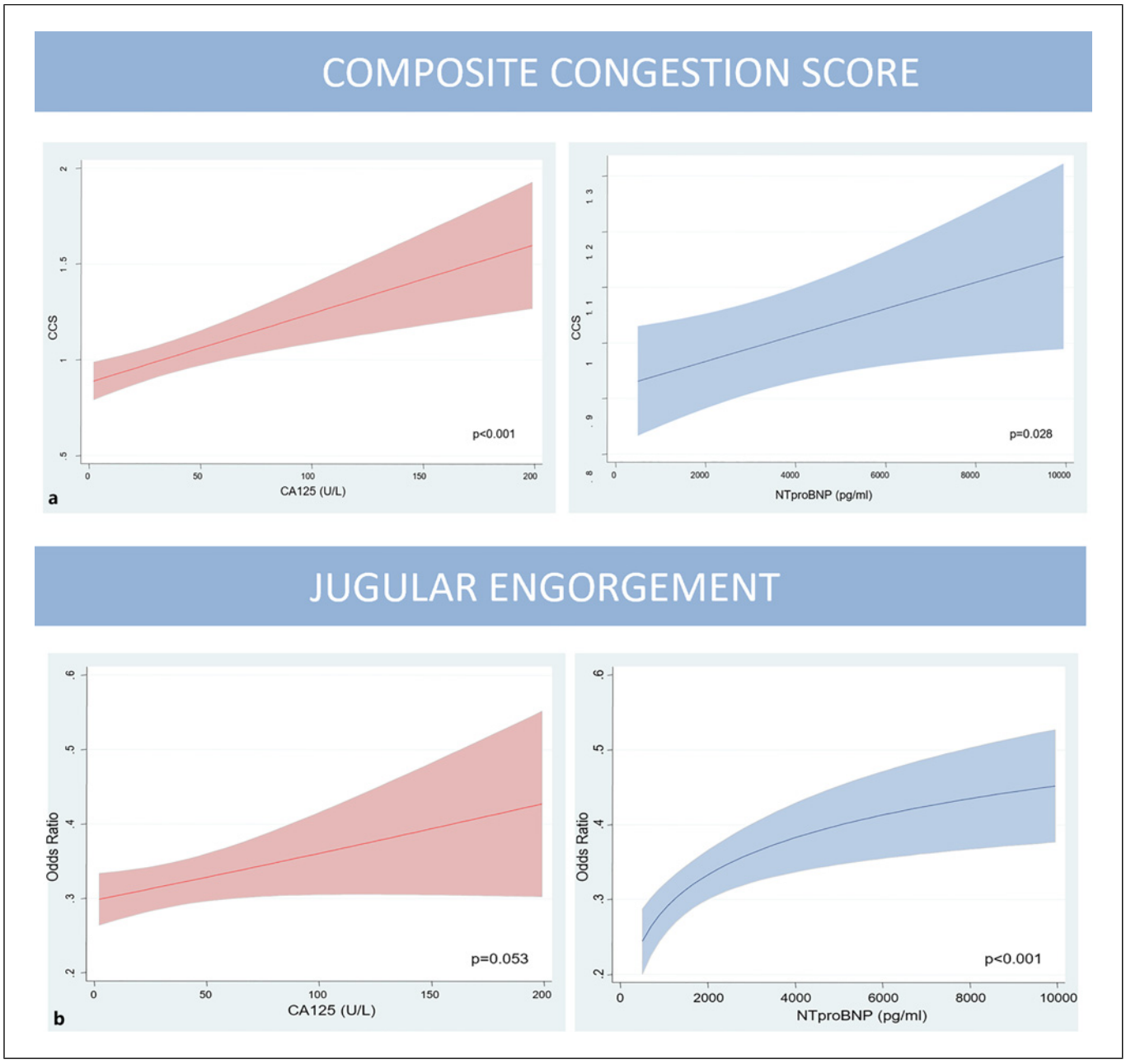
Increased plasma levels of NTproBNP and CA125 were found in patients with pathological lung B-lines (Table 2). Multivariate analyses revealed that CA125 ($p < 0.001$), but not NTproBNP ($p = 0.743$), was positively associated with the odds of presenting with pathological B-lines (Fig. 4a).

IVC Diameter

Patients with IVC diameter >20 mm showed higher NTproBNP and CA125 levels (Table 2). In the multivariable analysis, only NTproBNP remained independently associated with the risk of increased IVC diameter (Fig. 4b).

Discussion

In this subanalysis from the Cardioren registry, 45% of the patients with CHF who attended a routine clinical visit exhibited clinical data that were indicative of



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congestion in the ambulatory CHF setting. The circulating biomarkers were associated with different clinical and imaging parameters of FO; specifically, NTproBNP values were associated with the presence of parameters linked to intravascular congestion (jugular engorgement, orthopnea, and IVC diameter), whereas CA125 was related to signs of extravascular or tissue congestion (lower extremity edema and lung B-lines).

Role of the Circulating Biomarkers CA125 and NTproBNP in Identifying and Quantifying Congestion in an Outpatient Setting

CA125

In recent years, numerous publications have demonstrated the usefulness of plasma concentrations of CA125 as a biomarker in AHF [11, 14]. From the clinical perspective, CA125 provides information on the degree of

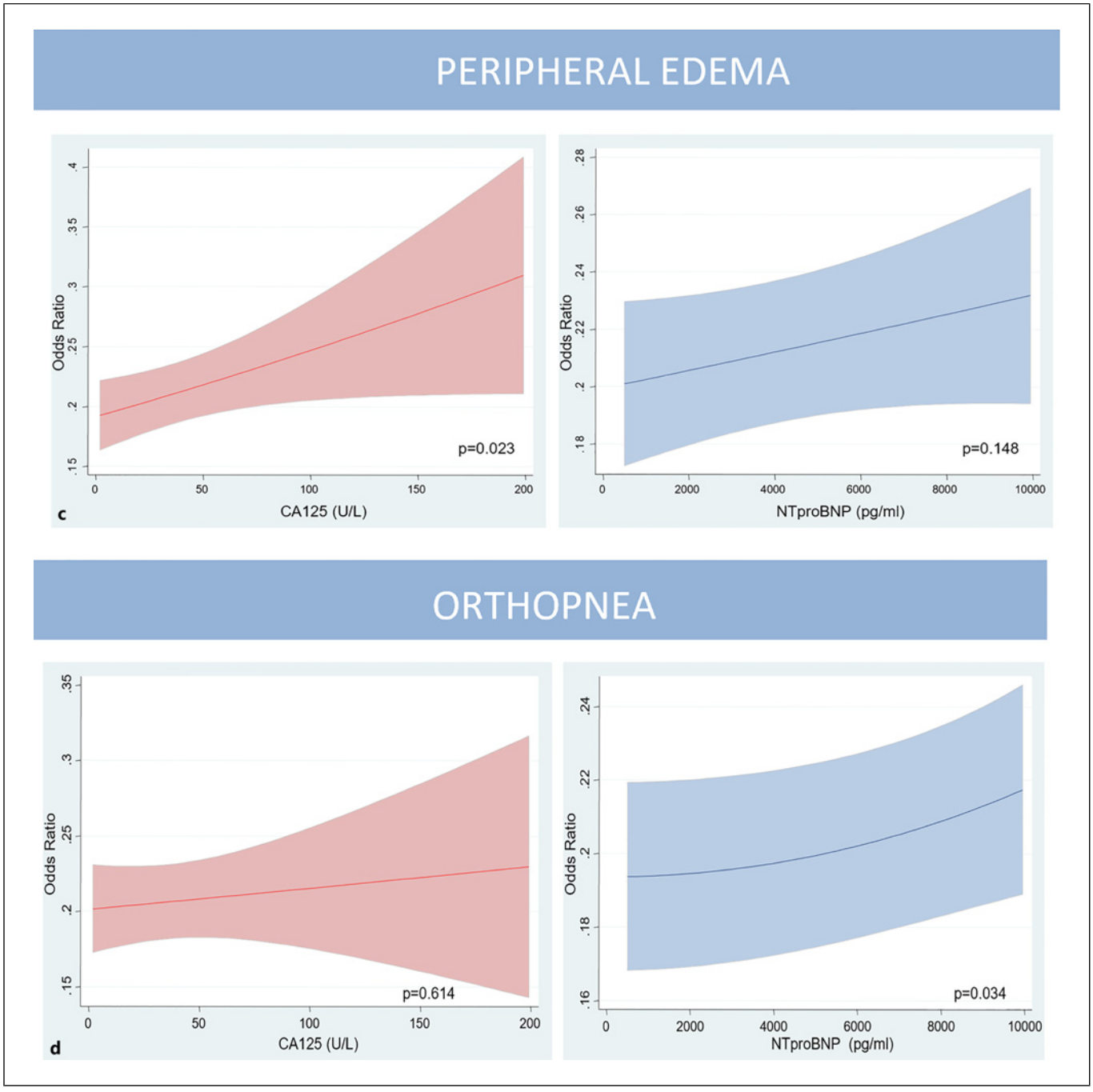
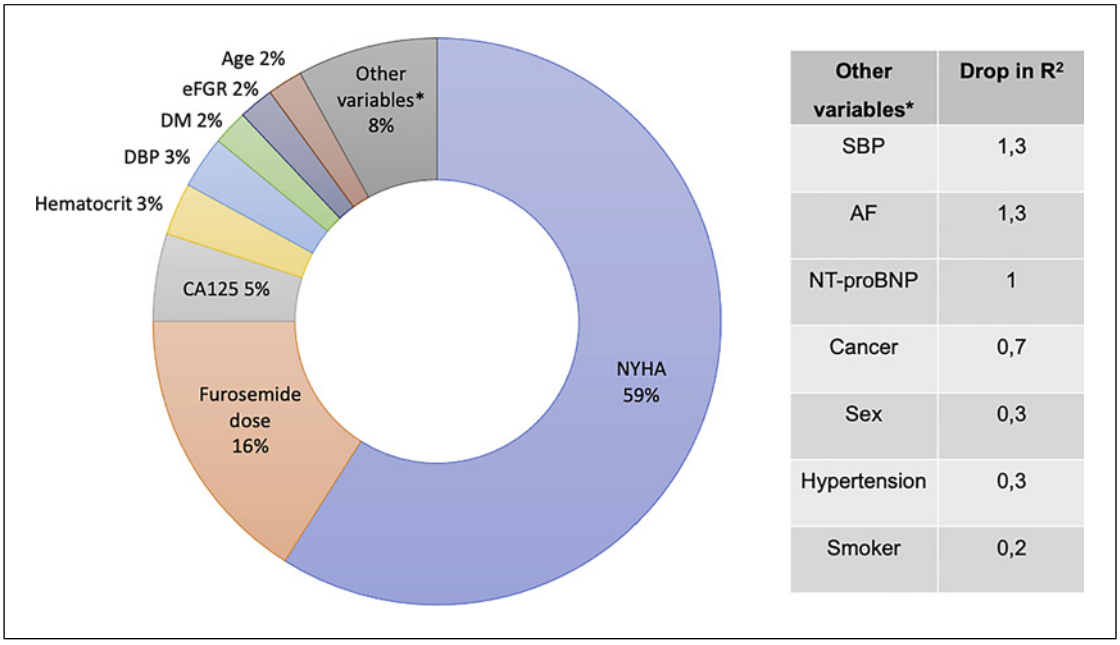


Fig. 2. Associations between CA125 and NTproBNP with **a** CCS (composite congestion score); **b** jugular engorgement; **c** peripheral edema; **d** orthopnea. The covariates included in the models were the New York Heart Association (NYHA) functional class, eGFR, the presence of diabetes mellitus, atrial fibrillation, systolic blood pressure, furosemide dose, and hematocrit.

congestion and is an established prognostic marker in AHF [10, 16, 35]. In this setting, a positive association has been observed with the presence of congestion, especially right-sided and extravascular FO, although some studies have also related it to intravascular congestion (diameter of inferior cava vein) [15, 36–38]. However, its performance in ambulatory CHF is less known [11, 17, 38]. Our findings make a pertinent contribution in this regard, as



Other variables*	Drop in R^2
SBP	1,3
AF	1,3
NT-proBNP	1
Cancer	0,7
Sex	0,3
Hypertension	0,3
Smoker	0,2

Fig. 3. Variables associated with quantitative clinical congestion score.

Table 2. Values of NTproBNP and CA125 according to the presence of clinical and imaging congestion parameters

	NTproBNP, pg/mL			CA125, U/mL		
	yes	no	*p* value	yes	no	*p* value
CCS >1	2,199 (933, 4,946)	906 (364, 2,050)	<0.001	18 (11, 41)	12 (8, 20)	<0.001
Peripheral edema	2,216 (1,054, 5,530)	1,191 (464, 2,839)	<0.001	21 (12, 60)	13 (8, 22)	<0.001
Jugular engorgement	2,500 (1,058, 5,455)	1,022 (382, 2,413)	<0.001	20 (12, 48)	12 (8, 21)	<0.001
Orthopnea	2,326 (745, 5,283)	1,238 (489, 2,871)	<0.001	17 (11, 47)	13 (9, 24)	<0.001
Presence of B-lines	2,107 (937, 4,211)	1,184 (486, 2,927)	<0.001	19 (11, 22)	13 (8, 23)	<0.001
Diameter of IVC >20 mm	2,884 (1,281, 5,653)	1,240 (514, 2,838)	<0.001	23 (12, 60)	13 (9, 23)	<0.001

Data are expressed as median and IQR. CCS, composite congestion score; IVC, inferior vena cava.

they confirm that higher levels of CA125 are associated with the presence and degree of clinical and imaging congestion (predominantly extravascular) parameters in patients with CHF [17]. In addition, the longer half-life of CA125 makes it a parameter of particular interest in the chronic HF scenario.

Natriuretic Peptides

While NPs are well-known markers of HF [23, 28], the evidence for their association with congestion is debatable. That is, while patients with HF who have left ventricular systolic dysfunction exhibit high NP values, right dysfunction does not seem to translate into an additional increase in NP. To elaborate, in patients with elevated NP values due to left predominant HF, the involvement of the right heart translates into elevations of NPs of much lesser magnitude [21]. Based on the current research, we confirm the usefulness of NPs in detecting intravascular congestion in patients presenting chronic HF [39].

Clinical Implications

This subanalysis reveals that subclinical or mild congestion is present in a significant portion (45% of the sample) of ambulatory patients with CHF. Diagnosing

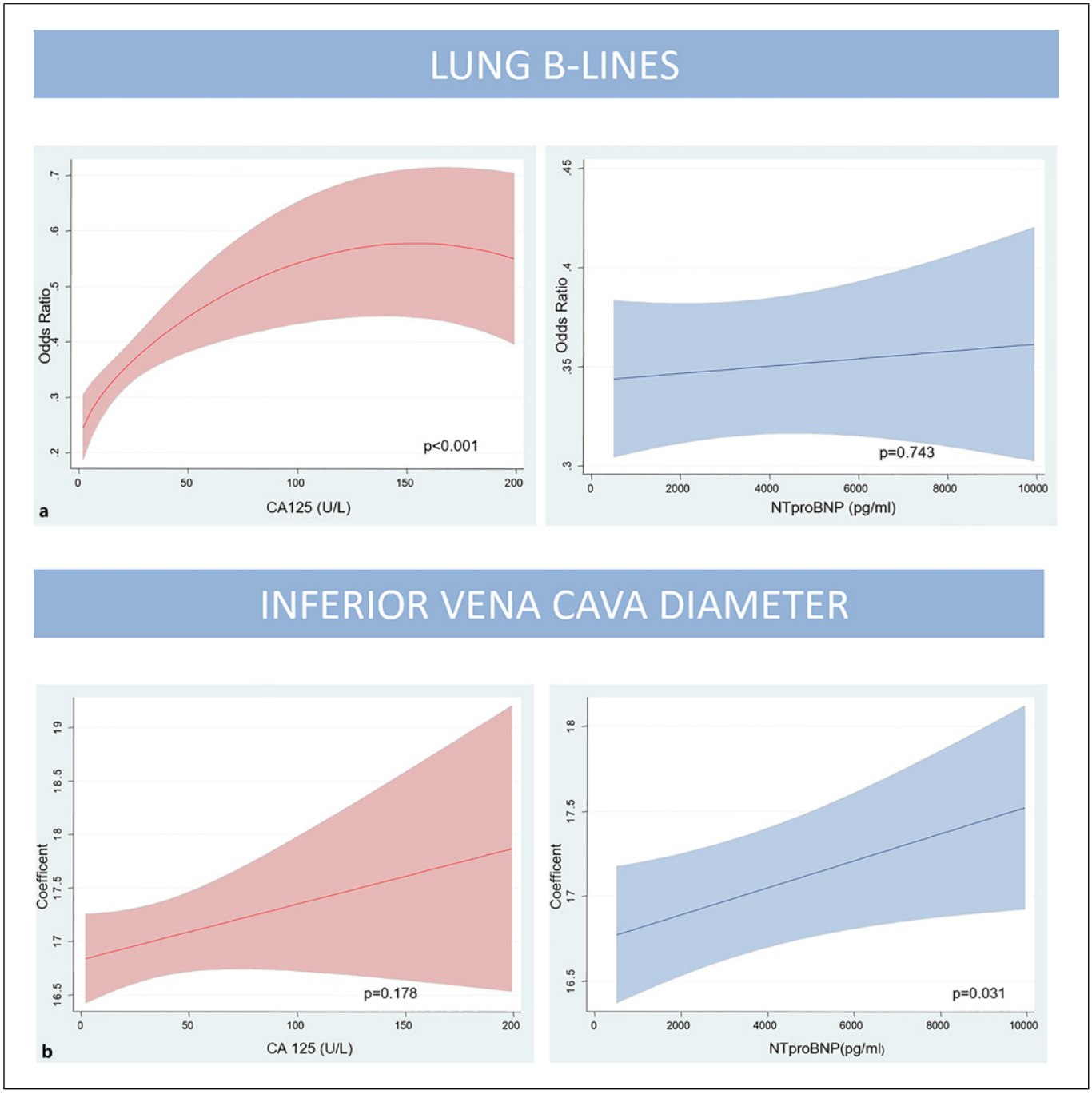


Fig. 4. Associations between CA125 and NTproBNP with **a** presence of lung B-lines; **b** IVC. The covariates included in the models were the New York Heart Association (NYHA) functional class, eGFR, the presence of diabetes mellitus, atrial fibrillation, systolic blood pressure, furosemide dose, and hematocrit.

and quantifying congestion in an outpatient setting can be particularly challenging. Notably, residual congestion is strongly linked to worse outcomes [2, 22]. In this context, routine biomarker assessment may enhance the understanding and identification of different congestion "phenotypes" [39].

To our knowledge, there is a lack of robust data on the role of circulating CA125 and NPs in defining the FO

profile of ambulatory CHF patients. Our findings contribute significantly to this area, as we confirm that both biomarkers provide complementary information. Therefore, we speculate that incorporating both biomarkers into clinical practice may improve the early detection of subclinical congestion and, therefore, the early diagnosis of worsening HF. Phenotyping congestion can also lead to improved volume management strategies [15, 37, 40]. For instance, patients with predominant tissue or extravascular congestion may benefit from more aggressive diuretic therapy or diuretics that increase vascular refill, such as sodium-glucose cotransporter 2 inhibitors or vaptans [20]. Conversely, patients with predominant intravascular congestion and fluid redistribution may benefit from vasodilator therapy and less aggressive diuretic strategies [40, 41].

Limitations

This study has several limitations that need to be mentioned. First, this is an observational study in which several confounders may have affected the results. Another limitation is that the echocardiographic assessment was not performed in 26% of the patients, which may have increased the selection bias. In addition, despite US parameters being obtained and evaluated by expert HF specialists, there was no external validation. Fourth, although this study encompassed several clinical and imaging parameters related to congestion, additional variables, such as pleural effusion, ascites, and other echocardiography parameters, were not assessed. Finally, laboratory determinations were not centralized, which may have introduced slight variability in the data.

Conclusions

Clinical signs of congestion are frequent in CHF. Importantly, higher CA125 and NTproBNP values were positively associated with FO parameters in CHF, with NTproBNP related to intravascular congestion parameters (jugular engorgement, orthopnea, and IVC diameter) and CA125 related to extravascular congestion parameters (lower limb edema and lung B-lines).

Statement of Ethics

This study protocol was reviewed and approved by Puerta de Hierro Hospital Committee, Approval No. H.U.P.H.: PI 232/20. Written informed consent to participate in the study has been obtained from all adult participants and all underaged participants' parent/legal guardian/next of kin. Strobe statement is available as supplementary data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jara Gayán, Marta Cobo, and Julio Nuñez participated in the conception and design of the document. Jara Gayán, Julio Nuñez, Ramón Bascompte, Pau Llacer, Isabel Zegrí, Rafael de la Espriella, Aleix Fort, Jorge Rubio, Zorba Blazquez, Ana Mendez, Inés Ponz, Adriana Rodriguez Chaverri, Pedro Caravaca Pérez, Alejandro Recio Mayoral, Clara Jiménez Rubio, Antonia Pomares, María José Soler, Paula Fluviá, Belén García Magallón, and Marta Cobo Marcos participated in the elaboration of the manuscript. José Luis Górriz, Luis Manzano, and Faeq Husain-Syed reviewed the document critically for important intellectual content. All the authors have approved the submitted version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Lucas C, Johnson W, Hamilton MA, Fonarow GC, Woo MA, Flavell CM, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. Am Heart J. 2000;140(6):840–7. https://doi.org/10.1067/mhj.2000.110933

2 Pellicori P, Cleland JGF, Zhang J, Kallvikbacka-Bennett A, Urbinati A, Shah P, et al. Cardiac dysfunction, congestion and loop diuretics: their relationship to prognosis in heart failure. Cardiovasc Drugs Ther. 2016;30(6):599–609. https://doi.org/10.1007/s10557-016-6697-7

3 Vecchi AL, Muccioli S, Marazzato J, Mancinelli A, Iacovoni A, De Ponti R. Prognostic role of subclinical congestion in heart failure outpatients: focus on right ventricular dysfunction. J Clin Med. 2021;10(22):5423. https://doi.org/10.3390/jcm10225423

4 Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, et al. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. Int J Cardiol. 2018;258:185–91. https://doi.org/10.1016/j.ijcard.2018.01.067

5 Peacock WF, Soto KM. Current techniques of fluid status assessment. Contrib Nephrol. 2010;164:128–42. https://doi.org/10.1159/000313726
6 Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG; et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12(5):423–33. https://doi.org/10.1093/eurjhf/hfq045
7 Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. Nat Rev Cardiol. 2020;17(10):641–55. https://doi.org/10.1038/s41569-020-0379-7
8 Miñana G, Palau P, Núñez J, Sanchis J. The tumor marker CA-125 and heart failure. Rev Esp Cardiol. 2010;63(10):1213–4. https://doi.org/10.1016/s1885-5857(10)70240-1
9 Miñana G, Núñez J, Sanchis J, Bodí V, Núñez E, Llàcer A. CA125 and immunoinflammatory activity in acute heart failure. Int J Cardiol. 2010;145(3):547–8. https://doi.org/10.1016/j.ijcard.2010.04.081
10 Núñez J, de la Espriella R, Miñana G, Santas E, Llácer P, Núñez E, et al. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. Eur J Heart Fail. 2021;23(9):1445–57. https://doi.org/10.1002/ejhf.2295
11 Huang F, Zhang K, Chen J, Cai Q, Liu X, Wang T, et al. Elevation of carbohydrate antigen 125 in chronic heart failure may be caused by mechanical extension of mesothelial cells from serous cavity effusion. Clin Biochem. 2013;46(16–17):1694–700. https://doi.org/10.1016/j.clinbiochem.2013.09.008
12 Llàcer P, Bayés-Genís A, Núñez J. Carbohydrate antigen 125 in heart failure. New era in the monitoring and control of treatment. Med Clin. 2019;152(7):266–73. https://doi.org/10.1016/j.medcli.2018.08.020
13 Núñez J, Sanchis J, Bodí V, Fonarow GC, Núñez E, Bertomeu-González V, et al. Improvement in risk stratification with the combination of the tumour marker antigen carbohydrate 125 and brain natriuretic peptide in patients with acute heart failure. Eur Heart J. 2010;31(14):1752–63. https://doi.org/10.1093/eurheartj/ehq142
14 Núñez J, Bayés-Genís A, Revuelta-López E, Ter Maaten JM, Miñana G, Barallat J, et al. Clinical role of CA125 in worsening heart failure: a BIOSTAT-CHF study subanalysis. JACC Heart Fail. 2020;8(5):386–97. https://doi.org/10.1016/j.jchf.2019.12.005
15 Núñez J, Llàcer P, García-Blas S, Bonanad C, Ventura S, Núñez JM, et al. CA125-Guided diuretic treatment versus usual care in patients with acute heart failure and renal dysfunction. Am J Med. 2020;133(3):370–80.e4. https://doi.org/10.1016/j.amjmed.2019.07.041
16 Núñez J, Llàcer P, Bertomeu-González V, Bosch MJ, Merlos P, García-Blas S, et al. Carbohydrate antigen-125-guided therapy in acute heart failure: chance-hf: a randomized study. JACC Heart Fail. 2016;4(11):833–43. https://doi.org/10.1016/j.jchf.2016.06.007
17 Kouris NT, Zacharos ID, Kontogianni DD, Goranitou GS, Sifaki MD, Grassos HE, et al. The significance of CA125 levels in patients with chronic congestive heart failure. Correlation with clinical and echocardiographic parameters. Eur J Heart Fail. 2005;7(2):199–203. https://doi.org/10.1016/j.ejheart.2004.07.015
18 Varol E, Ozaydin M, Dogan A, Kosar F. Tumour marker levels in patients with chronic heart failure. Eur J Heart Fail. 2005;7(5):840–3. https://doi.org/10.1016/j.ejheart.2004.12.008
19 Vizzardi E, Nodari S, D'Aloia A, Chiari E, Faggiano P, Metra M, et al. CA 125 tumoral marker plasma levels relate to systolic and diastolic ventricular function and to the clinical status of patients with chronic heart failure. Echocardiography. 2008;25(9):955–60. https://doi.org/10.1111/j.1540-8175.2008.00714.x
20 Docherty KF, McDowell K, Welsh P, Osmanska J, Anand I, de Boer RA, et al. Association of carbohydrate antigen 125 on the response to dapagliflozin in patients with heart failure. J Am Coll Cardiol. 2023;82(2):142–57. https://doi.org/10.1016/j.jacc.2023.05.011
21 Miñana G, de la Espriella R, Mollar A, Santas E, Núñez E, Valero E, et al. Factors associated with plasma antigen carbohydrate 125 and amino-terminal pro-B-type natriuretic peptide concentrations in acute heart failure. Eur Heart J Acute Cardiovasc Care. 2020;9(5):437–47. https://doi.org/10.1177/2048872620908033
22 Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21(2):137–55. https://doi.org/10.1002/ejhf.1369
23 Núñez J, Núñez E, Robles R, Bodí V, Sanchis J, Carratalá A, et al. Prognostic value of brain natriuretic peptide in acute heart failure: mortality and hospital readmission. Rev Esp Cardiol. 2008;61(12):1332–7. https://doi.org/10.1016/s1885-5857(09)60062-1
24 Mueller C, McDonald K, de Boer RA, Maisel A; Heart Failure Association of the European Society of Cardiology; Cleland JGF, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019;21(6):715–31. https://doi.org/10.1002/ejhf.1494
25 Lankeit M, Jiménez D, Kostrubiec M, Dellas C, Kuhnert K, Hasenfuß G, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. Eur Respir J. 2014;43(6):1669–77. https://doi.org/10.1183/09031936.00211613
26 Kang SH, Park JJ, Choi DJ, Oh IY, Kang SM, Yoon CH, et al. Prognostic valueof NT- proBNP in heart failure with preserved versus reduced EF. Heart. 2015;101(23):1881–8. https://doi.org/10.1136/heartjnl-2015-307782
27 Núñez J, Núñez E, Bayés-Genís A, Fonarow GC, Miñana G, Bodí V, et al. Long-term serial kinetics of N-terminal pro B-type natriuretic peptide and carbohydrate antigen 125 for mortality risk prediction following acute heart failure. Eur Heart J Acute Cardiovasc Care. 2017;6(8):685–96. https://doi.org/10.1177/2048872616649757
28 Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2017;318(8):713–20. https://doi.org/10.1001/jama.2017.10565
29 Cobo Marcos M, de la Espriella R, Gayán Ordás J, Llàcer P, Pomares A, Fort A, et al. Prevalence and clinical profile of kidney disease in patients with chronic heart failure. Insights from the Spanish cardiorenal registry. Rev Esp Cardiol. 2024;77(1):50–9. https://doi.org/10.1016/j.rec.2023.05.003
30 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726. https://doi.org/10.1093/eurheartj/ehab368
31 Ambrosy AP, Pang PS, Khan S, Konstam MA; EVEREST Trial Investigators; Fonarow GC, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34(11):835–43. https://doi.org/10.1093/eurheartj/ehs444
32 Josa-Laorden C, Giménez-López I, Rubio-Gracia J, Ruiz-Laiglesia F, Garcés-Horna V, Pérez-Calvo JI. Valor pronóstico de la medición del diámetro y colapso inspiratorio de la vena cava inferior en la insuficiencia cardiaca aguda [Prognostic value of measuring the diameter and inspiratory collapse of the inferior vena cava in acute heart failure]. Rev Clin Esp. 2016;216(4):183–90. https://doi.org/10.1016/j.rce.2015.11.012
33 Longino A, Martin K, Leyba K, Siegel G, Thai TN, Riscinti M, et al. Prospective evaluation of venous excess ultrasound for estimation of venous congestion. Chest. 2024;165(3):590–600. https://doi.org/10.1016/j.chest.2023.09.029

34 Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38(4):577–91. https://doi.org/10.1007/s00134-012-2513-4
35 Llàcer P, Núñez J, Manzano L, Cepeda Rodrigo JM, Salamanca Bautista P, Guzmán García M, et al. Carbohydrate antigen 125 (CA125) as a prognostic marker in the elderly with acute heart failure and preserved ejection fraction. Med Clin. 2022;159(4):164–70. https://doi.org/10.1016/j.medcli.2021.09.032
36 de la Espriella R, Núñez-Marín G, Codina P, Núñez J, Bayés-Genís A. Biomarkers to improve decision-making in acute heart failure. Card Fail Rev. 2023;9:e13. https://doi.org/10.15420/cfr.2023.08
37 Núñez J, de la Espriella R, Rossignol P, Voors AA, Mullens W, Metra M, et al. Congestion in heart failure: a circulating biomarker-based perspective. A review from the biomarkers working group of the heart failure association, European society of cardiology. Eur J Heart Fail. 2022;24(10):1751–66. https://doi.org/10.1002/ejhf.2664
38 Yilmaz MB, Zorlu A, Tandogan I. Plasma CA-125 level is related to both sides of the heart: a retrospective analysis. Int J Cardiol. 2011;149(1):80–2. https://doi.org/10.1016/j.ijcard.2009.12.003
39 de la Espriella R, Cobo M, Santas E, Verbrugge FH, Fudim M, Girerd N, et al. Assessment of filling pressures and fluid overload in heart failure: an updated perspective. Rev Esp Cardiol. 2023;76(1):47–57. https://doi.org/10.1016/j.rec.2022.07.009
40 de la Espriella R, Santas E, Zegri Reiriz I, Górriz JL, Cobo Marcos M, Núñez J. Quantification and treatment of congestion in heart failure: a clinical and pathophysiological overview. Nefrologia. 2021;S0211-6995(21)00114-4. https://doi.org/10.1016/j.nefro.2021.04.006
41 Sokolska JM, Sokolski M, Zymliński R, Biegus J, Siwołowski P, Nawrocka-Millward S, et al. Distinct clinical phenotypes of congestion in acute heart failure: characteristics, treatment response, and outcomes. ESC Heart Fail. 2020;7(6):3830–40. https://doi.org/10.1002/ehf2.12973