


# CA-125 variation in acute heart failure: a single-centre analysis

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## Abstract

**Aims** A decrease in carbohydrate antigen 125 (CA-125) predicts survival advantage in chronic heart failure (HF); the impact of its variation in acute HF is unknown. We studied the association of CA-125 decrease with prognosis in acute HF.

**Methods and results** We studied acute hospitalized HF patients. Predictors of admission and discharge CA-125 were determined by linear regression. Follow-up was 1 year; endpoint was all-cause death. The association of admission and discharge CA-125 with mortality was assessed using a Cox-regression analysis. A Cox-regression analysis was also used to assess the prognostic impact of CA-125 decrease during hospitalization. Analysis was stratified by length of hospital stay (LOS). We studied 363 patients, 51.5% male, mean age 75 ± 12 years, 51.5% ischaemic, 30.0% with preserved ejection fraction, and 57.3% with reduced ejection fraction; patients presented elevated comorbidity burden. Median LOS was 7 (5–11) days. In the subgroup of 262 patients with CA-125 measured both at admission and at discharge, we reported a significant increase in its levels: 56.0 (26.0–160.7) U/mL to 74.0 (32.3–195.0) U/mL. Independent predictors of admission CA-125 were higher BNP and lower creatinine. Predictors of discharge CA-125 were higher discharge BNP, lower discharge albumin, and younger age. Both admission and discharge CA-125 predicted mortality. During follow-up, 75 (31.8%) patients died. A decrease in CA-125 predicted a 68% reduction in the 1 year death risk only in patients with LOS > 10 days.

**Conclusions** Our results suggest that an early re-evaluation (>10 days) with CA-125 measurement after an acute HF hospitalization may be of interest in patient management.

**Keywords** CA-125; Acute heart failure; Biomarkers; Prognosis

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## Introduction

Heart failure (HF) is a complex systemic condition; neurohormonal and cytokine activation is one of its hallmarks and this activation is intimately associated with disease progression.<sup>1</sup>

In recent years, there has been a growing recognition and a renewed interest in new biomarkers in HF, specifically in diagnosis, prognosis, monitoring, and as a therapeutic guide.<sup>2</sup> However, most biomarkers still do not meet the required criteria for daily clinical practice, like availability, procedure standardization, and reasonable cost.<sup>2</sup> Ideal biomarkers for implementation should have good diagnostic accuracy and

be able to guide clinicians to when initiate and how to titrate therapy.<sup>3</sup>

Tumour markers are classically used for the screening, diagnosis, and stratification of cancer disease.<sup>4</sup> Recently, carbohydrate antigen 125 (CA-125), known for its utility in ovarian cancer monitoring, has been explored in the context of HF management.<sup>4–6</sup> CA-125 is a well-known biomarker, recently shown to be associated with mortality in systolic HF,<sup>7</sup> and the practical application of its elevation to predict clinical outcome in chronic HF is recognized.<sup>8</sup> A number of studies have consistently indicated that it could serve as both as congestion and prognostic biomarker.<sup>4</sup> The association with conges-

tion is not fully understood but may result from the fact that CA-125 is a transmembrane glycoprotein expressed in mesothelial membranes and therefore its up-regulation in HF may result from mesothelial cell activation due to mechanical stress and increased hydrostatic pressures.<sup>9</sup> CA-125 levels have been shown to closely correlate with HF severity and its variations are related with clinical outcomes in the chronic ambulatory context.<sup>10</sup> These results suggest a potential role for CA-125 in the monitoring and therapy guiding in HF.<sup>6,11</sup> Still, despite all these observations, the pathophysiological link between CA-125 and HF is not yet fully understood.<sup>4</sup>

We aimed to assess the variation of CA-125 during a hospitalization due to acute HF and to test the hypothesis that a CA-125 decrease would associate with survival advantage.

## Material and methods

A prospective acute HF registry was conducted in the Internal Medicine Department of Centro Hospitalar Universitário São João, Porto, Portugal, between March 2009 and December 2010. All patients hospitalized with the primary diagnosis of acute HF were eligible for inclusion in the registry. The 2008 European Society of Cardiology guidelines were used for the diagnosis of HF,<sup>12</sup> and diagnosis was made/confirmed during hospital stay. Patients with an acute coronary syndrome precipitating acute HF were immediately excluded at admission, and patients with no structural or functional abnormalities in the echocardiogram performed during hospital stay or in whom the attending physician considered that patients' symptoms were justified by other medical condition were additionally excluded despite acute HF being the admission diagnosis.

As part of the registry's protocol, a set of procedures took place in all patients. A complete physical examination was performed at admission and in the discharge day. Demographic data, comorbidities, and medication in use were recorded based on information provided by the patients and their relatives/care providers. A venous blood sample was collected on the admission and discharge day. Part of the blood was collected in serum separating tubes, immediately centrifuged (2573 g for 15 min), and then stored at  $-75^{\circ}\text{C}$  within 2 h, for future analysis. A transthoracic echocardiogram was performed during hospitalization. Patients with left ventricular ejection fraction  $\geq 50\%$  were considered as having preserved systolic function. Patients with ejection fraction between 40% and 49% were classified as having HF with mildly reduced ejection fraction and those with ejection fraction  $< 40\%$  as having HF with reduced ejection fraction (HFrEF). Within HFrEF patients, ejection fraction  $< 30\%$  was considered severe systolic dysfunction. B-type natriuretic peptide (BNP) determination is a routine laboratory procedure in our hospital; an Abbott chemiluminescent microparti-

cle immunoassay (two-step immunoassay) was used. Haemoglobin was obtained using an automated blood counter Sysmex<sup>®</sup> XE-5000. Serum creatinine was measured using conventional methods with an Olympus AU5400<sup>®</sup> automated clinical chemistry analyser Beckman-Coulter<sup>®</sup>.

Both patients and the physicians treating them were aware of the ongoing registry. Patient's treatment strategy, timing of discharge, and discharge medication were a decision of the attending physician only. Patients' vital status was ascertained by consulting hospital registries and by telephone contact with the patients or their relatives/care providers. When no information was obtained, we consulted the Registo Nacional de Utentes (RNU); RNU is a national platform that provides information on patient mortality. No patient was lost to follow-up.

The registry's protocol conformed to the ethical guidelines of the Declaration of Helsinki, and it was approved by the local ethics committee.

To analyse the variation of CA-125 during the acute HF episode, we retrospectively analysed a subgroup of patients in whom enough serum collected at registry inclusion was stored for CA-125 measurement at admission and discharge. To study if the decrease in CA-125 during hospitalization predicted a survival advantage, we followed patients for up to 1 year and all-cause mortality was the endpoint under analysis. CA-125 measurements of samples stored during study inclusion (2009 and 2010) were performed in 2018. The serum concentrations of CA-125 were determined by chemiluminescent microparticle immunoassay on the Architect i2000SR (Abbott Diagnostics, Abbott Park, IL, USA).

## Statistical analysis

Categorical variables are presented as counts and proportions. Continuous variables are presented as mean  $\pm$  standard deviation when normally distributed and as median (interquartile range, IQR) when non-normally distributed.

A Wilcoxon signed-rank test was used to compare admission and discharge CA-125. Predictors of admission and discharge CA-125 were determined by a linear regression analysis. Multivariate models included variables associated with CA-125 in a univariate approach. The association of admission and discharge CA-125 with 1 year all-cause mortality was assessed by a Cox-regression analysis. CA-125 at admission and discharge were assessed as a continuous (the variable was log-transformed for the analysis) as well as a categorical variable: both 35 U/mL (the upper limit of the normal reference range) and 60 U/mL cut-offs<sup>13,14</sup> were used. A multivariate model was built taking into consideration age, BNP, severe left ventricular dysfunction, ischaemic HF, and comorbidities. For the analysis of the prognostic value of

CA-125 at discharge, a second model including evidence-based therapy was also tested.

Admission and discharge CA-125 were compared using a Wilcoxon signed-rank test. Variation of CA-125 was calculated as  $(\text{admission CA} - 125 - \text{discharge CA} - 125) / \text{admission CA} - 125 \times 100$ . Patients were categorized in two groups: those with CA-125 increase and those with CA-125 decrease during hospitalization. Groups were compared:  $\chi^2$  test for categorical variables, Student's *t*-test for continuous normally distributed variables, and Mann–Whitney *U*-test when continuous variables presented a highly skewed distribution.

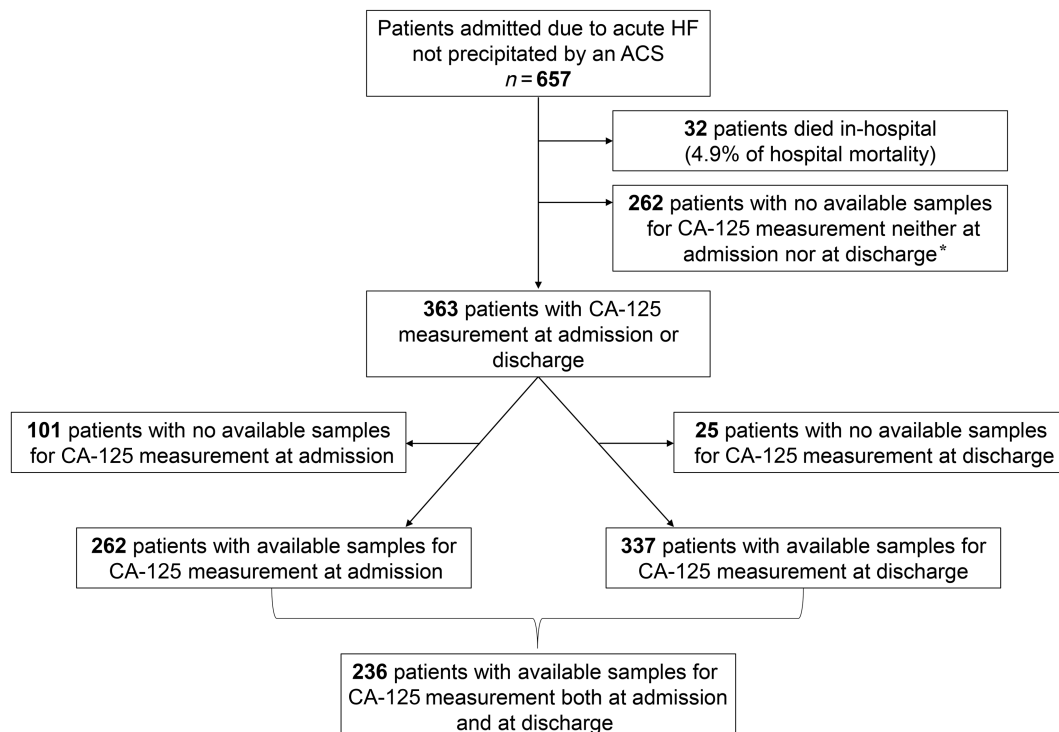
Survival curves in patients with CA-125 increase and decrease were calculated based on the Kaplan–Meier method. The association of CA-125 variation with 1 year survival was calculated using a Cox-regression analysis. Analysis was further stratified according to length of hospital stay (LOS):  $\leq 10$  and  $> 10$  days. Adjustments were made accounting for independent predictors of admission or discharge CA-125 as well as for variables differently distributed between patients with CA-125 increase or decrease during hospital stay.

The *P*-value considered for statistical significance was 0.05. Data were stored and analysed using SPSS software (IBM Corp, Armonk, NY, USA, Version 20.0).

## Results

From a group of 657 patients included in the acute HF registry described, a total of 363 patients hospitalized due to acute HF had available serum stored to measure CA-125 at admission or at discharge. The remaining 294 consisted of the 32 patients that died in-hospital and those in whom no serum samples were available for additional measurements. *Figure 1* shows the patients included in the registry and the subgroups of patients analysed in our study. Of note that valvular HF patients were practically inexistent (around 1%) among the subgroup of patients that were ultimately studied. Patients' characteristics are shown in *Table 1*. Men and women were equally represented, and mean age was  $75 \pm 12$  years. Patients had elevated comorbidity burden; however, no patient was on renal replacement therapy. Median LOS was 7 (5–11) days. Of these patients, 262 had CA-125 measured at admission and 337 had CA-125 measured at discharged (*Figure 1*). In 236 patients, serum was available to measure CA-125 both at admission and at discharge (*Figure 1*). Both admission and discharge CA-125 had highly skewed right tailed distributions. We observed a significant global increase in CA-125 levels from admission to discharge—median (IQR) from 56.0 (26.0–160.7) U/mL to 74.0 (32.3–195.0) U/mL,  $P < 0.001$ .

**Figure 1** Flow diagram of patients included in this study. \*The majority of patients with valvular HF ( $n = 130/294$ , 44.2%) were included in this group because their serum had already been used in other analysis. ACS, acute coronary syndrome; CA-125, carbohydrate antigen 125; HF, heart failure.



**Table 1** General patients' characteristics

	N = 363
Male sex, n (%)	187 (51.5)
Age (years), mean (SD)	75 (12)
Arterial hypertension, n (%)	284 (78.2)
Diabetes mellitus, n (%)	200 (55.1)
Atrial fibrillation, n (%)	158 (43.5)
HF aetiology	
Ischaemic, n (%)	187 (51.5)
Hypertensive, n (%)	76 (20.9)
Alcoholic, n (%)	21 (5.8)
Tachycardiomyopathy, n (%)	26 (7.2)
Idiopathic, n (%)	34 (9.4)
Valvular, n (%)	3 (0.8)
Other, n (%)	16 (4.4)
Left ventricular function	
Preserved ejection fraction, n (%)	109 (30.0)
Mildly reduced ejection fraction, n (%)	30 (10.7)
Reduced ejection fraction, n (%)	208 (57.3)
Length of hospital stay, n (%)	7 (5–11)
Beta-blocker at discharge, n (%)	287 (79.1)
ACEi and/or ARB at discharge, n (%)	298 (82.1)
MRA at discharge, n (%)	93 (25.6)
Furosemide at discharge, n (%)	345 (95.0)

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor 1 blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonists; SD, standard deviation.

Independent predictors of admission CA-125 were admission BNP (higher BNP was associated with higher levels of CA-125) and admission creatinine (higher creatinine was associated with lower CA-125). There was a non-significant trend for older patients to have lower CA-125 levels. *Table 2* shows the predictors of admission CA-125. Variables independently associated with discharge CA-125 were discharge BNP, discharge albumin, and age. Elevated BNP predicted elevated CA-125, just as at admission; lower albumin predicted higher CA-125 and CA-125 decreased with increasing age (*Table 3*).

Both admission and discharge CA-125 were associated with 1 year all-cause mortality (*Table 4*). Elevated CA-125 whether using the 35 U/mL cut-off and the 60 U/mL cut-off or analysing it as a continuous, log-transformed, variable more than doubled the risk of 1 year all-cause death. Considering the subgroup of 236 patients with CA-125 measurement both at admission and at discharge, the CA-125 variation during hospitalization had also a highly skewed distribution, this time left tailed; median (IQR) was  $-19.2$  ( $-54.3$  to  $8.2$ ) %. In 165 (69.9%) patients, the CA-125 increased during hospitalization and in the remaining, 30.1% CA-125 decreased. Patients with increase or decrease in CA-125 during hospitalization were globally similar except for the fact that patients with CA-125 decrease were younger (*Table 5*); moreover, no significant differences were detected in the particular subgroup of patients with LOS > 10 days (*Table 5*).

During 1 year of follow-up, 75 (31.8%) patients died. The decrease in CA-125 level during hospital admission was not associated with prognosis; however, in the subgroup of patients with hospitalizations longer than 10 days ( $n = 66$ , 28.0%), those with CA-125 decrease presented survival advantage. *Figure 2* shows the Kaplan–Meier survival curves according to CA-125 variation (increase or decrease) for patients hospitalized for up to 10 days or longer. Crude and one at a time adjustment to BNP and age associations of CA-125 decrease with survival in patients with admissions of  $\leq 10$  days or longer are shown in *Table 6*.

## Discussion

In our group of acute HF patients, we reported an increase in CA-125 during hospitalization. We reinforce previous studies

**Table 2** Predictors of admission carbohydrate antigen 125—linear regression: univariate and multivariate analysis

	$\beta$ coefficient (95% CI)	p-value	$\beta$ coefficient (95% CI)	p-value
Male sex	16.3 (–24.8; 57.4)	0.44	–1.4 (–3.0; 0.2)	0.09
Age (per year)	–2.0 (–3.6; –0.4)	0.02	14.0 (–5.6; 33.6)	0.16
Diabetes mellitus	15.0 (–5.5; 35.5)	0.15		
Arterial hypertension	–27.8 (–77.1; 21.6)	0.27		
Atrial fibrillation	7.5 (–34.2; 49.3)	0.72		
Reduced LVEF	28.5 (–15.7; 72.7)	0.21		
Adm NYHA class $\geq$ IV	–21.3 (–62.6; 19.9)	0.31		
Adm SBP (per 10 mmHg)	–1.8 (–8.9; 5.3)	0.61		
Rales and oedema at admission	32.1 (–9.4; 73.7)	0.13	28.8 (–11.2; 68.8)	0.16
Adm haemoglobin (per 1 g/dL)	3.6 (–6.6; 13.8)	0.49		
Adm creatinine (per 1 mg/dL)	–32.3 (–59.7; –4.9)	0.02	–47.0 (–73.8; –20.1)	0.001
Adm CRP (per 10 mg/L)	–1.2 (–4.7; 2.3)	0.50		
Adm sodium (per 10 mEq/L)	–6.1 (–47.1; 34.9)	0.77		
Adm albumin (per 1 g/L)	–5.3 (–9.7; –1.0)	0.02	–3.4 (–7.7; 0.9)	0.12
Adm total cholesterol (per 10 mg/dL)	–1.7 (–6.5; 3.1)	0.49		
Adm uric acid (per 1 mg/dL)	0.1 (–0.7; 0.8)	0.89		
Glycated haemoglobin (per 1%)	4.3 (–9.6; 18.3)	0.54		
Adm BNP (per 100 pg/mL)	2.9 (1.7; 4.1)	<0.001	2.9 (1.7; 4.1)	<0.001

Adm, admission; BNP, B-type natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

**Table 3** Predictors of discharge carbohydrate antigen 125—linear regression: univariate and multivariate analysis

	$\beta$ coefficient (95% CI)	<i>p</i> -value	$\beta$ coefficient (95% CI)	<i>p</i> -value
Male sex	26.6 (−13.3; 66.6)	0.19		
Age (per year)	−1.6 (−3.3; 0.0)	0.05	−2.4 (−4.1; −0.7)	0.007
Diabetes mellitus	10.7 (−9.4; 30.8)	0.29		
Arterial hypertension	−19.6 (−68.8; 29.6)	0.43		
Atrial fibrillation	9.4 (−31.1; 49.9)	0.65		
Reduced LVEF	23.1 (21.2; 67.3)	0.31		
Disch NYHA class $\geq$ III	52.7 (1.1; 104.3)	0.05	40.9 (−12.5; 94.3)	0.13
Disch SBP (per 10 mmHg)	−7.1 (−17.7; 3.5)	0.19		
Rales or oedema at discharge	33.7 (−10.5; 77.9)	0.13		
Disch haemoglobin (per 1 g/dL)	−1.0 (−10.9; 8.9)	0.84		
Disch creatinine (per 1 mg/dL)	−5.8 (−33.0; 21.4)	0.67		
Disch CRP (per 10 mg/L)	7.2 (−1.3; 15.6)	0.10		
Disch sodium (per 10 mEq/L)	−39.5 (−86.3; 7.2)	0.10		
Disch albumin (per 1 g/L)	−6.6 (−10.6; −2.8)	0.001	−6.8 (−11.3; −2.4)	0.003
Disch total cholesterol (per 10 mg/dL)	0.9 (−4.2; 6.0)	0.72		
Disch uric acid (per 1 mg/dL)	−0.2 (−0.9; 0.6)	0.62		
Glycated haemoglobin (per 1%)	5.3 (−8.5; 19.1)	0.45		
Disch BNP (per 100 pg/mL)	1.9 (0.6; 3.1)	0.003	1.4 (0.1; 2.7)	0.03

BNP, B-type natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; Disch, discharge; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

**Table 4** Admission and discharge CA-125 and 1 year mortality: crude and multivariate analysis

	Admission CA-125		Discharge CA-125	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
>35 U/mL				
Crude	2.25 (1.30–3.88)	0.004	3.02 (1.65–5.51)	<0.001
Multivariate Model 1 <sup>a/b</sup>	1.87 (1.05–3.32)	0.03	2.55 (1.37–4.72)	0.003
Multivariate Model 2 <sup>c</sup>			2.74 (1.47–5.09)	0.001
>60 U/mL				
Crude	2.35 (1.50–3.70)	<0.001	2.66 (1.69–4.17)	<0.001
Multivariate Model 1 <sup>a/b</sup>	2.12 (1.33–3.39)	0.002	2.47 (1.55–3.94)	<0.001
Multivariate Model 2 <sup>c</sup>			2.47 (1.55–3.95)	<0.001
Continuous: log(CA-125)				
Crude	2.54 (1.68–3.86)	<0.001	2.74 (1.77–4.25)	<0.001
Multivariate Model 1 <sup>a/b</sup>	2.39 (1.50–3.80)	<0.001	2.51 (1.55–4.07)	<0.001
Multivariate Model 2 <sup>c</sup>			2.40 (1.49–3.88)	<0.001

CA-125, carbohydrate antigen 125; CI, confidence interval; HR, hazard ratio.

CA-125 analysed both as a continuous and categorical variable (cut-offs used: 35 and 60 U/mL).

<sup>a</sup>For admission CA-125, adjustments to admission BNP (per 100 pg/mL), age (years), arterial hypertension and diabetes mellitus, ischaemic HF, severe left ventricular systolic dysfunction, anaemia, and renal dysfunction upon admission.

<sup>b</sup>For discharge CA-125, adjustments to discharge BNP (per 100 pg/mL), age (years), arterial hypertension and diabetes mellitus, ischaemic HF, severe left ventricular systolic dysfunction, anaemia, and renal dysfunction at discharge.

<sup>c</sup>Same as Model 1 also including angiotensin-converting enzyme inhibitors and/or angiotensin II receptor 1 blocker at discharge and beta-blocker at discharge.

suggesting the independent prognostic value of CA-125 in the acute HF setting. Additionally, we report that CA-125 for risk stratification in acute HF is relevant whether it is measured at admission or at discharge. CA-125 decrease has been associated with survival advantage in chronic ambulatory HF; however, in our acute HF patients, a decrease in CA-125 associated with survival advantage only in patients with hospitalizations longer than 10 days. Acute HF patients hospitalized for more than 10 days that show a decrease in CA-125 from admission to discharge have a 68% reduction in 1 year mortality risk and this survival advantage is independent of age and of BNP.

The reported half-life of CA-125 is of 5 days<sup>15</sup>; this long half-life may, in part, explain our results, mainly the associa-

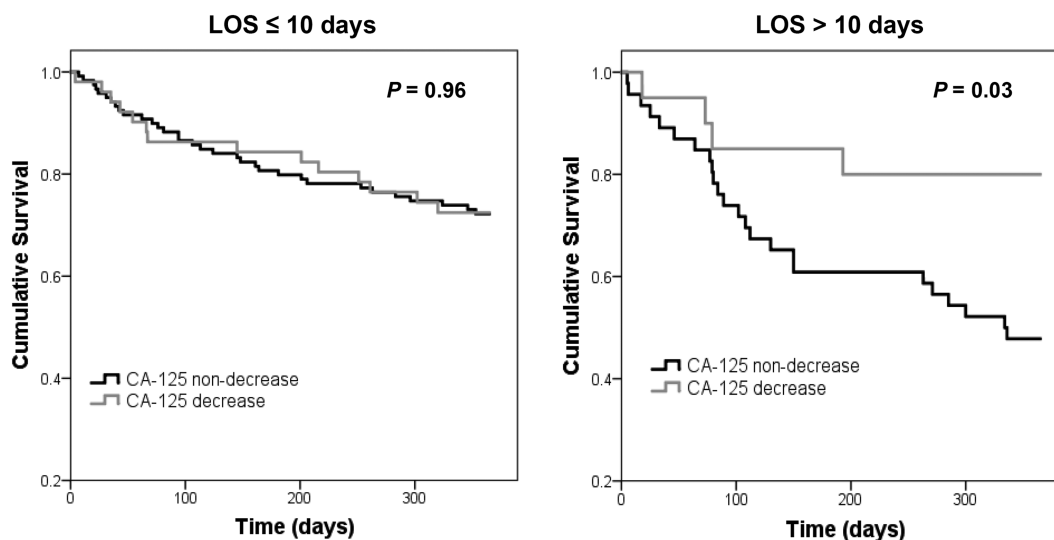
tion of CA-125 variation with prognosis only in patients with long hospitalizations. In short hospitalizations with close measurements of the biomarker, the second measurement would still reflect the initial factor related with decompensation and its severity. Given the long CA-125 half-life, daily changes in its levels may not be very informative; however, we can speculate that after two half-lives, a reassessment of CA-125 would already reflect response to treatment and clinical course and, therefore, predict prognosis. The overall increase in CA-125 reported in our population of acutely decompensated HF patients is intriguing and difficult to explain. Most patients had hospitalizations shorter than 10 days; in them, any CA-125 follow-up measurement would probably still reflect the harshness of decompensation. This circum-

**Table 5** Comparison between acute HF patients with CA-125 increase and CA-125 decrease during hospitalization

	CA-125 increase (n = 165, 69.9%)	CA-125 decrease (n = 71, 30.1%)	p-value
Male sex, n (%)	83 (50.3)	44 (62.0)	0.10
Age (years), mean (SD)	76 (12)	72 (13)	0.04
Diabetes mellitus, n (%)	88 (53.5)	37 (52.1)	0.86
Arterial hypertension, n (%)	131 (79.9)	51 (75.0)	0.41
Atrial fibrillation, n (%)	67 (40.6)	27 (38.0)	0.71
Ischaemic HF, n (%)	91 (55.2)	41 (57.7)	0.71
Left ventricular function			
Preserved ejection fraction, n (%)	56 (34.6)	18 (25.7)	
Mildly reduced ejection fraction, n (%)	18 (11.1)	4 (5.7)	
Reduced ejection fraction, n (%)	88 (54.4)	48 (68.5)	0.22
Coexisting infection, n (%)	80 (48.5)	30 (42.3)	0.38
1 year mortality, n (%)	57 (34.5)	18 (25.4)	0.16
In patients with length of hospital stay > 10 days			
	CA-125 increase (n = 46, 69.7%)	CA-125 decrease (n = 20, 30.3%)	
Male sex, n (%)	26 (56.5)	15 (75.0)	0.15
Age (years), mean (SD)	76 (13)	72 (11)	0.37
Diabetes mellitus, n (%)	29 (63.0)	10 (50.0)	0.32
Arterial hypertension, n (%)	36 (78.3)	14 (73.7)	0.69
Atrial fibrillation, n (%)	19 (41.3)	11 (55.0)	0.30
Ischaemic HF, n (%)	21 (45.7)	12 (60.0)	0.28
Left ventricular function			
Preserved ejection fraction, n (%)	21 (46.7)	7 (36.8)	
Mildly depressed ejection fraction, n (%)	1 (2.2)	1 (5.3)	
Reduced ejection fraction, n (%)	23 (51.1)	11 (57.9)	0.65
Coexisting infection, n (%)	30 (65.2)	11 (55.0)	0.43
1 year mortality, n (%)	24 (52.2)	4 (20.0)	0.02

CA-125, carbohydrate antigen 125; HF, heart failure; SD, standard deviation.

**Figure 2** The Kaplan–Meier survival curves in patients with carbohydrate antigen 125 (CA-125) decrease and non-decrease during hospitalization due to acute heart failure. Survival curves for patients with length of hospital stay (LOS) ≤ 10 days in the left panel and curves for patients with LOS > 10 days in the right panel.



stance may, at least partially, help to understand the observed rising trend of the biomarker. Natriuretic peptide levels have much shorter half-lives, and therefore, dramatic

drops during acute HF episodes in response to therapy have been reported.<sup>16</sup> With CA-125, probably due to its long half-life, variations are not so impressive.

**Table 6** Cox-regression analysis

CA-125 decrease	LOS ≤ 10 days		LOS > 10 days	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Crude	0.99 (0.53–1.84)	0.96	0.32 (0.11–0.93)	0.04
Adm BNP adjusted	0.90 (0.48–1.69)	0.74	0.34 (0.12–0.97)	0.04
Age adjusted	1.14 (0.61–2.14)	0.68	0.33 (0.11–0.96)	0.04

Adm, admission; BNP, B-type natriuretic peptide; CA-125, carbohydrate antigen 125; CI, confidence interval; HR, hazard ratio; LOS, length of hospital stay.

Crude and one at a time adjustments accounting for BNP and age. Analysis is performed separately in patients with length of hospital stay ≤ 10 and >10 days.

Admission and discharge BNP independently predicted admission and discharge CA-125, respectively, in accordance with their association with congestion. Neither New York Heart Association class nor the presence of hypervolaemia as assessed by pulmonary rales and/or peripheral oedema associated with CA-125. Eventually, this reflects the lack of specificity of typical HF signs and symptoms. In fact, classic clinical assessment of congestion through symptoms and signs has shown limited accuracy.<sup>17–19</sup> Current experts recommend an integrative multiparameter-based evaluation of congestion using clinical assessment, biomarkers, and supplemented with technical assessments.<sup>17–19</sup> Nevertheless, and despite these recommendations, a well-validated tool for the clinical assessment of congestion is still an unmet need.

A positive and independent association between CA-125 and clinical endpoints has been widely reported both in chronic and acute HF, both in patients with preserved and depressed systolic function.<sup>13,14,20,21</sup> Our results in acute HF suggest that CA-125 provides prognostic information either upon admission or at hospital discharge. This information is significant at both times and can have therapeutic implications.<sup>22</sup>

Our results give information that can be clinically relevant in identifying patients that could benefit from a closer follow-up and eventually additional therapeutic intervention in a vulnerable phase such as an acute HF episode. In recent years, CA-125 has emerged as a novel useful biomarker of congestion,<sup>11,23</sup> and we do believe our data empower the evidence for its potential role as a biomarker for clinical use in HF. CA-125 fulfils most of the required criteria for use in clinical practice as it is widely available, inexpensive, the measurement methods are standardized, and it is prognostic associated providing extra information over standard risk factors. Additionally, serial changes are prognostic related and may be potentially useful for therapy guiding.

The expression of the CA-125 antigen has been demonstrated in mesothelial cells lining the adult pleura, pericardium, and peritoneum.<sup>24</sup> The decrease of CA-125 levels with age has already been reported,<sup>25</sup> although the reasons for this reduction are still unknown. The fact that patients with a decrease in CA-125 during hospitalization were younger reinforces the association of CA-125 with age. Further studies should address this question because it is possible

that different cut-offs have to be used in different age strata. An association with creatinine and with albumin has never been described. Herein, we reported an inverse association with creatinine at admission and a direct association with albumin at discharge suggesting a role for both kidney and liver in the metabolism and/or clearance of CA-125; this issue should, eventually, be also further studied. The metabolism and clearance of CA-125 is not well understood,<sup>26</sup> and it is possible that CA-125 may be more than just a biomarker of congestion in HF.

Some study limitations are worth noting. The retrospective design and single-centre nature imply problems, namely, concerning data availability and generalizability. The small sample size of patients with both admission and discharge CA-125 measurement is a major setback. We identified an association of CA-125 decrease with survival advantage in the subgroup of patients with hospitalizations longer than 10 days; this was, however, a small subgroup with reduced number of events. Even so, such association remained valid after one at a time adjustment for major confounders. Importantly, it would have been interesting to also have measured CA-125 at 10 days from admission in patients already discharged; that would increase the number of patients with basal and over 10 days onwards CA-125 measurements to test the hypothesis that a decrease in CA-125 associates with a survival advantage in the acute HF setting. However, this was a retrospective analysis and early post-discharge blood collection was not part of the registry protocol. The fact that our population is mainly composed by non-valvular HF patients makes the study perhaps even stronger because valvular patients are a very particular group of patients that should probably be dealt with separately. It is also important to note that patients were prospectively recruited between 2009 and 2010 and CA-125 measurements were performed in 2018. Blood samples were immediately processed and stored at  $-75^{\circ}\text{C}$ ; however, the time elapsed between storage and analysis makes it impossible to totally guarantee the integrity of the samples. Still, the CA-125 measurements and distribution are consistent with values described in the literature. Furthermore, history of past neoplasia or concomitant active neoplasia, as well as data concerning coexisting auto-immune/inflammatory diseases should have been taken into consideration; however, these data were not systematically

collected. Lastly, one should bear in mind that, despite being a 21st century real-life acute HF population, it is not a completely contemporary HF population, because angiotensin receptor-neprilysin inhibitors and sodium-glucose co-transporter 2 inhibitors were not yet part of the HF armamentarium.

Despite the aforementioned limitations, this is the first study reporting CA-125 variation during acute HF hospitalizations. Our results suggest no place for CA-125 variation for risk stratification in HF decompensations, except for a possible role in the subgroup of patients with difficult compensation and long hospitalizations. Our results also suggest that an early re-evaluation (>10 days) after an acute HF decompensation with CA-125 measurement may be of potential in-

terest to patient management, such as in the ambulatory context.

## Conflict of interest

None declared.

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