Research Square

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sST2 and CA125 identify distinct biological phenotypes and predict one-year mortality in very old patients hospitalised for decompensated HFpEF

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Research Article

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Abstract

Background:

Risk stratification remains challenging in very old patients hospitalised for decompensated heart failure with preserved ejection fraction (HFpEF). Soluble suppression of tumorigenicity 2 (sST2) and carbohydrate antigen 125 (CA125) reflect complementary pathophysiological domains related to fibro-inflammatory stress and systemic congestion. We evaluated whether their combined assessment identifies distinct prognostic phenotypes.

Methods

Prospective observational cohort of 175 consecutive patients aged ≥ 80 years admitted for decompensated HFpEF. Four phenotypes were defined by sST2 (cut-off 35 ng/mL) and CA125 (cut-off 35 U/mL): both low, sST2 high only, CA125 high only, and both high. Primary endpoint was one-year all-cause mortality.

Results

Among 164 patients with complete biomarker data, one-year mortality ranged from 18% in the dual-low phenotype to 43% in the dual-high phenotype, with significant differences across phenotypes (log-rank p = 0.013). After multivariable adjustment, the both-high phenotype was associated with higher mortality compared with the both-low phenotype (HR 2.43, 95% CI 1.01–5.85; p = 0.048). Frailty and lower systolic blood pressure were also independent predictors, whereas BNP was not. When modelled continuously, sST2 was independently associated with mortality (HR 1.51 per SD, 95% CI 1.12–2.05; p = 0.007), with no evidence of non-linearity. Neither rehospitalisation nor the composite endpoint differed significantly across phenotypes.

Conclusions

Combined assessment of sST2 and CA125 identified distinct prognostic phenotypes in very old patients hospitalised for decompensated HFpEF. Concurrent elevation of both biomarkers was associated with higher one-year mortality, supporting further evaluation of multidimensional biomarker phenotyping in this understudied population.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is the dominant form of heart failure (HF) in older adults, accounting for more than half of all heart failure hospitalisations in patients aged over 75 years[1,2]. In very old patients[3], HFpEF adopts a particularly complex clinical expression, shaped by

multimorbidity, frailty, functional impairment, polypharmacy, and ageing-related biological mechanisms that often attenuate the discriminatory value of conventional prognostic tools[4,5].

HFpEF in the elderly is not merely a haemodynamic disorder but a systemic syndrome in which low-grade chronic inflammation, myocardial fibrosis, endothelial dysfunction, renal impairment, venous congestion, and biological vulnerability coexist and interact[6,7]. In this context, natriuretic peptides may lose discriminatory accuracy, motivating complementary biomarker strategies that integrate different dimensions of the disease[8,9].

Soluble suppression of tumorigenicity 2 (sST2) is the soluble decoy form of the interleukin-33 (IL-33) receptor, released in response to myocardial stress, inflammation, and profibrotic stimuli, promoting fibrosis and adverse structural remodelling[10,11]. Its levels are less influenced by age, sex, body mass index, and renal function than natriuretic peptides[12]. Elevated sST2 has been independently associated with disease severity and mortality, with prognostic value additive to NT-proBNP[11].

Carbohydrate antigen 125 (CA125) is a glycoprotein produced by mesothelial cells of the pleura, peritoneum, and pericardium[13]. In decompensated heart failure (DHF), venous congestion and elevated right-sided filling pressures drive its release, making it a sensitive surrogate of systemic fluid overload and serosal inflammation, complementary to neurohormonal markers[14,15].

The combined assessment of sST2 and CA125 may provide a broader representation of the pathophysiological burden of HFpEF: while sST2 predominantly reflects fibrotic, inflammatory, and structural remodelling pathways, CA125 reflects a distinct but mechanistically related dimension of systemic fluid overload[10,13]. Their concurrent elevation could therefore identify patients in whom fibro-inflammatory stress and congestion coexist, a potentially relevant phenotype in very old patients, in whom frailty and multimorbidity further influence prognosis[4,5].

Although each biomarker has individually shown prognostic value in unselected decompensated HF[11,14,15] and their prognostic roles may be complementary[16], whether their combined assessment refines risk stratification in very old patients hospitalised for decompensated HFpEF remains an unaddressed gap. We aimed to characterize biomarker-defined phenotypes based on sST2 and CA125 in a prospective cohort of patients aged 80 years or above hospitalised for decompensated HFpEF, to describe their clinical, biological, and echocardiographic correlates, and to evaluate their independent association with one-year all-cause mortality.

Material and Methods

Study Design and Population

This is a prospective observational cohort study including 175 consecutive patients aged 80 years or above, admitted for decompensated HFpEF to the Internal Medicine Department of Hospital

Universitario Ramón y Cajal, a tertiary referral centre in Madrid, Spain. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee (approval No. 332/21). All patients provided written informed consent. Decompensated HFpEF was defined as the rapid onset or worsening of symptoms and signs of heart failure, with a left ventricular ejection fraction ≥ 50% on echocardiography and objective evidence of raised left ventricular filling pressures or diastolic dysfunction, supported by natriuretic peptide elevation and/or echocardiographic criteria, in accordance with current ESC guidelines[1].

Patients with acute coronary syndrome as the primary cause of decompensation, severe valvular heart disease with indication for intervention, end-stage chronic kidney disease on renal replacement therapy, active malignancy, or conditions precluding adequate clinical follow-up were excluded.

Data collection

Demographic data, cardiovascular and non-cardiovascular medical history, vital signs, functional status, and pharmacological treatments were recorded at admission. Frailty was assessed using the FRAIL scale[17], and comorbidity burden was quantified using the Charlson Comorbidity Index (CCI)[18]. Clinical signs of congestion, including peripheral oedema, pulmonary crackles, and jugular venous distension, were systematically evaluated and quantified using the EVEREST congestion score[19]. Point-of-care ultrasound was used to assess the VExUS (Venous Excess Ultrasound) grading system[20], inferior vena cava diameter and collapsibility, and the presence of pleural effusion. Echocardiographic parameters were obtained after clinical stabilization during index hospitalization. Clinical data, routine laboratory tests, and outcomes were also recorded at scheduled post-discharge follow-up visits at 30, 90 days and one year.

Biomarker assessment and phenotype characterization

Venous blood for sST2 was sampled within 24 hours prior to hospital discharge, and CA125 was measured at admission by chemiluminescence (Alinity, Abbott Laboratories, Abbott Park, IL, USA), in keeping with its slower kinetics and its established role as a marker of sustained congestion rather than of acute change.

Laboratory parameters, including BNP, C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (eGFR), haemoglobin, albumin, and sodium, were measured from venous blood samples obtained within 24 hours of admission as part of standard clinical care. Additional blood samples were collected, processed according to standard operating procedures, and stored at the BioBank Hospital Ramón y Cajal-IRYCIS (National Registry of Biobanks B.0000678), integrated in the Biobanks and Biomodels Platform of the ISCIII (PT20/00045). Plasma aliquots were used for the determination of circulating soluble suppression of tumorigenicity 2 (sST2), using commercially available enzyme-linked

immunosorbent assay (ELISA) kits (Elabscience Biotechnology Co., Ltd., Wuhan, Hubei, China, Cat. No. E-EL-H6082).

Patients were classified into four mutually exclusive phenotypes by combining each biomarker dichotomised as high or low: Phenotype 1 (both low), Phenotype 2 (sST2 high only), Phenotype 3 (CA125 high only) and Phenotype 4 (both high). CA125 was dichotomised at the established clinical threshold of 35 U/mL. For sST2, a threshold of 35 ng/mL was used based on the prognostic cut-off established for the Presage assay[10,11]. Given potential differences across analytical platforms, sST2 was alternatively dichotomised at the cohort median (17.5 ng/mL) in a sensitivity analysis. Patients with a missing CA125 or predischarge sST2 value were excluded from the phenotype analyses.

Endpoints

The primary endpoint was one-year all-cause mortality. Secondary endpoints were one-year all-cause rehospitalisation and the composite of all-cause mortality or rehospitalisation at one year.

Statistical Analysis

Continuous variables were presented as median with interquartile range (IQR). Categorical variables were expressed as absolute frequencies and percentages. Baseline characteristics were compared across the four biomarker-defined phenotypes using the Kruskal-Wallis test or ANOVA for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate. The relationship between sST2 and CA125 was assessed with the Spearman rank correlation coefficient, given the skewed distribution of both biomarkers. Inflammatory markers (C-reactive protein and the neutrophil-to-lymphocyte ratio) were additionally compared by sST2 status (high versus low) using the Mann-Whitney U test.

Survival analyses were performed using the Kaplan-Meier method, with differences between groups assessed by the log-rank test. The overall log-rank test was used as the primary comparison across the four phenotypes. A log-rank test for trend was additionally performed as a supportive analysis.

Multivariable Cox proportional-hazards regression was used to evaluate the association between biomarker-defined phenotypes and all endpoints, with Phenotype 1 as the reference. Covariates were selected a priori on the basis of clinical relevance and established prognostic value in heart failure, and their number was deliberately limited given the number of events to avoid overfitting. The final model included the variables: age, sex, systolic blood pressure, baseline NYHA class, frailty (FRAIL score), BNP (standardized natural logarithm), and renal function (serum creatinine). The proportional-hazards assumption was verified using Schoenfeld residuals, globally and for each covariate, and was satisfied throughout. sST2 was additionally analysed as a continuous variable (per SD of its natural logarithm) and modelled as a restricted cubic spline.

The multiplicative sST2×CA125 interaction was tested as an exploratory analysis. As a sensitivity analysis, phenotypes were redefined using the cohort median sST2 threshold. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI).

A two-sided p value < 0.05 was considered statistically significant. All analyses were performed using Stata version 19 (StataCorp, College Station, TX, USA).

Results

Baseline profiles across biomarker-defined phenotypes

Of the patients enrolled, 164 had a measurable predischarge sST2 value and constituted the complete-case population for the phenotype analyses, distributed as Phenotype 1 (both low, n = 44), Phenotype 2 (sST2 high only, n = 14), Phenotype 3 (CA125 high only, n = 60) and Phenotype 4 (both high, n = 46). Baseline characteristics across phenotypes are presented in Table 1. As expected, the two defining biomarkers differed markedly by design (both p < 0.001), and BNP increased progressively from Phenotype 1 to Phenotype 4 (median 350 to 677 pg/mL; p < 0.001). The principal clinical difference was a progressive decline in body mass index towards Phenotype 4 (29.2 to 23.6 kg/m²; p < 0.001), and a higher Charlson comorbidity index in Phenotype 4 (median 4 [3–6]; p = 0.043). Atrial fibrillation (82.6%) and previous heart failure (84.8%) were also most frequent in Phenotype 4, although these differences did not reach statistical significance (p = 0.096 and p = 0.076, respectively). sST2 and CA125 were only weakly and non-significantly correlated (Spearman ρ = 0.15, p = 0.056).

Table 1
Clinical characteristics of the study population across the four sST2/CA125 phenotypes.

	Total (n = 164)	**Phenotype 1 sST2 ≤ 35, CA125 ≤ 35 (n = 44)**	**Phenotype 2 sST2 > 35, CA125 ≤ 35 (n = 14)**	**Phenotype 3 sST2 ≤ 35, CA125 > 35 (n = 60)**	**Phenotype 4 sST2 > 35, CA125 > 35 (n = 46)**	**p-value**
Demographics						
Age, years	88.0 [86.0–91.5]	88.5 [86.0–90.0]	89.5 [86.0–93.0]	88.0 [86.0–91.5]	89.5 [86.0–92.0]	0.687
Women	123 (75.0)	36 (81.8)	12 (85.7)	41 (68.3)	34 (73.9)	0.334
Medical history						
Hypertension	153 (93.3)	41 (93.2)	14 (100)	54 (90.0)	44 (95.7)	0.483
Diabetes mellitus	66 (40.2)	18 (40.9)	4 (28.6)	25 (41.7)	19 (41.3)	0.832
Atrial fibrillation	116 (70.7)	30 (68.2)	7 (50.0)	41 (68.3)	38 (82.6)	0.096
Ischaemic heart disease	20 (12.2)	4 (9.1)	1 (7.1)	8 (13.3)	7 (15.2)	0.754
COPD	56 (34.1)	16 (36.4)	3 (21.4)	22 (36.7)	15 (32.6)	0.724
Chronic kidney disease (moderate–severe)	58 (35.4)	12 (27.3)	5 (35.7)	20 (33.3)	21 (45.7)	0.321
Prior NYHA class III/IV	39 (23.8)	9 (20.5)	4 (28.6)	12 (20.0)	14 (30.4)	0.564

Data are given as n (%) or median [P25–P75]. Phenotypes were defined by discharge sST2 (cut-off 35 ng/mL) and admission CA125 (cut-off 35 U/mL): P1 both low, P2 sST2-high only, P3 CA125-high only, P4 both high. p-values from the Kruskal–Wallis test (continuous variables) and the chi-squared or Fisher's exact test (categorical variables); follow-up events were compared across phenotypes with the log-rank test; values < 0.05 in bold. Albumin available in 157 patients and furosemide dose in 115. VExUS measured at discharge. Abbreviations: COPD chronic obstructive pulmonary disease, NYHA New York Heart Association, CCI Charlson Comorbidity Index, LVEF left ventricular ejection fraction, VExUS venous excess ultrasound, SBP systolic blood pressure, BMI body mass index, FRAIL fatigue-resistance-ambulation-illness-loss of weight, BNP B-type natriuretic peptide, CA125 carbohydrate antigen 125, sST2 soluble suppression of tumorigenicity 2, CRP C-reactive protein, eGFR estimated glomerular filtration rate, MDRD-4 Modification of Diet in Renal Disease (4-variable), ACE-I angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, MRA mineralocorticoid receptor antagonist, SGLT2 sodium-glucose cotransporter 2.

	Total (n = 164)	Phenotype 1 sST2 ≤ 35, CA125 ≤ 35 (n = 44)	Phenotype 2 sST2 > 35, CA125 ≤ 35 (n = 14)	Phenotype 3 sST2 ≤ 35, CA125 > 35 (n = 60)	Phenotype 4 sST2 > 35, CA125 > 35 (n = 46)	p-value
Demographics						
Prior heart failure	116 (70.7)	28 (63.6)	8 (57.1)	41 (68.3)	39 (84.8)	0.076
Comorbidity burden						
Charlson Comorbidity Index (CCI), median [P25–P75]	3 [2–5]	3 [2–4]	2.5 [1–4]	3 [2–5]	4 [3–6]	0.043
Echocardiographic parameters						
LVEF, %	63.1 [58.9–67.8]	63.8 [60.0–67.7]	63.2 [58.5–70.4]	63.1 [58.7–67.1]	62.4 [55.6–68.9]	0.733
VExUS score ≥ 1 (discharge)	18 (11.0)	3 (6.8)	2 (14.3)	7 (11.7)	6 (13.0)	0.761
Pleural effusion	49 (29.9)	9 (20.5)	6 (42.9)	19 (31.7)	15 (32.6)	0.355
Symptoms and signs at discharge						
Dyspnoea	14 (8.5)	3 (6.8)	0 (0)	10 (16.7)	1 (2.2)	0.030
Jugular venous distension	15 (9.1)	5 (11.4)	0 (0)	6 (10.0)	4 (8.7)	0.629
Crackles	69 (42.1)	16 (36.4)	3 (21.4)	28 (46.7)	22 (47.8)	0.243
Peripheral edema	34 (20.7)	8 (18.2)	2 (14.3)	14 (23.3)	10 (21.7)	0.885

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Demographics						
EVEREST score, median [P25–P75]	1 [0–2]	1 [0–2]	1 [0–1]	1 [1–2]	1 [1–2]	0.073
Vital and physical signs						
SBP, mmHg	137.5 [119.5–153.0]	140.0 [118.5–155.5]	140.0 [122.0–150.0]	140.5 [126.0–161.5]	130.0 [115.0–147.0]	0.207
Heart rate, bpm	82.5 [70.0–97.5]	83.0 [74.0–96.0]	83.5 [69.0–93.0]	80.0 [64.5–104.5]	85.0 [70.0–96.0]	0.934
BMI, kg/m²	26.1 [22.6–30.8]	29.2 [24.9–33.4]	27.8 [25.0–33.6]	25.2 [22.4–29.0]	23.6 [22.1–26.7]	< 0.001
Frailty						
FRAIL score (0–5), median [P25–P75]	3 [2–4]	3 [1.5–4]	4 [2–4]	3 [2–4]	4 [2–4]	0.546
Laboratory parameters						
BNP, pg/mL	524 [340–914]	350 [184–545]	426 [379–722]	558 [427–1047]	677 [477–1102]	< 0.001
CA125, U/mL	49.5 [23.4–122.0]	17.5 [12.9–25.1]	18.5 [12.5–30.0]	79.1 [48.3–162.5]	98.2 [55.4–146.9]	< 0.001

Data are given as n (%) or median [P25–P75]. Phenotypes were defined by discharge sST2 (cut-off 35 ng/mL) and admission CA125 (cut-off 35 U/mL): P1 both low, P2 sST2-high only, P3 CA125-high only, P4 both high. p-values from the Kruskal–Wallis test (continuous variables) and the chi-squared or Fisher's exact test (categorical variables); follow-up events were compared across phenotypes with the log-rank test; values < 0.05 in bold. Albumin available in 157 patients and furosemide dose in 115. VExUS measured at discharge. Abbreviations: COPD chronic obstructive pulmonary disease, NYHA New York Heart Association, CCI Charlson Comorbidity Index, LVEF left ventricular ejection fraction, VExUS venous excess ultrasound, SBP systolic blood pressure, BMI body mass index, FRAIL fatigue-resistance-ambulation-illness-loss of weight, BNP B-type natriuretic peptide, CA125 carbohydrate antigen 125, sST2 soluble suppression of tumorigenicity 2, CRP C-reactive protein, eGFR estimated glomerular filtration rate, MDRD-4 Modification of Diet in Renal Disease (4-variable), ACE-I angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, MRA mineralocorticoid receptor antagonist, SGLT2 sodium-glucose cotransporter 2.

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Demographics						
sST2, ng/mL	17.5 [9.9–52.1]	13.1 [6.5–17.2]	53.3 [45.0–81.7]	10.7 [7.7–16.6]	71.9 [50.7–102.0]	< 0.001
CRP, mg/L	15.0 [6.0–44.2]	21.8 [4.0–75.2]	30.3 [6.5–120.1]	11.7 [6.4–23.2]	20.1 [6.3–43.3]	0.288
Neutrophil-to-lymphocyte ratio	4.7 [3.0–7.9]	4.0 [2.6–8.0]	5.2 [4.3–11.7]	4.6 [3.2–7.7]	4.9 [3.0–8.3]	0.429
Haemoglobin, g/dL	11.6 [10.3–12.8]	11.6 [10.3–12.9]	12.1 [10.8–12.5]	12.0 [10.3–13.3]	11.4 [10.3–12.6]	0.588
Creatinine, mg/dL	1.23 [0.88–1.67]	1.06 [0.86–1.44]	1.20 [0.88–1.93]	1.25 [0.92–1.65]	1.39 [0.94–1.87]	0.200
eGFR (MDRD-4), mL/min/1.73m²	47.9 [29.8–61.8]	49.1 [38.1–67.4]	47.7 [24.3–59.0]	49.3 [31.0–61.1]	40.0 [27.7–55.9]	0.184
Serum sodium, mmol/L	140.0 [137.0–142.0]	140.0 [138.5–143.0]	139.5 [137.0–141.0]	140.5 [137.0–142.0]	138.0 [136.0–142.0]	0.114
Serum chloride, mmol/L	102.0 [97.5–104.0]	101.0 [96.5–104.5]	103.0 [101.0–104.0]	102.0 [98.0–104.0]	101.0 [98.0–104.0]	0.820

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Demographics						
Albumin, g/dL	3.13 [2.89–3.39]	3.27 [2.95–3.49]	2.90 [2.82–3.31]	3.17 [2.91–3.37]	3.00 [2.85–3.31]	0.139
Treatment at discharge						
SGLT2 inhibitors	146 (89.0)	40 (90.9)	13 (92.9)	55 (91.7)	38 (82.6)	0.434
ARB / ACE-I	86 (52.4)	29 (65.9)	8 (57.1)	29 (48.3)	20 (43.5)	0.157
Beta-blockers	98 (59.8)	28 (63.6)	6 (42.9)	38 (63.3)	26 (56.5)	0.483
Aldosterone antagonists (MRA)	20 (12.2)	4 (9.1)	0 (0)	8 (13.3)	8 (17.4)	0.311
Oral furosemide dose, mg/day, median [P25–P75]	60 [40–80]	60 [40–80]	40 [40–80]	70 [40–80]	60 [40–100]	0.778
Thiazides	8 (4.9)	2 (4.5)	2 (14.3)	3 (5.0)	1 (2.2)	0.333
Follow-up events (1 year)						
All-cause mortality	48 (29.3)	8 (18.2)	4 (28.6)	16 (26.7)	20 (43.5)	0.043
All-cause rehospitalisation	83 (50.6)	20 (45.5)	8 (57.1)	31 (51.7)	24 (52.2)	0.584
Death or rehospitalisation	99 (60.4)	24 (54.5)	9 (64.3)	35 (58.3)	31 (67.4)	0.288

Data are given as n (%) or median [P25–P75]. Phenotypes were defined by discharge sST2 (cut-off 35 ng/mL) and admission CA125 (cut-off 35 U/mL): P1 both low, P2 sST2-high only, P3 CA125-high only, P4 both high. p-values from the Kruskal–Wallis test (continuous variables) and the chi-squared or Fisher's exact test (categorical variables); follow-up events were compared across phenotypes with the log-rank test; values < 0.05 in bold. Albumin available in 157 patients and furosemide dose in 115. VExUS measured at discharge. Abbreviations: COPD chronic obstructive pulmonary disease, NYHA New York Heart Association, CCI Charlson Comorbidity Index, LVEF left ventricular ejection fraction, VExUS venous excess ultrasound, SBP systolic blood pressure, BMI body mass index, FRAIL fatigue-resistance-ambulation-illness-loss of weight, BNP B-type natriuretic peptide, CA125 carbohydrate antigen 125, sST2 soluble suppression of tumorigenicity 2, CRP C-reactive protein, eGFR estimated glomerular filtration rate, MDRD-4 Modification of Diet in Renal Disease (4-variable), ACE-I angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, MRA mineralocorticoid receptor antagonist, SGLT2 sodium-glucose cotransporter 2.

Clinical outcomes

During one-year follow-up, 48 of the 164 patients (29%) died. All-cause mortality was lowest in Phenotype 1 (18%) and highest in Phenotype 4 (43%), with intermediate values in Phenotypes 2 and 3 (29% and 27%, respectively). Kaplan–Meier analysis showed significant differences in mortality across the four phenotypic groups (log-rank test, p = 0.043). A supportive log-rank test for trend was also significant (p = 0.013) (Fig. 1). In multivariable analysis, Phenotype 4 was independently associated with higher one-year all-cause mortality compared with Phenotype 1 (HR 2.43, 95% CI 1.01–5.85; p = 0.048), whereas the single-biomarker-high phenotypes were not (Phenotype 2 HR 1.62, 95% CI 0.47–5.54; Phenotype 3 HR 1.49, 95% CI 0.61–3.64). Frailty (HR 1.92 per point, 95% CI 1.46–2.53; p < 0.001) and lower systolic blood pressure (HR 0.98 per mmHg, 95% CI 0.97–0.99; p = 0.003) were also independently associated with mortality, whereas BNP was not (p = 0.552). Full model estimates are shown in Table 2. The proportional-hazards assumption was satisfied globally (global Schoenfeld test, p = 0.820) and for every covariate.

Table 2
Multivariable Cox regression analysis for all-cause mortality

Variable	Hazard ratio (HR)	95% CI	p value
Clinical and demographic covariates			
Age at admission (per year)	1.03	0.95–1.12	0.440
Female sex	0.91	0.44–1.85	0.787
Systolic BP (per mmHg)	0.98	0.97–0.99	0.003
NYHA functional class	0.73	0.39–1.36	0.325
Frailty score	1.92	1.46–2.53	< 0.001
BNP (standardized natural logarithm)	0.91	0.66–1.24	0.552
Creatinine at admission (per mg/dL)	1.08	0.71–1.65	0.711
Biomarker-defined phenotypes (ref: P1)			
P2—High sST2 / Low CA125	1.62	0.47–5.54	0.444
P3—Low sST2 / High CA125	1.49	0.61–3.64	0.387
P4—High sST2 / High CA125	2.43	1.01–5.85	0.048

Adjusted for age, sex, systolic blood pressure, NYHA functional class, frailty score, BNP, and creatinine at admission. Biomarker phenotypes: P1 (Low sST2/Low CA125, reference); P2 (High sST2/Low CA125); P3 (Low sST2/High CA125); P4 (High sST2/High CA125). BP blood pressure, CI confidence interval, HR hazard ratio, NYHA New York Heart Association

When both biomarkers were modelled as standardised log-transformed continuous variables, sST2 was independently associated with one-year mortality (HR 1.51 per SD, 95% CI 1.12–2.05; p = 0.007), showing

a graded association with no significant departure from linearity on restricted cubic spline analysis (overall p = 0.029; test for non-linearity p = 0.466; Fig. 2), whereas CA125 did not reach statistical significance as a continuous predictor (HR 1.17 per SD, 95% CI 0.85–1.62; p = 0.335).

In exploratory interaction analyses, both biomarkers were modelled as standardised continuous variables. A joint test of the sST2 main effect, the CA125 main effect and their interaction was statistically significant (χ^2=8.73; p = 0.033), whereas the multiplicative interaction term itself was not significant (p = 0.457). Consistent results were obtained when continuous sST2 was tested against dichotomised CA125 (high vs. low, cut-off 35 U/mL), with the interaction term was again non-significant (p = 0.995). When both biomarkers were instead modelled as dichotomous variables, neither the interaction term (HR 1.01, p = 0.989) nor the joint test (p = 0.211) reached statistical significance.

For the secondary endpoints, neither one-year all-cause rehospitalisation nor the composite of death or rehospitalisation differed significantly across phenotypes (log-rank test, p = 0.584 and p = 0.288, respectively) (Supplementary Figures S1 and S2). In multivariable analysis, Phenotype 4 was not independently associated with rehospitalisation (HR 1.39, 95% CI 0.72–2.68; p = 0.333) or the composite endpoint (HR 1.37, 95% CI 0.76–2.48; p = 0.292) compared with Phenotype 1.

Sensitivity analysis

When phenotypes were redefined using the cohort median sST2 threshold (17.5 ng/mL) instead of 35 ng/mL, the independent association of Phenotype 4 with all-cause mortality was preserved (HR 2.37, 95% CI 1.00–5.63; log-rank for trend p = 0.018).

Discussion

In this prospective cohort of patients aged 80 years or above hospitalized for decompensated HFpEF, an understudied population, a biomarker phenotype combining sST2 and CA125 stratified one-year all-cause mortality. The dual-high phenotype (Phenotype 4) carried more than twice the adjusted risk of death compared with the both-low phenotype, while isolated elevation of either biomarker was not independently associated with mortality. Modelled continuously, sST2 showed a consistent, graded association with mortality, and the signal was specific to death rather than rehospitalisation.

Soluble ST2 and the fibro-inflammatory axis in the very old

In our cohort, sST2 showed a graded, approximately linear association with one-year mortality, and, notably, remained an independent predictor after adjustment, whereas BNP did not. This suggests that sST2 may provide prognostic information independently of the natriuretic peptide in this setting.

This pattern is consistent with the biological properties of sST2, which reflects the fibrotic, inflammatory and structural-remodelling axis of heart failure[10] and, unlike natriuretic peptides, is relatively independent of age, sex, body mass index and renal function[12], a property of particular value in the multimorbid

octogenarian, in whom natriuretic peptides are harder to interpret. Elevated sST2 has been associated with adverse outcomes beyond NT-proBNP in broader heart failure populations[11], and our findings extend this observation to the very old. The absence of significant departure from linearity on restricted cubic spline analysis (Fig. 2) further indicates that the prognostic signal is not an artefact of the chosen cut-off, supporting the use of a pragmatic dichotomy for phenotypic classification.

CA125 and the complementary dimension of congestion

CA125 is a sensitive marker of systemic venous congestion and serosal inflammation rather than myocardial stretch[13,14]. In our cohort, however, CA125 was not independently associated with mortality, either as a continuous variable (HR 1.17 per SD, p = 0.335) or as an isolated categorical elevation (Phenotype 3 versus Phenotype 1, HR 1.49, p = 0.387). This contrasts with sST2, which retained independent prognostic value as a continuous variable. The weak correlation between the two markers (Spearman ρ = 0.15) suggest that they capture largely distinct dimensions of the disease; the prognostic relevance of CA125 appeared to emerge primarily when it coexisted with sST2 elevation (Phenotype 4), identifying a subgroup with particularly high biological vulnerability that was not apparent with isolated elevation of either biomarker.

Combined sST2-CA125 phenotyping and interaction analysis

A central question is whether the risk associated with concurrent elevation of sST2 and CA125 reflects independent biomarker effects or an interaction between the two pathways. The descriptive pattern in our cohort, an independent effect of sST2, no independent effect of CA125, and a significant effect only when both were elevated, suggests that concurrent elevation identifies a particularly high-risk phenotype, but does not establish whether this reflects additive or synergistic effects. Consistent with this, the multiplicative sST2×CA125 interaction term was not statistically significant (p = 0.457); nonetheless, given the modest sample size and event count, this study was only powered to detect a large interaction effect, and the non-significant interaction term cannot exclude a smaller interaction effect. Taken together, these findings do not provide evidence of a multiplicative interaction, although the biological and prognostic relationship between the two biomarkers warrants specific testing in larger cohorts adequately powered for interaction analysis.

Combined sST2-CA125 assessment and prior evidence

The most directly comparable evidence comes from a sub-study of the IMPROVE-HF trial, in which the prognostic association of sST2 with the burden of recurrent cardiovascular and renal hospitalisations was modulated by CA125, being apparent only when CA125 was elevated, whereas no such modulation was observed for all-cause mortality[16]. Notably, the endpoint specificity in our cohort is the reverse: the association of the combined sST2–CA125 phenotype was apparent for mortality, but not for rehospitalisation. This divergence may reflect the distinct population studied (patients aged 80 years or above with HFpEF, versus a younger, mixed ejection-fraction cohort with renal dysfunction).

Rehospitalisation in the very old may be more strongly influenced by non-cardiac and social factors, which may dilute the prognostic signal of cardiac-specific biomarkers for this endpoint. These observations are consistent with a companion analysis by our group in a related very old HFpEF cohort, in which biomarker-defined congestion profiles based on BNP and CA125 carried prognostic information beyond the ejection-fraction classification, with combined elevation associated with mortality and isolated CA125 elevation with rehospitalisation[15].

A more vulnerable phenotype

The phenotype was associated with mortality but not with rehospitalisation or the composite endpoint. Beyond the multifactorial and competing-risk nature of rehospitalisation in this population, commonly influenced by comorbidity burden, functional status, and social factors rather than cardiac-specific biology, the coexistence of fibro-inflammatory and congestive signals captured by sST2 and CA125 may more closely track the lethal trajectory of the syndrome. This mortality-specific behaviour should be regarded as hypothesis-generating and warrants confirmation.

Geriatric context: frailty, multimorbidity and biological vulnerability

In the phenotype-adjusted model, frailty and lower systolic blood pressure were also independently associated with mortality, underscoring that prognosis in the very old integrates biological and functional vulnerability[5]; importantly, the biomarker phenotype remained independently associated with mortality after adjustment for frailty and BNP. The progressive decline in body mass index towards Phenotype 4, together with its higher comorbidity burden, may reflect a more advanced, catabolic disease phenotype, in keeping with the reverse-epidemiology of body mass repeatedly described in heart failure; this association was not formally tested and should be regarded as exploratory.

Clinical implications

From a clinical standpoint, the combined assessment of sST2 and CA125 may provide complementary biological information. The proposed phenotype may help identify a particularly high-risk subgroup for closer surveillance and earlier goals-of-care discussions, and supports a multidimensional approach to risk stratification, integrating biological, functional and clinical information, in a population in which conventional tools perform poorly[10]. Whether this phenotype could also help tailor decongestive or other therapeutic strategies remains speculative and was not addressed in this study. These implications remain hypothesis-generating and require prospective validation.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, its single-centre design may limit external generalizability, and validation in independent cohorts is warranted. Second, the sample size and the number of events remain relatively modest, which may limit the precision of multivariable estimates, particularly for secondary analyses, and the statistical power to

detect interactions or differences in small subgroups. Third, sST2 and CA125 were measured at a single time point; serial assessments during follow-up may carry additional prognostic information not captured in the present analysis. Fourth, frailty was assessed using the FRAIL scale, which, while validated and widely used, may not fully capture all dimensions of biological vulnerability. Finally, the 35 ng/mL sST2 threshold was established using the Presage® ST2 assay, whereas sST2 was measured using the Elabscience ELISA in this study. Given potential differences across analytical platforms, this threshold should be considered pragmatic rather than assay-validated; however, sensitivity analysis using the cohort-specific median yielded concordant results.

Conclusions

In patients aged 80 years or above hospitalised for decompensated HFpEF, combined elevation of sST2 and CA125 was independently associated with increased one-year mortality, whereas isolated elevation of either biomarker was not. These hypothesis-generating findings suggest that integrating complementary biological pathways may refine risk stratification in this understudied population and warrant validation in independent cohorts.

Declarations

Conflicts of interest.

The authors declare that they have no competing interests.

Ethics approval and consent to participate.

The study was approved by the Clinical Research Ethics Committee of Hospital Universitario Ramón y Cajal (approval No. 332/21) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

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Figures

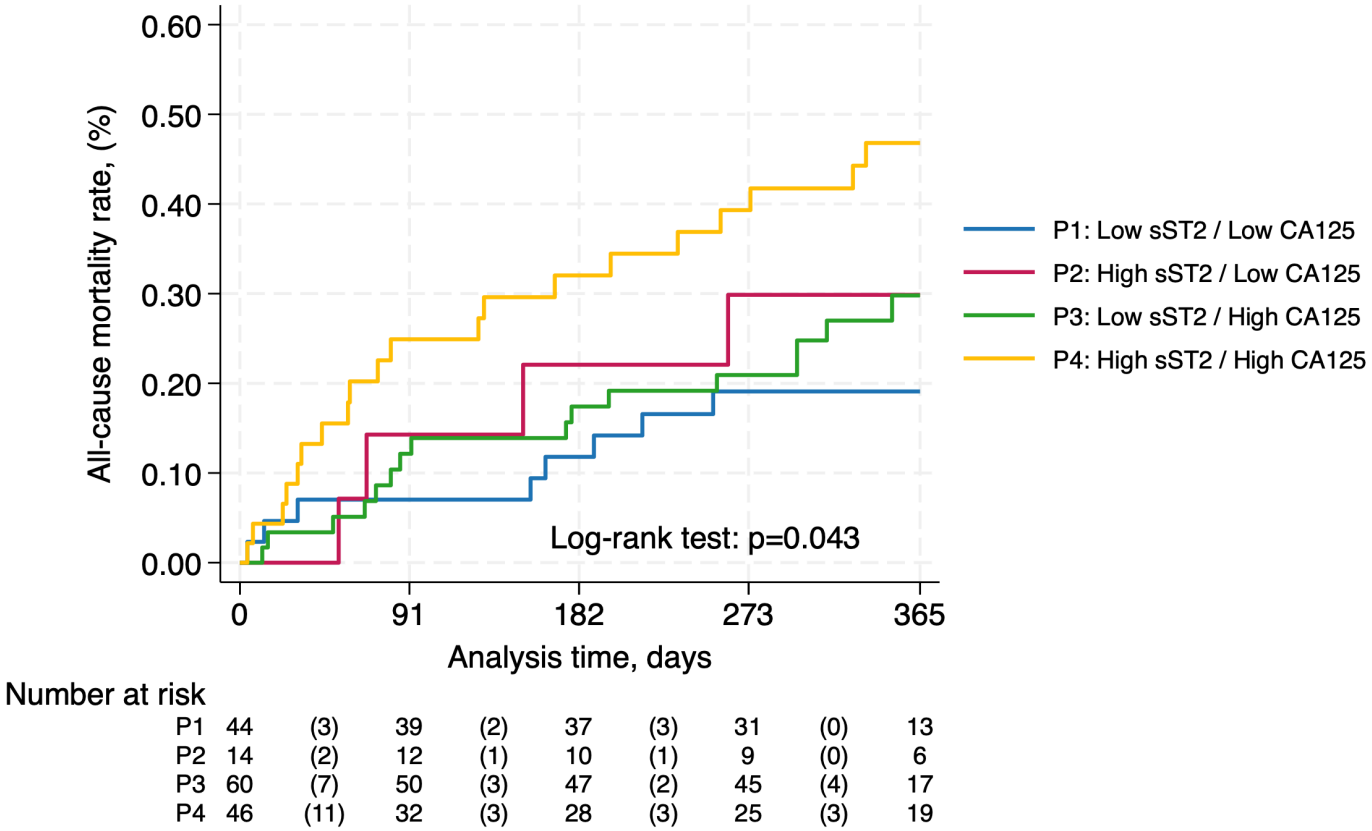


Figure 1

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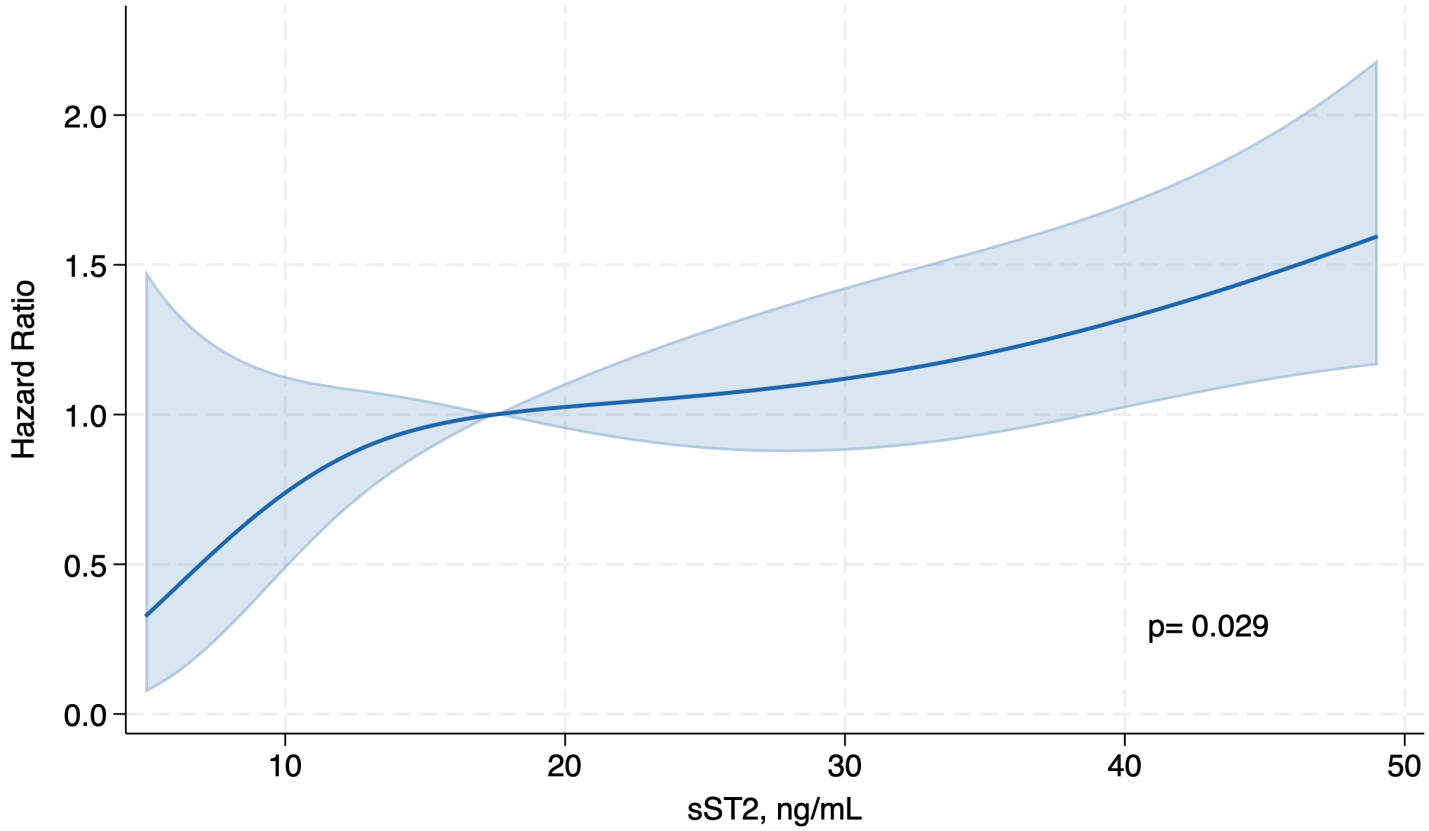


Figure 2

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