

BASELINE SERUM HS-CRP, IL-6, AND NT-PROBNP IN RELATION TO 6-MONTH RIGHT VENTRICULAR DECOMPENSATION IN CHRONIC LUNG DISEASE-ASSOCIATED PULMONARY HYPERTENSION

POČETNE VREDNOSTI SERUMSKIH HS-CRP, IL-6 I NT-PROBNP U ODNOSU NA ŠESTOMESEČNU DEKOMPENZACIJU DESNE KOMORE KOD PLUĆNE HIPERTENZIJE POVEZANE SA HRONIČNOM BOLEŠĆU PLUĆA

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Summary

Background: Right ventricular decompensation in chronic lung disease-associated pulmonary hypertension (CLD-PH) is associated with systemic inflammatory activation and increasing myocardial stress. High-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) reflect complementary components of the inflammatory response, whereas N-terminal pro-B-type natriuretic peptide (NT-proBNP) indicates myocardial wall stress; however, their baseline concentrations and the value of their combined assessment in predicting 6-month decompensation severity remain insufficiently characterised.

Methods: This single-centre retrospective cohort included 120 patients with right heart catheterisation-confirmed CLD-PH. Baseline serum hs-CRP, IL-6, and NT-proBNP concentrations were compared among groups defined by subsequent 6-month right ventricular decompensation status and severity; their relationships with pulmonary vascular load and right ventricular function were examined, while multivariable Cox regression, sequential model comparison, and 1,000-resample bootstrap validation were used to evaluate their individual and combined prognostic value. TAPSE was retained as an echocardiographic reference measure.

Results: During follow-up, 48 patients (40.0%) developed right ventricular decompensation. Baseline serum hs-

Kratak sadržaj

Uvod: Dekompenzacija desne komore kod plućne hipertenzije sa pridruženom hroničnom bolešću pluća (CLD-PH) je povezana sa sistemskom inflamatornom aktivacijom i povećanim stresom miokarda. Visokosenzitivni C-reaktivni protein (hs-CRP) i interleukin-6 (IL-6) odražavaju komplementarne komponente inflamatornog odgovora, dok N-terminalni pro-B-tip natrijum-uretskog peptida (NT-proBNP) ukazuje na stres zida miokarda. Međutim, povezanost njihovih početnih koncentracija sa naknadnom težinom dekompenzacije tokom 6-mesečnog perioda, kao i značaj njihove kombinovane procene, još uvek nisu dovoljno razjašnjeni.

Metode: Ova retrospektivna kohortna studija sprovedena u jednom centru je obuhvatila 120 pacijenata sa CLD-PH potvrđenom kateterizacijom desnog srca. Početne koncentracije hs-CRP, IL-6 i NT-proBNP u serumu su poređene između grupa definisanih statusom i težinom naknadne dekompenzacije desne komore tokom 6 meseci. Ispitivane su njihove povezanosti sa plućnim vaskularnim opterećenjem i funkcijom desne komore, dok su multivariabilna Cox-ova regresija, sekvencijalno poređenje modela i validacija pomoću »bootstrap« metode sa 1.000 ponovljenih uzoraka korišćeni za procenu njihovih pojedinačnih i kombinovanih prognostičkih vrednosti. TAPSE je zadržan kao referentna ehokardiografska mera.

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CRP, IL-6, and NT-proBNP concentrations increased progressively from the group that remained free of decompensation to the groups that subsequently developed non-severe and severe decompensation, and higher concentrations were associated with greater pulmonary vascular resistance and poorer right ventricular functional indices. After multivariable adjustment, each 1-standard-deviation increase in hs-CRP and NT-proBNP was associated with a higher risk of decompensation, with hazard ratios of 1.637 (95% CI 1.167–2.296; $P=0.004$) and 1.808 (95% CI 1.253–2.611; $P=0.002$), respectively, whereas IL-6 and TAPSE did not retain independent associations. NT-proBNP showed the highest discrimination among the individual markers, with an AUC of 0.759 (95% CI 0.673–0.845), while the three-marker serum panel achieved an AUC of 0.823 (95% CI 0.747–0.898). Adding the serum panel to the basic clinical model increased the AUC from 0.751 to 0.841 ($P=0.014$); adding TAPSE produced only a small, non-significant increase to 0.846 ($P=0.527$).

Conclusion: Higher baseline hs-CRP, IL-6, and NT-proBNP concentrations were associated with greater subsequent 6-month right ventricular decompensation severity in patients with CLD-PH. Their combined assessment integrated information on systemic inflammation and myocardial stress and improved short-term risk discrimination beyond a parsimonious reference model comprising PVR and 6MWD, whereas TAPSE contributed limited additional prognostic information.

Keywords: hs-CRP, IL-6, NT-proBNP, chronic lung disease, pulmonary hypertension

Introduction

Chronic lung disease-associated pulmonary arterial hypertension (CLD-PAH) is characterised by sustained pulmonary vascular stress, systemic inflammatory activation, and progressive right ventricular pressure loading, all of which become more pronounced as right ventricular compensation begins to fail (1–3). Among routinely accessible circulating markers, high-sensitivity C-reactive protein (hs-CRP) reflects the hepatic acute-phase response. It provides an integrated measure of low-grade systemic inflammation (4, 5), whereas interleukin-6 (IL-6), an upstream proinflammatory cytokine, participates in pulmonary vascular inflammatory signalling through pathways that include gp130/JAK/STAT3 signalling (6, 7). Although hs-CRP and IL-6 are closely related, they do not provide identical biological information: IL-6 reflects proximal cytokine signalling, whereas hs-CRP represents a downstream systemic acute-phase response (8, 9). As pulmonary vascular resistance rises, the right ventricle faces increasing pressure and wall stress; NT-proBNP, released in response to myocardial stretch, therefore represents a complementary biochemical dimension more

Rezultati: Tokom praćenja, kod 48 pacijenata (40,0%) se razvila dekompenzacija desne komore. Početne koncentracije hs-CRP, IL-6 i NT-proBNP u serumu su progresivno rasle od grupe koja je ostala bez dekompenzacije do grupa kod kojih se naknadno razvila dekompenzacija blažeg stepena i teška dekompenzacija, dok su više koncentracije bile povezane sa većim plućnim vaskularnim otporom i lošijim pokazateljima funkcije desne komore. Nakon multivarijabilnog prilagođavanja, svako povećanje hs-CRP i NT-proBNP za jednu standardnu devijaciju bilo je povezano sa većim rizikom od dekompenzacije, uz hazardne količnike od 1,637 (95% CI 1,167–2,296; $P=0,004$) i 1,808 (95% CI 1,253–2,611; $P=0,002$), respektivno, dok IL-6 i TAPSE nisu zadržali nezavisnu povezanost. NT-proBNP je pokazao najveću diskriminativnu sposobnost među pojedinačnim markerima, sa AUC od 0,759 (95% CI 0,673–0,845), dok je serumski panel sa sva tri markera postigao AUC od 0,823 (95% CI 0,747–0,898). Dodavanje serumskog panela osnovnom kliničkom modelu povećalo je AUC sa 0,751 na 0,841 ($P=0,014$); naknadno uključivanje TAPSE-a dovelo je samo do malog, statistički neznčajnog povećanja na 0,846 ($P=0,527$).

Zaključak: Više početne koncentracije hs-CRP, IL-6 i NT-proBNP bile su povezane sa većom naknadnom težinom dekompenzacije desne komore tokom 6 meseci kod pacijenata sa CLD-PH. Njihova kombinovana procena objedinila je informacije o sistemskej inflamaciji i miokardnom stresu i poboljšala kratkoročnu diskriminaciju rizika u odnosu na štedljiv referentni model koji je obuhvatao PVR i 6MWD, dok je TAPSE pružio ograničene dodatne prognostičke informacije.

Ključne reči: hs-CRP, IL-6, NT-proBNP, hronična bolest pluća, plućna hipertenzija

closely related to the cardiac consequences of pulmonary vascular disease than to inflammation itself (10). Considered together, hs-CRP, IL-6, and NT-proBNP may characterise the progression from inflammatory and vascular stress to clinically relevant right ventricular dysfunction more comprehensively than any single marker.

TAPSE is a widely used echocardiographic measure of longitudinal right ventricular contraction. However, its dependence on loading conditions and ventricular geometry limits its ability to represent the broader systemic processes accompanying decompensation (11). In the present study, TAPSE was therefore retained as a functional reference against which the serum inflammatory and cardiac-stress biomarker profile could be evaluated, rather than being treated as a co-primary laboratory indicator.

Previous studies have generally evaluated inflammatory markers, natriuretic peptides, or echocardiographic indices separately, leaving the relationship between baseline circulating inflammatory and cardiac-stress markers and subsequent graded right ventricular decompensation

insufficiently characterised. It also remains uncertain whether hs-CRP provides prognostic information beyond IL-6 and NT-proBNP, and whether their combined assessment improves risk discrimination beyond a parsimonious model based on pulmonary vascular load and functional capacity. Accordingly, this study was designed to determine whether baseline serum hs-CRP, IL-6, and NT-proBNP concentrations were associated with subsequent 6-month right ventricular decompensation severity in patients with CLD-PH, to examine their relationships with pulmonary vascular load and right ventricular function, and to determine the individual and combined prognostic value of these circulating markers, with TAPSE retained as an echocardiographic reference measure.

Materials and Methods

Study design and participants

This single-centre retrospective cohort study consecutively identified patients with CLD-PH who were hospitalised and treated at our hospital between December 1, 2024, and October 31, 2025. Baseline and 6-month outcome data through April 30, 2026, were extracted retrospectively from electronic inpatient records, outpatient records, and routinely documented clinical telephone follow-up records; no investigator-initiated follow-up contact or intervention was undertaken for the present analysis. The date on which a patient first completed serum biomarker measurements and echocardiography during a clinically stable period was defined as baseline, and 120 patients were included in the analysis. Clinical stability was defined as the absence of respiratory tract infection or acute exacerbation of chronic lung disease during the preceding 4 weeks and the absence of an acute cardiovascular event at baseline. Blood sampling was designated as day 0; arterial blood gas analysis and resting SpO₂ were obtained within 24 h, echocardiography and the 6MWD within 48 h, and right heart catheterisation and pulmonary function testing including DLCO within 7 days of blood collection. Supplemental oxygen, diuretic therapy, and PH-directed therapy were maintained without change throughout this baseline assessment window. The Medical Ethics Committee of Ganzhou Fifth People's Hospital approved the study, and all participants signed informed consent forms.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) a definite diagnosis of chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), bronchiectasis, or another chronic hypoxic

lung disease; (3) precapillary PH confirmed by right heart catheterisation, defined as mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR > 2 Wood units (WU), with a clinical classification consistent with Group 3 CLD-PH according to the 2022 ESC/ERS Guidelines; (4) complete baseline measurements of serum hs-CRP, IL-6, and NT-proBNP, with echocardiography completed within 48 h; (5) no right ventricular decompensation, as defined in this study, at baseline; (6) complete 6-month outcome data, or occurrence of the primary endpoint within 6 months.

The exclusion criteria were as follows: (1) respiratory tract infection, acute exacerbation of COPD, or acute exacerbation of ILD within 4 weeks before baseline; (2) concomitant acute pulmonary embolism, acute coronary syndrome, myocarditis, or a recent severe arrhythmia; (3) left ventricular ejection fraction (LVEF) $< 50\%$, moderate-to-severe left-sided valvular disease, or another left heart disease sufficient to cause elevated pulmonary artery pressure; (4) chronic thromboembolic pulmonary hypertension (CTEPH), or another form of PH unrelated to chronic lung disease; (5) active malignant tumor, systemic infection, autoimmune disease, or hematological disease; (6) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², or decompensated cirrhosis. Left heart disease was excluded by the PAWP criterion together with echocardiographic assessment of LVEF and left-sided valvular disease. CTEPH was excluded by ventilation/perfusion lung scanning; patients with mismatched perfusion defects underwent CT pulmonary angiography and were excluded if chronic thromboembolic obstruction was identified. Other causes of precapillary PH were excluded on the basis of clinical history, relevant laboratory testing, and imaging according to the 2022 ESC/ERS clinical classification.

Right heart catheterisation

Right heart catheterisation was performed under local anaesthesia, with the patient in the supine position, and a 7 F balloon-tipped flow-directed catheter was inserted through the right internal jugular vein or femoral vein; the pressure transducer was zeroed at the level of the midaxillary line, and mean right atrial pressure (mRAP), mean pulmonary artery pressure (mPAP), and pulmonary artery wedge pressure (PAWP) were recorded at end-expiration. Cardiac output (CO) was measured by thermodilution, and the mean was calculated after three consecutive measurements differing by no more than 10% had been obtained. The cardiac index was calculated by dividing CO by body surface area, and pulmonary vascular resistance (PVR) was calculated as (mPAP–PAWP)/CO.

Serum biomarker measurement and analytical quality control

After fasting for at least 8 h, 5 mL of antecubital venous blood was collected from each patient in the early morning and placed in a vacuum collection tube containing a clot activator and separator gel; after standing at room temperature for 30 min, the sample was centrifuged at $1,500\times g$ for 10 min at 4°C . The separated serum was aliquoted into 300 μL portions within 2 h after collection and stored at -80°C . Before measurement, the samples were slowly thawed at $2\sim 8^{\circ}\text{C}$, and only one freeze-thaw cycle was permitted for each sample. The actual interval from blood collection to centrifugation was a median of 42 min (IQR 38–47; range 35–58 min), and serum aliquots were frozen a median of 53 min after centrifugation (IQR 41–66; range 28–82 min); all samples were frozen within 2 h of collection. The median storage duration before analysis was 162 days (IQR 91–244; maximum 338 days), and all three biomarkers were analysed within the same two-week analytical period. Samples with gross hemolysis, lipemia, or icterus were excluded before aliquoting and recollected when possible. Storage duration did not differ significantly among the no-decompensation, non-severe, and severe groups (Kruskal–Wallis $P=0.684$).

Serum hs-CRP was measured using the Cardiac C-Reactive Protein (Latex) High Sensitive assay (CRPHS; Roche Diagnostics, Mannheim, Germany; reagent no. 04628918190) on a cobas c 501 analyser, and results were reported in mg/L. Calibration was performed using Calibrator f.a.s. Proteins (no. 11355279216), with traceability to the IFCC/BCR/CAP CRM 470 reference preparation. The analytical measurement range was 0.15–20.0 mg/L, the lower detection limit was 0.15 mg/L, and the functional sensitivity was 0.30 mg/L; samples above the analytical range were remeasured using the instrument's 1:15 rerun dilution, although no study sample required dilution. CRP T Control N and Precinorm Protein were used as low- and high-level internal quality-control materials at target concentrations of approximately 4.34 and 9.06 mg/L, respectively; the laboratory acceptance limits were target $\pm 10\%$, and the within-run CVs were 1.0% and 1.2%, with between-run CVs of 2.6% and 1.3%, respectively. Serum IL-6 was measured using the Human IL-6 ELISA Kit (Assay Genie, Dublin, Ireland; catalogue no. AEES00163), with an analytical sensitivity of 0.94 pg/mL and a standard-curve range of 1.56–100 pg/mL; the operational lower limit of quantification was set at 1.56 pg/mL, corresponding to the lowest calibrator. All study samples fell within this range and were analysed in duplicate without predilution, with intra-assay coefficients of variation of 5.06%–5.96% and inter-assay coefficients of variation of 6.06%–8.49%. Patient samples were randomly coded and distributed across three microplates, and each plate included the same

pooled-serum quality-control sample, yielding an interplate CV of 6.7%. After incubation, washing, and colour development, absorbance was read at 450 nm using a Synergy H1 multimode microplate reader (Agilent BioTek), and concentrations were calculated from a four-parameter logistic standard curve. Duplicate results were averaged when their coefficient of variation did not exceed 15%; five samples exceeding this threshold were reassayed. Laboratory personnel performing the assay were blinded to 6-month outcome status.

NT-proBNP was measured using the Elecsys proBNP II electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany; reagent no. 09315284190) on a cobas e 801 analyser. Calibration was performed using proBNP II CalSet, and the assay is traceable to pure synthetic NT-proBNP(1–76) by weight. The analytical measurement range was 5–35,000 pg/mL, with a blank limit of 3 pg/mL, a limit of detection of 5 pg/mL, and a limit of quantification of 50 pg/mL. PreciControl Cardiac II was analysed daily at approximately 140 and 4,846 pg/mL; the within-run CVs were 1.5% and 1.8%, and the between-run CVs were 2.9% at both levels. Samples above the analytical range were to be diluted 1:2 with Diluent Universal according to the manufacturer's protocol, although no study sample required dilution. Hemolysis, icterus, and lipemia were screened before analysis; specimens exceeding the manufacturer-validated interference limits for haemoglobin (1,000 mg/dL), bilirubin (25 mg/dL), or Intralipid (1,500 mg/dL) were not accepted for measurement, and no included sample exceeded these limits. The three serum markers were prespecified to represent complementary biochemical domains: hs-CRP as a downstream acute-phase indicator, IL-6 as a marker of cytokine-mediated inflammatory activation, and NT-proBNP as a marker of myocardial stress. The principal analyses therefore focused on baseline concentration differences according to subsequent decompensation severity, their relationships with hemodynamic and right ventricular functional measures, and the incremental value of their combined assessment.

Echocardiography

Transthoracic echocardiography was performed using an ultrasound system (EPIQ ELITE) and an X5-1 phased-array transducer (Philips Healthcare); patients were placed in the left lateral decubitus position and connected to electrocardiographic monitoring, and standard parasternal and apical views were acquired during quiet breathing. TAPSE was measured by M-mode echocardiography in the apical four-chamber view, with the sampling line passing through the lateral tricuspid annulus adjacent to the right ventricular free wall and kept as parallel as possible to the direction of longitudinal motion;

the maximum displacement from end-diastole to peak systole was then measured. RV fractional area change (RV-FAC) was measured from an RV-focused apical four-chamber view by tracing the RV endocardial border at end-diastole and end-systole. It was calculated as $[(RV \text{ end-diastolic area} - RV \text{ end-systolic area}) / RV \text{ end-diastolic area}] \times 100\%$. Echocardiographic measurements used for analysis were performed by two sonographers with more than 5 years of experience who were blinded to serum biomarker values and follow-up outcomes. In 30 randomly selected examinations, intraobserver/interobserver intraclass correlation coefficients were 0.95/0.92 for TAPSE and 0.93/0.89 for RV-FAC, respectively. PaO_2 was measured by arterial blood gas analysis and resting SpO_2 by pulse oximetry after at least 10 min of rest; patients not receiving long-term oxygen therapy were assessed on room air, whereas those receiving long-term oxygen were tested at their prescribed resting flow, which was kept unchanged during testing. Pulmonary function testing, including percent-predicted DLCO, was performed according to ERS/ATS technical standards with routine equipment calibration and acceptability and repeatability checks. The 6-minute walk distance (6MWD) was measured in a 30-m indoor corridor using standardised instructions and encouragement, with supplemental oxygen maintained at the patient's usual flow rate when prescribed; World Health Organisation functional class (WHO-FC) was assigned at baseline by the treating PH physician according to the 2022 ESC/ERS criteria.

Outcome definition and follow-up

The primary outcome was the first occurrence of right ventricular decompensation within 6 months after baseline, defined as new or progressively worsening systemic venous congestion or manifestations of low cardiac output accompanied by at least one of the following: (1) an unplanned outpatient assessment with intensification of oral diuretic therapy; (2) unplanned hospitalisation for right heart failure; (3) a requirement for intravenous loop diuretics; (4) the use of inotropic or vasoactive agents because of low cardiac output or circulatory instability; or (5) PH-related or right heart failure-related death. The first qualifying event determined event time and decompensation severity: non-severe decompensation comprised criterion (1) without concurrent hospitalisation, intravenous treatment, inotropic or vasoactive support, or death, whereas severe decompensation comprised a first qualifying event meeting any of criteria (2)–(5). Subsequent events during follow-up did not alter the severity category assigned at the first qualifying event.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 27.0 (IBM Corp). The distributions of continuous variables were first examined using the Shapiro–Wilk test. Normally distributed data were expressed as the mean $\pm$ standard deviation, with comparisons between two groups performed using the independent-samples *t* test and comparisons among three groups performed using one-way analysis of variance; skewed data were expressed as the median and interquartile range and were analysed using the Mann–Whitney *U* test or Kruskal–Wallis test, respectively. Categorical variables were expressed as numbers and percentages and analysed using the χ^2 test or Fisher's exact test. Ordered biomarker changes across the three decompensation severity groups were evaluated using Spearman rank correlation with severity coded as 0, 1, and 2; following a significant Kruskal–Wallis test, pairwise biomarker comparisons were performed using Dunn's test with Holm adjustment, and Hodges–Lehmann location shifts with 10,000-bootstrap 95% confidence intervals were reported as effect-size estimates. Correlations were assessed using Spearman correlation analysis, followed by partial correlation analysis after adjustment for age, sex, type of chronic lung disease, and percent-predicted diffusing capacity of the lung for carbon monoxide (DLCO); the *Figure 1* correlation analyses were exploratory, and their unadjusted *P* values were interpreted descriptively. PVR, hs-CRP, IL-6, and NT-proBNP were natural-log transformed before Cox modelling because of their skewed distributions, and all continuous predictors were standardised to *z* scores after transformation where applicable; hazard ratios therefore represent a 1-standard-deviation increase in the corresponding predictor. Factors associated with right ventricular decompensation were examined using Cox proportional hazards regression, with hazard ratios and 95% confidence intervals reported; hs-CRP, IL-6, and NT-proBNP were entered as serum biomarkers, while TAPSE was included as an echocardiographic reference variable. For sequential model comparisons, a parsimonious reference model containing $\ln(PVR)$ and 6MWD was defined on clinical grounds to represent pulmonary vascular load and functional capacity while limiting model complexity in view of the 48 outcome events; this model was not intended to represent a comprehensive clinical risk score. Multicollinearity was evaluated using variance inflation factors, and the proportional hazards assumption was examined using Schoenfeld residuals; model fit was compared using the likelihood ratio test and Akaike information criterion (AIC), while discrimination was expressed using the Harrell C-index.

Because all patients who remained event-free completed 6 months of follow-up, discrimination at

6 months was assessed using standard binary ROC analysis with 6-month decompensation status as the state variable; for multivariable models, the test variable was the corresponding Cox-model linear predictor. Harrell's C-index quantified concordance across observed event times, whereas the 6-month AUC quantified discrimination at the prespecified 6-month endpoint; pairwise AUC comparisons used DeLong's test, and nested Cox models were compared using the likelihood-ratio test. Six-month Brier scores were calculated from Cox-predicted 6-month risks. The full model was internally validated using 1,000 bootstrap resamples, with optimism-corrected C-index, 6-month AUC, Brier score, and calibration slope reported. *Supplementary File S1* provides variable transformations, standardisation constants, model-specific coefficients, Cox linear predictors, baseline survival at 6 months, and risk-calculation formulas. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Study population and baseline characteristics

During the 6-month follow-up period, 48 patients (40.00%) developed right ventricular decompensation, including 22 with non-severe decompensation and 26 with severe decompensation. All 22 patients in the non-severe group had an unplanned outpatient assessment with intensification of oral diuretic therapy as their first qualifying event. Among the 26 patients in the severe group, 26 required hospitalisation for right heart failure, 24 received intravenous loop diuretics, 8 received inotropic or vasoactive support, and 3 died from PH or right heart failure during follow-up; these severe-event components were not mutually exclusive. Demographic characteristics, the distribution of underlying lung diseases, pulmonary function, and resting oxygenation were generally comparable between groups; however, patients who developed decompensation had a longer duration of chronic lung disease than those who remained free of decompensation ($P = 0.006$, *Table I*).

Table I Baseline demographic and clinical characteristics according to 6-month right ventricular decompensation status.

	Overall (n=120)	No decompensation group (n=72)	Decompensation group (n=48)	Test statistic	P value
Age, years	63.27±8.03	62.78±7.90	64.02±8.26	t=-0.829	0.409
Male, n (%)	79 (65.83)	46 (63.89)	33 (68.75)	$\chi^2=0.303$	0.582
BMI, kg/m ²	23.04±3.46	23.40±3.60	22.50±3.20	t=1.39	0.167
Smoking history, n (%)	81 (67.50)	47 (65.28)	34 (70.83)	$\chi^2=0.405$	0.524
Hypertension, n (%)	46 (38.33)	26 (36.11)	20 (41.67)	$\chi^2=0.376$	0.540
Diabetes mellitus, n (%)	24 (20.00)	13 (18.06)	11 (22.92)	$\chi^2=0.425$	0.514
Duration of chronic lung disease, years	8.00 (5.00, 11.25)	7.00 (5.00, 10.00)	9.00 (6.00, 14.25)	Z=-2.747	0.006
Chronic obstructive pulmonary disease, n (%)	70 (58.33)	42 (58.33)	28 (58.33)	$\chi^2=0.149$	0.928
Interstitial lung disease, n (%)	36 (30.00)	21 (29.17)	15 (31.25)	-	-
Bronchiectasis and other diseases, n (%)	14 (11.67)	9 (12.50)	5 (10.42)	-	-

Table II Baseline serum hs-CRP, IL-6, and NT-proBNP concentrations according to subsequent right ventricular decompensation severity.

	No decompensation group (n=72)	Non-severe group (n=22)	Severe group (n=26)	Test statistic	P value	Trend r_s	Trend P value
hs-CRP, mg/L	1.91 (1.34, 2.52)	2.59 (1.91, 2.75)	3.22 (2.52, 4.36)	H=22.436	<0.001	0.426	<0.001
IL-6, pg/mL	6.04 (4.24, 9.00)	8.55 (5.60, 12.29)	10.77 (7.65, 12.54)	H=13.088	0.001	0.331	<0.001
NT-proBNP, pg/mL	331.05 (216.82, 523.97)	489.15 (361.05, 676.70)	777.35 (645.02, 951.08)	H=28.667	<0.001	0.48	<0.001

Note: Trend r_s denotes the Spearman rank correlation between biomarker concentration and subsequent decompensation severity coded as 0, 1, and 2. Adjusted pairwise comparisons and effect-size estimates with 95% confidence intervals are provided in *Supplementary Table S2*.

Supplementary Table I Adjusted pairwise comparisons of baseline serum biomarkers across subsequent decompensation severity groups.

Predictor transformation and standardisation constants.			
Predictor	Transformation	Mean	SD
PVR	ln (PVR)	1.670582	0.389178
6MWD	None	328.000000	78.588386
hs-CRP	ln (hs-CRP)	0.809042	0.538473
IL-6	ln (IL-6)	1.974897	0.631498
NT-proBNP	ln (NT-proBNP)	6.064850	0.715122
TAPSE	None	18.769167	2.366247

Location shifts are expressed as the higher-severity group minus the lower-severity group. Pairwise P values were obtained from Dunn's tests and adjusted within each biomarker using the Holm method; 95% confidence intervals for Hodges-Lehmann location shifts were obtained from 10,000 percentile bootstrap resamples.

Baseline serum biomarker profiles according to subsequent decompensation severity

Baseline serum hs-CRP, IL-6, and NT-proBNP concentrations were progressively higher from the group that remained free of decompensation to the groups that subsequently developed non-severe and severe decompensation, defining a graded baseline

Supplementary Table S1 Model Specification and Equations for 6-Month Right Ventricular Decompensation Risk.

Model equations

Reference model: $LP = 0.735118 \times Z\ln(PVR) - 0.199088 \times Z6MWD$; $S_0(6 \text{ months}) = 0.640221$

Reference + three serum biomarkers: $LP = 0.648258 \times Z\ln(PVR) - 0.047008 \times Z6MWD + 0.457858 \times Z\ln(\text{hs-CRP}) + 0.259041 \times Z\ln(\text{IL-6}) + 0.685763 \times Z\ln(\text{NT-proBNP})$; $S_0(6 \text{ months}) = 0.696641$

Reference + TAPSE: $LP = 0.623467 \times Z\ln(PVR) - 0.203650 \times Z6MWD - 0.482774 \times ZTAPSE$; $S_0(6 \text{ months}) = 0.651776$

Full combined model: $LP = 0.589918 \times Z\ln(PVR) - 0.057536 \times Z6MWD + 0.492957 \times Z\ln(\text{hs-CRP}) + 0.217640 \times Z\ln(\text{IL-6}) + 0.592484 \times Z\ln(\text{NT-proBNP}) - 0.241089 \times ZTAPSE$; $S_0(6 \text{ months}) = 0.698776$

Risk calculation formula: 6-month risk = $1 - S_0(6 \text{ months})^{\Lambda} \exp(LP)$, where LP denotes the Cox-model linear predictor. $Z = (\text{transformed value} - \text{mean})/\text{SD}$.

biomarker profile associated with subsequent clinical deterioration (*Table II*, *Supplementary Table S1*). NT-proBNP showed the strongest correlation with decompensation severity ($r=0.480$, $P<0.001$), while all three serum markers remained positively associated with PVR and inversely associated with TAPSE and RV-FAC after adjustment for age, sex, chronic lung disease type, and percent-predicted DLCO. Pulmonary artery pressure and right-sided chamber dimensions also increased with severity, whereas cardiac index and several measures of right ventricular function declined; these changes were interpreted as hemodynamic and functional correlates of the serum biomarker profile (*Figure 1*).

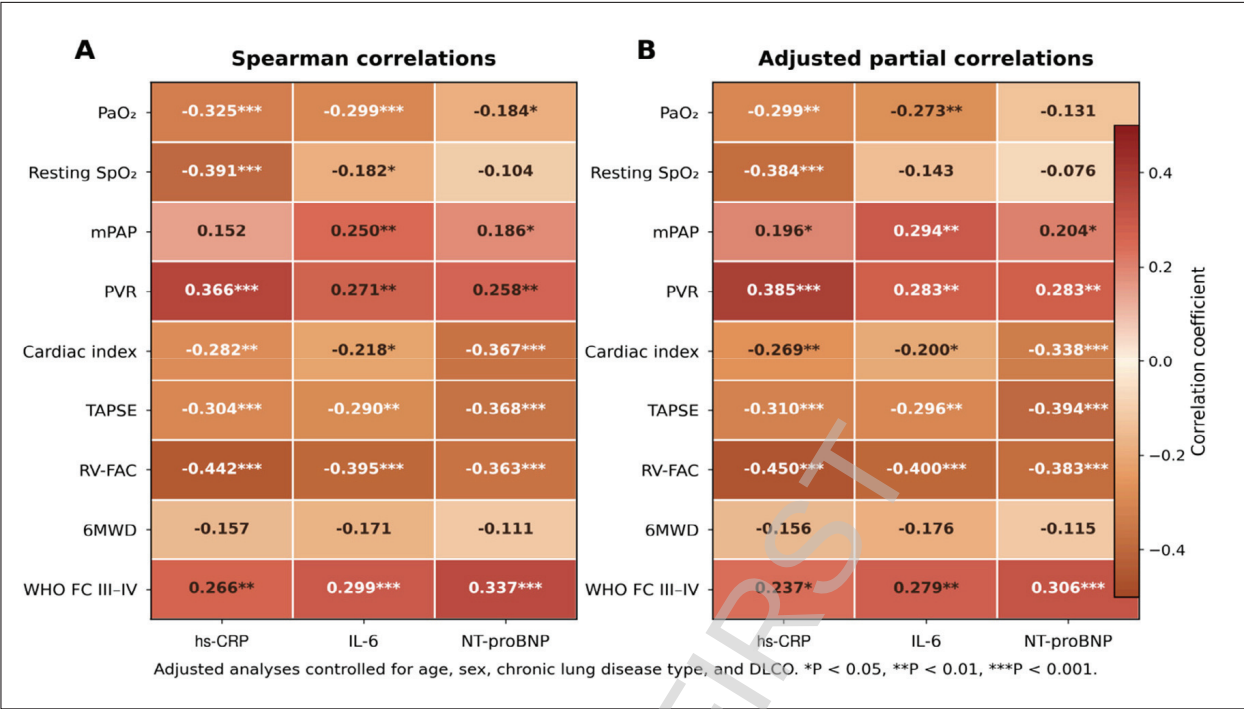


Figure 1 Correlation heatmaps of serum inflammatory and cardiac-stress biomarkers with oxygenation, hemodynamic, functional, and clinical measures.

(A) Spearman correlations of serum hs-CRP, IL-6, and NT-proBNP with PaO₂, resting SpO₂, mPAP, PVR, cardiac index, TAPSE, RV-FAC, 6MWD, and WHO functional class III-IV; (B) partial correlations after adjustment for age, sex, chronic lung disease type, and percent-predicted DLCO. The values shown are correlation coefficients; *P<0.05, **P<0.01, and ***P<0.001. These correlation analyses were exploratory, and the displayed P values were not adjusted for multiplicity.

Independent associations of serum biomarkers with right ventricular decompensation

In univariable Cox analyses, higher hs-CRP, IL-6, and NT-proBNP concentrations were associated with increased risk of right ventricular decompensation, as were higher pulmonary artery pressure, higher PVR, and poorer WHO functional class; higher cardiac index and TAPSE were associated with lower risk. After multivariable adjustment, PVR, hs-CRP, and NT-proBNP remained independently associated with decompensation within 6 months, with adjusted hazard ratios of 1.804 (95% CI 1.276–2.550), 1.637 (95% CI 1.167–2.296), and 1.808 (95% CI 1.253–2.611), respectively (all P≤0.004). The association of IL-6 was attenuated after simultaneous adjustment, while TAPSE and 6MWD also did not retain independent statistical significance (Table III).

Individual and combined prognostic value of the serum biomarker panel

Among the individual serum markers, NT-proBNP showed the highest discriminative ability, with an AUC of 0.759 (95% CI 0.673–0.845). Adding IL-6 to hs-CRP increased the AUC numerically,

while further inclusion of NT-proBNP increased the AUC of the three-marker serum panel to 0.823 (95% CI 0.747–0.898); the three-marker model performed significantly better than the hs-CRP-only model (P=0.011) and the hs-CRP plus IL-6 model (P=0.019). The parsimonious reference model had an AUC of 0.751, which increased to 0.841 (95% CI 0.770–0.913) after addition of the three serum biomarkers; the increase was significant by DeLong's test (P=0.014), while both AIC and the 6-month Brier score decreased. Further addition of TAPSE increased the AUC only from 0.841 to 0.846, which was not significant by DeLong's test (P=0.527); the corresponding nested Cox-model comparison for adding TAPSE was also non-significant (LR χ^2 =1.927, df=1, P=0.165) (Table IV, Figure 2).

Survival analysis and model validation

Exploratory Kaplan–Meier analyses using cohort-derived Youden cutoffs showed lower 6-month decompensation-free survival among patients with higher hs-CRP, IL-6, or NT-proBNP concentrations and among those with lower TAPSE; these plots were used for visualisation, whereas continuous-variable Cox analyses remained primary

Table III Univariable and multivariable Cox proportional hazards analyses of factors associated with 6-month right ventricular decompensation.

Variable	Uni-variable β	SE	Wald z	Univariable HR (95% CI)	P value	Multi-variable β	SE	Wald z	Adjusted HR (95% CI)	P value	VIF
Age	0.134	0.144	0.93	1.143 (0.862–1.515)	0.353	-	-	-	-	-	-
Mean pulmonary artery pressure	0.451	0.121	3.723	1.571 (1.238–1.992)	<0.001	-	-	-	-	-	-
Pulmonary vascular resistance	0.753	0.162	4.656	2.124 (1.547–2.917)	<0.001	0.59	0.177	3.342	1.804 (1.276–2.550)	<0.001	1.236
Cardiac index	-0.673	0.141	-4.768	0.510 (0.387–0.673)	<0.001	-	-	-	-	-	-
6-minute walk distance	-0.253	0.137	-1.85	0.776 (0.594–1.015)	0.064	-0.058	0.151	-0.381	0.944 (0.702–1.270)	0.703	1.054
WHO functional class III-IV	0.664	0.293	2.266	1.942 (1.094–3.449)	0.023	-	-	-	-	-	-
hs-CRP	0.7	0.158	4.44	2.014 (1.478–2.742)	<0.001	0.493	0.173	2.857	1.637 (1.167–2.296)	0.004	1.31
IL-6	0.591	0.156	3.786	1.805 (1.330–2.451)	<0.001	0.218	0.159	1.369	1.243 (0.910–1.698)	0.171	1.259
NT-proB-NP	0.805	0.17	4.743	2.237 (1.604–3.121)	<0.001	0.592	0.187	3.163	1.808 (1.253–2.611)	0.002	1.253
TAPSE	-0.649	0.152	-4.268	0.523 (0.388–0.704)	<0.001	-0.241	0.175	-1.379	0.786 (0.558–1.107)	0.168	1.242

Table IV Apparent model fit and predictive performance for 6-month right ventricular decompensation.

Model	Included variables	AIC	Harrell C-index	6-month AUC (95% CI)	6-month Brier score	LR χ^2	df	P value
Reference model	ln(PVR), 6MWD	416.402	0.751	0.751 (0.664–0.839)	0.2	-		-
Reference + three serum biomarkers	Reference model + ln(hs-CRP), ln(IL-6), ln(NT-proBNP)	389.579	0.841	0.841 (0.770–0.913)	0.162	32.823	3	<0.001
Reference + TAPSE	Reference model + TAPSE	407.648	0.77	0.802 (0.724–0.879)	0.181	10.754	1	0.001
Full combined model	Reference model + three serum biomarkers + TAPSE	389.652	0.842	0.846 (0.777–0.916)	0.158	34.75	4	<0.001

Note: All performance estimates in Table IV are apparent development-cohort estimates. Likelihood-ratio statistics compare each expanded model with the reference model; the full model contained six 1-df predictors. The comparison of the full model with the »Reference + three serum biomarkers« model yielded LR $\chi^2=1.927$, df=1, P=0.165. Harrell's C-index and the 6-month AUC were calculated separately; their identical rounded values in the reference model (0.751) and the reference + three-serum-biomarker model (0.841) reflect rounding of independently calculated estimates.

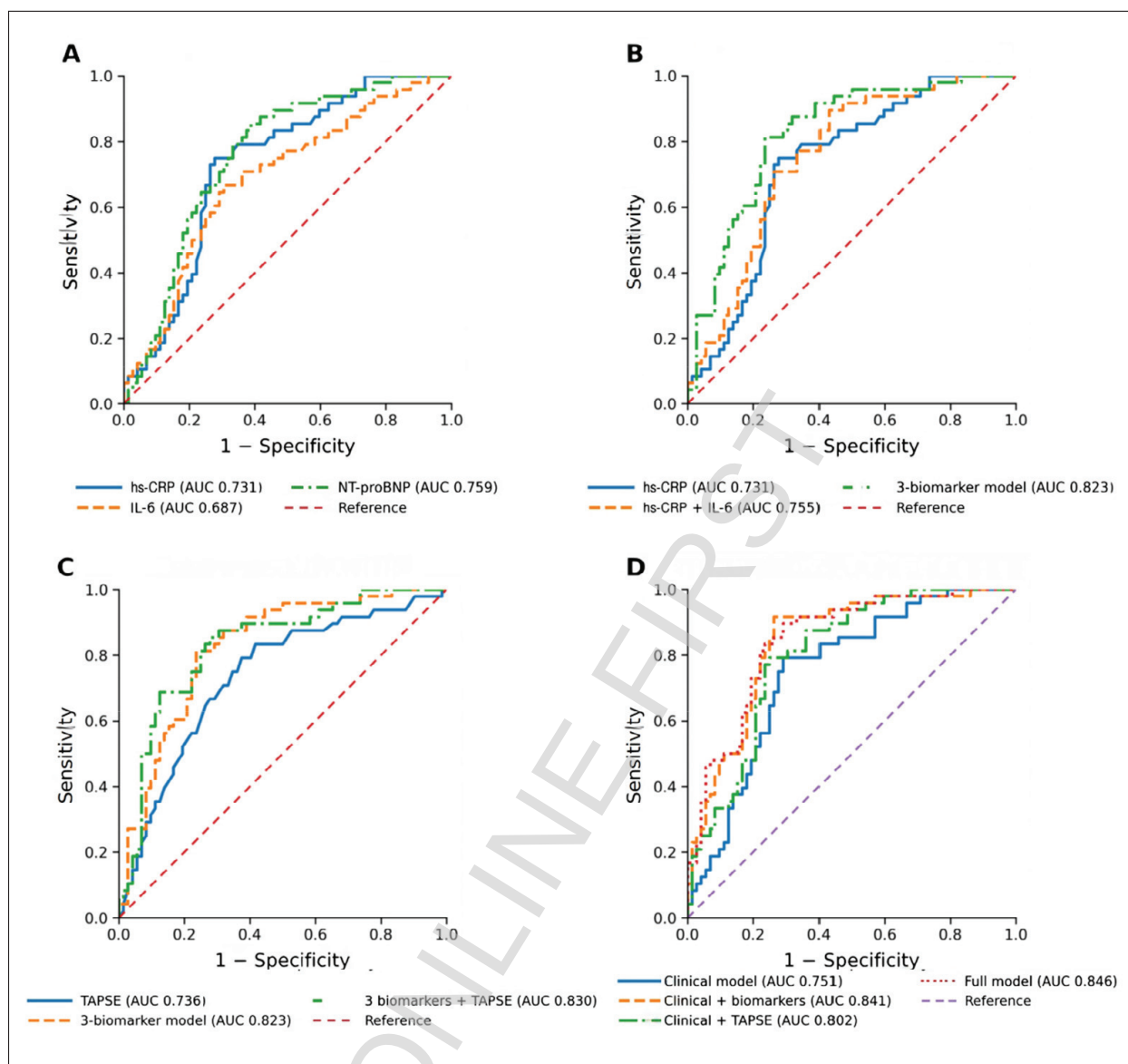


Figure 2 Receiver operating characteristic curves for individual biomarkers and sequential prediction models of 6-month right ventricular decompensation.

(A) Discriminative performance of serum hs-CRP, IL-6, and NT-proBNP as individual biomarkers; (B) stepwise comparison of the hs-CRP model, the hs-CRP plus IL-6 model, and the three-marker serum model incorporating hs-CRP, IL-6, and NT-proBNP; (C) comparison of TAPSE alone, the three-biomarker model, and the three-biomarker plus TAPSE model; (D) incremental predictive performance of the basic clinical model, the clinical model plus three serum biomarkers, the clinical model plus TAPSE, and the full combined model.

(Figure 3). When patients were divided into tertiles of risk predicted by the full model, 3, 17, and 28 decompensation events occurred in the low-, intermediate-, and high-risk groups, respectively. The survival curves of the three groups were clearly separated (log-rank $\chi^2=40.510$, $P<0.001$). The apparent full-model C-index, 6-month AUC, and 6-month Brier score were 0.842, 0.846, and 0.158, respectively; after 1,000-resample bootstrap

correction, the corresponding values were 0.820, 0.823, and 0.177, with a calibration slope of 0.832, indicating modest optimism in the development sample. Decision curve analysis showed that, within a threshold probability range of 0.10–0.50, both the reference + three-serum-biomarker model and the full model showed relatively high and similar net benefit; these analyses were exploratory (Figure 4).

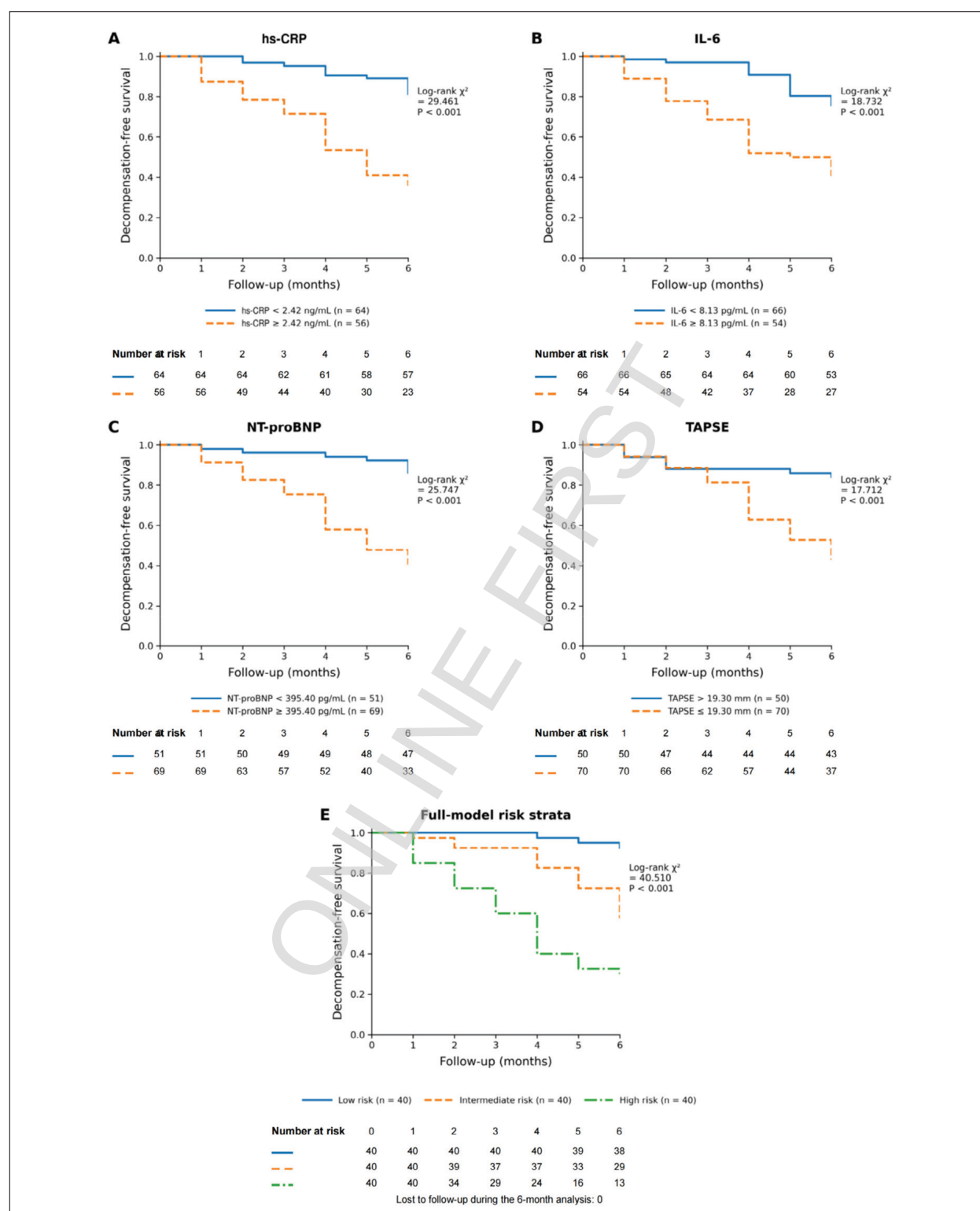


Figure 3 Kaplan–Meier curves of 6-month decompensation-free survival according to baseline serum biomarkers, TAPSE, and model-derived risk strata.

(A) Decompensation-free survival according to baseline hs-CRP dichotomised at the cohort-derived Youden cutoff; (B) decompensation-free survival according to baseline IL-6 dichotomised at the cohort-derived Youden cutoff; (C) decompensation-free survival according to baseline NT-proBNP dichotomised at the cohort-derived Youden cutoff; (D) decompensation-free survival according to TAPSE at the cohort-derived Youden cutoff of 19.30 mm; (E) decompensation-free survival across low-, intermediate-, and high-risk groups defined by tertiles of the predicted risk from the full model. These cutoffs were derived from the same cohort and are shown for exploratory visualisation only; they should not be interpreted as validated clinical thresholds. No included patient was lost to follow-up before completion of the 6-month outcome assessment.

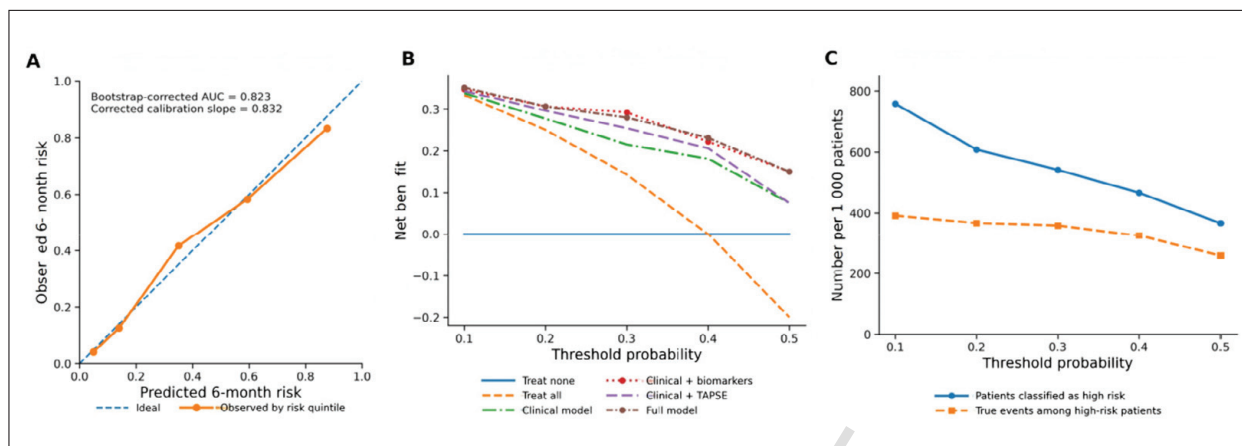


Figure 4 Internal validation and clinical utility of the full model for predicting 6-month right ventricular decompensation.

(A) Apparent and bootstrap-corrected calibration curves comparing the predicted and observed probabilities of right ventricular decompensation; (B) decision curve analysis comparing the net benefits of the basic clinical model, the clinical model plus three serum biomarkers, the clinical model plus TAPSE, and the full combined model, together with the treat-all and treat-none strategies, across a range of threshold probabilities; (C) clinical impact curve of the full model showing the number of patients classified as high risk and the number of true decompensation events among high-risk patients at different threshold probabilities. The full model included $\ln(\text{PVR})$, 6MWD, $\ln(\text{hs-CRP})$, $\ln(\text{IL-6})$, $\ln(\text{NT-proBNP})$, and TAPSE.

Discussion

This study identified a graded baseline serum inflammatory and cardiac-stress biomarker profile associated with subsequent right ventricular decompensation severity in patients with CLD-PH. Baseline hs-CRP, IL-6, and NT-proBNP concentrations were progressively higher in patients who subsequently developed more severe decompensation and were consistently related to greater pulmonary vascular load and poorer right ventricular function; after adjustment for relevant clinical variables, hs-CRP and NT-proBNP retained independent associations with the 6-month outcome. The three-marker serum panel improved model fit and discrimination when added to the parsimonious reference model comprising PVR and 6MWD, whereas TAPSE added little information, indicating that the study's main contribution lies in integrated biochemical assessment rather than in building a comprehensive multimodal prediction model.

hs-CRP is a sensitive acute-phase reactant that integrates the downstream effects of circulating proinflammatory cytokines and is widely used to quantify low-grade systemic inflammatory activity (12). In chronic lung disease, persistent airway and parenchymal inflammation, recurrent hypoxemic stress, endothelial dysfunction, and right ventricular pressure loading may all contribute to an amplified systemic inflammatory response (13, 14). In the present cohort, baseline hs-CRP was progressively higher across groups defined by subsequent decompensation severity and was associated with lower oxygenation, higher PVR, and poorer right ventricular functional indices; importantly, its association with subsequent decompensation persisted after

adjustment for other clinical and laboratory variables. The persistence of this association suggests that hs-CRP captured inflammatory information related to subsequent decompensation; however, because hs-CRP was measured only once in an observational cohort, the present data do not establish a causal contribution of systemic inflammation.

IL-6 represents a more proximal component of inflammatory activation than hs-CRP and participates in pulmonary vascular immune signalling and acute-phase responses (15). Higher baseline IL-6 concentrations in patients who subsequently developed more severe decompensation, together with their associations with PVR and right ventricular functional measures, were consistent with greater inflammatory activity at baseline; however, IL-6 did not retain an independent association after hs-CRP, NT-proBNP, PVR, and other variables were considered simultaneously. This attenuation may reflect shared information with hs-CRP and other correlated variables, but measurement variability, limited sample size, and model overfitting may also have contributed; therefore, the absence of an independent association should not be interpreted as evidence for or against a causal role of IL-6.

NT-proBNP is more closely related to downstream right ventricular functional decompensation. As PVR and right ventricular pressure load increase, its circulating level usually rises and is associated with worsening right ventricular function, higher clinical risk, and poorer prognosis (16–18). This may explain why NT-proBNP showed the highest discriminative ability among the individual markers and retained an independent association in multivariable analysis; unlike hs-CRP and IL-6, which characterise different

levels of systemic inflammatory activity, NT-proBNP more directly reflects the downstream myocardial consequences of sustained pulmonary vascular loading.

Finally, lower TAPSE was consistent with more severe decompensation and poorer decompensation-free survival, but its effect was attenuated in the multivariable model, and adding it to the serum biomarker model did not significantly improve predictive performance. TAPSE mainly reflects longitudinal right ventricular systolic function; although it is simple to obtain, it should be interpreted in the context of overall RV geometry, loading conditions, and complementary measures of RV function (19, 20). This result does not negate the role of TAPSE in evaluating right ventricular function, but suggests that a single echocardiographic parameter may partly overlap with information provided by PVR, NT-proBNP, and other changes in right ventricular function.

The incremental performance of the serum panel supports a multidimensional biochemical interpretation of right ventricular decompensation. hs-CRP, IL-6, and NT-proBNP are not interchangeable measures: IL-6 represents cytokine-mediated inflammatory activation, hs-CRP reflects the downstream systemic acute-phase response, and NT-proBNP indicates myocardial wall stress. Importantly, hs-CRP remained independently associated with the 6-month outcome in a model that also included NT-proBNP, supporting nonredundant information beyond myocardial stress; IL-6 was retained because it was a prespecified upstream inflammatory marker, although its attenuated multivariable association means that the three-marker panel should be interpreted as a biologically complementary construct rather than as three independent predictors. Accordingly, the value examined here is primarily pathophysiological complementarity and model-level incremental information; assay accessibility, cost, and turnaround time were not formally evaluated. Together, these markers captured information not fully represented by PVR and 6MWD, as shown by the reduction in AIC and 6-month Brier score and the increase in AUC after adding the panel to the reference model. From a clinical biochemistry perspective, this represents the principal finding of the study, because a serum-based panel may refine short-term risk stratification while remaining complementary to hemodynamic and echocardiographic assessment. Further inclusion of TAPSE produced only a numerical improvement in model performance, and the between-model comparison did not reach statistical significance; the bootstrap-corrected calibration slope of 0.832 and the reduction in discrimination after optimism correction indicate some model optimism, so the full model should be regarded as exploratory, while the decision-curve results remain internal evidence and cannot yet support clinical implementation.

We should not overlook the limitations of this study: it had a single-centre retrospective

design, the sample size and number of outcome events were limited, and the full model contained a relatively large number of variables; a 6-month follow-up was also insufficient for evaluating long-term prognosis. In addition, each biomarker was measured only once during a clinically stable period, making it impossible to determine whether serial increases in hs-CRP, IL-6, or NT-proBNP preceded clinical decompensation; residual inflammatory confounding also cannot be excluded, even though patients with recent respiratory infection, acute exacerbation, systemic infection, autoimmune disease, and active malignancy were excluded. Future studies should externally validate these findings in multicenter prospective cohorts and compare the stability of simplified models with that of serial measurement strategies.

Conclusion

Higher baseline hs-CRP, IL-6, and NT-proBNP concentrations were associated with greater subsequent right ventricular decompensation severity in patients with CLD-PH, linking the baseline inflammatory and myocardial-stress profile with short-term clinical outcomes. The combined serum panel improved short-term risk discrimination beyond the parsimonious reference model comprising PVR and 6MWD, although its value remains complementary to established hemodynamic and echocardiographic assessment. Prospective external validation and longitudinal biomarker measurements are required before this laboratory-based approach can be incorporated into routine risk assessment.

Consent for publication

All authors gave final approval of the version to be published.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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