











Original article

Association between Venous Excess Ultrasound (VExUS) Score and Serum CA-125 Levels in Patients with Heart Failure and Left Ventricular Systolic Dysfunction: A Prospective Pilot Study

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ABSTRACT

Introduction: Heart failure (HF) remains a major cause of morbidity and mortality worldwide. Accurate assessment of congestion is fundamental in patients with worsening HF, yet physical examination and chest radiography may underestimate its severity. Carbohydrate antigen 125 (CA-125) has emerged as a biomarker associated with congestion severity and prognosis in HF. However, its relationship with ultrasound-defined systemic venous congestion using the Venous Excess Ultrasound (VExUS) score has not been evaluated.

Material and methods: We conducted a prospective, cross-sectional, single-center pilot study including ambulatory patients with previously diagnosed chronic HF with reduced ejection fraction and with clinical suspicion of worsening heart failure. At inclusion, blood samples were obtained for CA-125 measurement and transthoracic echocardiography with VExUS assessment was performed during the same visit, prior to treatment adjustment. The primary objective was to determine the association between VExUS score and CA-125 levels.

Results: Fifty-four patients were included. A moderate positive correlation was observed between VExUS grade and CA-125 (Spearman $\rho=0.46$, $p<0.001$). In multivariable analysis adjusting for age, ejection fraction and serum creatinine, VExUS grade remained independently associated with CA-125 ($\beta = 0.387$, $p = 0.001$).

Discussion: In patients with HF and left ventricular systolic dysfunction, CA-125 levels correlate with ultrasound-defined systemic venous congestion. CA-125 may represent an accessible biomarker reflecting congestion severity in ambulatory clinical settings.

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Asociación entre la puntuación de ultrasonido de exceso venoso (VExUS) y los niveles séricos de CA-125 en pacientes con insuficiencia cardíaca y disfunción sistólica del ventrículo izquierdo: un estudio piloto prospectivo

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RESUMEN

Introducción: La insuficiencia cardíaca (IC) sigue siendo una de las principales causas de morbilidad y mortalidad a nivel mundial. La evaluación precisa de la congestión es fundamental en pacientes con IC progresiva; sin embargo, la exploración física y la radiografía de tórax pueden subestimar su gravedad. El antígeno carbohidrato 125 (CA-125) ha surgido como un biomarcador asociado a la gravedad de la congestión y al pronóstico en la IC. No obstante, su relación con la congestión venosa sistémica definida por ecografía mediante la puntuación de exceso venoso por ultrasonido (VExUS) no se ha evaluado.

Material y métodos: Realizamos un estudio piloto prospectivo, transversal y unicéntrico que incluyó pacientes ambulatorios con IC crónica previamente diagnosticada, con fracción de eyección reducida y con sospecha clínica de empeoramiento de la insuficiencia cardíaca. Al inicio del estudio, se obtuvieron muestras de sangre para la medición de CA-125 y se realizó una ecocardiografía transtorácica con evaluación VExUS durante la misma visita, antes del ajuste del tratamiento. El objetivo principal fue determinar la asociación entre la puntuación VExUS y los niveles de CA-125.

Resultados: Se incluyeron cincuenta y cuatro pacientes. Se observó una correlación positiva moderada entre el grado VExUS y el CA-125 (Spearman $\rho=0,46$, $p<0,001$). En el análisis multivariante, ajustando por edad, fracción de eyección y creatinina sérica, el grado VExUS se mantuvo asociado de forma independiente con el CA-125 ($\beta = 0,387$, $p = 0,001$).

Discusión: En pacientes con insuficiencia cardíaca y disfunción sistólica del ventrículo izquierdo, los niveles de CA-125 se correlacionan con la congestión venosa sistémica definida por ecografía. El CA-125 podría representar un biomarcador accesible que refleje la gravedad de la congestión en entornos clínicos ambulatorios.

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1. INTRODUCTION

Heart failure (HF) affects 1–2% of the adult population and more than 10% of individuals aged ≥ 70 years [1-3]. The majority of hospitalizations for HF occur primarily due to congestion rather than to low cardiac output. Congestion is a central pathophysiological component of HF decompensation [4, 5]. In this context, biomarkers and imaging tools have gained relevance due to low accuracy of physical exam to detect congestion [6, 7]. Although natriuretic peptides remain the standard biochemical markers, other approaches such as CA-125 and VExUS have gained popularity due to its lower cost, and because they have demonstrated prognostic and congestion-related value [8, 9].

Carbohydrate antigen 125 (CA-125), traditionally used in

oncology [10], has emerged as a biomarker associated with congestion severity, functional class, hemodynamic parameters, and prognosis in HF [11-18]. Elevated CA-125 levels have been correlated with peripheral edema, pleural effusion, and inferior vena cava diameter, in some settings outperforming NT-proBNP in congestion assessment [13, 14]. The Venous Excess Ultrasound (VExUS) score, introduced by Beaubien-Souligny et al. [19], allows objective grading of systemic venous congestion through evaluation of inferior vena cava diameter and Doppler patterns of hepatic, portal, and intrarenal veins. In clinical practice, VExUS has become a useful tool as clinical assessment alone may lack sensitivity to distinguish vascular from tissue congestion [17, 18]. Although VExUS has been associated with adverse renal outcomes in surgical patients [19], its relationship with circulating congestion biomarkers such as CA-125 has not been established.

Therefore, this study aimed to determine the correlation between VExUS-defined congestion and serum CA-125 levels in ambulatory patients with HF and left ventricular systolic dysfunction.

2. MATERIAL AND METHODS

2.1. STUDY DESIGN AND POPULATION

This was a prospective, cross-sectional, analytical, single-center pilot study conducted at the Heart Failure Clinic of a tertiary cardiovascular center. Consecutive ambulatory patients with previously diagnosed chronic HF and reduced ejection fraction (LVEF $\leq 40\%$) who presented with clinical suspicion of decompensation were included. All patients were receiving guideline-directed medical therapy prior to evaluation. Assessments were performed before any adjustment of treatment. Inclusion criteria were age >18 years, prior diagnosis of chronic HF with reduced ejection fraction, and clinical suspicion of worsening heart failure. Exclusion criteria included severe hepatic disease (Child-Pugh C), dialysis-dependent chronic kidney disease, hemodynamic instability, or inability to obtain adequate ultrasound windows. The study was approved by the local Ethics and Research Committees and conducted in accordance with the Declaration of Helsinki.

2.2. STUDY PROCEDURES

After informed consent, blood samples were obtained for CA-125 measurement using chemiluminescent immunoassay (Roche platform). On the same visit, transthoracic echocardiography and VExUS assessment were performed using a General Electric Vivid E95 system. Standard echocardiographic measurements followed current recommendations. LVEF was calculated using Simpson's biplane method. Additional parameters included TAPSE, right ventricular dimensions, and diastolic function indices. VExUS grading (0–3) was determined based on inferior vena cava diameter and Doppler patterns of hepatic, portal, and intrarenal veins as originally described. VExUS assessments were performed prior to the availability of laboratory results, including CA-125 levels, ensuring that sonographers were effectively blinded to biomarker values at the time of image acquisition and interpretation.

2.3. STATISTICAL ANALYSIS

Categorical variables were expressed as frequencies and percentages. Our independent variable was VExUS grade (ordinal 0–3) and the dependent variable was serum CA-125

level (U/mL). Continuous variables were expressed as mean \pm standard deviation or median with interquartile range according to distribution. Normality was assessed using the Shapiro–Wilk test. Correlation between VExUS grade and CA-125 was evaluated using Spearman's rank correlation coefficient. Differences in CA-125 levels across VExUS grades were analyzed using Kruskal–Wallis test. An exploratory multivariable linear regression model was constructed using log-transformed CA-125 as dependent variable and VExUS grade, age, LVEF, and serum creatinine as covariates. A two-sided p-value <0.05 was considered statistically significant. Analyses were performed using Stata version 18.

3. RESULTS

54 patients were included. Mean age was 55.0 ± 15.1 years, 41 patients (75.9%) were male, and mean left ventricular ejection fraction was $28.2 \pm 9.3\%$. Table 1 describes baseline characteristics of the included cohort. Serum CA-125 median concentration was 19.9 U/mL (interquartile range [IQR] 50.4 U/mL). According to VExUS classification, 29 patients (53.7%) were categorized as VExUS grade 0, 4 (7.4%) as grade I, 4 (7.4%) as grade II, and 17 (31.5%) as grade III systemic venous congestion.

Table 1: Baseline Clinical and Laboratory Characteristics of the Study Population

Variable	Value
Age (years), mean \pm SD	55.0 \pm 15.1
Male sex, n (%)	41 (75.9%)
Hypertension, n (%)	27 (50.0%)
Diabetes mellitus, n (%)	17 (31.5%)
Ischemic heart disease, n (%)	30 (55.6%)
NYHA class I, n (%)	17 (31.5%)
NYHA class II, n (%)	22 (40.7%)
NYHA class III, n (%)	13 (24.1%)
NYHA class IV, n (%)	2 (3.7%)
Orthopnea, n (%)	46 (85.2%)
Peripheral edema, n (%)	31 (57.4%)
Left ventricular ejection fraction (%), mean \pm SD	28.2 \pm 9.3
Serum creatinine (mg/dL), mean \pm SD	1.36 \pm 0.62
NT-proBNP (ng/mL), median [Q1–Q3]	2590.5 [828.2–10130.5]
CA-125 (U/mL), median [Q1–Q3]	19.9 [13.2–63.6]

Differences in CA-125 concentrations across VExUS grades were statistically significant (Kruskal–Wallis $P = 0.0027$). Importantly, these differences followed that higher VExUS correlated with higher CA-125 values as represented by a Spearman rank correlation of $\rho = 0.459$, $p < 0.001$; see Table 2 and Figure 1. In an exploratory multivariable linear regression model using log-transformed CA-125 as the

dependent variable, VExUS grade remained independently associated with CA-125 ($\beta = 0.387$, $p = 0.001$) after adjusting for LVEF, age, and serum creatinine. As expected, LVEF showed an inverse association with CA-125 ($\beta = -0.034$, $p = 0.044$), and age demonstrated borderline significance ($p = 0.053$). Serum creatinine was not significantly associated with CA-125 ($p = 0.143$).

4. DISCUSSION

In this prospective pilot study of ambulatory patients with heart failure and reduced ejection fraction, we found a statistically significant positive correlation between ultrasound-defined systemic venous congestion and serum CA-125 levels. Importantly, this association occurred even

Table 2: Association Between VExUS Congestion Grade and Serum CA-125 Levels

VExUS Grade (n)	Mean \pm SD (U/mL)	Median [Q1–Q3] (U/mL)	Range (U/mL)
0 (29)	30.13 \pm 41.01	14.60 [9.10–26.40]	4.00–165.80
I (4)	21.68 \pm 8.31	19.40 [17.90–23.18]	14.30–33.60
II (4)	111.33 \pm 60.79	102.70 [63.40–150.62]	56.50–183.40
III (17)	138.32 \pm 217.00	53.30 [16.60–159.30]	9.20–854.50

Kruskal–Wallis test: $H = 14.12$, $p = 0.0027$.

A sensitivity analysis excluding extreme CA-125 values (above the 95th percentile; >230.4 U/mL, $n=3$) showed consistent results, with a similar correlation between VExUS grade and CA-125 ($\rho = 0.39$, $p = 0.005$). In multivariable analysis, VExUS grade remained independently associated with CA-125 ($\beta = 0.28$, $p = 0.011$). The overall model explained a moderate proportion of variance in CA-125 levels ($R^2 = 0.34$). The wide variability observed reflects the known skewed distribution of CA-125 levels in patients with advanced congestion.

after adjusting for key clinical variables such as LVEF, age, and renal function.

CA-125 progressively increased across higher VExUS congestion grades. The moderate positive correlation observed ($\rho = 0.459$) suggests a meaningful biological gradient between increasing venous congestion severity and CA-125 elevation. Importantly, this association persisted after adjustment for age, LVEF, and creatinine, indicating that the relationship between VExUS grade and CA-125 is not solely explained by the high filling pressures that NT-proBNP captures or renal function. Notably, although more than half of the cohort was classified as VExUS grade 0, a graded association remained evident across congestion categories. Additionally, the lower mean CA-125 observed in VExUS grade I compared to grade 0 likely reflects the small sample size and variability within this subgroup. Importantly, VExUS grade I represents a mild or borderline degree of congestion, which may not be clearly distinguishable from grade 0 in ambulatory patients. This may result in overlapping biomarker levels between these categories, particularly in small samples.

Previous studies have demonstrated associations between CA-125 and clinical or echocardiographic markers of congestion, including peripheral edema, pleural effusion, and inferior vena cava diameter [11–14]. However, these studies did not evaluate a structured ultrasound-based grading system of systemic venous congestion. Our findings extend existing evidence by demonstrating a relationship between CA-125 and VExUS grading [19].

From a pathophysiological perspective, elevated intracardiac filling pressures that are transmitted backward to the systemic venous circulation, leading to venous hypertension and organ congestion, characterize heart failure. This increase in venous pressure promotes fluid extravasation into interstitial and serosal compartments, resulting in pleural effusion, ascites, and tissue edema.

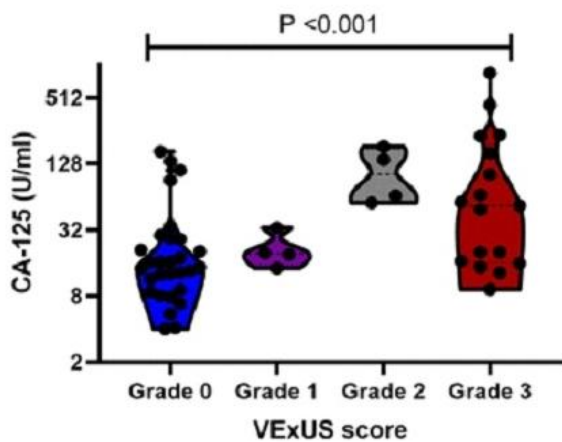


Figure 1: Violin plot illustrating the association between VExUS congestion grade (0–III) and serum CA-125 levels (U/mL) in patients with heart failure and left ventricular systolic dysfunction. A moderate positive correlation was observed between congestion severity and CA-125 concentration (Spearman $\rho = 0.459$, $p < 0.001$).

NT-proBNP also showed a significant correlation with VExUS grade (Spearman $\rho = 0.70$, $p < 0.001$), which was stronger than that observed for CA-125. In regression analysis, NT-proBNP demonstrated a higher explanatory capacity ($R^2 = 0.52$ vs. 0.23 for CA-125).

VExUS provides a non-invasive assessment of this systemic venous congestion by evaluating venous flow patterns and inferior vena cava dynamics. Sustained venous hypertension and fluid accumulation lead to mechanical stretch and activation of mesothelial cells lining serosal surfaces, which respond by increasing the synthesis and release of CA-125 in response to mechanical stress and inflammatory signaling. This mechanistic pathway supports the biological plausibility of CA-125 as a biomarker reflecting systemic venous congestion in patients with heart failure [16, 20, 21]. The VExUS score was initially developed as a tool to quantify systemic venous congestion in critically ill patients. However, its use has progressively expanded beyond the intensive care setting, with emerging evidence supporting its application in cardiorenal syndromes and heart failure populations. Recent studies suggest that VExUS may provide clinically relevant information for congestion assessment in non-critical settings, including ambulatory patients, complementing traditional clinical and biochemical evaluation [19, 22, 23].

In our cohort, NT-proBNP showed a stronger correlation with VExUS-defined congestion compared to CA-125. This finding is expected given that natriuretic peptides reflect myocardial wall stress and intracardiac pressures. However, CA-125 remained significantly associated with systemic venous congestion, supporting its role as a biomarker reflecting the systemic congestion phenotype. These findings suggest that both biomarkers may provide complementary information rather than representing interchangeable measures.

From a clinical standpoint, CA-125 may represent an accessible biomarker reflecting objective venous congestion severity. In healthcare environments where advanced ultrasound protocols or natriuretic peptides are not readily available, CA-125 could serve as a complementary tool to support congestion assessment and therapeutic decision-making. Although it was not the purpose of this study, CA-125 has been evaluated as a biomarker to guide decongestive therapy in heart failure. Trials such as CHANCE-HF and LEVO-CHOP have demonstrated that CA-125-guided strategies may improve clinical outcomes by optimizing diuretic therapy and congestion management. In this context, the observed association between VExUS-defined congestion and CA-125 levels provides additional support for the use of CA-125 as a clinically meaningful marker of systemic congestion [24, 25].

5. CONCLUSIONS

In ambulatory patients with heart failure and reduced

ejection fraction, serum CA-125 levels were independently associated with VExUS-defined systemic venous congestion. These findings support the potential role of CA-125 as an accessible biomarker reflecting objective congestion severity. Larger multicenter studies are required to confirm these results and determine their clinical implications.

6. LIMITATIONS

This study has limitations. It was conducted at a single center with a relatively small sample size and a cross-sectional design, which precludes causal inference. Additionally, the distribution of VExUS grades was skewed, with a limited number of patients in intermediate categories (Grades I and II), which may have reduced the statistical robustness of comparisons across individual groups. Invasive hemodynamic validation was not performed, and multivariable analyses should be considered exploratory. Additionally, VExUS assessment is operator-dependent. Nevertheless, the prospective design and simultaneous acquisition of biochemical and ultrasound measurements strengthen the internal validity of our observations.

7. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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