que precisa mayor atención. Una fortaleza de la presente encuesta es su carácter no remunerado, libre, opcional y anónimo y, por tanto, sin sesgos en las posibles respuestas, lo que confiere un valor adicional y diferenciador a pesar de su bajo porcentaje de respuestas. En definitiva, se hace necesario llevar a cabo estudios más específicos que permitan conocer con exactitud la percepción de los cardiólogos de las GPC. Esto ayudará a los profesionales a implementar y a adaptar mejor las GPC a una realidad clínica, siempre con el objetivo final de mejorar la salud cardiovascular de los pacientes que atendemos en la práctica clínica habitual.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

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Clinical applications of CA125 in patients with heart failure: a case series

Aplicaciones clínicas del CA125 en pacientes con insuficiencia cardiaca: una serie de casos

To the Editor,

In recent years, antigen carbohydrate 125 (CA125) has emerged as a promising biomarker for monitoring congestion, guiding diuretic therapy, and risk stratification of patients with heart failure (HF).[1] Recent evidence of novel applications of CA125 has come to light, such as identifying the patient's congestion phenotype to tailor diuretic therapy.[2,3] Nonetheless, several factors should be considered to interpret CA125 correctly. In this article, we report a case series of 6 patients that illustrate the applicability of CA125 in different clinical scenarios. Table 1 summarizes their clinical characteristics.

CA125 is a large transmembrane glycoprotein synthesized by mesothelial cells that is widely used to monitor ovarian cancer. However, elevated values can also be found in other hydropic conditions such as HF.[1] Several studies have con-

Table 1 – Clinical characteristics of the six case studies.

	Case 1		*Case 2*		*Case 3*		*Case 4*		*Case 5*		*Case 6*	
Sex	Female		Male		Male		Male		Female		Male	
Age, y	73		75		76		53		82		77	
CV risk factors	No CV risk factors		HT, type 2 DM, former smoker		HT, former smoker		DLP		HT, DLP, type 2 DM, TIA in 2008		HT, DLP, type 2 DM, BMI 31, former smoker	
Other	Atrial fibrillation Mitral and aortic mechanical prostheses Gastric adenocarcinoma		COPD OSA		COPD Atrial fibrillation CKD stage G3bA2		Atrial flutter Hypertrophic cardiomyopathy		Atrial fibrillation HF with recent hospitalization		COPD Atrial fibrillation CKD stage G3aA1 Peripheral artery disease	
	Initial visit	*Follow-up (72 h)*	*Initial visit*	*Follow-up (3 weeks)*	*Initial visit*	*Follow-up (3 weeks)*	*Initial visit*	*Follow-up (3 weeks)*	*Initial visit*	*Follow-up (5 months)*	*Initial visit*	*Follow-up (1 month)*
Symptoms	–	–	Progressive peripheral edema and exertional dyspnea. NYHA II	Clinical improvement NYHA class I	Worsening dyspnea NYHA class III Cough and mucus	Clinical improvement NYHA class I	Anasarca NYHA III	Clinical improvement NYHA II	Constitutional syndrome	–	Worsening dyspnea and peripheral edema NYHA IV	Clinical improvement
Physical examination	LA: bilateral rales Peripheral edema: 2/4 Weight: 54 kg (+ 4 in 1 week) JVD: +	LA: normal Peripheral edema: 1/4 Weight: 51.5 kg (−2.3) JVD: –	LA: bilateral rales in bases Peripheral edema: 3/4 Weight: 64.3 kg JVD: +	LA: normal Peripheral edema: 1/4 Weight: 51.7 kg (−13) JVD: –	LA: bilateral rales and rhonchi Peripheral edema: 0/4 Weight: 69 kg JVD: –	LA: normal Peripheral edema: 0/4 Weight: 66 kg JVD: –	LA: bilateral rales Peripheral edema: 4/4 Weight: 112 kg (+ 4 in 2 weeks) JVD: +	LA: normal Peripheral edema: 0/4 Weight: 98 (−14) JVD: –	LA: normal Peripheral edema: 0/4 Weight: 64.1 kg JVD: –	LA: normal Peripheral edema: 0/4 Weight: 57 kg (7) JVD: –	LA: basal hypophonesis Peripheral edema: 3/4 Weight: 120 kg JVD: +	LA: normal Peripheral edema: 0/4 Weight: 110 kg (−10) JVD: –
Echocardiogram	LVEF: 50% TAPSE: 14 mm and dilated RV Severe TR IVC: 21 mm	IVC: 18 mm	LVEF: 20% TAPSE: 15 mm sPAP: 38 mmHg IVC: 25 mm	IVC: 15 mm	LVEF: 55% TAPSE: 18 mm sPAP: 37 mmHg IVC: 20 mm	IVC: 17 mm	LVEF: 61% TAPSE: 13 mm IVC: 22 mm	IVC: 19 mm	LVEF > 57% sPAP: 35 mmHg IVC: 15 mm	IVC: 13 mm	LVEF: 54% TAPSE: 13 mm and dilated RV sPAP: 71 mmHg Severe TR IVC: 28 mm	IVC: 22 mm

Table 1 (*Continued*)

	Case 1		*Case 2*		*Case 3*		*Case 4*		*Case 5*		*Case 6*	
Pulmonary ultrasound	–	–	Bilateral pleural effusion B-lines in 6/8 pulmonary quadrants	Resolution of pleural effusion and reduction of B-lines 2/8 quadrants	Bilateral pleural effusion Diffuse B-lines	Resolution of pleural effusion and B-lines	–	–	–	–	Bilateral pleural effusion No B-lines Ascites IAP: 18 mmHg	Resolution of pleural effusion
Renal venous flow pattern	–	–	Monophasic	Continuous	–	–	–	–	Continuous	Continuous	Monophasic	Continuous
Portal venous flow pattern	–	–	Pulsatile (>50%)	Continuous	Continuous	Continuous	–	–	Continuous	Continuous	–	–
CA 125 (U/mL)	68 (baseline 23)	–	234	29	112 (previous 80)	71	768 (baseline 14) → 1201 (72 h)	33	90	35	439 (previous 350)	75
NT-ProBNP (pg/mL)	1821	1431	25 362	5693	1900	1694	1986 (baseline 970)	1304	1446	1446	5233 (previous 5233)	4000
Creatinine (mg/dL)	–	–	1.1	1.50	1.88	1.68	–	–	0.8	0.8	2.1	1.7
Other findings			MRIc: dilated cardiomyopathy with biventricular dysfunction.		Elevated CRP				Abdominal, pelvic, and thoracic CT-scan: endometrioid carcinoma (stage IV)			
Treatment adjustment	+ Furosemide sc 120 mg during 72 h + Chlorthalidone 25 mg/48 h		+ Furosemide 120 mg sc during 72 h + Chlorthalidone 25 mg/24 h + Dapagliflozin 10 mg/24 h		+ Dapagliflozin 10 mg/24 h + Furosemide 40 mg/12 h + Chlorthalidone 25 mg		+ Furosemide 120 mg s.c during 72 h + Chlorthalidone 25 mg/24 h + Dapagliflozin 10 mg/24 h				+ Furosemide sc 250 mg during 72 h + Chlorthalidone 25 mg/24 h + Hypertonic saline	

BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: computed tomography; CV: cardiovascular; DLP: dyslipidemia; DM: diabetes mellitus; ECG: electrocardiogram; HF: heart failure; HT: hypertension; IVC: inferior vena cava; JVD: jugular vein distention; LA: lung auscultation; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MRIc: cardiac magnetic resonance imaging; NT-proBNP: N-terminal brain natriuretic peptide; NYHA: New York Heart Association; OSA: obstructive sleep apnea; RV: right ventricle; sc, subcutaneous; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TIA: transitory ischemic attack; TR: tricuspid regurgitation.

firmed its prognostic value mainly in acute HF (AHF) with reduced or preserved left ventricular ejection fraction (LVEF).[1] In a sub-analysis of the BIOSTAT-CHF study,[4] CA125 was strongly correlated with 1-year mortality risk and the composite of death and HF readmissions in 2516 patients with HF. Furthermore, it provided additive prognostic value over traditional risk factors such as N-terminal prohormone of brain natriuretic peptide (NT-ProBNP).

Patient 1 illustrates how to utilize the predictive power of CA125. She was a 73-year-old woman with chronic HF of valvular etiology in whom elevated CA125 levels (68 U/mL; previous: 23 U/mL) were detected in a routine follow-up, without meaningful variations in NT-ProBNP values (1821 pg/mL previous: 1518 pg/mL). The patient denied symptoms and had minimal peripheral edema. Echocardiography revealed a dilated inferior vena cava, dilated right ventricle (RV) with systolic dysfunction, and severe tricuspid regurgitation (TR). Based on these findings, despite being asymptomatic, we intensified diuretic therapy. On the follow-up visit, the patient had lost 2.3 kg, and peripheral edema had resolved. Monitoring the trajectory of CA125 in this patient allowed for early detection of HF decompensation and timely treatment that helped prevent hospitalization.

Conversely, CA125 has the potential for both monitoring and guiding HF treatment. The CHANCE-HF trial[2] compared a CA125-guided therapy vs standard of care in 380 patients discharged for AHF. Diuretics were intensified when CA125 increased or persisted elevated and downtitrated when CA125 decreased. The study demonstrated that CA125-guided therapy was superior to standard of care in reducing the risk of 1-year death or AHF readmission. Fig. 1 illustrates how our patients' CA125 levels decreased after the intensification of diuretic therapy in parallel with the improvement of signs/symptoms of congestion.

A good example of the use of CA125 to monitor diuretic therapy is patient 2, a 75-year-old man with a history of chronic obstructive pulmonary disease (COPD) who was admitted to hospital with AHF. Both NT-ProBNP (25 362 pg/mL) and CA125 were elevated (234 U/mL). B-lines and bilateral pleural effusion were present on lung ultrasound. Intrarenal venous flow pattern (VFP) was monophasic, and portal VFP was pulsatile (>50%). During admission, the patient received high doses of intravenous furosemide (200 mg/day), 15 mg/day of tolvaptan, and 25 mg/day of chlortalidone. Fourteen days after discharge, the patient had lost 13 kg, congestion had disappeared, and ultrasound parameters of venous congestion (intrarenal and portal VFP) normalized. In accordance with the resolution of the signs and symptoms of congestion there was a substantial decrease in congestion biomarkers (CA125, 29 U/mL; NT-ProBNP, 5693 pg/mL), reaffirming our decision to downtitrate diuretic therapy.

A novel application of CA125 is to classify HF patients based on their congestion phenotype in intravascular or tissue congestion.[5] This distinction is important because they have different pathophysiology and thus, require different treatment. CA125 helps identify HF patients with predominant tissue congestion that may benefit from aggressive diuretic therapy targeting interstitial fluid such as tolvaptan, sodium-glucose cotransporter-2 inhibitors (SGLT2i), or hypertonic saline. On the other hand, NT-ProBNP, jugular vein distention (JVD), and venous excess ultrasound score (VExUS) may help identify patients with predominant intravascular congestion who may not have an increase in total blood volume, but rather a dysregulation of blood distribution and, therefore, benefit from vasodilators and a conservative diuretic strategy.

Patient 3 exemplifies the tissue congestion phenotype. He was a 76-year-old man with right-side HF as a consequence of pulmonary hypertension and severe COPD who came to our clinic with progressive dyspnea due to a COPD exacerbation. The patient had no signs of intravascular congestion (NT-ProBNP was stable, no JVD and the VExUS was 0). However, CA125 was elevated (112 U/mL; previous: 80 U/mL) and he presented bilateral pleural effusion and B-lines on pulmonary ultrasound (signs of pulmonary tissue congestion). Identifying the patient's phenotype helped tailor the diuretic therapy he received, by intensifying oral diuretic therapy (furosemide 120 mg/day plus chlorthalidone 25/48 h) and adding dapagliflozin 10 mg/day. Three weeks later, CA125 levels dropped to 71 U/mL, and pleural effusion and B-lines disappeared.

When interpreting CA125 levels, it is important to consider 2 aspects. Firstly, CA125 has a long half-life (5.1–12 days)[1] and may remain elevated or even increase the first days of decompensation. This is the case of patient 4, a 53-year-old man with hypertrophic cardiomyopathy and RV dysfunction who was referred to our outpatient clinic due to worsening symptoms and clinical evidence of volume overload. Blood analysis showed elevated CA125 (768 U/mL). As the patient did not require hospital admission, ambulatory diuretic therapy intensification with 120 mg/day of subcutaneous furosemide + 25 mg/day of chlorthalidone was initiated. Three days later, the patients had lost 12 kg, and peripheral edema had resolved. Surprisingly, CA125 levels continued to increase (1201 U/mL). Knowing the kinetics of CA125 and given the favorable course of other markers of decongestion, we decided not to modify treatment. The patient evolved favorably and CA125 concentrations eventually dropped. Therefore, serial measurements during the first days of admission are not recommended. A reasonable approach is to measure CA125 on admission and 7–10 days after the initial measurement. Secondly, CA125 should be evaluated with the patient's clinical context and other parameters of congestion. A good example is patient 5, an 82-year-old woman with a recent episode of AHF who was evaluated in our clinic 5 months after discharge. She had unintentionally lost 7 kg, and CA125 had risen (35–90 U/mL) despite absent signs of congestion (VExUS 0, absence of serosal effusion and NT-ProBNP similar to baseline). In light of this incongruency, we requested a computerized tomography scan and discovered a stage IV endometrioid carcinoma. A valuable lesson was learnt: increased CA125 levels in the absence of objective evidence of congestion (ideally with ultrasound techniques) must alert physicians to the possibility of malignancies.

Lastly, CA125 might outperform NT-ProBNP in patients with predominant RV dysfunction or systemic congestion, especially if they present severe TR.[3,6] Moreover, CA125 levels are not influenced by age, LVEF, or eGFR (1), making it attractive for monitoring patients with concomitant heart and kidney dysfunction. By contrast, NT-ProBNP reflects predo-

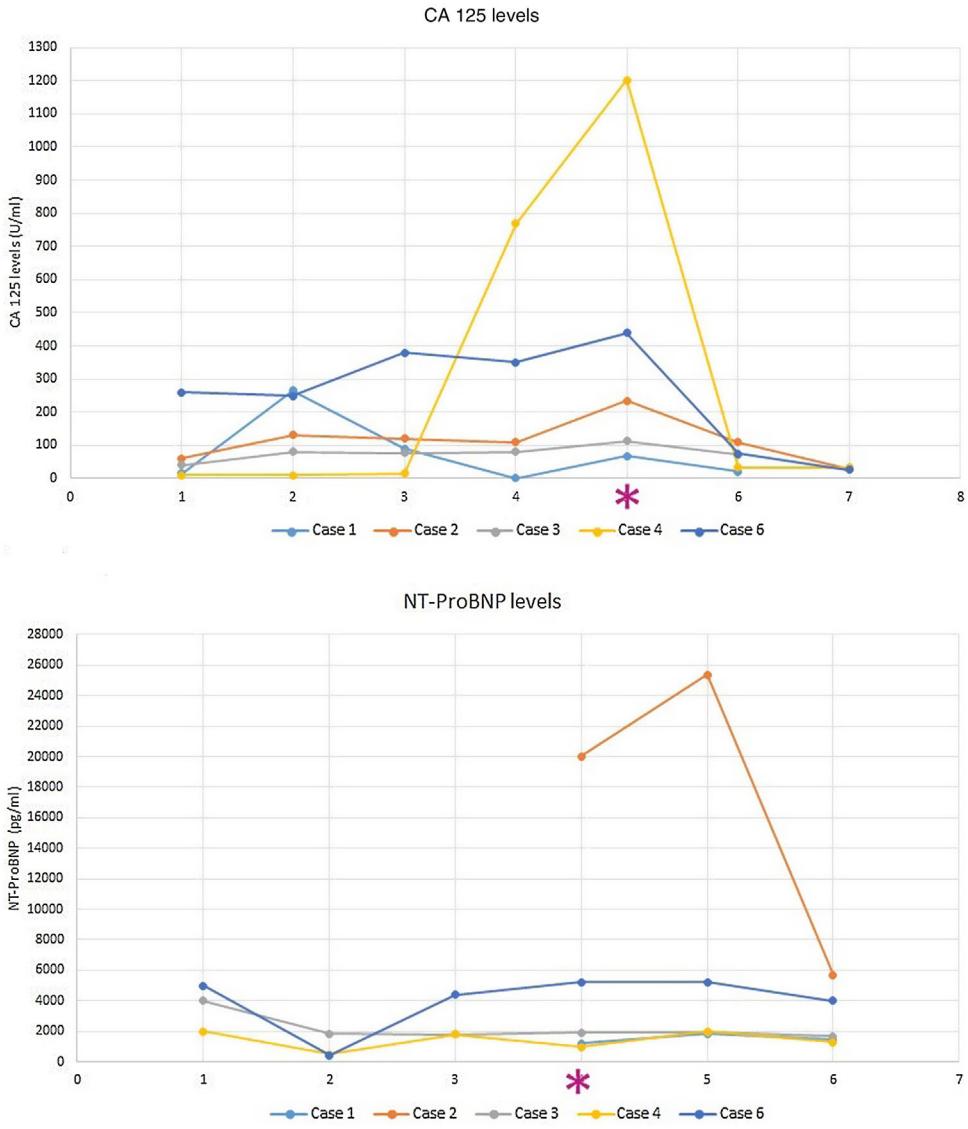

Fig. 1 – CA125 and NT-ProBNP values during heart failure decompensation of the cases 1, 2, 3, 4, and 6. The asterisks (*) mark initiation of diuretics.

minant left-sided HF. *Patient 6* represents a clinical scenario in which CA125 has demonstrated to be superior to NT-ProBNP: preserved LVEF, right-sided HF, chronic kidney disease and/or TR. He was a 77-year-old man with a history of COPD, atrial fibrillation, and chronic kidney disease who was admitted with progressive dyspnea and peripheral edemas along with JVD. The patient also presented ascites with elevated intra-abdominal pressure (18 mmHg) and bilateral pleural effusion. Blood analysis revealed higher CA125 levels (439 U/mL) than previous ambulatory determination (350 U/mL), but NT-ProBNP was similar (5233 pg/mL at admission; 4938 pg/mL in prior visit). Echocardiography showed a dilated RV with systolic dysfunction and severe TR. An intensive diuretic regimen with 250 mg of furosemide (continuous intravenous perfusion), hypertonic saline, and 25 mg/day of chlorthalidone was initiated. After successful decongestion, CA125 dropped to 75 U/mL (at 3-month follow-up). However, NT-ProBNP remained elevated, failing to reflect clinical improvement. The same occurs in patients 4 and 5. Note how NT-ProBNP remained similar to baseline (failing to predict HF-decompensation), while CA125 peaked (Fig. 1). In summary, both biomarkers are complementary and should be used in combination with clinical signs/symptoms and emergent ultrasound techniques to better characterize congestion and help us tailor diuretic therapy in our daily clinical practice.

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Authors' contribution

L. Fuertes Kenneally and S. Villar are equally first authors. All authors have participated in the work and have reviewed and agree with the contents of the article.

Conflicts of interest

The authors declare no conflicts of interest.

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One-year outcomes in patients with COVID-19 and clinical heart failure or elevated NT-proBNP

Evolución clínica a un año en pacientes con COVID-19 asociada a insuficiencia cardiaca descompensada o elevación del NT-proBNP

To the Editor,

The unique pathophysiology of COVID-19 and the complex interactions between the heart, the lungs and the inflammatory response have led some experts to propose the concept of biochemical heart failure (HF).[1] To further assess this concept, we designed a dedicated substudy of the large CARD-COVID registry in order to investigate long-term clinical outcomes and quality of life among COVID-19 patients with either clinical HF or isolated elevated NT-proBNP during the index admission.

Table 1 – Baseline characteristics, drug therapy, vitals, and laboratory data according to clinical diagnosis of acute heart failure or isolated NT-proBNP elevation.

Variable	All patients (*N* = 222)	NT-proBNP without clinical HF (*n* = 145)	Clinical diagnosis of AHF (*n* = 77)	*P*
Baseline characteristics and coexisting disorder				
Age (years)	75.2 ± 13.6	73.4 ± 13.9	78.6 ± 12.6	.007
Sex (male)	138 (62.2)	96 (66.2)	42 (54.6)	.088
Hypertension	152 (68.5)	90 (62.1)	62 (80.5)	.005
Diabetes	61 (27.5)	34 (23.5)	27 (35.1)	.049
Dyslipidemia	124 (55.9)	77 (53.1)	47 (61.0)	.279
Smoking habit	28 (12.6)	20 (13.8)	8 (10.4)	.467
Obesity	36 (16.2)	19 (13.1)	17 (22.1)	.084
Peripheral artery disease	36 (16.2)	24 (16.6)	12 (15.6)	.882
Ischemic stroke	36 (16.2)	19 (13.1)	17 (22.1)	.069
Coronary artery disease	33 (14.9)	24 (16.6)	9 (11.7)	.349
Chronic heart failure	40 (18.0)	23 (15.9)	17 (22.1)	.251