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Cholestatic Liver Dysfunction and Systemic Congestion in Acute Heart Failure: Prognostic Interaction Between Alkaline Phosphatase and CA125

Juan Esteban Oyuela Rodríguez
Hospital Ramon y Cajal: Hospital Universitario Ramon y Cajal
Pau Llàcer
paullacer@hotmail.com

Hospital Ramon y Cajal: Hospital Universitario Ramon y Cajal https://orcid.org/0000-0002-0988-0599
François Croset
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Alberto Pérez Nieva
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Jorge Campos
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Marina García Melero
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Carlos Pérez
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Marina Vergara
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Andrés Paúl Cevallos Castro
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
María Pumares
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Cristina Fernández
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Martin Fabregate
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Beatriz Del Hoyo Cuenda
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal
Esteban Pérez Pisón
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal

Luis Manzano
Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal

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Abstract

Background: Congestive hepatopathy is a recognized complication of right-sided venous congestion in acute heart failure (AHF). Alkaline phosphatase (AP) reflects cholestatic liver dysfunction, while CA125 serves as a surrogate of systemic serosal congestion. We aimed to evaluate the prognostic impact of AP and its interaction with CA125 in patients hospitalized for AHF.

Methods: We conducted a retrospective observational study including 735 patients hospitalized for AHF. Patients were classified according to AP and CA125 levels using predefined cutoffs (AP >141 U/L; CA125 >54.6 U/mL). The primary outcome was a composite of all-cause mortality and unplanned heart failure rehospitalization during follow-up, censored at one year. All-cause mortality was evaluated as a secondary endpoint. Cox proportional hazards regression with interaction terms was used for multivariable analysis

Results: Median age was 88 years and 66.9% were women. During follow-up, 387 patients (53.1%) experienced the primary composite endpoint. Elevated AP alone was not associated with increased risk of adverse outcomes (HR 0.94; 95% CI 0.53–1.66; p=0.830). However, concurrent elevation of AP and CA125 identified a high-risk subgroup with markedly increased composite endpoint risk (HR 1.98; 95% CI 1.40–2.80; p<0.001) and all-cause mortality (HR 2.10; 95% CI 1.39–3.11; p<0.001). The interaction between AP and CA125 was statistically significant for both endpoints (p<0.001).

Conclusions: In old patients with AHF, the prognostic impact of elevated AP is critically dependent on concomitant systemic congestion reflected by elevated CA125. In contrast, elevated AP without concomitant CA 125 elevation was not independently associated with adverse outcomes.

Introduction

Acute heart failure (AHF) is a complex clinical syndrome that triggers a cascade of systemic consequences resulting from impaired cardiac function and elevated intracardiac filling pressures[1]. Right-sided venous congestion plays a central role in these systemic effects, leading to dysfunction of multiple visceral organs, including the liver. In this context, chronic hepatic venous congestion may result in the development of congestive hepatopathy[2].

Congestive hepatopathy is characterized by the presence of structural heart disease with impaired right ventricular function, together with signs and symptoms of right side congestion, including jugular venous distension, hepatomegaly, hepatojugular reflux, peripheral edema, or ascites, elevated cholestasis markers, such as alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), and total bilirubin, following the exclusion of alternative causes of liver damage[2–4]. Previous studies have shown that elevated cholestasis enzymes correlate with poorer prognosis, as evidenced by an increased risk of readmissions and mortality among patients experiencing AHF[5–8].

AP represents a robust biochemical marker of cholestasis, reflecting both intrahepatic and extrahepatic bile flow impairment. Given its synthesis at the canalicular membrane of hepatocytes, elevations in AP may reflect increased canalicular enzyme expression or biliary obstruction, even in the absence of concomitant hyperbilirubinemia, making it particularly sensitive for the detection of early or congestion-related cholestasis[3,9].Plasma levels of carbohydrate antigen 125 (CA125) are elevated in most patients with (AHF) and have emerged as a surrogate marker of systemic congestion and predominant right-sided dysfunction[10]. CA125 is a high–molecular-weight glycoprotein produced by mesothelial cells, and its elevation reflects serosal irritation and fluid accumulation driven by increased hydrostatic pressure and mechanical stress secondary to venous congestion[10]. Elevated CA125 levels are independently associated with worse prognosis, including increased risk of mortality and rehospitalization[11].

However, whether the prognostic significance of AP is uniform across patients with AHF or whether it depends on the broader context of systemic congestion remains unknown. Given that CA125 reflects serosal fluid accumulation and right-sided venous congestion, the same pathophysiological mechanism driving congestive hepatopathy, we hypothesized that elevated AP may carry a differential prognostic impact depending on the degree of systemic congestion as reflected by CA125.

This study aims to assess the prognostic value of AP for long-term outcomes in patients hospitalized with AHF and to examine its interaction with CA125.

Materials and Methods

Study design and patients

This study is based on the UICA Registry (Unidad de Insuficiencia CArdiaca), an ongoing prospective single-center cohort of consecutive patients hospitalized for AHF and followed up in the Heart Failure Unit of the Internal Medicine Department at Ramón y Cajal University Hospital, a tertiary referral center in Madrid, Spain. Between January 2020 and July 2025, a total of 1408 patients were consecutively enrolled. Patients without measurement of AP or bilirubin during index admission were excluded (n = 673), leaving a final study sample of 735 patients. The diagnosis of AHF was established by the attending physician according to current guidelines[12]. Demographic data, medical history, physical examination findings, 12-lead electrocardiogram, standard laboratory tests, echocardiographic parameters, and pharmacological therapies during hospitalization and at discharge were prospectively recorded using standardized electronic questionnaires. The UICA Registry was approved by the Research Ethics Committee of Ramón y Cajal University Hospital (protocol reference: 052/18), and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Biomarkers measurements

Venous blood samples obtained within 24 hours of admission were used to measure B-type natriuretic peptide (BNP), CA125, AP, total bilirubin, GGT, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), using standard automated assays at the local laboratory.

Measures and Definition of Exposures

Patients were classified according to serum AP and CA125 levels. Elevated AP was defined as > 141 U/L, a threshold previously validated as a clinically meaningful cut-off for congestive hepatopathy in heart failure[2]. CA125 was dichotomized at the median value of the study population (54.6 U/mL). Based on these two thresholds, patients were categorized into four mutually exclusive groups: (1) low AP and low CA125; (2) low AP with elevated CA125; (3) elevated AP with low CA125; and (4) concurrent elevation of both markers.

Follow-up and Endpoints

The primary endpoint was a composite of all-cause mortality and unplanned heart failure rehospitalization during follow-up, censored at one year. All-cause mortality was the secondary endpoint.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR], as appropriate. Categorical variables are expressed as frequencies (percentages)

Patients were classified into four groups according to alkaline phosphatase and CA-125 levels, as previously described. Group comparisons were performed using the $\chi 2$ test for categorical variables and ANOVA or the Kruskal-Wallis test for continuous variables, depending on data distribution. To evaluate the modulating effect of CA125 on the association between AP and clinical outcomes, we stratified the analysis by median CA125 levels (≤ 54.6 U/mL and > 54.6 U/mL). Survival analysis was performed using the Kaplan–Meier method and the log-rank test to compare the survival curves between patients according to the categories. Associations were assessed using Cox proportional hazard regression, and p-values for interactions were calculated. Risk estimates were expressed as hazard ratios (HR) with 95% confidence interval (95% CI).

All variables listed in Table 1 were tested for multivariable adjustment based on prior knowledge/biological plausibility, regardless of their univariate p-value. The linearity assumption for continuous variables was tested, and transformations using fractional polynomials were applied as needed. A parsimonious model was subsequently derived using backward stepwise selection guided by clinical judgment. The covariates included in the multivariable model for all the endpoints were age, B-type natriuretic peptide, edema, cumulative intravenous furosemide dose during hospitalization, total bilirubin, gamma-glutamyl transferase, presence of jugular venous distension, heart rate, hemoglobin and systolic blood pressure

Table 1
Baseline Characteristics. Two categories are based on Alkaline phosphatase levels.

Variables	Total (n = 735)	Low Alkaline phosphatase (n = 636)	High Alkaline phosphatase (n = 99)	p value
Demographic parameters and medical history				
Age,years	88 (84–91)	87 (84–91)	88 (83–91)	0.336
Female, sex n (%)	492 (66.9)	431 (67.7)	61 (61.2)	0.226
Hypertension, n (%)	662 (90.7)	576 (90.5)	86 (86.7)	0.253
Crhonic Kidney disease, n(%)	533 (72.5)	459 (72.2)	74 (74.8)	0.593
Diabetes Mellitus type 2, n (%)	273 (37.1)	228 (35.8)	45 (45.4)	0.066
COPD, n (%)	199 (27)	169 (26.5)	30 (30.3)	0.437
Atrial Fibrillation, n (%)	456 (62)	387 (60.8)	69 (69.7)	0.092
Ischemic heart disease, n (%)	143 (19.4)	119 (18.7)	24 (24.2)	0.196
Valvular disease, n (%)	154 (20.9)	126 (19.8)	28 (28.2)	0.054
Hepatic disease, n (%)	25 (3.40)	19 (2.9)	6 (6)	0.117
Days of hospitalization (d)	6 (4–8)	5 (4–8)	6 (4–9)	0.159
Physical examination				
NYHA class (%)	52 (7.15)	46 (7.30)	6 (6.19)	0.843
I	472 (64.92)	411 (65.24)	61 (62.89)	
II	193 (26.55)	165 (26.19)	28 (28.8)	
III	10 (1.38)	8 (1.27)	2 (2.06)	
IV				
Systolic Blood Pressure, mmHg	132 (117–150)	133 (117–150)	130 (114–147)	0.584

COPD: Chronic Obstructive Pulmonary Disease; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; TAPSE: Tricuspid Annular Plane Systolic Excursion; eGFR: estimated Glomerular Filtration Rate: BNP: B-type Natriuretic Peptide; CA125: Carbohydrate Antigen 125; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: Gamma Glutamyl Transferse; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; MRA: Mineral Receptor Antagonists; SGLT2i: Sodium-glucose Co-transporter-2 Inhibitors.

*: Data were available for a limited number of patients, 435.

Variables	Total (n = 735)	Low Alkaline phosphatase (n = 636)	High Alkaline phosphatase (n = 99)	p value
Demographic parameters and medical history				
Diastolic Blood Pressure, mmHg	72 (63–83)	72 (63–83)	71 (63–82)	0.723
Heart rate, bpm	80 (70–93)	80 (69–93)	81 (71–95)	0.354
Peripheral edema, n (%)	490 (66.6)	415 (65.25)	75 (75.6)	0.039
Pleural effusion, n (%)	251 (34.1)	207 (32.5)	44 (44.4)	0.020
Jugular vein distention, n (%)*	188 (25.5)	163 (25.6)	25 (25)	0.93
Ascites, n (%)*	20 (4.64)	11 (2.99)	9 (14.2)	< 0.001
Echocardiogram				
LVEF n (%)	61 (53-67.8)	60.9 (54–68)	61.1 (52–68)	0.843
Tricuspid regurgitation, n (%)	434 (65.46)	363 (63.8)	71 (75.5)	0.027
PAPS, mmHg	50 (39.6–59.4)	48.7 (39.5–56.8)	51.4 (40.2–66.3)	0.091
TAPSE, cm	2.0 (1.8–2.3)	2.0 (1.8–2.3)	1.9 (1.7–2.2)	0.042
Laboratory test				
Creatinine, mg/dL	1.2 (0.92–1.6)	1.18 (0.9–1.6)	1.36 (0.9–1.9)	0.069
eGFR, ml/min/1.73m^2	47.6 (33.5–63.6)	47.8 (34.1–64.1)	45.8 (29.3–61.6)	0.149
Urea	61 (44–87)	60 (43–85)	70 (51–102)	0.008
Sodium, mEq/L	138 (135–141)	139 (136–141)	138 (135–140)	0.022

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*: Data were available for a limited number of patients, 435.

Variables	Total (n = 735)	Low Alkaline phosphatase (n = 636)	High Alkaline phosphatase (n = 99)	p value
Demographic parameters and medical history				
Potassium, mEq/L	4.43 (4.1–4.9)	4.41 (4.08–4.88)	4.62 (4.2–4.98)	0.010
Chloride, mEq/L	103 (99–106)	103 (99–106)	104 (99–107)	0.358
Hemoglobine, g/dL	12 (10.4–13.4)	12 (10.4–13.4)	11.7 (11–13.4)	0.618
Leukocytes, x10³/µL	8.42 (6.57–10.9)	8.45(6.6–10.9)	7.83(6.1–10.6)	0.263
Total proteins, g/dL	6.2 (5.8–6.6)	6.2(5.8–6.6)	6.2(5.7–6.6)	0.889
Albumin, g/dL	3.06 (2.77–3.32)	3.09(2.79–3.33)	2.97(2.67–3.19)	0.003
AST, U/L	21 (16–18)	21 (16–28)	25.5(18–41)	< 0.001
ALT, U/L	15 (10–24)	14(10–23)	20(14-40.5)	< 0.001
GGT, U/L	45 (26–82)	39 (25-66.5)	121 (64–233)	< 0.001
Bilirubin, mg/dL	0.65 (0.49–0.97)	0.64(0.45–0.94)	0.76(0.47–1.24)	0.018
BNP, pg/mL	582 (315.4-1064.9)	558 (331.2–1035)	761.6(432.8–1297)	0.007
CA125, U/L	54.3 (25.4–120)	49.4(24.5-110.3)	104.5(42-169.6)	0.001
Treatment				
ACEI/ARB/ARNI, n (%)	190 (25.85)	174 (27.3)	16 (16.1)	0.018
Betablokers, n (%)	403 (54.98)	350 (55.12)	53 (54.08)	0.848
SGLT2i, n (%)	191 (26.13)	164 (25.95)	27 (27.2)	0.780

COPD: Chronic Obstructive Pulmonary Disease; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; TAPSE: Tricuspid Annular Plane Systolic Excursion; eGFR: estimated Glomerular Filtration Rate: BNP: B-type Natriuretic Peptide; CA125: Carbohydrate Antigen 125; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: Gamma Glutamyl Transferse; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; MRA: Mineral Receptor Antagonists; SGLT2i: Sodium-glucose Co-transporter-2 Inhibitors.

*: Data were available for a limited number of patients, 435.

Variables	Total (n = 735)	Low Alkaline phosphatase (n = 636)	High Alkaline phosphatase (n = 99)	p value
Demographic parameters and medical history				
MRAm n(%)				
Furosemide, n (%)	473 (64.35)	409 (64.31)	64 (64.6)	0.948
Furosemide dose, mg	240 (120–440)	240 (120–425)	300 (160–560)	0.129
Events				
All-cause mortality and/or heart failure hospitalization, n(%)	387 (53.09)	317 (50.32)	70 (70.1)	< 0.001
All-cause mortality, n (%)	279 (38.32)	230 (36.57)	49 (49.4)	0.014
COPD: Chronic Obstructive Pulmonary Disease; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; TAPSE: Tricuspid Annular Plane Systolic Excursion; eGFR: estimated Glomerular Filtration Rate: BNP: B-type Natriuretic Peptide; CA125: Carbohydrate Antigen 125; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: Gamma Glutamyl Transferse; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; MRA: Mineral Receptor Antagonists; SGLT2i: Sodium-glucose Co-transporter-2 Inhibitors.				
*: Data were available for a limited number of patients, 435.				

A two-sided p-value of < 0.05 was considered statistically significant for all analyses. All survival analyses were performed using STATA18, 1 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics

A total of 735 patients were included in the analysis. The median age was 88 years (IQR 84–91), 492 patients (66.9%) were women, and 533 (72.5%) had preserved left ventricular ejection fraction (LVEF ≥50%). The most prevalent comorbidities were arterial hypertension (90.1%), chronic kidney disease (71.0%), atrial fibrillation (62.0%), and type 2 diabetes mellitus (37.1%). Median (IQR) AP was 88 U/L (70-115), median (IQR) CA125 was 54.3 U/mL (25.4-119.6), and median BNP (IQR) was 581.8 pg/mL (315.4-1064.9). Overall, 99 patients (13.6%) had AP >141 U/L and 397 patients (54.0%) had CA125 above the cohort median. Detailed baseline characteristics, including clinical, biochemical, and echocardiographic parameters, are presented in Table 1.

Baseline profiles across AP and CA125 categories

Patients with elevated AP (>141 U/L) were comparable to those with normal AP in terms of age, sex, comorbidity burden, LVEF, and most pharmacological treatments. However, they presented a more severe congestive profile, with higher prevalence of peripheral edema, pleural effusion, and ascites, as well as echocardiographic evidence of right heart dysfunction, including lower TAPSE and more frequent tricuspid regurgitation. Biochemically, elevated AP was associated with higher serum urea, potassium, GGT, bilirubin, AST, ALT, and CA125, and lower albumin levels. (Table 2).

When patients were stratified into four groups according to combined AP and CA125 levels, a clear gradient of clinical and biochemical severity emerged across categories (Table 2). The most adverse profile was observed in patients with concurrent elevation of both biomarkers (high AP/high CA125), who had the longest hospital stays, the highest rates of pleural effusion, ascites, and jugular venous distension, the lowest TAPSE values, and the greatest prevalence of tricuspid regurgitation and atrial fibrillation. Biochemically, this group exhibited the most pronounced hepatic and neurohormonal derangements, with the highest GGT, bilirubin, BNP, and CA125 levels and the lowest albumin concentrations. In contrast, patients with low AP and low CA125 represented the least congested group with the most favorable biochemical profile.

Association between the levels of Alkaline phosphatase, CA125, and adverse outcomes

Composite endpoint

During a median follow-up of 237 days (IQR 72–447), 387 patients (53.1%) experienced the primary composite endpoint of all-cause mortality or unplanned heart failure rehospitalization. Patients with elevated AP had significantly higher event rates compared to those with normal AP (70.1% vs. 50.3%, p<0.001). Similarly, patients with CA125 above the cohort median had higher event rates than those below the median (58.9% vs. 41.1%, p=0.004).

When patients were stratified into four groups according to combined AP and CA125 levels, a progressive gradient of risk was observed: C1 (low AP/low CA125): 46.2%; C2 (low AP/high CA125): 54.1%; C3 (high AP/low CA125): 58.6%; and C4 (high AP/high CA125): 75.7% (p≤0.001). Kaplan–Meier analysis confirmed higher cumulative event rates with increasing biomarker burden, with the highest incidence observed in patients with concurrent elevation of both markers (Figure 1).

This differential association of AP, according to CA125, persisted significantly after multivariate adjustment (p-value for interaction < 0.001).Compared to the lower baseline risk group (AP <141 U/L and CA125 (≤54.6 U/mL), patients with AP high and CA125≤54.6 U/ ml did not show a higher risk of adverse events (HR: 0,94, CI 95 %= 0.53–1.66, p =0.830). Conversely, those with high AP and CA125>54.6 U/ml confirmed identifying a subgroup at higher risk for the composite endpoint (HR 1.98; 95% CI 1.40–2.80; p < 0.001). When we analyzed the association between AP along the continuum and adverse events across CA125 strata, there was a numerical signal of greater association between higher AP levels in those patients with high CA125 despite non-significant differential association (p-value for interaction=0.129). (Figure 2)

All-cause mortality

During a median follow-up of 341 days (IQR 127–511), 274 patients (38.3%) died. Patients with high AP presented higher rates of all-cause mortality endpoint (49.4 % vs 36.57 %, p =0.014). When stratifying the predictive value of AP across CA125≤54.6 vs >54.6 U/ml, we were able to reclassify the risk of patients (C1:39.3%, C2:46.1 %, C3: 48.7 %, and C4: 60.1 %, p=<0.001). Kaplan–Meier plots showed divergent trajectories among categories, with a higher risk for patients with high AP and high CA125, without overt differences for the other groups (Figure 3). The interaction between AP and CA125 remained statistically significant after multivariable adjustment (p-value for interaction <0.001). Relative to the reference group (AP <141 U/L and CA125 ≤54.6 U/mL), patients with elevated AP and low CA125 did not demonstrate a significantly higher risk of all-cause mortality (HR 0.49, 95% CI 0.21–1.17; p=0.109). In contrast, those with elevated AP and high CA125 showed a markedly increased mortality risk (HR 2.10, 95% CI 1.39–3.11; p<0.001). When we analyzed the association between AP along the continuum and all-cause mortality across CA125 strata, a significant interaction was observed (p-value for interaction = 0.002). (Figure 4). Among patients with CA125 above the median, each 1 U/L increase in alkaline phosphatase was associated with a significant increase in mortality risk (HR 1.004, 95% CI 1.001–1.007, p = 0.003). In contrast, among patients with CA125 at or below the median, higher alkaline phosphatase levels were not significantly associated with all-cause mortality (HR 0.995, 95% CI 0.989–1.002, p = 0.137).

Discussion

The main findings of this study can be summarized as follows. In a large cohort of very old patients hospitalized with AHF, elevated AP was associated with a more severe congestive profile and worse clinical outcomes. However, this prognostic signal was not uniform: the adverse impact of elevated AP was entirely contingent on the presence of concomitant systemic congestion as reflected by CA125. Patients with elevated AP in the absence of elevated CA125 showed no significant increase in risk, whereas those with concurrent elevation of both biomarkers represented a distinct high-risk phenotype with markedly increased mortality and rehospitalization. Together, these findings support a model in which hepatic cholestasis and systemic congestion interact synergistically to define a particularly vulnerable subgroup among older patients with AHF.

Congestive hepatopathy and cholestasis in acute heart failure

Hepatic dysfunction is a well-recognized but frequently underappreciated complication of right-sided venous congestion in heart failure. Elevated filling pressures transmitted to the hepatic venous system result in sinusoidal congestion, hepatocellular injury, and impaired bile flow, ultimately manifesting as cholestatic liver dysfunction[2,3]. AP, as a marker of canalicular membrane integrity and bile flow, has been proposed as a sensitive indicator of early or subclinical congestive hepatopathy, detectable even in the absence of hyperbilirubinemia[9,13]. Consistent with this, our data showed that elevated AP was

associated with echocardiographic markers of right heart dysfunction, including lower TAPSE and higher prevalence of tricuspid regurgitation, as well as clinical signs of right-sided congestion such as jugular venous distension, ascites, and peripheral edema, in line with prior studies demonstrating that cholestasis markers correlate with the severity of right ventricular dysfunction and venous congestion in AHF[13,14].

Previous work has shown that elevated GGT, bilirubin, and AP are independently associated with worse outcomes in heart failure[5–8]. Our results extend these observations by demonstrating that the prognostic value of AP is not independent of the broader congestion context. Notably, elevated AP in isolation did not significantly predict adverse outcomes. Rather than representing a paradox, this finding may reflect a clinically meaningful distinction: AP elevation without concomitant systemic congestion may indicate a more localized or hemodynamically limited form of hepatic involvement, in which sufficient physiological reserve remains to withstand the acute decompensation episode. In contrast, when hepatic cholestasis coexists with systemic serosal congestion, it signals a more globally decompensated state characterized by limited compensatory capacity and greater biological vulnerability. In this setting, increased right-sided filling pressures may simultaneously impair hepatic venous drainage and reduce hepatic arterial perfusion, creating a dual mechanism of hepatocellular and cholestatic injury that amplifies the prognostic signal of either marker alone[2,3,8,14].

CA125 as a modulator of prognostic risk: the systemic congestion context

CA125 is a high-molecular-weight glycoprotein produced by mesothelial cells lining the pleura, peritoneum, and pericardium[10]. Its elevation in AHF reflects increased hydrostatic pressure and mechanical stress on serosal surfaces driven by venous congestion, and it has emerged as one of the most robust biomarkers of systemic fluid overload and right-sided dysfunction in this setting[10]. Elevated CA125 is independently associated with mortality and rehospitalization in AHF, and its prognostic value has been demonstrated across different scenarios[11].

The key finding of our study is that CA125 does not merely add independent prognostic information to AP but rather acts as a contextualizing factor that determines whether AP elevation translates into increased clinical risk. This interaction suggests that the biological significance of hepatic cholestasis in AHF cannot be assessed in isolation but must be interpreted within the framework of systemic congestion burden. From a pathophysiological standpoint, this is coherent: hepatic venous congestion and serosal fluid accumulation share a common upstream mechanism, elevated right-sided filling pressures, and their co-occurrence likely reflects a more advanced and sustained elevation of venous pressure that overwhelms both hepatic and serosal compensatory mechanisms simultaneously.

This concept aligns with the emerging framework of organ-specific congestion phenotyping in heart failure, in which different biomarkers reflect distinct but interrelated compartments of the congestion syndrome. Our data suggests that combining markers of hepatic congestion and systemic serosal

congestion may provide a more complete biological portrait of the decompensated state than either marker alone[15].

In this context, lower albumin levels observed in patients with elevated alkaline phosphatase may reflect a broader systemic profile related to congestion, hemodilution, inflammation, renal dysfunction, or impaired hepatic synthetic function, potentially favoring extravascular fluid accumulation[16].

A high-risk hepatosystemic congestion phenotype

The concurrent elevation of AP and CA125 identified a clinically distinct subgroup characterized by the most severe congestive profile, the greatest hepatic and neurohormonal derangements, the longest hospital stays, and the highest rates of adverse outcomes. The adjusted hazard ratio for all-cause mortality in this group was 2.07 (95% CI 1.38–3.10) and for the composite endpoint 1.98 (95% CI 1.40–2.80), compared to the low AP/low CA125 reference group. Consistent with prior studies [5,6,17,18,20], patients with evidence of hepatic involvement during AHF decompensation also exhibited a higher prevalence of peripheral edema, required greater cumulative doses of intravenous loop diuretics, and experienced longer lengths of stay, observations made in an elderly population admitted to internal medicine wards without vasopressor support or overt hemodynamic instability.

This phenotype shares conceptual similarities with previously described congestion profiles in AHF that combine markers of hemodynamic stress, systemic fluid overload, and end-organ dysfunction[2,19]. What our study adds is a specific characterization of the hepatic dimension of this syndrome, linking cholestatic liver dysfunction, a marker of sustained right-sided venous hypertension, with systemic serosal congestion as a joint determinant of prognosis. The coexistence of these two processes may reflect a distinct biological state in which hepatic and systemic congestion mutually amplify their adverse prognostic impact.

Clinical implications

Our findings have several potential clinical implications. First, AP should not be interpreted as a prognostic marker in isolation in patients with AHF. Its adverse prognostic signal emerges only in the context of elevated CA125, suggesting that the two biomarkers should be evaluated jointly rather than independently. A simple bedside classification based on AP and CA125 levels at admission may help identify patients at highest risk who may benefit from more aggressive decongestion strategies, closer monitoring, and earlier escalation of care.

Second, the null prognostic finding for elevated AP with low CA125 should not be interpreted as reassuring in all cases. These patients may represent an earlier or more localized stage of congestive hepatopathy that has not yet progressed to systemic serosal involvement. Serial monitoring of both biomarkers during hospitalization and at follow-up may help detect progression toward the high-risk phenotype before clinical deterioration occurs.

Third, our results reinforce the concept that congestion in AHF is a multidimensional syndrome that cannot be fully captured by a single biomarker, clinical sign, or imaging parameter. Integrated biomarker profiling, combining markers of myocardial stress, systemic congestion, and end-organ dysfunction, may provide more actionable risk stratification than any individual parameter alone[15,17,20].

Limitations

This study has several limitations that should be considered when interpreting the findings. First, its retrospective, single-center design limits generalizability, and the results should be validated in cohorts and other settings. Second, nearly half of the original registry population was excluded due to missing AP or bilirubin measurements, which may introduce selection bias; as the characteristics of excluded patients were not systematically compared to those included, the direction and magnitude of this potential bias cannot be fully assessed. Third, although multivariable adjustment was performed for clinically relevant covariates, residual confounding from unmeasured variables cannot be excluded. Fourth, biomarker measurements were obtained at a single time point at admission, without serial assessments during hospitalization or at follow-up; dynamic changes in AP and CA125 during decongestion therapy, which may carry additional prognostic information, were therefore not evaluated. Fifth, the diagnosis of congestive hepatopathy was not formally established in individual patients; rather, AP was used as a biochemical surrogate of cholestatic liver dysfunction, and the absence of invasive hemodynamic measurements precluded direct quantification of right-sided filling pressures. Finally, frailty was not formally assessed despite the very advanced age of this cohort (median 88 years), and its potential confounding effect on both biomarker levels and clinical outcomes cannot be excluded.

Conclusion

In very old patients hospitalized with AHF, the prognostic impact of elevated AP is critically dependent on the presence of concomitant systemic congestion as reflected by CA125. Patients with concurrent elevation of both biomarkers represent a high-risk subgroup with markedly increased mortality and rehospitalization. These findings support combined AP and CA125 assessment at admission as a pragmatic tool for risk stratification, highlighting the value of integrated biomarker profiling beyond single-marker approaches in the management of AHF.

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Tables

Table 1. Baseline Characteristics. Two categories are based on Alkaline phosphatase levels.

Variables	Total (n= 735)	Low Alkaline phosphatase (n=636)	High Alkaline phosphatase (n=99)	p value
Demographic parameters and medical history				
Age,years	88 (84-91)	87 (84-91)	88 (83-91)	0.336
Female, sex n (%)	492 (66.9)	431 (67.7)	61 (61.2)	0.226
Hypertension, n (%)	662 (90.7)	576 (90.5)	86 (86.7)	0.253
Crhonic Kidney disease, n(%)	533 (72.5)	459 (72.2)	74 (74.8)	0.593
Diabetes Mellitus type 2, n (%)	273 (37.1)	228 (35.8)	45 (45.4)	0.066
COPD, n (%)	199 (27)	169 (26.5)	30 (30.3)	0.437
Atrial Fibrillation, n (%)	456 (62)	387 (60.8)	69 (69.7)	0.092
Ischemic heart disease, n (%)	143 (19.4)	119 (18.7)	24 (24.2)	0.196
Valvular disease, n (%)	154 (20.9)	126 (19.8)	28 (28.2)	0.054
Hepatic disease, n (%)	25 (3.40)	19 (2.9)	6 (6)	0.117
Days of hospitalization (d)	6 (4-8)	5 (4-8)	6 (4-9)	0.159
Physical examination				
NYHA class (%)				
I	52 (7.15)	46 (7.30)	6 (6.19)	0.843
II	472 (64.92)	411 (65.24)	61 (62.89)	
III	193 (26.55)	165 (26.19)	28 (28.8)	
IV	10 (1.38)	8 (1.27)	2 (2.06)	
Systolic Blood Pressure, mmHg	132 (117-150)	133 (117-150)	130 (114-147)	0.584
Diastolic Blood Pressure, mmHg	72 (63-83)	72 (63-83)	71 (63-82)	0.723
Heart rate, bpm	80 (70-93)	80 (69-93)	81 (71-95)	0.354
Peripheral edema, n (%)	490 (66.6)	415 (65.25)	75 (75.6)	0.039
Pleural effusion, n (%)	251 (34.1)	207 (32.5)	44 (44.4)	0.020
Jugular vein distention, n (%)*	188 (25.5)	163 (25.6)	25 (25)	0.93
Ascites, n (%)*	20 (4.64)	11 (2.99)	9 (14.2)	< 0.001

Echocardiogram				
LVEF n (%)	61 (53-67.8)	60.9 (54-68)	61.1 (52-68)	0.843
Tricuspid regurgitation, n (%)	434 (65.46)	363 (63.8)	71 (75.5)	0.027
PAPS, mmHg	50 (39.6-59.4)	48.7 (39.5-56.8)	51.4 (40.2-66.3)	0.091
TAPSE, cm	2.0 (1.8-2.3)	2.0 (1.8-2.3)	1.9 (1.7-2.2)	0.042
Laboratory test				
Creatinine, mg/dL	1.2 (0.92-1.6)	1.18 (0.9- 1.6)	1.36 (0.9 – 1.9)	0.069
eGFR, ml/min/1.73m^2	47.6 (33.5-63.6)	47.8 (34.1-64.1)	45.8 (29.3-61.6)	0.149
Urea	61 (44-87)	60 (43-85)	70 (51-102)	0.008
Sodium, mEq/L	138 (135-141)	139 (136-141)	138 (135-140)	0.022
Potassium, mEq/L	4.43 (4.1-4.9)	4.41 (4.08-4.88)	4.62 (4.2-4.98)	0.010
Chloride, mEq/L	103 (99-106)	103 (99-106)	104 (99-107)	0.358
Hemoglobine, g/dL	12 (10.4-13.4)	12 (10.4-13.4)	11.7 (11 – 13.4)	0.618
Leukocytes, x10³/µL	8.42 (6.57-10.9)	8.45(6.6-10.9)	7.83(6.1-10.6)	0.263
Total proteins, g/dL	6.2 (5.8-6.6)	6.2(5.8-6.6)	6.2(5.7-6.6)	0.889
Albumin, g/dL	3.06 (2.77-3.32)	3.09(2.79-3.33)	2.97(2.67-3.19)	0.003
AST, U/L	21 (16-18)	21 (16-28)	25.5(18-41)	< 0.001
ALT, U/L	15 (10-24)	14(10-23)	20(14-40.5)	< 0.001
GGT, U/L	45 (26-82)	39 (25-66.5)	121 (64-233)	< 0.001
Bilirubin, mg/dL	0.65 (0.49-0.97)	0.64(0.45-0.94)	0.76(0.47-1.24)	0.018
BNP, pg/mL	582 (315.4-1064.9)	558 (331.2 – 1035)	761.6(432.8-1297)	0.007

CA125, U/L	54.3 (25.4-120)	49.4(24.5-110.3)	104.5(42-169.6)	0.001
Treatment				
ACEI/ARB/ARNI, n (%)	190 (25.85)	174 (27.3)	16 (16.1)	0.018
Betablokers, n (%)	403 (54.98)	350 (55.12)	53 (54.08)	0.848
SGLT2i, n (%)	191 (26.13)	164 (25.95)	27 (27.2)	0.780
MRAm n(%)				
Furosemide, n (%)	473 (64.35)	409 (64.31)	64 (64.6)	0.948
Furosemide dose, mg	240 (120-440)	240 (120-425)	300 (160-560)	0.129
Events				
All-cause mortality and/or heart failure hospitalization, n(%)	387 (53.09)	317 (50.32)	70 (70.1)	< 0.001
All-cause mortality, n (%)	279 (38.32)	230 (36.57)	49 (49.4)	0.014

COPD: Chronic Obstructive Pulmonary Disease; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; TAPSE: Tricuspid Annular Plane Systolic Excursion; eGFR: estimated Glomerular Filtration Rate: BNP: B-type Natriuretic Peptide; CA125: Carbohydrate Antigen 125; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: Gamma Glutamyl Transferse; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; MRA: Mineral Receptor Antagonists; SGLT2i: Sodium-glucose Co-transporter-2 Inhibitors.

*: Data were available for a limited number of patients, 435.

Table 2. Baseline Characteristics. 4 categories based on FAL and CA125 levels.

Variables	Total (n=735)	Categorie 1: Low FAL/LowCA125 (n=309)	Categorie 2: Low FAL/High CA125 (n=327)	Categorie 3: High FAL/low CA125 (n=29)	Categorie 4: High FAL/High CA125 (n=70)	*p value*
Demographic parameters and medical history						
Age, years	88 (84-91)	87 (83-91)	88 (84-91)	88 (85-91)	89 (83-92)	0.645
Female sex. n (%)	492 (66.94)	215 (69.58)	216 (66.06)	22 (75.86)	39 (55.71)	0.106
Hypertension, n (%)	662 (90.07)	276 (89.32)	300 (91.74)	28 (96.55)	58 (82.86)	0.084
Diabetes mellitus, n (%)	273 (37.14)	103 (33.33)	125 (38.23)	16 (55.17)	29 (41.43)	0.083
Chronic kidney disease, n (%)	553 (72.5)	218 (70.6)	241 (73.7)	25 (86.2)	49 (70)	0.286
COPD, n (%)	199 (27.07)	91 (29.45)	78 (23.85)	7 (24.14)	23 (32.86)	0.271
Atrial Fibrilation, n (%)	456 (62.04)	173 (55.99)	214 (65.44)	16 (55.17)	53 (75.71)	0.006
Ischemic heart disease, n (%)	143 (19.46)	59 (19.09)	60 (18.35)	6 (20.69)	18 (25.71)	0.560
Valvular disease, n (%)	154 (20.95)	54 (17.48)	72 (22.02)	9 (31.03)	19 (27.14)	0.118
Hepatic disease, n (%)	25 (3.40)	7 (2.27)	12 (3.67)	0 (0)	6 (8.57)	0.046
Alcohol consume, n (%)	18 (2.45)	6 (1.94)	8 (2.45)	0 (0)	4 (5.71)	0.242
Days of hospitalization, (d)	6 (4-8)	5 (3-7)	6 (4-9)	5 (3-8)	6 (4-9)	0.009
Physical examination						

NYHA class (%)						0.425
I II III IV	52 (7.15) 472 (64.92) 193 (26.55) 10 (1.38)	27 (8.82) 185 (60.46) 89 (29.08) 5 (1.63)	19 (5.86) 226 (69.75) 76 (23.46) 3 (0.93)	1 (3.45) 19 (65.52) 9 (31.03) 0 (0)	5 (7.35) 42 (61.76) 19 (27.94) 2 (2.94)	
Systolic Blood Pressure, mmHg	132 (117-150)	133 (118-150)	132 (114-150)	136 (118-154)	128 (114-147)	0.706
Diastolic Blood Pressure, mmHg	72 (63-83)	72 (63-82)	73 (64-85)	71 (63-78)	71 (63-84)	0.707
Heart rate, bpm	80 (70-93)	79 (69-92)	80 (70-94)	79 (72-86)	83.5 (71-100)	0.338
Peripheral edema, n (%)	490 (66.67)	208 (67.31)	207 (63.30)	19 (65.52)	56 (80)	0.062
Pleural effusion, n (%)	251 (34.15)	82 (26.54)	125 (38.23)	13 (44.83)	31 (44.29)	0.002
Jugular vein distention, n (%)*	188 (25.58)	89 (28.80)	74 (22.63)	3 (10.34)	22 (31.43)	0.047
Ascitis, n (%)*	20 (4.64)	2 (1.16)	9 (4.62)	0 (0)	9 (19.57)	<0.001
Echocardiogram						
LVEF n (%)	61 (53-68)	62 (55-68)	60 (51-67.5)	63 (56-73)	60 (50-67)	0.048
LVEF≥50% n (%)	602 (81.9)	264 (85.4)	257 (79)	27 (93)	54 (77)	0.036
Septum, mm	1,2 (1.04-1.36)	1.2 (1.04-1.39)	1.19 (1.02-1.34)	1.19 (1.1-1.33)	1.2 (1.1-1.4)	0.407
TAPSE, mm	1.97 (1.75-2.31)	2.04 (1.8-2.39)	1.96 (1.69-2.2)	2.03 (1.8-2.29)	1.79 (1.6-2.1)	0.001
PASP, mmHg	50 (40-60)	47.5 (40-58)	50 (39 -56)	47.5 (40.2-64.3)	53.2 (40-67.5)	0.300

Tricuspid regurgitation, n (%)	434 (65.46)	173 (63.14)	190 (64.41)	19 (67.86)	52 (78.79)	0.109
Laboratory tests						
Creatinine, mg/dL	1.2 (0.92-1.6)	1.14 (0.87-1.56)	1.22 (0.92-1.58)	1.35 (0.99-1.91)	1.36 (0.91-1.9)	0.165
eGFR, ml/min/1.73m^2	47.5(33.4-63.6)	47.9(33.8-64.9)	47.4(34.8-62.6)	40.7(28.2-53.7)	46 (30.8-67.3)	0.218
Urea, mg/dL	61 (44-87)	57 (41-82)	63 (45-87)	58 (49-115)	70.5 (51-102)	0.009
Sodium, mEq/L	138 (135-141)	138 (135-141)	139 (136-141)	138 (135-139)	137 (134-140)	0.081
Potassium, mEq/L	4.43 (4.1-4.9)	4.37 (4-4.8)	4.4 (4.1-4.9)	4.7 (4.25-4.9)	4.6 (4.2-4.9)	0.050
Chloride, mEq/L	103 (99-106)	103 (98-106)	103 (100-106)	103 (100-106)	104 (99-107)	0.730
Hemoglobin, g/dL	12 (10.4-13.4)	12 (10.4-13.6)	12 (10.4-13.3)	11.2 (9.9-12.2)	12 (10.7-13.6)	0.205
Leukocytes, mcg/L	8.42 (6.57-10.9)	8.4 (6.5-11.4)	8.57 (6.8-11)	9.2 (7.1-11.5)	7.4 (6-10.4)	0.296
Total proteins, g/dL	6.2 (5.8-6.6)	6.3 (5.8-6.7)	6.12 (5.7-6.5)	6.4 (5.7-6.8)	6.2 (5.6-6.6)	0.003
Albumin, g/dL	3.06 (2.77-3.32)	3.09 (2.8-3.3)	3.08 (2.7-3.3)	2.94 (2.78-3.35)	2.9 (2.61-3.14)	0.024
AST/GOT, UI/lt	21 (16-18)	20 (16-27)	22 (16-29)	20 (15-37)	26 (20-41)	0.003
ALT/GPT, UI/lt	15 (10-24)	14 (10-22)	15 (10-24)	18 (14-36)	23 (13-46)	0.001
GGT, UI/lt	45 (26-82)	36 (24-66)	44 (27-70)	108 (60-202)	121 (70-241)	0.001
Bilirrubin, g/dL	0.65 (0.49-0.97)	0.58 (0.41-0.82)	0.7 (0.5-1.03)	0.5 (0.4-0.74)	0.9 (0.53-1.38)	0.001
Alkaline phosphatase, U/lt	88 (71 – 113)	83 (67-102)	84 (69-104)	163 (152-192)	169 (154-206)	0.001
BNP, pg/mL	582 (315.4-	470 (245.2-860)	680 (374.5-	563 (241-865)	824.9 (473-	<0.001

	1064.9)		1177)		1327)	
CA125, U/ml	54.3 (25.4-120)	25.9 (16.5-39.4)	114.2 (79-180)	24.1 (18-36.3)	140.8 (99-222)	0.001
Treatment						
ACEI/ARB, n (%)	190 (25.85)	85 (39.72)	89 (37.24)	5 (26.32)	11 (20.37)	0.048
Betablokers, n (%)	403 (54.98)	176 (57.14)	174 (53.21)	17 (58.62)	36 (52.17)	0.713
SGLT2i, n (%)	191 (26.13)	74 (23.95)	90 (27.8)	7 (24.14)	20 (28.57)	0.673
Furosemida, n (%)	473 (64.35)	194 (62.78)	215 (67.75)	18 (62.07)	46 (65.71)	0.866
Furosemide dose, mg	240 (120-450)	240 (120-420)	240 (120-440)	160 (120-240)	390 (160-580)	0.018
Events						
All-cause death and/or heart failure hospitalization, n(%)	387 (53.09)	142 (46.25)	175 (54.18)	17 (58.62)	53 (75.71)	<0.001
Mortality, n (%)	279 (38.32)	100 (32.57)	130 (40.37)	8 (27.59)	41 (58.57)	<0.001

Legend: COPD: Chronic Obstructive Pulmonary Disease; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; eGFR: estimated Glomerular Filtration Rate: BNP: B-type Natriuretic Peptide; CA125: Carbohydrate Antigen 125; AST: aspartate amino transferase; ALT: alanine amino transferase; GGT: gamma glutamyl transferse; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; MRA: Mineral Receptor Antagonists; SGLT2i: Sodium-glucose Co-transporter-2 Inhibitors

*: Data on jugular vein distension and ascites were available for a limited number of patients.

Figures

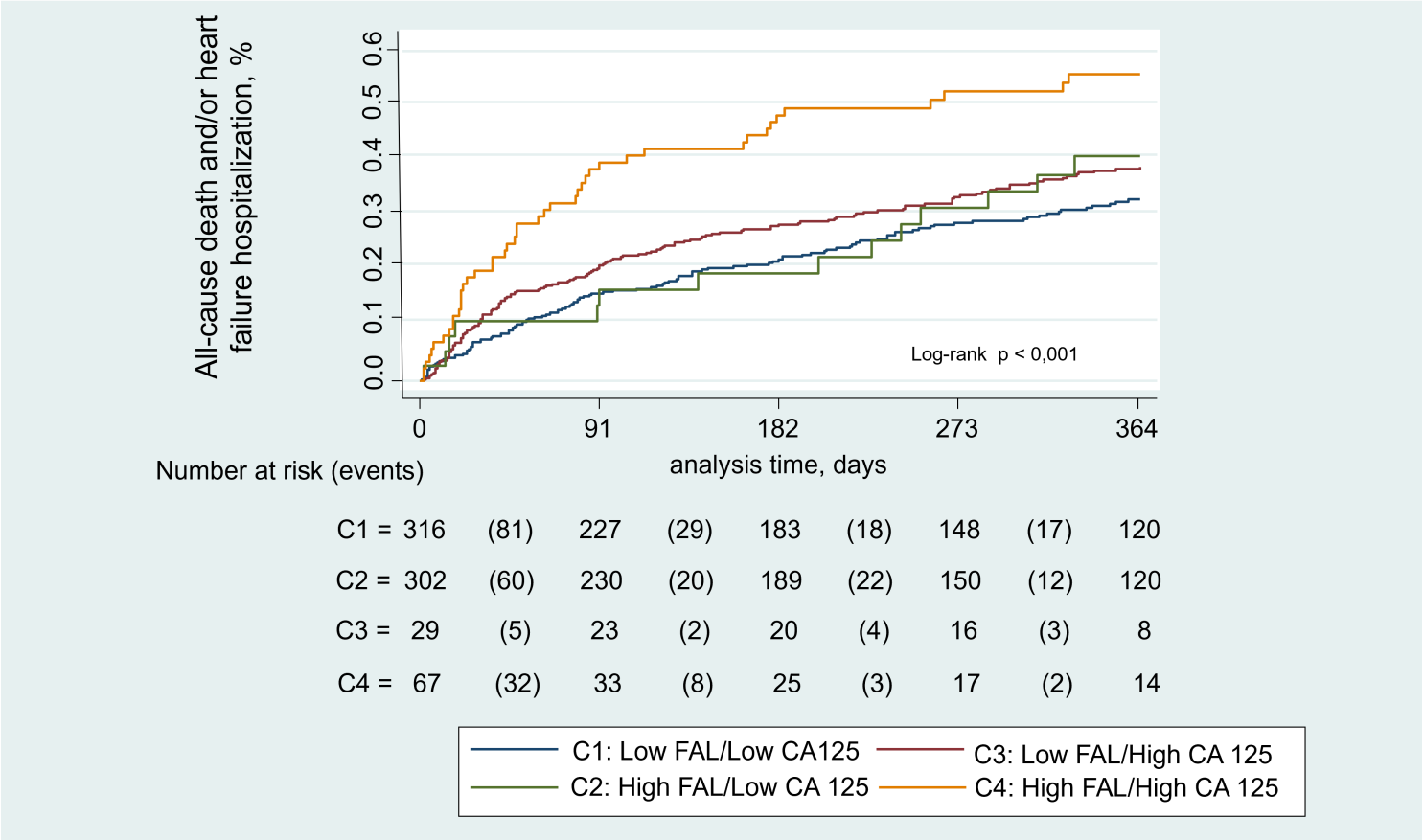


Figure 1

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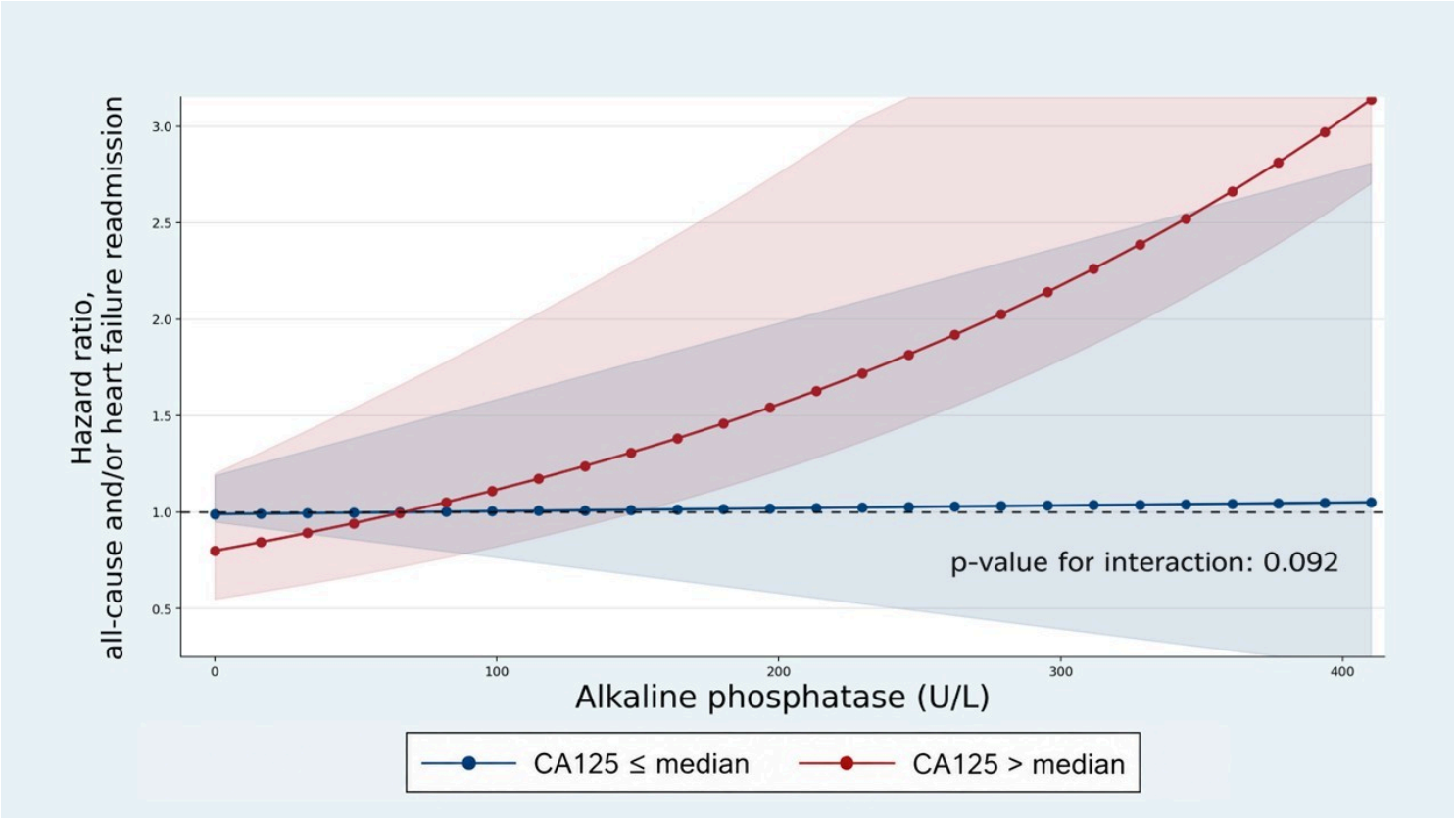


Figure 2

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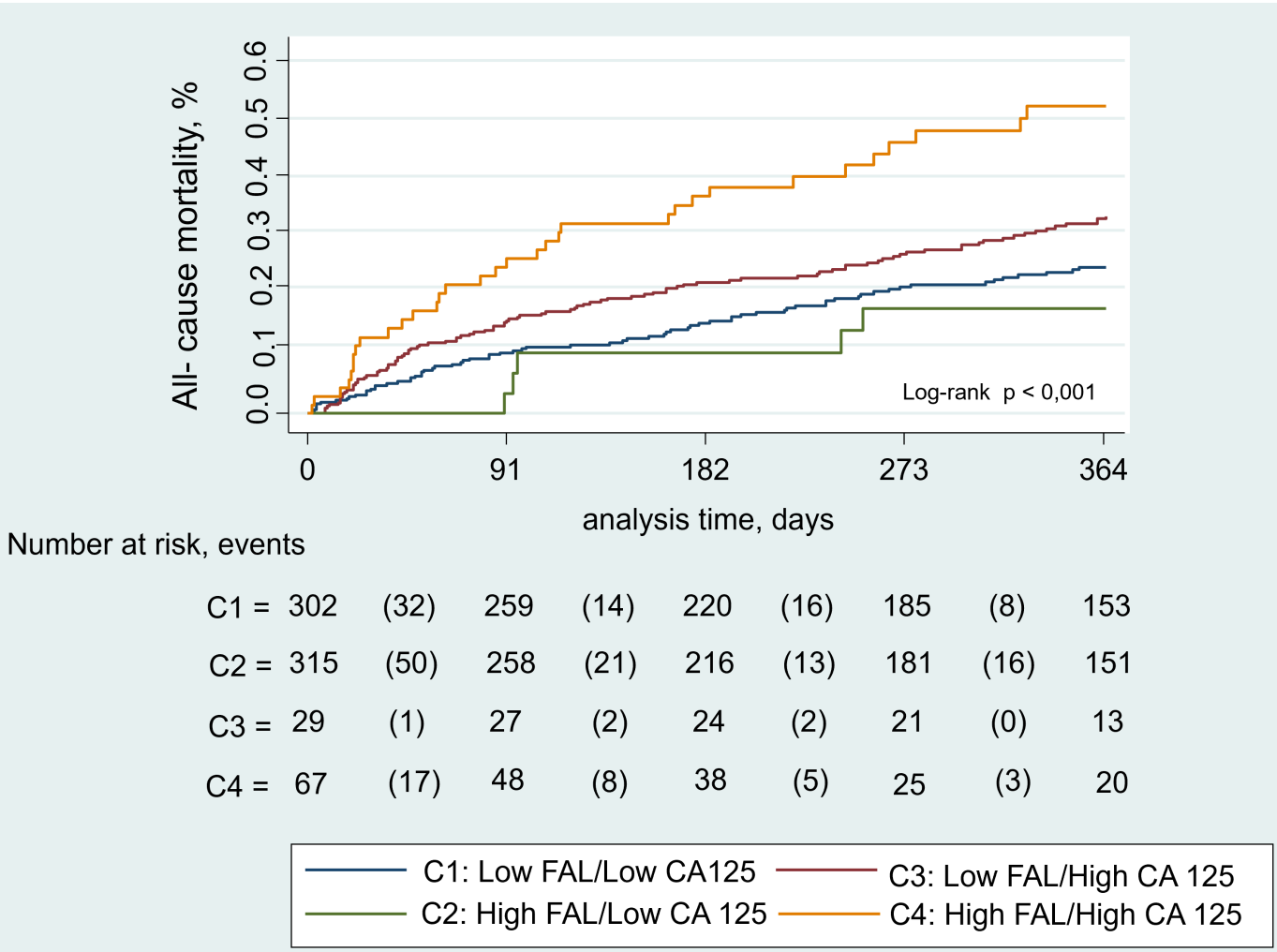


Figure 3

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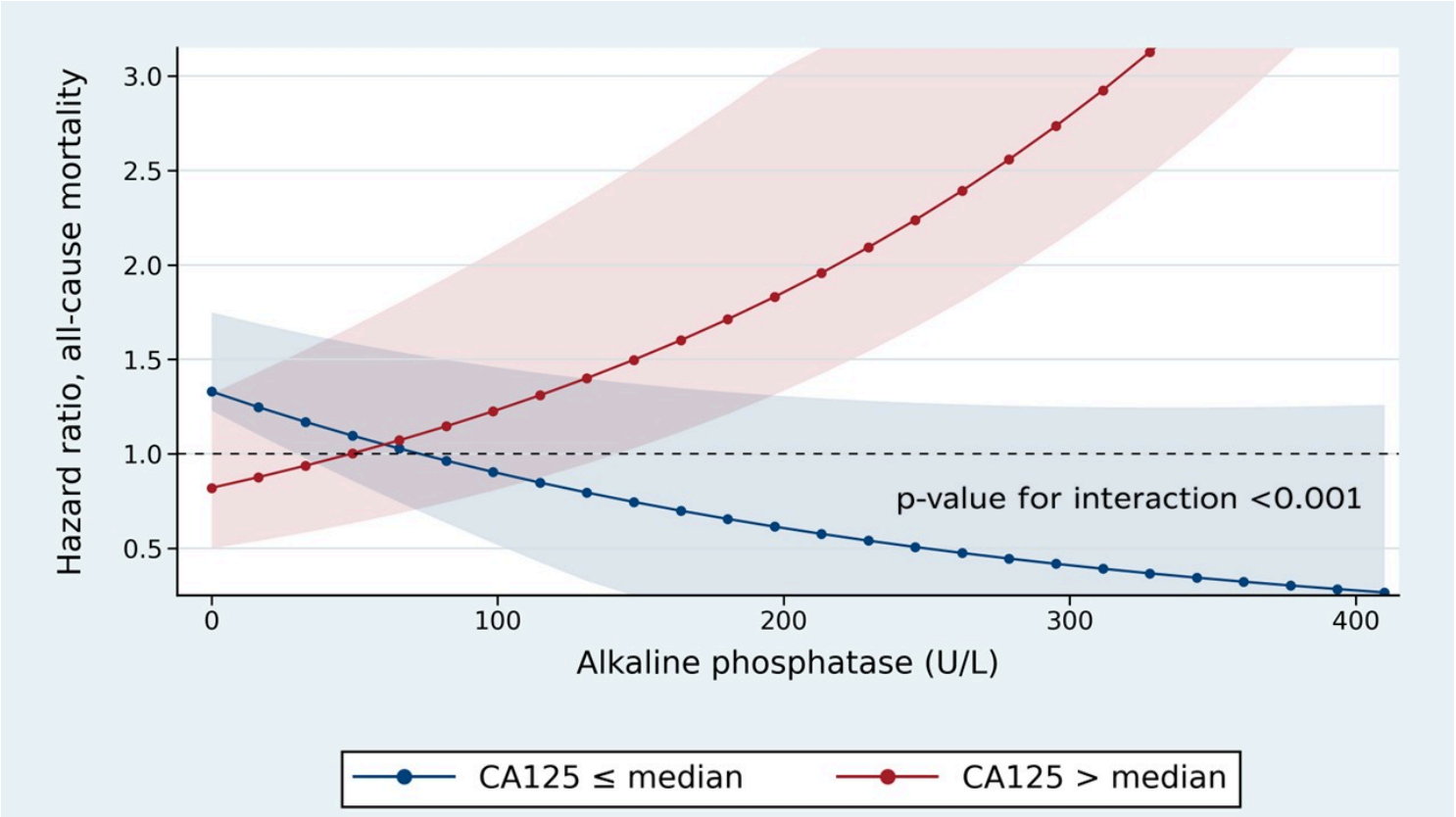


Figure 4

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