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CA125 versus NT-proBNP for Assessing Congestion and Predicting In-Hospital Mortality in Very Old Patients with Acute Heart Failure

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Abstract

Purpose

Very old patients with acute heart failure (AHF) are underrepresented in biomarker studies despite frequent congestion, frailty and in-hospital mortality. We compared carbohydrate antigen 125 (CA125) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) for congestion assessment and in-hospital mortality prediction.

Methods

This prospective single-centre observational study included consecutive patients aged ≥ 80 years diagnosed with AHF who were admitted to an acute geriatric unit. Congestion, geriatric assessment, CA125 and NT-proBNP were evaluated within 24 hours of admission. Associations with congestion were assessed using group comparisons, correlations and restricted cubic splines. Mortality discrimination was assessed using receiver operating characteristic curves.

Results

We included 210 patients (mean age 89.8 [SD 5.3]; 75.2% women; 88.1% frail). CA125 showed a weak, non-significant positive correlation with inferior vena cava diameter (Spearman ρ = 0.127; p = 0.067) and was numerically higher in patients with inferior vena cava diameter ≥ 21 mm, jugular venous distension and severe congestion. NT-proBNP was not significantly associated with the congestion measures evaluated. Twenty-two patients (10.5%) died during hospitalisation. The AUC for in-hospital mortality was 0.708 (95% CI 0.615–0.801) for CA125 and 0.733 (95% CI 0.620–0.846) for NT-proBNP. Spline analyses suggested increasing mortality risk with CA125 concentrations up to approximately 125 U/mL, whereas the NT-proBNP association became statistically significant only at approximately 13,000 pg/mL.

Conclusion

In very old patients admitted with AHF, CA125 demonstrated more consistent, although non-significant, association with systemic congestion than NT-proBNP. Both biomarkers showed moderate discrimination for in-hospital mortality, supporting a potentially complementary role in cardiogeriatric assessment.

Key summary points

Aim: To compare CA125 and NT-proBNP as markers of congestion and predictors of in-hospital mortality in patients aged 80 years or older admitted with acute heart failure.

Findings: CA125 showed a more consistent, albeit non-significant, association with systemic congestion, whereas NT-proBNP was not significantly associated with any of the congestion measures evaluated. Both biomarkers displayed moderate discrimination for in-hospital mortality. Spline modelling suggested a progressive increase in mortality risk with rising CA125 concentrations, reaching statistical significance across part of the concentration range.

Message: CA125 and NT-proBNP may provide complementary information in very old patients with acute heart failure, with CA125 potentially adding value to the assessment of systemic congestion and short-term mortality risk.

Introduction

Heart failure (HF) is a major cause of hospitalisation and mortality in older adults, and its clinical burden rises markedly with age [1–3]. Patients in their eighties and nineties admitted with acute heart failure (AHF) frequently have multimorbidity, polypharmacy, functional dependence and frailty. These characteristics influence presentation, treatment tolerance and prognosis, yet very old and frail patients remain underrepresented in HF research [3, 6]. This evidence gap is particularly relevant to geriatric medicine because biomarker results in this population need to be interpreted alongside functional status and frailty rather than as isolated biological measurements.

Congestion is a main clinical feature of AHF and an important therapeutic target. Its assessment is challenging in very old patients because signs and symptoms may be heterogeneous, atypical or difficult to quantify. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is widely used for HF diagnosis and prognostic assessment, but its concentrations are strongly influenced by age, renal function and cardiac phenotype [7]. Moreover, natriuretic peptides predominantly reflect myocardial wall stress and filling pressures and may not fully capture peripheral or systemic congestion. Recent studies of decongestion and clinical congestion scores support a multimodal approach to congestion assessment [8, 9].

Carbohydrate antigen 125 (CA125), a glycoprotein best known as oncological biomarker, has emerged as a marker of serosal inflammation and systemic congestion in HF [10, 11]. Previous studies have linked CA125 to peripheral oedema, pleural effusion, inferior vena cava (IVC) dilatation, right-sided dysfunction and intrarenal venous congestion [12–15]. CA125 is also less dependent on glomerular filtration than NT-proBNP, a potentially important advantage in geriatric populations with a high prevalence of chronic kidney disease [16]. Its associations with haemodynamic severity and adverse outcomes have been reported in both acute and chronic HF cohorts [17–19], and meta-analyses and recent reviews have reinforced its potential prognostic role [20–23]. However, most published cohorts are considerably younger than patients commonly admitted to acute geriatric units, and evidence on in-hospital mortality in the oldest old remains limited.

This study aimed to compare CA125 and NT-proBNP, measured at admission, as markers of clinical and ultrasonographic congestion and predictors of in-hospital mortality in patients aged ≥ 80 years admitted with AHF. We hypothesised that CA125 would correlate more closely with systemic congestion and

would provide short-term prognostic information complementary to NT-proBNP and comprehensive geriatric assessment.

Methods

Study design and population

We performed a prospective, longitudinal, single-centre observational study (OCTA-HF cohort) in the Acute Geriatric Unit of Hospital Universitario Central de la Cruz Roja San José y Santa Adela, Madrid, Spain. Consecutive patients were recruited between 9th March 2023 and 1st March 2024. Eligible patients were aged ≥80 years and admitted with AHF according to the 2021 European Society of Cardiology criteria [1]. Exclusion criteria were age <80 years, absence of informed consent, active malignancy, or a clinical decision to adopt a palliative approach because of advanced end-organ disease. The present analysis focuses on congestion at admission and mortality during the index hospitalisation.

Clinical and geriatric assessment

A standardised assessment was completed within the first 24 hours of admission. Demographic characteristics, living situation, cardiovascular risk factors, comorbidities and chronic HF treatment were recorded. Comorbidity burden was quantified using the Charlson Comorbidity Index [24]. Comprehensive geriatric assessment included assessment of functional status using the Barthel Index [25], frailty using the Clinical Frailty Scale (CFS) [26], nutritional status using the Mini Nutritional Assessment-Short Form [27], and medication review. Polypharmacy was defined as the regular use of five or more medications.

Assessment of congestion

Congestion assessment included peripheral oedema, jugular venous distension, hepatomegaly and orthopnoea. Bedside point-of-care ultrasonography (Philips Lumify S4-1; Philips Ultrasound, Bothell, WA, USA) was used to measure IVC diameter and identify the presence of pleural effusion. A modified composite congestion score (CCS), based on the clinical congestion score used by Núñez et al. in the BIOSTAT-CHF CA125 analysis [28], was calculated from orthopnoea, jugular venous distension and peripheral oedema. Orthopnoea and jugular venous distension each contributed one point. Oedema was scored as 0 for absent, ankle or below-knee oedema and 1 for above-knee oedema. CCS was categorised as no congestion (0), mild congestion (1-2) or severe congestion (3). For spline analyses, no/mild congestion was compared with severe congestion. Transthoracic echocardiographic assessment followed standard reporting recommendations [29].

Biomarker measurements

Blood samples were obtained within the first 24 hours of admission and processed according to institutional laboratory procedures. CA125 was measured using a luminescence immunometric assay (VITROS CA125; Ortho Clinical Diagnostics, Madrid, Spain), and NT-proBNP was measured using a fluorescence immunoassay (VIDAS NT-proBNP2; bioMérieux, Marcy-l'Étoile, France). Results are expressed as U/mL and pg/mL, respectively.

Outcomes and statistical analysis

The outcomes of this analysis were (1) clinical and ultrasonographic congestion at admission and (2) all-cause in-hospital mortality. Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range), and categorical variables as numbers and percentages. Between-group comparisons were performed using Student's t test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Spearman's rank correlation was used to assess the relationship between CA125 and continuous congestion measures.

Receiver operating characteristic (ROC) curves were constructed to assess discrimination for in-hospital mortality and to identify cut-offs maximising the balance between sensitivity and specificity. Restricted cubic spline logistic regression models were used to explore non-linear associations between continuous biomarker concentrations and peripheral oedema, severe CCS and in-hospital mortality. Knots were placed at the 10th, 50th and 90th percentiles. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and Stata version 17.0 (StataCorp, College Station, TX, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Universidad Alfonso X el Sabio (approval No. 2023_03/179; 8 March 2023). Written informed consent was obtained from participants or, when appropriate, their legally authorised representatives.

Results

Cohort characteristics

A total of 210 patients were included. The mean age was 89.8 (SD 5.3) years and 158 (75.2%) were women. Frailty was present in 185 patients (88.1%; CFS ≥5), the mean Barthel Index score was 64.1 (SD 30.9), and HF with preserved ejection fraction was the predominant phenotype (80.2%). Chronic kidney disease was present in 45.7% of patients. Median CA125 and NT-proBNP concentrations were 46.7 (24.1-108.0) U/mL and 5906 (3070-11,599) pg/mL, respectively. Congestion was frequent: 65.6% had an IVC diameter ≥21 mm, 79% had pleural effusion, 53.3% had jugular venous distension, and 11.4% had severe CCS (Table 1).

Table 1. Selected baseline characteristics of the study cohort.

Characteristic	Overall cohort (N = 210)
Age, years, mean (SD)	89.8 (5.3)
Women, n (%)	158 (75.2)
Nursing-home residence, n (%)	81 (38.6)
Barthel Index, mean (SD)	64.1 (30.9)
Clinical Frailty Scale, mean (SD)	5.88 (1.28)
Frailty, CFS ≥5, n (%)	185 (88.1)
Charlson Comorbidity Index, mean (SD)	3.64 (1.90)
Hypertension, n (%)	182 (86.7)
Diabetes mellitus, n (%)	64 (30.5)
Chronic kidney disease, n (%)	96 (45.7)
Ischaemic heart disease, n (%)	44 (21.0)
Atrial fibrillation, n (%)	142 (67.9)
HF with preserved ejection fraction, n (%)	166 (80.2)
CA125, U/mL, median (IQR)	46.7 (24.1–108.0)
NT-proBNP, pg/mL, median (IQR)	5906 (3070–11,599)
Creatinine, mg/dL, mean (SD)	1.3 (0.72)
eGFR (CKD-EPI), mL/min/1.73 m^2, mean (SD)	47.5 (18.2)
Haemoglobin, g/dL, mean (SD)	11.74 (2.01)
IVC diameter ≥21 mm, n (%)	137 (65.6)
Pleural effusion, n (%)	166 (79.0)
Jugular venous distension, n (%)	112 (53.3)
Orthopnoea, n (%)	106 (50.5)
Severe congestion, CCS = 3, n (%)	24 (11.4)

Abbreviations: CA125, carbohydrate antigen 125; CCS, composite congestion score; CFS, Clinical Frailty Scale; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; HF, heart failure; IVC, inferior vena cava; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

CA125, NT-proBNP and congestion

CA125 showed weak, non-significant positive correlations with IVC diameter (Spearman ρ = 0.127; p = 0.067) and CCS (ρ = 0.102; p = 0.139). CA125 concentrations were numerically higher in patients with an IVC diameter ≥21 mm than in those with an IVC diameter <21 mm (51.6 [27.5–116.0] vs 40.3 [18.2–87.9] U/mL; p = 0.140), in patients with versus without jugular venous distension (51.7 [27.5–112.5] vs 42.6 [19.8–97.3] U/mL; p = 0.140), and in patients with severe versus no/mild congestion (74.1 [29.8–141.0] vs 44.8 [23.8–96.9] U/mL; p = 0.106). Differences according to oedema category and orthopnoea were not statistically significant. By contrast, NT-proBNP concentrations did not differ significantly across the congestion variables evaluated (Table 2).

Table 2. CA125 and NT-proBNP concentrations according to congestion measures.

Congestion measure	CA125, U/mL	p	NT-proBNP, pg/mL	p
IVC diameter		0.140		0.334
IVC <21 mm	40.3 (18.2–87.9)		5738 (3062–12,852)	
IVC ≥21 mm	51.6 (27.5–116.0)		5925 (3085–11,571)	
Jugular venous distension		0.140		0.334
No jugular venous distension	42.6 (19.8–97.3)		5174 (3017–11,079)	
Jugular venous distension	51.7 (27.5–112.5)		6345 (3098–13,386)	
Orthopnoea		0.486		0.454
No orthopnoea	46.8 (25.2–91.5)		6201 (3062–13,277)	
Orthopnoea	48.4 (23.5–127.0)		5696 (3105–10,885)	
CCS		0.106		0.783
No/mild congestion (CCS 0–2)	44.8 (23.8–96.9)		5906 (3145–11,486)	
Severe congestion (CCS 3)	74.1 (29.8–141.0)		6102 (2219–13,638)	

Values are presented as median (IQR).

Abbreviations: CA125, carbohydrate antigen 125; CCS, composite congestion score; IQR, interquartile range; IVC, inferior vena cava; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Restricted cubic spline analyses were consistent with these group comparisons. For peripheral oedema, the CA125 curve was relatively flat at lower concentrations and rose progressively above approximately 100 U/mL; confidence intervals widened at higher concentrations and the association was not statistically significant (Fig. 1a). NT-proBNP showed no clear association with peripheral oedema (Fig. 1b).

For severe congestion assessed using the CCS, the CA125 curve rose most steeply up to approximately 120 U/mL and then plateaued, although the association was not statistically significant (Fig. 2a). NT-proBNP showed no clear association with severe congestion assessed using the CCS (Fig. 2b).

CA125 and NT-proBNP as predictors of in-hospital mortality

Twenty-two of 210 patients died during the index hospitalisation (10.5%). CA125 showed moderate discrimination for in-hospital mortality, with an AUC of 0.708 (95% CI 0.615–0.801). A cut-off of approximately 59 U/mL yielded a sensitivity of 72.7% and a specificity of 60.1%. NT-proBNP also showed moderate discrimination (AUC 0.733, 95% CI 0.620–0.846); a cut-off of approximately 5900 pg/mL yielded a sensitivity of 80.0% and a specificity of 53.0% (Table 3).

Table 3. Discrimination of in-hospital mortality by CA125 and NT-proBNP based on ROC curve analysis

Biomarker	AUC (95% CI)	Approximate cut-off	Sensitivity	Specificity
CA125	0.708 (0.615–0.801)	59 U/mL	72.7%	60.1%
NT-proBNP	0.733 (0.620–0.846)	5900 pg/mL	80.0%	53.0%

Abbreviations: AUC, area under the curve; CA125, carbohydrate antigen 125; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROC, receiver operating characteristic.

Spline modelling showed different concentration–risk profiles. For CA125, the estimated odds of in-hospital mortality rose steeply up to approximately 125 U/mL and then declined gradually, with the 95% confidence interval indicating a statistically significant association over part of the curve (Fig. 3a). NT-proBNP showed a positive, approximately linear association with in-hospital mortality, with the lower bound of the 95% confidence interval exceeding an odds ratio of 1 at concentrations above approximately 13,000 pg/mL (Fig. 3b).

Discussion

In this prospective cohort of very old patients admitted with AHF, CA125 showed more consistent numerical trends in relation to clinical and ultrasonographic markers of systemic congestion than NT-proBNP. CA125 concentrations were numerically higher in patients with a dilated IVC, jugular venous distension, and severe congestion assessed using the CCS, and spline analyses suggested increasing odds of peripheral oedema and severe congestion over parts of the CA125 concentration range. None of these congestion relationships reached conventional statistical significance, so the findings should be interpreted as exploratory trends rather than definitive associations. NT-proBNP, in contrast, showed no clear association with the congestion measures evaluated. For in-hospital mortality, both biomarkers had moderate and numerically similar discrimination on ROC analysis, while spline modelling suggested different concentration–risk profiles: the estimated odds of mortality associated with CA125 rose steeply up to approximately 125 U/mL and then declined gradually, whereas those associated with NT-

proBNP increased progressively, with statistical significance observed only above approximately 13,000 pg/mL.

The relationship between CA125 and systemic congestion is biologically plausible and consistent with previous work. CA125 is produced by mesothelial cells and appears to respond to serosal stretch, venous congestion and inflammatory activation [10, 30-32]. Llàcer et al. reported independent associations between CA125 and peripheral oedema, pleural effusion and IVC diameter ≥21 mm in AHF [13]. Miñana et al. identified pleural effusion, tricuspid regurgitation severity, age, NT-proBNP and peripheral oedema among the principal determinants of CA125 concentrations [12]. In addition, CA125, but not NT-proBNP, has been associated with congestive intrarenal venous flow [14], and CA125 has shown particular prognostic value in AHF with severe tricuspid regurgitation [33]. These observations, together with prior systematic evidence [34], support the concept that CA125 captures a systemic and predominantly right sided/extravascular component of congestion that is not fully represented by natriuretic peptides.

This distinction may be particularly relevant in geriatric AHF. In our cohort, the mean age was almost 90 years, 88% of patients were frail, nearly half had chronic kidney disease and four in five had HF with preserved ejection fraction. NT-proBNP is an established marker of myocardial wall stress and remains essential for HF diagnosis and prognosis, but its interpretation is modified by renal dysfunction, age and ventricular phenotype [7]. In previous AHF analyses, renal function, left ventricular systolic dysfunction and age were major determinants of NT-proBNP, whereas congestion variables had a smaller influence [12]. CA125 is less dependent on renal clearance, and this different biology may explain why the two biomarkers may be complementary rather than competing tests [16]. Evidence in HF with preserved ejection fraction and in older AHF populations likewise supports the clinical relevance of CA125 in phenotypes characterised by systemic congestion and multimorbidity [35-37].

Our congestion findings did not reach statistical significance despite directionally consistent patterns for CA125. Several characteristics of the cohort may have contributed. Congestion was highly prevalent, reducing contrast between clinically defined groups, and only 24 patients had severe congestion assessed using the CCS. In addition, congestion in very old adults is multidimensional and clinical signs may have limited sensitivity and interobserver reproducibility. Studies of residual congestion and contemporary reviews of the congestion phenotype emphasise that no single bedside sign adequately captures total congestion burden [38,39]. These limitations reinforce the value of combining physical examination, point-of-care ultrasound and biomarkers rather than expecting any single measure to define congestion accurately. Recent data from chronic HF also show that CA125 and NT-proBNP provide different information when congestion is assessed comprehensively [40].

The in-hospital mortality analysis provides a second clinically relevant signal. CA125 and NT-proBNP both showed moderate discrimination for in-hospital mortality. The difference between their AUCs should not be interpreted as evidence of superiority without a formal statistical comparison. However, the spline curves suggested that the mortality association emerged over different concentration ranges.

The estimated odds of mortality associated with CA125 rose rapidly up to approximately 125 U/mL and then declined gradually, whereas the association with NT-proBNP did not reach statistical significance until approximately 13,000 pg/mL. This pattern is compatible with complementary pathophysiological information: CA125 may integrate systemic congestion and serosal inflammation, whereas NT-proBNP primarily reflects cardiac wall stress. A 2025 pilot study specifically evaluating CA125 kinetics in relation to in-hospital mortality reported that an increase in CA125 during admission was associated with higher in-hospital mortality [41]. A 2026 systematic review of congestion biomarkers in AHF also identified CA125 as providing complementary information to natriuretic peptides for congestion assessment and prognosis [42]. Because only 22 in-hospital deaths occurred in our cohort, these findings remain exploratory and require external validation before specific thresholds are used clinically.

The potential clinical appeal of CA125 is its availability, low cost and relative stability, together with previous evidence supporting its use to monitor decongestion and guide diuretic treatment. Serial CA125 changes have been associated with clinical course [43], and the CHANCE-HF randomised study showed the feasibility of CA125-guided therapy in AHF [44]. A subsequent randomised study in patients with AHF and renal dysfunction also evaluated CA125-guided diuretic treatment [45]. Nevertheless, our study did not test a CA125-guided treatment strategy, did not assess serial biomarker kinetics during admission, and cannot establish that treatment intensification based on CA125 improves outcomes. The present findings therefore support further investigation of risk phenotyping and hypothesis generation rather than treatment recommendations.

The geriatric context is central to the interpretation of these results. Our cohort was characterised by substantial functional dependence and frailty, making it more representative of patients managed in acute geriatric practice than many previous biomarker cohorts [3-6]. Biomarkers should therefore complement, not replace, geriatric assessment. A clinically useful cardiogeriatric model would integrate congestion phenotype, renal function, cardiac biomarkers and measures of vulnerability such as the Barthel Index and CFS [24-27].

Strengths and limitations

Strengths of this study include its prospective design, consecutive recruitment, the inclusion of a cohort of very old patients with AHF, which remains scarcely represented in the literature**,** systematic comprehensive geriatric assessment, and parallel evaluation of CA125 and NT-proBNP against both clinical and point-of-care ultrasound measures of congestion.

Several limitations should be acknowledged. First, this was a single-centre study with a modest sample size, and only 22 in-hospital deaths occurred, which limits statistical precision and restricts multivariable modelling because of the risk of overfitting. Second, congestion was assessed clinically and by ultrasound, both of which are operator-dependent and subject to inter-observer variability; moreover, right ventricular function and detailed venous Doppler parameters were not systematically available. Third,

biomarker measurements were obtained at admission only, which precluded the evaluation of serial changes during decongestion. Fourth, multiple congestion comparisons were exploratory and were not adjusted for multiplicity, so the findings should be considered hypothesis-generating. Finally, the cut-offs derived from ROC analyses were data-driven and require external validation.

Conclusion

In very old patients hospitalised with AHF, CA125 showed a more consistent, although non-significant, association with systemic congestion than NT-proBNP, which was not significantly associated with any of the congestion measures assessed. Both biomarkers demonstrated moderate discrimination for in-hospital mortality, with distinct concentration-risk patterns in spline analyses. These findings suggest a potential complementary role for CA125 and NT-proBNP within a comprehensive cardiogeriatric assessment that also incorporates frailty, function and renal status. Further multicentre studies incorporating serial biomarker measurements and externally validated thresholds are needed before CA125-guided short-term management can be recommended in this population.

Abbreviations

CA125
carbohydrate antigen 125
CCS
composite congestion score
IQR
interquartile range
IVC
inferior vena cava
NT-proBNP
N-terminal pro-B-type natriuretic peptide.

Declarations

Author contributions: Conceptualisation, J.J.-H.; methodology, J.J.-H.; investigation, J.J.-H. and N.G.-C.; data curation, J.J.-H. and A.M-N.; writing - original draft, J.J.-H.; writing - review and editing, J.J.-H., M.R., M.Q.-F., R.T. and F.J.G.-P.; supervision, M.R., M.Q.-F. and F.J.G.-P. All authors reviewed and approved the final manuscript.

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Consent to participate: Written informed consent was obtained from all participants or, when appropriate, their legally authorised representatives.

Data availability: Data are available from the corresponding author on reasonable request, subject to applicable privacy and ethical restrictions.

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Figures

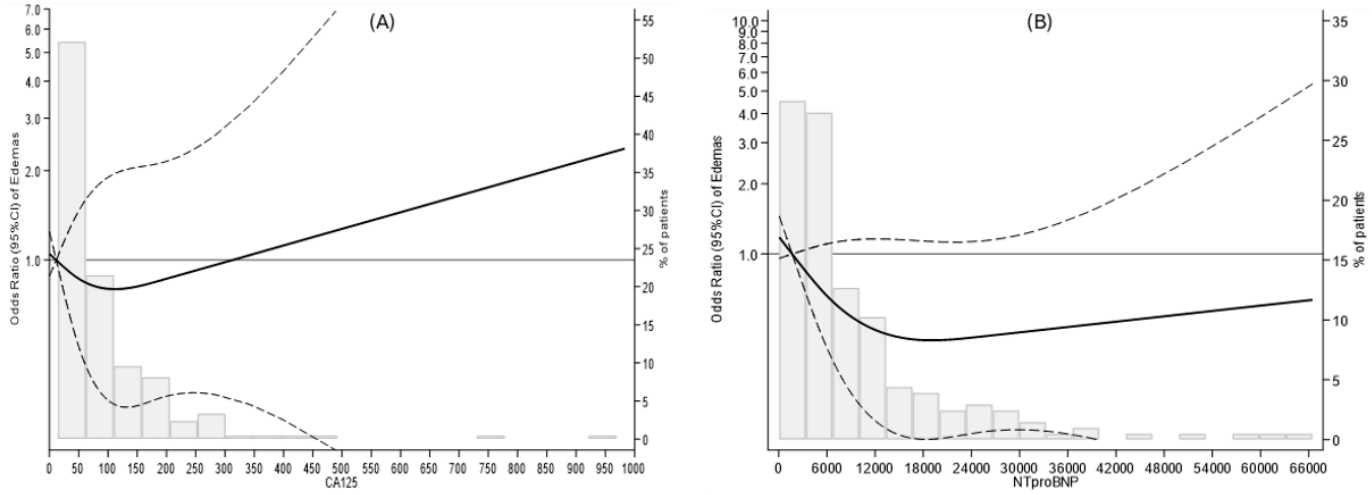

Figure 1

Restricted cubic spline analyses for peripheral oedema according to (a) CA125 and (b) NT-proBNP. Solid lines represent odds ratios, and dashed lines represent 95% confidence intervals. Histograms show the distribution of biomarker concentrations

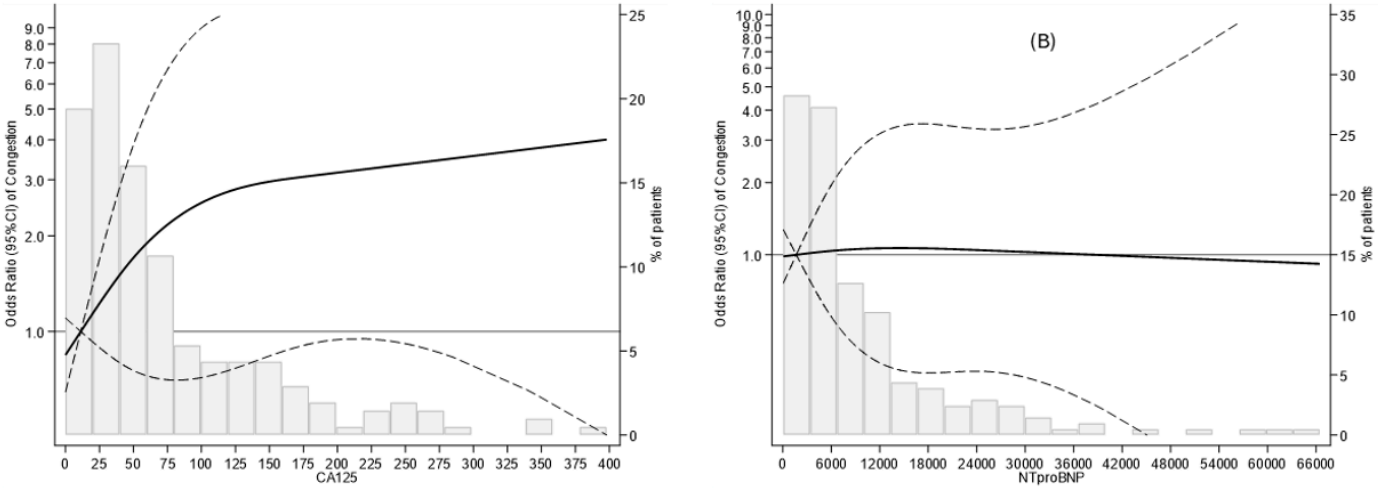

Figure 2

Restricted cubic spline analyses for severe congestion according to the composite congestion score (CCS) for (a) CA125 and (b) NT-proBNP. Solid lines represent odds ratios, and dashed lines represent 95% confidence intervals. Histograms show the distribution of biomarker concentrations

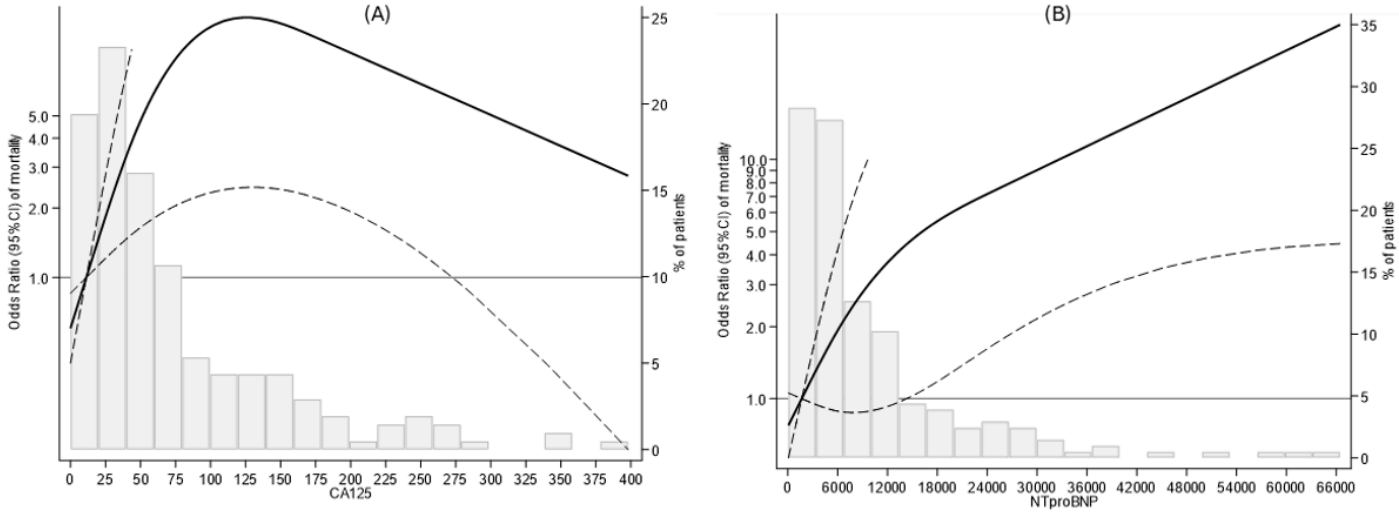

Figure 3

Restricted cubic spline analyses for in-hospital mortality according to (a) CA125 and (b) NT-proBNP. Solid lines represent odds ratios, and dashed lines represent 95% confidence intervals. Histograms show the distribution of biomarker concentrations