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Multimarker cardiocirculatory patterns at ICU admission and mortality in non- cardiac critically ill patients: a retrospective study

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Abstract

Background:

Elevated cardiac biomarkers are frequently observed in critically ill patients, even in the absence of primary cardiac disease. Although N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) are each associated with adverse outcomes, the clinical relevance of their combined assessment in non-cardiac ICU populations remains uncertain. We investigated whether the joint distribution of NT-proBNP and hs-cTnT at ICU admission delineates distinct cardiocirculatory patterns associated with short-term mortality. In a single-center retrospective cohort of 827 consecutive non-cardiac ICU patients, biomarkers were dichotomized at cohort-specific medians, and patients were classified into four cardiocirculatory patterns. The primary outcome was 30-day all-cause mortality.

Results:

The identified cardiocirculatory patterns differed significantly with respect to baseline characteristics and markers of hemodynamic instability, metabolic stress, systemic inflammation, and organ dysfunction. Thirty-day survival varied markedly across patterns (log-rank $p < 0.001$). After adjustment for disease severity using the Sequential Organ Failure Assessment (SOFA) score, only the combined high NT-proBNP/high hs-cTnT pattern was independently associated with increased 30-day mortality (adjusted hazard ratio 1.51; 95% CI 1.16–1.97; $p = 0.002$). Isolated elevation of either NT-proBNP or hs-cTnT alone was not independently associated with mortality.

Conclusions:

In non-cardiac critically ill patients, the combined assessment of NT-proBNP and hs-cTnT at ICU admission identifies distinct cardiocirculatory patterns with divergent clinical profiles and prognoses. This multimarker phenotyping approach provides prognostic information beyond isolated biomarker interpretation and may enhance early risk stratification in the ICU setting.

Introduction

Critically ill patients frequently develop profound cardiovascular and circulatory stress, even in the absence of primary cardiac disease (1, 2). Systemic inflammation, hypoxaemia, haemodynamic instability, catecholamine exposure and renal dysfunction contribute to complex alterations in cardiac loading conditions and myocardial integrity (1, 3). Consequently, biochemical markers traditionally considered “cardiac” are commonly elevated in non-cardiac intensive care unit (ICU) populations and carry important prognostic information (4–6). Nevertheless, the pathophysiological interpretation and

clinical implications of these biomarker elevations in non-cardiac critical illness remain incompletely understood (7, 8).

High-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) reflect distinct yet complementary pathophysiological dimensions of cardiovascular stress. Elevated hs-cTnT in critically ill patients most often indicates myocardial injury related to supply–demand mismatch, inflammatory myocardial depression or microcirculatory dysfunction rather than acute coronary syndromes (9–11). Indeed, recent angiographic data demonstrate that while acute plaque rupture is infrequent in septic patients with elevated troponin, up to two-thirds harbor underlying obstructive coronary artery disease, suggesting that critical illness unmasks a vulnerable coronary substrate via Type 2 myocardial infarction (12). In contrast, NT-proBNP primarily reflects haemodynamic load, ventricular wall stress, neurohumoral activation and impaired renal clearance, serving as a surrogate marker of global cardiocirculatory strain (6, 13–15).

Although the prognostic value of hs-cTnT and NT-proBNP has been consistently demonstrated in both cardiac and non-cardiac ICU cohorts, most prior studies have focused on the isolated predictive performance of individual biomarkers (4, 9, 13, 16–21). Reliance on a single marker, however, may inadequately capture the heterogeneity of cardiovascular responses to critical illness (22). From a pathophysiological standpoint, combined assessment of myocardial injury and haemodynamic stress may delineate biologically meaningful cardiocirculatory phenotypes more effectively than either marker alone (23).

Non-cardiac ICU populations provide a unique context for such multimarker phenotyping. In contrast to cardiac cohorts, where biomarker elevations are often driven by underlying structural heart disease or acute coronary pathology, non-cardiac critical illness allows cardiovascular biomarkers to be evaluated primarily as integrative indicators of systemic circulatory stress and host response severity. This setting minimizes confounding by overt cardiac diagnoses and enables exploration of distinct cardiocirculatory stress patterns across heterogeneous critical illness syndromes.

To our knowledge, the combined prognostic implications of NT-proBNP- and hs-cTnT-defined cardiocirculatory patterns have not been systematically evaluated in non-cardiac ICU populations. We therefore hypothesised that the joint distribution of NT-proBNP and hs-cTnT at ICU admission identifies discrete cardiocirculatory patterns associated with distinct short-term prognoses. Specifically, we aimed to classify patients into four biomarker-based patterns and to examine their associations with 30-day mortality, independent of overall illness severity.

Data collection

We conducted a retrospective analysis of clinical records from adult patients (≥ 18 years) consecutively admitted to the ICU of the University Hospital in Kraków, Poland, between January 2021 and December 2022. Patients admitted for acute cardiac conditions, including acute coronary syndrome, acute decompensated heart failure, out-of-hospital cardiac arrest, or pulmonary embolism, were excluded. For

all included patients, both hs-cTnT and NT-proBNP were measured at ICU admission as part of routine diagnostics. Both biomarkers were analysed in the central hospital laboratory using standardized immunoassay platforms validated for clinical use (enzyme-linked immuno-chemiluminescent assay [ECLIA] on a Cobas Pro analyzer; Roche Diagnostics GmbH, Mannheim, Germany). Additional clinical variables—including demographics, comorbidities, laboratory findings, organ support modalities, and clinical outcomes—were retrieved from the hospital's electronic medical record system. The intensity of vasoactive and inotropic support on ICU admission was quantified using the Vasoactive–Inotropic Score (VIS), a validated composite measure reflecting the cumulative burden of pharmacological cardiovascular support (24). The Sequential Organ Failure Assessment (SOFA) score was calculated for each patient using clinical and laboratory data obtained within the first 24 hours of ICU admission.

The primary outcome was 30-day all-cause mortality, ascertained through the Polish National Electronic Population Registration System. Patients with incomplete data for hs-cTnT, NT-proBNP, SOFA score, or survival status were excluded from the analysis.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (25). A completed STROBE checklist indicating where each item is addressed in the manuscript is provided as Supplementary Table S1. A flowchart depicting the patient inclusion process is shown in Fig. 1.

Ethical Considerations

This retrospective study was approved by the Bioethics Committee of the Jagiellonian University (approval number 118.0043.1.160.2024). Given the retrospective design and use of anonymized data, the requirement for individual informed consent was waived. All procedures were conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its subsequent amendments.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables are expressed as absolute numbers and percentages. Normality of distribution was assessed using visual inspection and the Shapiro–Wilk test. As most variables were non-normally distributed, non-parametric methods were applied throughout the analyses.

Pattern definition

Patients were categorized into four cardiocirculatory patterns based on the joint distribution of NT-proBNP and hs-cTnT concentrations measured at ICU admission. For each biomarker, cohort-specific median values served as cut-off points to define "low" and "high" categories. This approach resulted in four patterns: Low NT-proBNP / Low hs-cTnT, High NT-proBNP / Low hs-cTnT, Low NT-proBNP / High hs-cTnT, and High NT-proBNP / High hs-cTnT. Median-based stratification was chosen to ensure balanced

group sizes, reduce the influence of extreme values, and avoid the use of arbitrary clinical thresholds in a heterogeneous non-cardiac ICU population, in which biomarker elevations frequently reflect systemic cardiocirculatory stress rather than specific cardiac pathology.

Comparative and survival analyses

Between-pattern comparisons of baseline characteristics and laboratory, hemodynamic, and severity variables were performed using the Kruskal–Wallis test for continuous data and the χ^2 test or Fisher's exact test, as appropriate, for categorical data. When overall group differences were statistically significant, post hoc pairwise comparisons were conducted using Dunn's test with Holm correction for multiple testing. Adjusted p-values are reported. Time-to-event analyses were performed using Cox proportional hazards regression to evaluate the association between cardiocirculatory patterns and 30-day all-cause mortality. Patterns were first analysed in unadjusted models and subsequently adjusted for global illness severity using the Sequential Organ Failure Assessment (SOFA) score. Adjustment for SOFA was chosen to account for overall illness severity and global organ failure, while allowing evaluation of incremental cardiocirculatory dysfunction reflected by NT-proBNP and hs-cTnT beyond the SOFA framework. The proportional hazards assumption was assessed using Schoenfeld residuals. Effect estimates are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). To address potential information loss associated with median-based dichotomisation, complementary analyses were performed modelling hs-cTnT and NT-proBNP as continuous variables after log-transformation. Joint associations between biomarkers and 30-day mortality were explored using generalised additive models, generating two-dimensional risk surfaces. These analyses were conducted both without adjustment and adjusted for SOFA score to visualise the joint biomarker effect at a constant level of illness severity. Formal assessment of a non-linear biomarker interaction was performed by comparing SOFA-adjusted additive and two-dimensional smooth models using likelihood ratio testing. To facilitate integrative visualization of complex multidimensional relationships, chord diagrams were generated, i.e.: baseline characteristics and comorbidities showing statistically significant differences across patterns ($p < 0.05$) were linked to cardiocirculatory patterns, with link weights proportional to $-\log10$(p-values) (panel A. Chord plots were used for descriptive visualization only and did not replace inferential statistical analyses presented in tables.

All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using R software (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria). Sample size adequacy was confirmed by power analysis conducted in G*Power.

Results

Clinical characteristics of study subjects

A total of 827 non-cardiac critically ill patients were included in the analysis. The median age was 67 years (IQR, 59–76), and 70.7% of the participants were male. Admissions were predominantly medical (59.5%), with the remainder following surgical procedures. The overall 30-day all-cause mortality rate was 46.7% (n = 386).

Clinical characteristics according to cardiocirculatory patterns

Baseline clinical characteristics stratified by NT-proBNP × hs-cTnT–defined cardiocirculatory patterns are summarized in Table 1. Median NT-proBNP and hs-cTnT concentrations at ICU admission were used as cohort-specific cut-off values to define low and high biomarker categories. The median NT-proBNP concentration was 1486 pg/mL and the median hs-cTnT concentration was 48.9 ng/L. Based on these thresholds, 287 patients (34.7%) were classified as Low NT-proBNP / Low hs-cTnT, 126 (15.2%) as High NT-proBNP / Low hs-cTnT, 126 (15.2%) as Low NT-proBNP / High hs-cTnT, and 288 (34.9%) as High NT-proBNP / High hs-cTnT.

Table 1
Baseline clinical characteristics according to NT-proBNP × hs-cTnT cardiocirculatory patterns

Parameter	Low NT-proBNP / Low hs-cTnT (n = 287, 34.7%)	High NT-proBNP / Low hs-cTnT (n = 126, 15.2%)	Low NT-proBNP / High hs-cTnT (n = 126, 15.2%)	High NT-proBNP / High hs-cTnT (n = 288, 34.9%)	p value
Age, years, median (IQR)	57.0 (44.5–67.0)	67.0 (59.0–74.0)	61.0 (44.2–67.8)	69.0 (60.0–76.0)	< 0.001
Male sex, n (%)	199 (69.3)	71 (56.3)	87 (69.0)	185 (64.2)	0.059
BMI[a], median (IQR) *	27.8 (24.7–31.8)	27.3 (24.5–32.2)	26.9 (24.3–31.1)	27.7 (24.5–31.7)	0.642
Comorbidities					
Arterial hypertension, n (%)	130 (45.3)	72 (57.1)	47 (37.3)	185 (64.2)	< 0.001
COPD, n (%)	22 (7.7)	20 (15.9)	3 (2.4)	29 (10.1)	0.002
Ischemic heart disease, n (%)	31 (10.8)	27 (21.4)	12 (9.5)	76 (26.4)	< 0.001
Diabetes mellitus, n (%)	67 (23.3)	38 (30.2)	25 (19.8)	89 (30.9)	0.045
Chronic kidney disease, n (%)	16 (5.6)	16 (12.7)	3 (2.4)	70 (24.3)	< 0.001
Chronic hepatic failure, n (%)	5 (1.7)	5 (4.0)	6 (4.8)	14 (4.9)	0.197
Heart failure, n (%)	19 (6.6)	31 (24.6)	6 (4.8)	87 (30.2)	< 0.001
Active malignancy, n (%)	23 (8.0)	14 (11.1)	11 (8.7)	34 (11.8)	0.438
History of stroke, n (%)	8 (2.8)	10 (7.9)	8 (6.3)	19 (6.6)	0.094
Admission diagnosis category					

Admission diagnosis categories were mutually exclusive, and each patient was assigned to a single predominant diagnosis at ICU admission. [b]Shock of any etiology included patients with circulatory failure secondary to non-cardiac causes such as hypovolemia, trauma, internal hemorrhage, anaphylaxis, metabolic or neurogenic shock.

Parameter	Low NT-proBNP / Low hs-cTnT (n = 287, 34.7%)	High NT-proBNP / Low hs-cTnT (n = 126, 15.2%)	Low NT-proBNP / High hs-cTnT (n = 126, 15.2%)	High NT-proBNP / High hs-cTnT (n = 288, 34.9%)	p value
Respiratory failure, n (%)	82 (28.6)	31 (24.6)	29 (23.0)	110 (38.2)	0.003
Sepsis, n (%)	21 (7.3)	9 (7.1)	31 (24.6)	60 (20.9)	< 0.001
Shock of any etiology[b], n (%)	111 (38.5)	57 (45.2)	20 (15.9)	61 (21.3)	< 0.001
Postoperative, n (%)	73 (25.3)	29 (23.0)	46 (36.5)	55 (19.2)	0.002

Admission diagnosis categories were mutually exclusive, and each patient was assigned to a single predominant diagnosis at ICU admission. [b]Shock of any etiology included patients with circulatory failure secondary to non-cardiac causes such as hypovolemia, trauma, internal hemorrhage, anaphylaxis, metabolic or neurogenic shock.

Patient age and comorbidity burden differed significantly across patterns. Individuals with concomitant elevation of both NT-proBNP and hs-cTnT were older and more frequently had cardiovascular comorbidities, including arterial hypertension, ischemic heart disease, and chronic kidney disease. In contrast, patients in the Low NT-proBNP / Low hs-cTnT pattern were generally younger and less burdened by chronic cardiovascular conditions (Table 1 and Supplementary Fig. 1).

Clinical, laboratory, and organ dysfunction parameters at ICU admission differed significantly across the four cardiocirculatory patterns (Table 2). A clear stepwise deterioration was observed for markers of circulatory failure and metabolic stress, with progressively higher lactate concentrations and lower mean arterial pressure across patterns, culminating in the most pronounced derangements among patients with concomitant elevation of both biomarkers (High NT-proBNP / High hs-cTnT). This group also required the highest intensity of vasoactive and inotropic support, as reflected by greater VIS values at admission. Markers of organ dysfunction displayed a consistent phenotype-dependent pattern. Renal and hepatic dysfunction were most pronounced in the High NT-proBNP / High hs-cTnT pattern, as indicated by markedly elevated creatinine and bilirubin concentrations, along with the highest SOFA scores. Similarly, markers of inflammatory and infectious burden, including high-sensitivity C-reactive protein and procalcitonin, increased across patterns and reached the highest levels in patients with dual biomarker elevation. Respiratory impairment, assessed using the PaO_2/FiO_2 ratio, differed significantly between patterns and was lowest in the High NT-proBNP / High hs-cTnT group, underscoring the systemic nature of circulatory and organ dysfunction in these patients. In contrast, erythrocyte indices demonstrated a modest decline across patterns, whereas platelet counts showed greater variability and only borderline statistical significance. Overall, patients with simultaneous elevation of NT-proBNP and hs-cTnT consistently exhibited the most severe hemodynamic instability, multisystem organ dysfunction,

and inflammatory activation at ICU admission. To identify which specific between-phenotype contrasts contributed to the overall group differences observed in Table 2, post hoc pairwise comparisons were performed using Dunn’s test with Holm correction (Supplementary Table S2).

Table 2
Clinical, laboratory, and prognostic parameters on ICU admission according to NT-proBNP × hs-cTnT cardiocirculatory patterns

Parameter	Low NT-proBNP / Low hs-cTnT (n = 287, 34.7%)	High NT-proBNP / Low hs-cTnT (n = 126, 15.2%)	Low NT-proBNP / High hs-cTnT (n = 126, 15.2%)	High NT-proBNP / High hs-cTnT (n = 288, 34.9%)	p value
Lactate, mmol/L	1.5 (1.0–2.6)	1.7 (1.2–3.4)	2.2 (1.4–4.5)	2.2 (1.3–4.4)	< 0.001
Arterial pH	7.3 (7.3–7.4)	7.3 (7.2–7.4)	7.3 (7.2–7.4)	7.3 (7.2–7.4)	< 0.001
Mean arterial pressure, mmHg	83.3 (70.0–96.7)	76.7 (60.0–92.9)	78.3 (60.0–90.0)	75.0 (60.0–90.0)	< 0.001
Heart rate, bpm	90.0 (70.0–102.5)	90.0 (75.0–110.0)	90.0 (75.0–110.0)	95.0 (80.0–110.0)	0.003
Noradrenaline dose, µg/kg/min	0.0 (0.0–0.1)	0.1 (0.0–0.3)	0.1 (0.0–0.4)	0.1 (0.0–0.3)	< 0.001
VIS score at admission to the ICU	5.0 (0.0–10.0)	10.0 (2.0–30.0)	15.0 (5.0–35.8)	12.0 (2.0–30.0)	< 0.001
NT-proBNP, pg/mL	317.0 (116.5–778.5)	3133.5 (2049.5–5638.0)	526.0 (194.5–995.5)	6865.0 (3507.5–16638.5)	< 0.001
hs-cTnT, ng/L	15.5 (6.8–25.6)	27.9 (19.6–35.5)	123.5 (73.5–242.2)	172.7 (90.2–595.6)	< 0.001
PaO_2/FiO_2 ratio	182.6 (96.6–354.7)	182.2 (99.6–262.6)	248.5 (124.1–402.9)	155.4 (84.4–281.9)	< 0.001
Creatinine, µmol/L	75.0 (57.0–103.0)	118.0 (68.8–179.0)	98.0 (62.5–133.0)	148.0 (93.0–289.0)	< 0.001
Total bilirubin, µmol/L	10.0 (5.0 – 17.0)	12.0 (6.0 – 21.0)	10.0 (7.0–19.0)	13.0 (7.0–21.0)	0.011
Hemoglobin, g/dL	12.5 (10.8–13.9)	11.1 (9.6–13.0)	11.6 (9.9–13.4)	11.4 (9.5–13.3)	< 0.001
Platelet count, $\times 10^9$/L	209.0 (157.0–282.0)	202.5 (127.8–305.5)	185.0 (125.0–238.0)	194.0 (121.0–268.0)	0.049

Comparisons across NT-proBNP × hs-cTnT cardiocirculatory patterns were performed using the Kruskal–Wallis test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Parameter	Low NT-proBNP / Low hs-cTnT (n = 287, 34.7%)	High NT-proBNP / Low hs-cTnT (n = 126, 15.2%)	Low NT-proBNP / High hs-cTnT (n = 126, 15.2%)	High NT-proBNP / High hs-cTnT (n = 288, 34.9%)	p value
Procalcitonin, ng/mL	0.3 (0.1–0.9)	0.6 (0.2–8.1)	0.4 (0.1–1.2)	1.6 (0.5–9.6)	< 0.001
SOFA score	9.0 (7.0–11.0)	11.0 (8.0–13.0)	10.0 (8.0–12.0)	11.0 (9.0–14.0)	< 0.001
ICU length of stay, days	12.0 (6.0–24.0)	13.0 (4.2–22.0)	11.0 (4.0–23.8)	9.0 (3.0–17.0)	< 0.001
Hospital length of stay, days	20.0 (12.0–32.0)	18.0 (11.0–32.8)	18.0 (8.0–30.8)	15.0 (8.0–28.0)	0.003
30-day all-cause mortality, n (%)	107 (37.3%)	58 (46.0%)	49 (38.9%)	172 (59.7%)	< 0.001
Comparisons across NT-proBNP × hs-cTnT cardiocirculatory patterns were performed using the Kruskal–Wallis test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.					

Abbreviations: bpm, beats per minute; hs-cTnT, high-sensitivity cardiac troponin T; ICU, intensive care unit; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SOFA, Sequential Organ Failure Assessment; VIS, vasoactive–inotropic score.

Data are presented as median (interquartile range)

Association of NT-proBNP × hs-cTnT cardiocirculatory patterns with 30-day mortality

Thirty-day mortality differed substantially among patterns, ranging from 107/287 (37.3%) in the Low NT-proBNP / Low hs-cTnT group to 172/288 (59.7%) in the High NT-proBNP / High hs-cTnT group (Table 2). Kaplan–Meier survival analysis demonstrated significant differences in 30-day mortality across NT-proBNP × hs-cTnT-defined cardiocirculatory patterns (log-rank $p < 0.001$; Fig. 2). The lowest survival probability was observed in patients with concomitant elevation of both biomarkers (High NT-proBNP / High hs-cTnT), whereas patients with low concentrations of both NT-proBNP and hs-cTnT exhibited the most favourable survival. Patterns characterized by isolated elevation of either NT-proBNP or hs-cTnT demonstrated intermediate survival trajectories. These survival differences mirror the progressive increase in age, comorbidity burden, and markers of circulatory and organ dysfunction observed across patterns at ICU admission (Tables 1 and 2). Although partial crossing of survival curves was observed during early follow-up, overall between-group differences remained statistically significant.

In unadjusted Cox proportional hazards regression, the High NT-proBNP / High hs-cTnT pattern was associated with a markedly increased hazard of 30-day all-cause mortality compared with the Low NT-proBNP / Low hs-cTnT reference pattern (Table 3). Isolated elevation of NT-proBNP showed a trend toward higher mortality risk, whereas isolated elevation of hs-cTnT was not significantly associated with 30-day mortality in unadjusted analyses.

Table 3
Cox proportional hazards regression for 30-day mortality by NT-proBNP × hs-cTnT patterns.

Pattern (NT-proBNP / hs-cTnT)	Unadjusted HR (95% CI)	p-value	SOFA-adjusted HR (95% CI)	p-value
Low NT-proBNP / Low hs-cTnT	Reference	–	Reference	–
High NT-proBNP/ Low hs-cTnT	1.50 (0.97–2.31)	0.066	1.14 (0.82–1.58)	0.436
Low NT-proBNP / High hs-cTnT	1.11 (0.72–1.72)	0.633	1.06 (0.76–1.50)	0.722
High NT-proBNP / High hs-cTnT	2.32 (1.64–3.29)	< 0.001	1.51 (1.16–1.97)	0.002
SOFA score (per 1 point)	1.13 (1.10–1.17)	< 0.001	1.11 (1.08–1.15)	< 0.001
Hazard ratios are reported with Low NT-proBNP / Low hs-cTnT as the reference pattern.				

After adjustment for global illness severity using the SOFA score at ICU admission, only the combined High NT-proBNP / High hs-cTnT pattern remained independently associated with increased 30-day mortality. Neither isolated NT-proBNP elevation nor isolated hs-cTnT elevation demonstrated a statistically significant association with mortality after adjustment. The SOFA score itself was a strong independent predictor of adverse outcome.

To summarise SOFA-adjusted mortality risk across the four predefined cardiocirculatory patterns, a patterns-based heatmap was generated (Fig. 3A). This visualisation demonstrated a graded increase in adjusted 30-day mortality from the Low NT-proBNP / Low hs-cTnT pattern to the High NT-proBNP / High hs-cTnT pattern, with intermediate risk observed in patterns characterised by isolated elevation of either biomarker.

When hs-cTnT and NT-proBNP were modelled as continuous variables without adjustment, their association with 30-day mortality was largely additive, as reflected by a near-planar risk surface with approximately parallel contour lines (Supplementary Figure S2). This pattern suggests that, in the unadjusted setting, both biomarkers predominantly capture overall disease severity rather than distinct cardiocirculatory mechanisms. After adjustment for SOFA score, continuous modelling demonstrated a graded joint association between hs-cTnT and NT-proBNP and predicted 30-day mortality (Fig. 3B), with the highest risk observed in patients with concomitant elevations of both biomarkers. Formal

comparison of SOFA-adjusted additive and two-dimensional models did not demonstrate a statistically significant non-linear interaction between hs-cTnT and NT-proBNP (likelihood ratio test p = 0.123). Importantly, the four median-based cardiocirculatory patterns corresponded to clinically interpretable regions of this continuous joint biomarker–risk landscape, supporting their use as a pragmatic representation of an underlying continuous cardiocirculatory risk continuum rather than discrete biological categories.

Discussion

In this study, we demonstrated that combined assessment of NT-proBNP and hs-cTnT at ICU admission identifies distinct cardiocirculatory patterns among non-cardiac critically ill patients, characterized by markedly different clinical profiles and short-term outcomes. Patients with concurrent elevation of both biomarkers (High NT-proBNP / High hs-cTnT pattern) exhibited the greatest severity of organ dysfunction and the poorest 30-day survival, an association that persisted after adjustment for global illness severity using the SOFA score.

Previous studies evaluating cardiac biomarkers in critically ill populations have predominantly focused on single disease entities—most commonly sepsis—or on patients with primary cardiac diagnoses (26–29). Moreover, the majority of available evidence has examined the prognostic relevance of individual biomarkers, either cardiac troponins or natriuretic peptides, in isolation (4, 9, 18–20, 30). Although elevations of hs-cTnT and NT-proBNP are frequently observed in non-cardiac critical illness, their pathophysiological interpretation and integrated prognostic meaning in this setting remain incompletely understood (7, 8). Typically, in critically ill patients, elevated cardiac troponin concentrations are most often attributed to type II myocardial ischemia, microcirculatory impairment, and myocardial stress, rather than to acute plaque rupture (4, 5, 9). In contrast, in ICU patients, NT-proBNP is regarded as an integrative marker of cardiocirculatory stress and haemodynamic burden (31, 32).

Concurrently, there is increasing recognition that multimarker strategies may better capture the heterogeneity of cardiovascular responses to critical illness than single-marker approaches (33–36). This conceptual framework is consistent with prior multimarker phenotyping approaches in cardiovascular medicine. Notably, Testani et al. demonstrated that combined interpretation of natriuretic peptides and renal biomarkers identifies distinct cardiorenal patterns with markedly different clinical profiles and prognoses in patients with heart failure, despite similar degrees of renal dysfunction. Analogously, our findings suggest that in non-cardiac critical illness, the joint distribution of NT-proBNP and hs-cTnT delineates clinically meaningful cardiocirculatory patterns that are not adequately captured by isolated biomarker assessment (37). To our knowledge, such a joint phenotyping strategy has not been systematically explored in exclusively non-cardiac ICU populations, thereby addressing an important gap in the current literature.

Although patients admitted primarily for acute cardiac conditions were explicitly excluded from our study, elevations in NT-proBNP and hs-cTnT were common and prognostically informative in this non-

cardiac ICU cohort. This observation supports the concept that cardiovascular stress and myocardial injury are integral components of critical illness, even in the absence of overt cardiac syndromes (23, 31). In this context, natriuretic peptides and troponins likely reflect a complex interplay of myocardial strain, microvascular dysfunction, hypoxia, systemic inflammation, neurohumoral activation, and impaired clearance, rather than isolated cardiomyocyte necrosis or decompensated heart failure (23).

Importantly, phenotypic stratification based on the joint biomarker profile revealed distinct patterns of extra-cardiac organ dysfunction. The High NT-proBNP / High hs-cTnT pattern was characterized by more pronounced circulatory failure and multisystem involvement, including elevated lactate concentrations, worse renal and hepatic function, higher inflammatory markers, impaired gas exchange, and increased vasopressor requirements. These findings suggest that combined biomarker elevation identifies a state of advanced cardiocirculatory failure embedded within generalized multi-organ dysfunction, rather than merely reflecting pre-existing chronic cardiovascular disease.

To address potential limitations related to median-based dichotomisation, we performed complementary analyses modelling hs-cTnT and NT-proBNP as continuous variables. In unadjusted analyses, both biomarkers demonstrated largely independent and cumulatively informative associations with mortality, rather than a synergistic interaction, consistent with their role as general markers of overall illness severity. After adjustment for SOFA score, continuous modelling revealed a graded joint biomarker–risk landscape, with the highest predicted mortality observed in patients with concomitant elevations of both hs-cTnT and NT-proBNP. Importantly, the four median-based cardiocirculatory patterns corresponded to clinically interpretable regions of this continuous risk surface, supporting their use as a pragmatic clinical abstraction of an underlying continuous cardiocirculatory risk continuum rather than discrete biological entities.

Patients with the High NT-proBNP / High hs-cTnT pattern were older and more frequently burdened with cardiovascular comorbidities such as hypertension, ischemic heart disease, and chronic kidney disease. Age is known to influence baseline concentrations of both natriuretic peptides and troponins and also serves as a surrogate for cumulative comorbidity burden (32, 38–40). Nevertheless, the persistence of strong associations between the combined biomarker phenotype and markers of tissue hypoperfusion, inflammation, and organ dysfunction suggests that this pattern primarily reflects acute pathophysiological processes, whereas age and comorbidity burden likely modulate the magnitude of the clinical response by limiting physiological reserve during critical illness (41). Accordingly, we deliberately adopted an adjustment strategy based on global illness severity using the SOFA score rather than including age and individual comorbidities in the primary multivariable model, in order to avoid overadjustment and attenuation of biologically meaningful associations embedded within the biomarker profiles (42, 43). Prior studies have reported age-dependent attenuation of the prognostic performance of cardiac biomarkers in critically ill and cardiovascular populations, likely reflecting competing risks and multimorbidity in older patients (38–40, 44, 45). These observations provide important biological context for interpreting biomarker signals across age strata but do not necessarily imply effect modification requiring formal interaction modelling in the present study.

Simultaneous interpretation of NT-proBNP and hs-cTnT at ICU admission may help inform early, pathophysiology-oriented risk stratification in non-cardiac critical illness. Patients with concomitant elevation of both biomarkers appear to represent a high-risk subgroup, in whom closer hemodynamic surveillance, a lower threshold for echocardiographic evaluation, and early recognition of evolving circulatory failure may be warranted. This multimarker approach is consistent with emerging concepts positioning critical illness as a systemic cardiocirculatory disorder rather than a series of isolated organ failures (46, 47). In this context, incorporating cardiac biomarker profiles into routine ICU assessment may contribute to a more integrated understanding of disease severity and physiological reserve, potentially supporting more individualised clinical decision-making.

Limitations

Several limitations of this study should be acknowledged. First, this was a single-center retrospective analysis, which limits causal inference and may reduce the generalizability of the findings to other ICU populations with different case-mix, admission pathways, or treatment protocols. Second, cardiac biomarker measurements were obtained at ICU admission only; therefore, temporal trends and biomarker trajectories could not be evaluated, precluding assessment of dynamic cardiocirculatory responses during critical illness. Third, although patients admitted for primary cardiac diagnoses were excluded, the presence of subclinical or unrecognized cardiac pathology cannot be entirely ruled out and may have influenced both biomarker concentrations and outcomes. In addition, echocardiographic data were not systematically available, preventing adjustment for baseline or acute alterations in cardiac structure and function that could modulate NT-proBNP or hs-cTnT levels. Fourth, cardiocirculatory patterns were defined using median-based cut-offs, which, while methodologically transparent and distribution-driven, may not correspond to clinically established thresholds. Alternative phenotyping strategies, including clinically informed cut-offs or data-driven clustering approaches, might yield partially different pattern boundaries. Fifth, although multivariable analyses were adjusted for global illness severity using the SOFA score, residual confounding related to unmeasured variables—such as detailed fluid balance, cumulative vasopressor exposure, mechanical ventilation parameters, or pre-existing cardiovascular disease—cannot be excluded. Importantly, the choice to adjust exclusively for SOFA score represents a deliberate methodological decision aligned with the study objective of cardiocirculatory pattern recognition and pathophysiological interpretation, rather than a limitation imposed by data availability. Alternative adjustment strategies, including models incorporating age and comorbidities, might yield different effect estimates and should be explored in future studies. Moreover, post hoc pairwise comparisons and chord diagram visualizations were exploratory in nature and should be interpreted as hypothesis-generating rather than confirmatory. Formal sensitivity analyses were not conducted and this should be considered as an additional limitation of the present study. In particular, we did not test the stability of the results across alternative biomarker cut-offs, adjustment sets, or phenotyping approaches, which may affect the generalizability and robustness of the observed associations. Finally, no independent external validation cohort was available, and the prognostic performance of the proposed patterns should be confirmed in prospective, multicenter studies before broader clinical implementation. Future studies should validate these cardiocirculatory patterns in

independent cohorts, explore biomarker dynamics over time, and assess whether phenotype-guided monitoring or therapeutic strategies can improve outcomes. Integration of circulating biomarkers with echocardiographic or invasive hemodynamic assessments may further refine cardiocirculatory phenotyping in critically ill patients.

Conclusions

In a non-cardiac ICU population, combined assessment of NT-proBNP and high-sensitivity cardiac troponin T identifies distinct cardiocirculatory patterns with fundamentally different clinical characteristics and short-term mortality risks. Only the pattern characterized by concurrent elevation of both biomarkers was independently associated with increased 30-day mortality after adjustment for illness severity. These findings underscore the clinical relevance of multimarker-based cardiocirculatory phenotyping beyond isolated biomarker interpretation in critically ill patients.

Abbreviations

BMI Body Mass Index
CI Confidence Interval
COPD Chronic Obstructive Pulmonary Disease
ECLIA Electrochemiluminescence Immunoassay
HR Hazard Ratio
hs-cTnT High-sensitivity Cardiac Troponin T
ICU Intensive Care Unit
IQR Interquartile Range
KM Kaplan–Meier
MAP Mean Arterial Pressure
NT-proBNP N-terminal pro-B-type Natriuretic Peptide
PaO_2/FiO_2 Partial Pressure of Arterial Oxygen to Fraction of Inspired Oxygen Ratio
SOFA Sequential Organ Failure Assessment
STROBE Strengthening the Reporting of Observational Studies in Epidemiology
VIS Vasoactive–Inotropic Score

Declarations

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Not applicable

Author contributions

MT, RŚ, WS, JK, PK, JD, AK, TD contributed to conceptualization, methodology, and investigation.

MM, KC, KF, MJ, GP, AS, KP, WI, MZ contributed to investigation, data curation, literature review, and visualization.

MT contributed to formal analysis, validation, writing – original draft, visualization, project administration, resources, writing – review & editing, and funding acquisition.
MT, AD, and EL critically reviewed the manuscript, contributed to methodology, writing – review & editing, and supervised the study. All authors read and approved the final version of the manuscript.

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Data availability

The underlying data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to appropriate institutional permissions and ethical oversight.

Ethics approval and consent to participate

The study protocol was approved by the Komisja ds. Etyki Badań Naukowych Uniwersytetu Jagiellońskiego – Collegium Medicum (Bioethics Committee of the Jagiellonian University – Collegium Medicum, Kraków, Poland; approval no. 118.0043.1.160.2024). As this study involved only the analysis of existing anonymized data and posed no risk to participants, the Institutional Review Board waived the requirement for obtaining informed consent, in accordance with Polish national regulations and the EU General Data Protection Regulation (GDPR, Regulation (EU) 2016/679). The study was conducted in accordance with the principles of the Declaration of Helsinki and reported in compliance with the STROBE Statement.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with improving the clarity, grammar, and readability of the text. All scientific content, data analysis, interpretation of results, and conclusions were developed by the authors without the use of generative AI. The final version of the manuscript was carefully reviewed and edited by the authors, who take full responsibility for the content of the work.

Consent for publication

Due to the retrospective observational use of routinely collected data with informed consent waived there is no requirement to seek consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

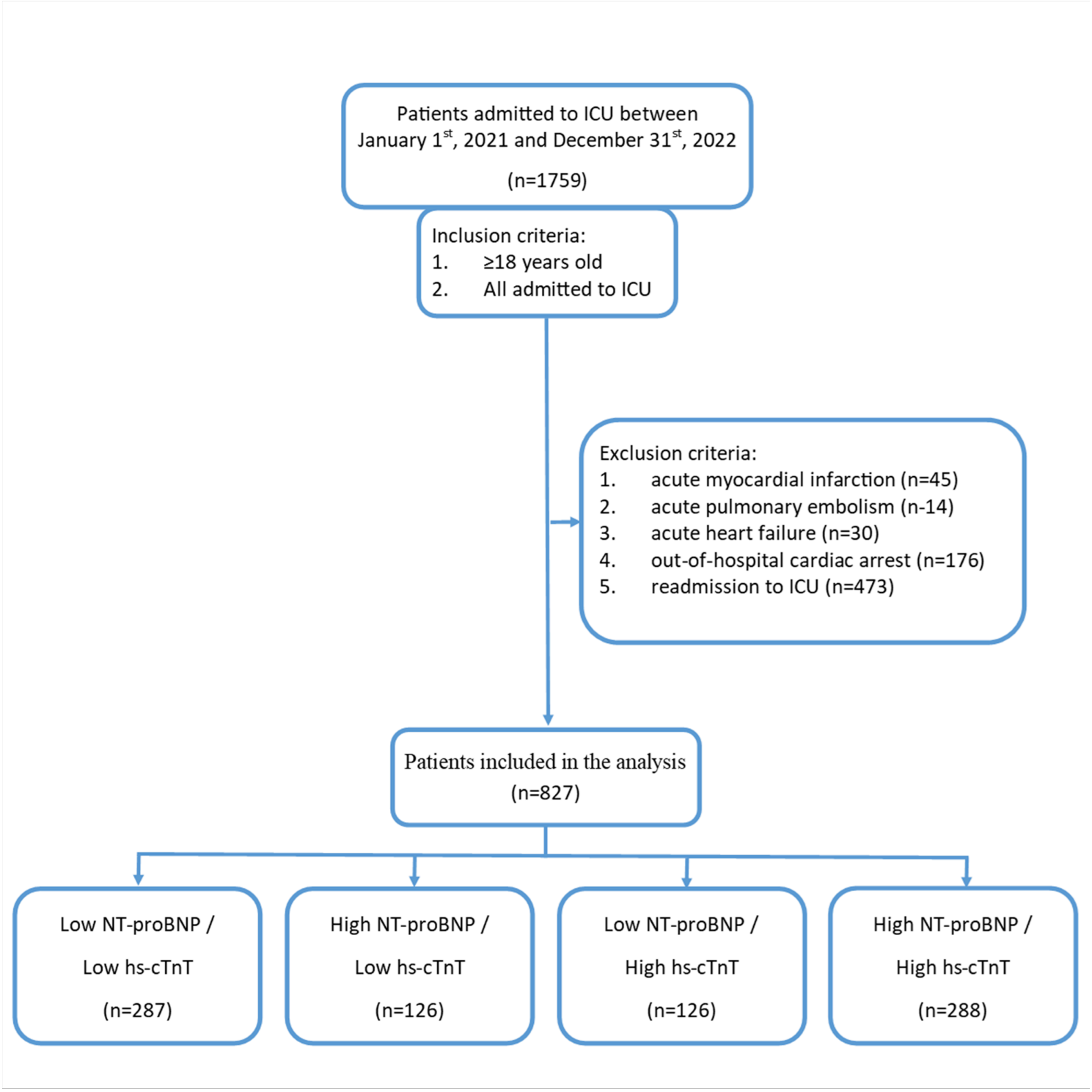

Figure 1

Flowchart of the study group

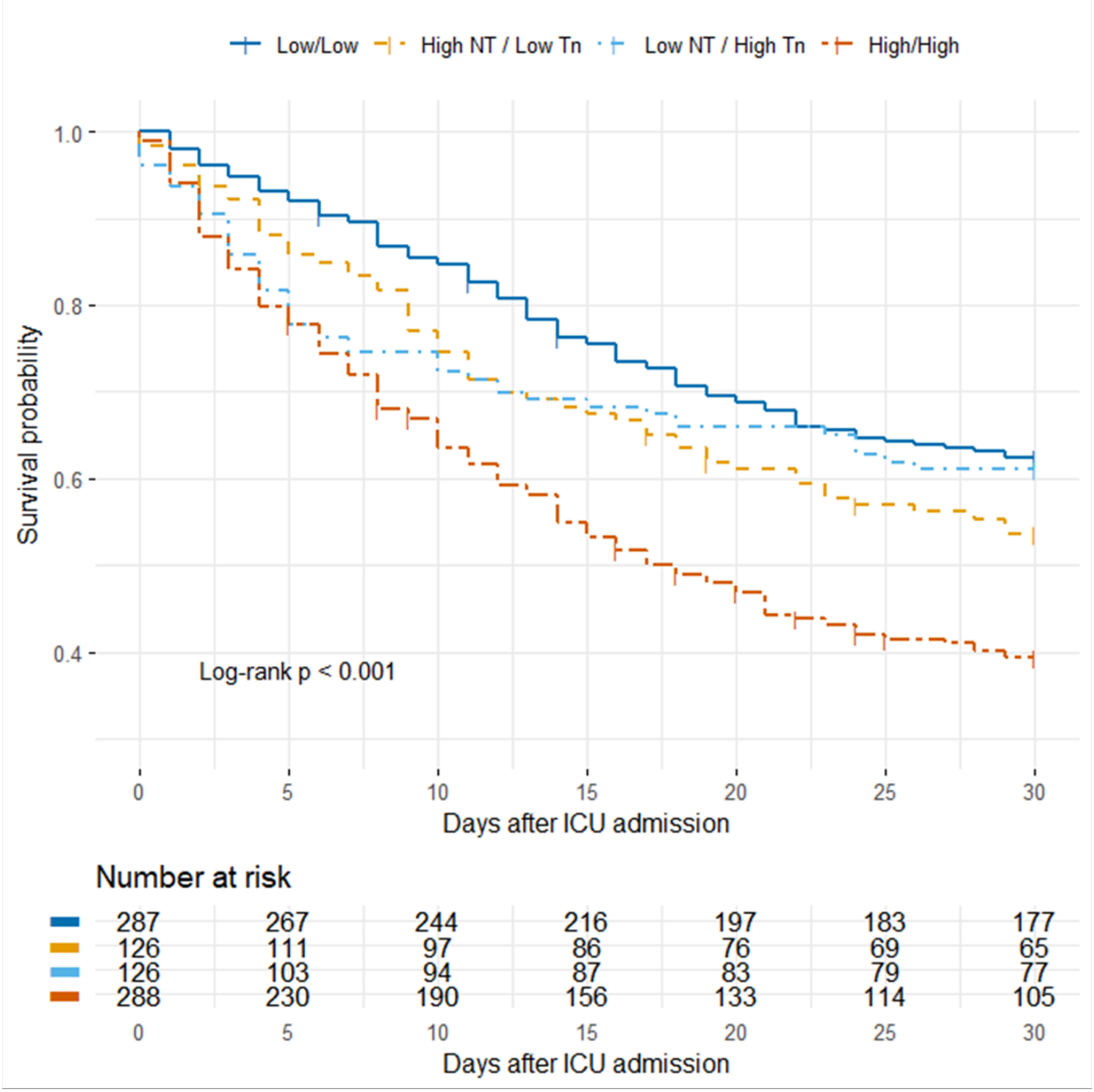

Figure 2

Kaplan–Meier survival curves stratified by NT-proBNP × hs-cTnT patterns.

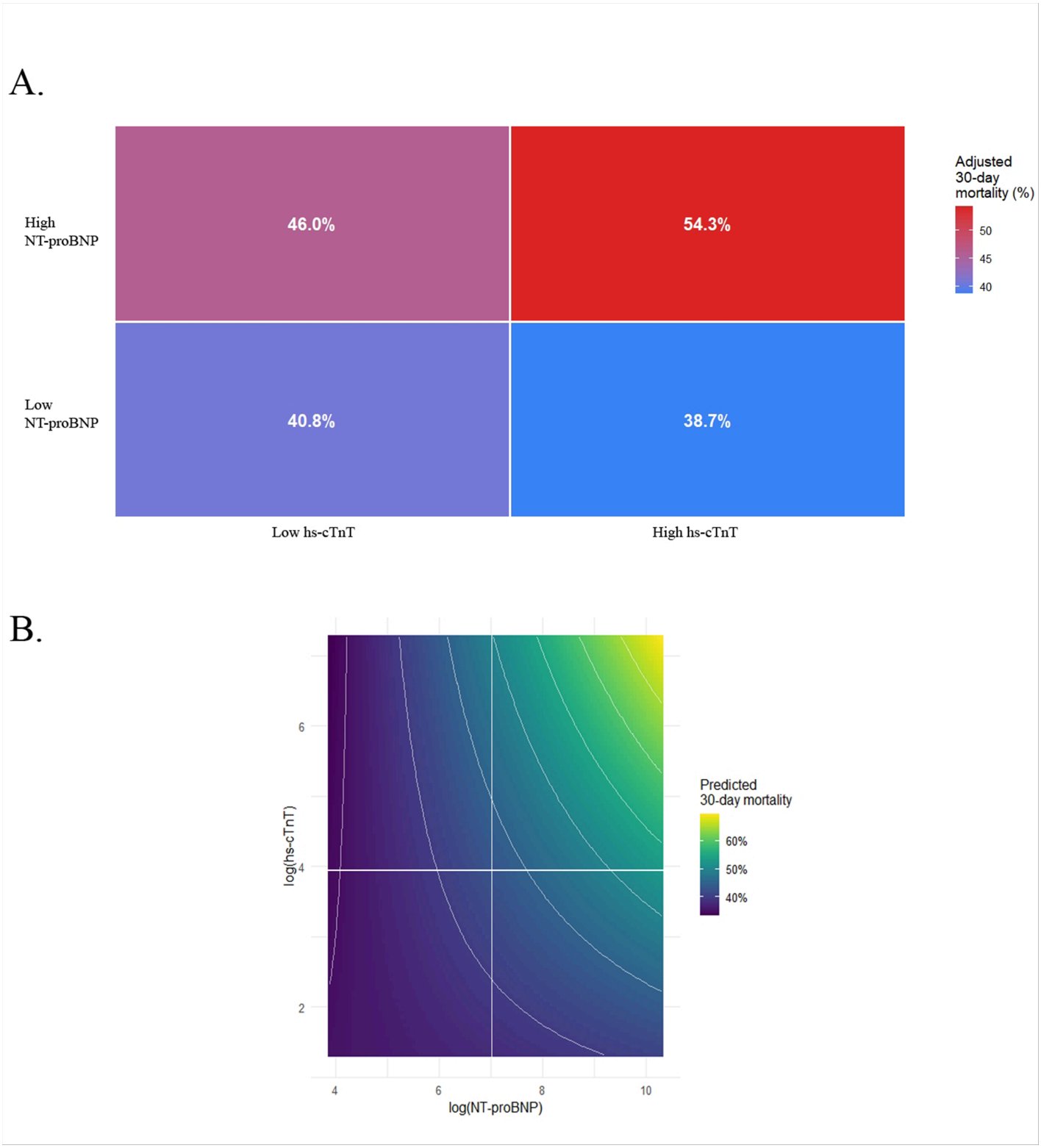

Figure 3

Visual exploration of cardiocirculatory patterns and mortality risk

A: Heatmap illustrating SOFA-adjusted predicted 30-day mortality across NT-proBNP ×hs-cTnT–defined cardiocirculatory patterns (colour intensity reflects increasing mortality risk across patterns, with estimates standardized to the cohort median SOFA value).

B: SOFA-adjusted two-dimensional risk surface illustrating the continuous joint association of NT-proBNP and hs-cTnT and predicted 30-day mortality (the surface was derived from a Cox proportional hazards model adjusted for SOFA score to visualize the joint biomarker effect at a constant level of illness severity; white vertical and horizontal lines indicate median values of hs-cTnT and NT-proBNP, illustrating the four cardiocirculatory patterns as cross-sections of the continuous joint biomarker–risk landscape).

Supplementary Files

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