

Pre-operative albumin outperforms NHANES-derived composite nutritional-immune-inflammatory indices for predicting adverse outcomes in pediatric congenital heart surgery: a single-center study with internal validation

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Abstract

Nutritional-immune-inflammatory indices derived from the National Health and Nutrition Examination Survey (NHANES) have been validated for prognostication in adults, but their utility in pediatric congenital heart disease (CHD) surgery remains unknown. We retrospectively analyzed 1,838 pediatric CHD surgeries from the Pediatric Intensive Care database, evaluating seven NHANES-derived indices (PNI, NLR, PLR, SII, SIRI, MLR, CALLY) and comparing them against serum albumin alone for predicting a composite outcome of in-hospital death or prolonged length of stay. Albumin was the strongest individual predictor (AUC = 0.690, 95% CI: 0.653–0.727), outperforming all composite indices. A multivariable model combining albumin, NLR, and SIRI achieved modest improvement (AUC = 0.722; optimism-corrected: 0.717; 5-fold CV: 0.718 ± 0.036). Age was the strongest effect modifier (p -interaction < 0.0001), with superior performance in infants < 1 year (AUC = 0.719) and complex CHD (AUC = 0.802). External validation using MIMIC-III was precluded by data structure limitations. Pre-operative serum albumin alone, a simple and inexpensive biomarker, outperforms complex NHANES-derived composite indices in pediatric CHD surgery. These findings caution against directly translating adult-derived risk tools to pediatric populations.

Introduction

Congenital heart disease (CHD) is the most common congenital anomaly, affecting approximately 1% of live births worldwide [1]. Despite advances in surgical techniques and perioperative care, postoperative morbidity and mortality remain substantial, particularly among neonates and infants with complex CHD [2, 3]. Accurate preoperative risk stratification is essential for optimizing perioperative management, counseling families, and allocating intensive care resources.

Nutritional status and systemic inflammation are increasingly recognized as critical determinants of surgical outcomes [4, 5]. In adult populations, composite indices integrating nutritional and inflammatory markers — such as the prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), monocyte-to-lymphocyte ratio (MLR), and the CALLY index — have been extensively validated for prognostication across various surgical disciplines, including cardiac surgery [6–11]. These indices, many originally derived from or validated in NHANES cohorts, offer the advantage of being inexpensive and routinely available from standard preoperative laboratory tests.

However, the applicability of these adult-derived indices to pediatric populations is uncertain. Children, particularly infants, possess fundamentally different hematopoietic and immune systems [12]. Age-related changes in lymphocyte counts, inflammatory responses, and nutritional reserve may substantially alter the performance and optimal thresholds of these composite indices [13]. Moreover, the relative contribution of individual components — such as albumin, a hepatic protein with both nutritional and negative acute-phase properties — may differ between adult and pediatric surgical populations [14].

To date, no study has systematically evaluated NHANES-derived composite nutritional-immune-inflammatory indices in the context of pediatric CHD surgery. We therefore conducted this study to evaluate the predictive value of preoperative PNI, NLR, PLR, SII, SIRI, MLR, and CALLY for adverse outcomes after pediatric CHD surgery, compare their performance against serum albumin alone, and determine whether age-related differences modify their predictive utility.

Results

Patient flow and baseline characteristics

Of the initial cohort, 1,838 pediatric CHD surgeries met the inclusion criteria after excluding diagnostic procedures (Supplementary Figure S1). The composite adverse outcome occurred in 476 patients (25.9%), including 22 in-hospital deaths (1.2%). Patients with adverse outcomes had significantly lower preoperative albumin, higher NLR, SIRI, and MLR compared with those without (all $p<0.001$, Table 1). The median age at surgery was 1.0 year (IQR: 0-3 years), and 46.4% were male.

Table 1. Baseline characteristics stratified by composite adverse outcome status.

Variable	Overall	No Event	Event	Statistic	P-value
Age (years)	1.9 (2.7)	2.3 (2.8)	0.9 (2.1)	11.311	0.0
<1y	1166 (63.4%)	766 (56.2%)	400 (84.0%)		
1-3y	328 (17.8%)	293 (21.5%)	35 (7.4%)		
3-6y	208 (11.3%)	182 (13.4%)	26 (5.5%)		
6-12y	119 (6.5%)	107 (7.9%)	12 (2.5%)		
≥12y	17 (0.9%)	14 (1.0%)	3 (0.6%)		
Male	852 (46.4%)	621 (45.6%)	231 (48.5%)		
Female	986 (53.6%)	741 (54.4%)	245 (51.5%)		
Surgery duration (min)	116 (64)	100 (49)	162 (80)	-16.015	0.0
Post-op LOS (days)	12.4 (24.9)	7.4 (2.5)	26.6 (45.9)	-9.087	0.0
Albumin (g/L)	44.0 (3.9)	44.7 (3.2)	41.5 (5.1)	10.517	0.0
Neutrophil (×10 ⁹ /L)	3.11 (1.82)	2.94 (1.34)	3.65 (2.78)	-4.871	0.0
Lymphocyte (×10 ⁹ /L)	4.97 (1.95)	5.02 (1.94)	4.84 (1.98)	1.513	0.1307
Platelet (×10 ⁹ /L)	345 (101)	343 (96)	352 (117)	-1.391	0.1649
Monocyte (×10 ⁹ /L)	0.59 (0.31)	0.54 (0.22)	0.76 (0.46)	-9.224	0.0
CRP (mg/L)	4.4 (4.3)	4.0 (2.7)	5.2 (6.6)	-2.542	0.0116
Triglycerides (mmol/L)	1.48 (0.89)	1.48 (0.89)	1.49 (0.88)	-0.218	0.8278
PNI	29.3 (9.8)	29.4 (9.8)	28.7 (10.0)	1.146	0.2524
NLR	0.80 (0.92)	0.73 (0.81)	1.00 (1.16)	-4.222	0.0
PLR	79.3 (38.5)	77.7 (36.2)	84.5 (44.8)	-2.708	0.007
SII	264 (272)	244 (250)	327 (327)	-4.566	0.0
SIRI	0.52 (1.08)	0.38 (0.39)	0.98 (2.04)	-5.735	0.0
MLR	0.14 (0.10)	0.12 (0.06)	0.19 (0.16)	-8.491	0.0
CALLY	7.74 (9.11)	8.03 (8.27)	7.04 (10.83)	1.067	0.2868

Univariate analysis

Serum albumin demonstrated the strongest individual predictive performance (AUC=0.690; OR per 1 g/L decrease: 0.92, 95% CI: 0.90-0.94, p<0.0001, Table 2). Among NHANES-derived indices, MLR (AUC=0.645) and SIRI (AUC=0.605) showed moderate associations. The remaining indices – PNI

(AUC=0.519, p=0.342), NLR (AUC=0.546, p=0.001), PLR (AUC=0.532, p=0.067), and SII (AUC=0.552, p=0.002) – performed poorly (all AUC<0.56).

Table 2. Univariate logistic regression results.

Predictor	N	Events	OR	CI lo	CI hi	P	AUC
PNI	1370	315	0.992	0.979	1.005	0.2453	0.519
NLR	1603	384	1.358	1.18	1.563	<0.0001	0.546
PLR	1603	384	1.004	1.001	1.007	0.0032	0.532
SII	1603	384	1.001	1.001	1.002	<0.0001	0.552
SIRI	1603	384	2.66	2.106	3.359	<0.0001	0.605
MLR	1603	384	1210.038	301.412	4857.786	<0.0001	0.645
CALLY	574	171	0.985	0.96	1.01	0.2461	0.615
Albumin	1379	317	0.812	0.783	0.841	<0.0001	0.69
Lymphocyte	1603	384	0.954	0.899	1.013	0.1258	0.524
Neutrophil	1603	384	1.218	1.143	1.297	<0.0001	0.548

Multivariable model comparison

Among the five models tested (Table 3), the albumin+NLR+SIRI model achieved the highest AUC (0.722), outperforming both albumin alone (AUC=0.690) and the Core 4 composite model (AUC=0.544). The addition of NLR and SIRI to albumin yielded modest improvements.

Table 3. Multivariable model AUC comparison.

Model	AUC
Albumin alone	0.6901878486517314
Core 4 (PNI+NLR+PLR+SII)	0.5441570751523359
Albumin + NLR + SII	0.6881576769728428
Albumin + NLR + SIRI	0.7215827879334987
Albumin + SIRI + MLR	0.6970074475287746

Internal validation

The albumin+NLR+SIRI model demonstrated stable internal validation. Bootstrap optimism correction yielded a corrected AUC of 0.7174 with minimal optimism (0.0041). Stratified 5-fold cross-validation

produced a mean AUC of 0.718 ± 0.036 . The model was well-calibrated (Brier: 0.145; Hosmer-Lemeshow $\chi^2=10.69$, $p=0.220$). Supplementary Table S1 summarizes the full internal validation metrics.

Subgroup and interaction analyses

Age was the strongest effect modifier (p -interaction < 0.0001 , Figure 1). The model performed well in infants < 1 year (AUC=0.719) but poorly in children ≥ 5 years (AUC=0.545). Among CHD subtypes, discrimination was excellent in great vessel anomalies (AUC=0.833) and complex CHD (AUC=0.802). Surgery duration significantly modified performance (p -interaction < 0.0001). No interaction was observed with sex ($p=0.99$).

Sensitivity analyses and external validation

The albumin+NLR+SIRI model remained robust across sensitivity analyses (Supplementary Table S2), maintaining AUC values of 0.733 (LOS > 80 th percentile) and 0.742 (LOS > 90 th percentile). Performance was reduced in older children (≥ 1 year, AUC=0.613) and after excluding neonates (AUC=0.613).

The MIMIC-III cohort comprised 631 pediatric CHD surgeries from 334 unique admissions (event rate 27.6%). However, fundamental data structure limitations precluded clean pre-operative external validation. Pre-operative albumin was available in only 12 admissions (1.9%), rendering the locked albumin+NLR+SIRI model unvalidatable. Using early post-operative laboratory values as surrogates, CBC-based indices showed reduced discrimination (Supplementary Figure S2).

Discussion

In this cohort of 1838 pediatric CHD surgeries, we systematically evaluated preoperative NHANES-derived nutritional-immune-inflammatory composite indices against serum albumin alone. The principal finding is that albumin – a single, inexpensive biomarker – outperforms all complex composite indices for predicting adverse outcomes after pediatric CHD surgery. Adding NLR and SIRI to albumin yields only modest improvement (optimism-corrected AUC: 0.717 vs 0.690).

The poor performance of traditional composite indices (PNI, NLR, PLR, SII) in our pediatric cohort contrasts sharply with their established utility in adult cardiac surgery. In adults, PNI consistently predicts postoperative complications with AUC values ranging from 0.70 to 0.80 [18], and NLR has been validated as a strong predictor across multiple cohorts [6]. This discrepancy likely reflects fundamental age-related differences in hematological and inflammatory physiology. Infants have higher baseline lymphocyte counts, more robust hematopoietic reserve, and different inflammatory cytokine profiles [12, 19]. Ratio-based indices that depend on circulating immune cell counts may lose discriminative power when both numerator and denominator vary with developmental stage.

Albumin emerged as the dominant predictor, consistent with its dual role as a nutritional marker and negative acute-phase reactant. Preoperative hypoalbuminemia has been consistently linked to adverse surgical outcomes across diverse populations, including pediatric cardiac surgery [20, 21]. The superior

performance of albumin alone suggests that in pediatric CHD patients, the nutritional component captured by albumin may be more prognostically relevant than the inflammatory components. Alternatively, the hepatic acute-phase response to preoperative physiologic stress – reflected by decreased albumin synthesis – may more sensitively indicate the child's overall physiologic reserve than peripheral blood cell ratios [22].

Among the NHANES indices, SIRI (which incorporates monocyte count) and MLR showed the strongest associations, suggesting that monocyte-mediated inflammatory pathways may be particularly relevant in pediatric CHD prognosis. Monocytes and macrophages play central roles in tissue remodeling, wound healing, and the inflammatory response to cardiopulmonary bypass [23].

Age was the strongest effect modifier, with the model performing well in infants < 1 year but poorly in older children. This likely reflects differences in the preoperative physiologic state and age-related differences in the inflammatory response to cardiopulmonary bypass [24]. These findings suggest that age-specific models or indices may be necessary for optimal risk stratification across the pediatric age range.

The attempt to externally validate our model using MIMIC-III highlights a critical challenge in pediatric cardiac surgery research: the scarcity of publicly available critical care databases with both structured pre-operative laboratory data and precise procedure timing. This underscores the need for prospective multi-center registries with standardized, time-stamped data collection protocols.

Strengths of this study include systematic evaluation of seven NHANES-derived indices in a well-characterized pediatric CHD cohort, comprehensive internal validation (bootstrap, cross-validation, calibration, interaction tests), and adequate event counts for multivariable modeling. Limitations include the single-center retrospective design, the composite outcome combining death and prolonged LOS, CRP availability in only 31.2% of patients, and the unsuccessful external validation attempt. The model requires prospective validation in cohorts with standardized pre-operative laboratory timing.

In conclusion, preoperative serum albumin is a simple, readily available, and effective predictor of adverse outcomes after pediatric CHD surgery, outperforming complex NHANES-derived composite indices. Age is the most important effect modifier. These findings underscore the need for pediatric-specific nutritional-immune-inflammatory indices and caution against direct translation of adult-derived risk stratification tools to pediatric populations.

Methods

Study design and data source

This retrospective cohort study used data from the Pediatric Intensive Care (PIC) database, a publicly available, de-identified, pediatric-specific intensive care database maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology [15]. The PIC database contains

comprehensive clinical data from children admitted to critical care units at a large children's hospital in China between 2010 and 2018. Institutional review board approval was obtained by the original database developers, and the requirement for individual patient consent was waived. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All methods were performed in accordance with the relevant guidelines and regulations.

Study population

We identified patients with CHD (ICD-10 codes Q20-Q28) who underwent cardiac surgery. Inclusion criteria were: (1) age < 18 years at surgery; (2) documented cardiac surgery procedure; and (3) available preoperative laboratory data. Patients undergoing diagnostic procedures (angiocardiology, angiography) without therapeutic intervention were excluded. For patients with multiple surgeries during the same admission, only the first surgery was analyzed.

Data extraction and NHANES index definitions

Preoperative laboratory values were extracted from the closest measurement within 7 days before surgery (30 days for lipid and glucose measurements to account for fasting requirements). Collected parameters included serum albumin, absolute neutrophil, lymphocyte, monocyte, and platelet counts, white blood cell count, C-reactive protein (CRP), triglycerides, HDL cholesterol, glucose, and total cholesterol.

The following indices were calculated using standard formulas: PNI = Albumin (g/dL) + 5 x Lymphocyte ($\times 10^9/L$) [16]; NLR = Neutrophil / Lymphocyte [6]; PLR = Platelet / Lymphocyte [7]; SII = Platelet x Neutrophil / Lymphocyte [8]; SIRI = Monocyte x Neutrophil / Lymphocyte [9]; MLR = Monocyte / Lymphocyte [10]; CALLY = Albumin (g/dL) x Lymphocyte / (CRP (mg/dL) x 10) [11]. Serum albumin was measured in g/L and converted to g/dL (divide by 10) for index calculations.

Outcome definition

The primary outcome was a composite of in-hospital mortality or prolonged postoperative length of stay (LOS), defined as exceeding the 75th percentile (13 days). This composite was chosen because in-hospital mortality alone was infrequent (22 deaths, 1.2%), and prolonged LOS is a clinically relevant endpoint reflecting postoperative morbidity and resource utilization [17].

Statistical analysis

Baseline characteristics were compared between outcome groups using Student's t-test or chi-square test as appropriate. Univariate logistic regression was performed for each predictor. Multivariable models compared five predictor combinations: (1) albumin alone; (2) Core 4 (PNI, NLR, PLR, SII); (3) albumin + NLR+SII; (4) albumin + NLR+SIRI; and (5) albumin+SIRI + MLR.

Discrimination was assessed using the area under the receiver operating characteristic curve (AUC). Calibration was evaluated using the Hosmer-Lemeshow test and Brier score. Restricted cubic splines (4 knots) explored non-linear dose-response relationships. Internal validation included bootstrap optimism

correction (1,000 resamples), stratified 5-fold cross-validation, and Youden index optimization. Subgroup analyses with formal interaction tests examined effect modification by age, sex, CHD subtype, and surgery duration. Sensitivity analyses varied the LOS threshold, excluded neonates, and tested alternative outcome definitions. All statistical tests were two-sided, and $p < 0.05$ was considered significant. Analyses used Python 3.12 with statsmodels 0.14 and scikit-learn 1.4.

External validation

We attempted external validation using the Medical Information Mart for Intensive Care (MIMIC)-III v1.4 database [25]. Pediatric patients (< 18 years) with ICD-9 codes for CHD (745.x-747.x) who underwent cardiac surgery (ICD-9 procedure codes 35.x-39.x) were identified. However, MIMIC-III does not record procedure datetime, and analysis of ICU admission timing revealed near-simultaneous hospital and ICU admission (median 0.2 hours), indicating that most laboratory measurements were obtained post-operatively. Consequently, we used the first available laboratory values within 48 hours of ICU admission as early post-operative surrogates.

Declarations

Competing interests

The authors declare that they have no competing interests.

Funding Declaration

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contribution

LPC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: LPC. Acquisition, analysis, or interpretation of data: XC and LPC. Drafting of the manuscript: XC. Critical revision of the manuscript for important intellectual content: LPC. Statistical analysis: XC. Supervision: LPC. All authors read and approved the final manuscript.

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Data Availability

The PIC database is publicly available through PhysioNet (<https://physionet.org/content/picdb/>). The MIMIC-III v1.4 database is available through PhysioNet (<https://physionet.org/content/mimiciii/1.4/>). The analytical code used in this study is available from the corresponding author upon reasonable request.

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Figures

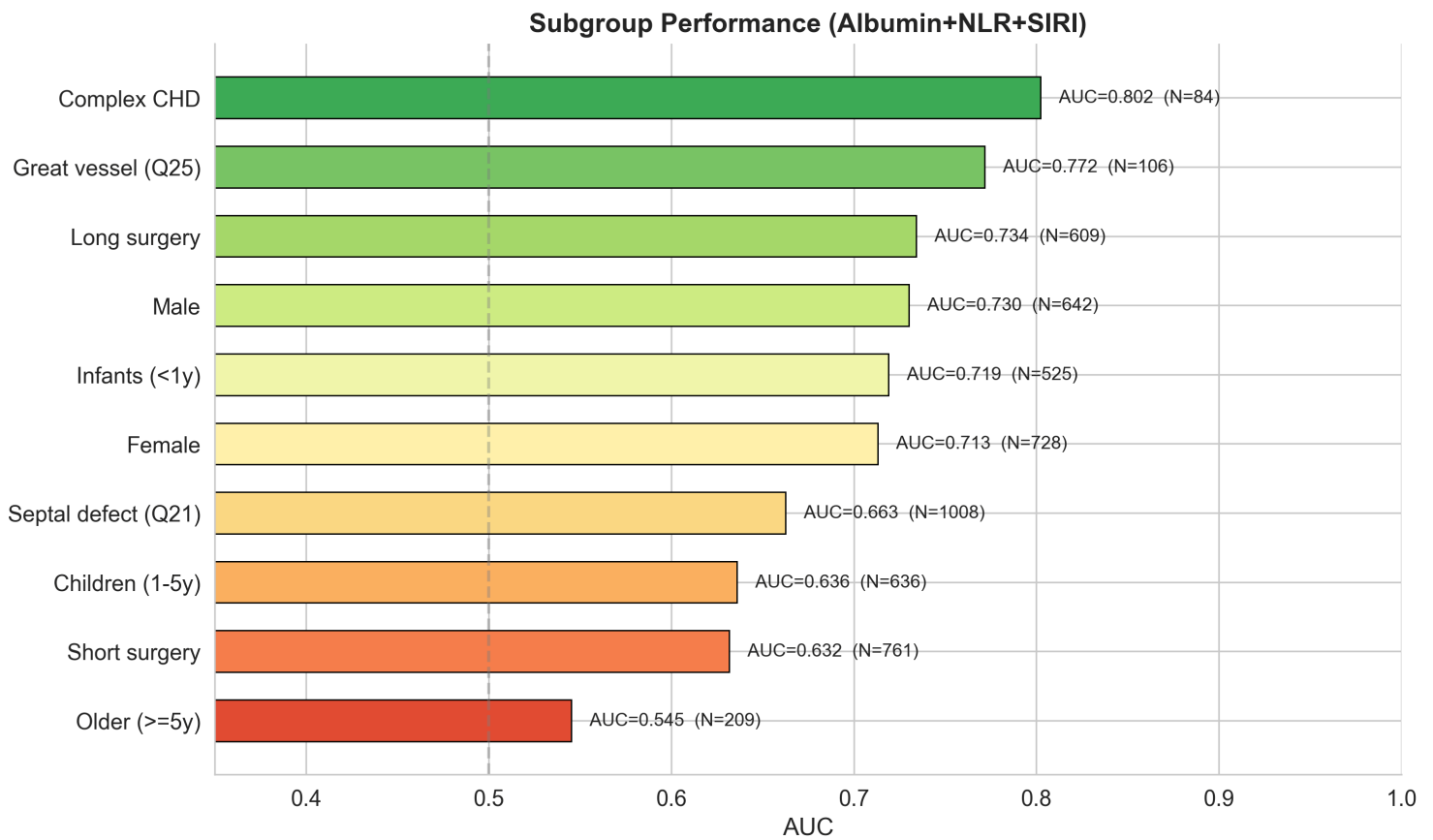


Figure 1

Model performance (AUC) across clinical subgroups. Age was the strongest effect modifier (p -interaction<0.0001), with superior performance in infants <1 year (AUC=0.719) and complex CHD subtypes (AUC=0.802). Bars represent AUC with 95% confidence intervals.

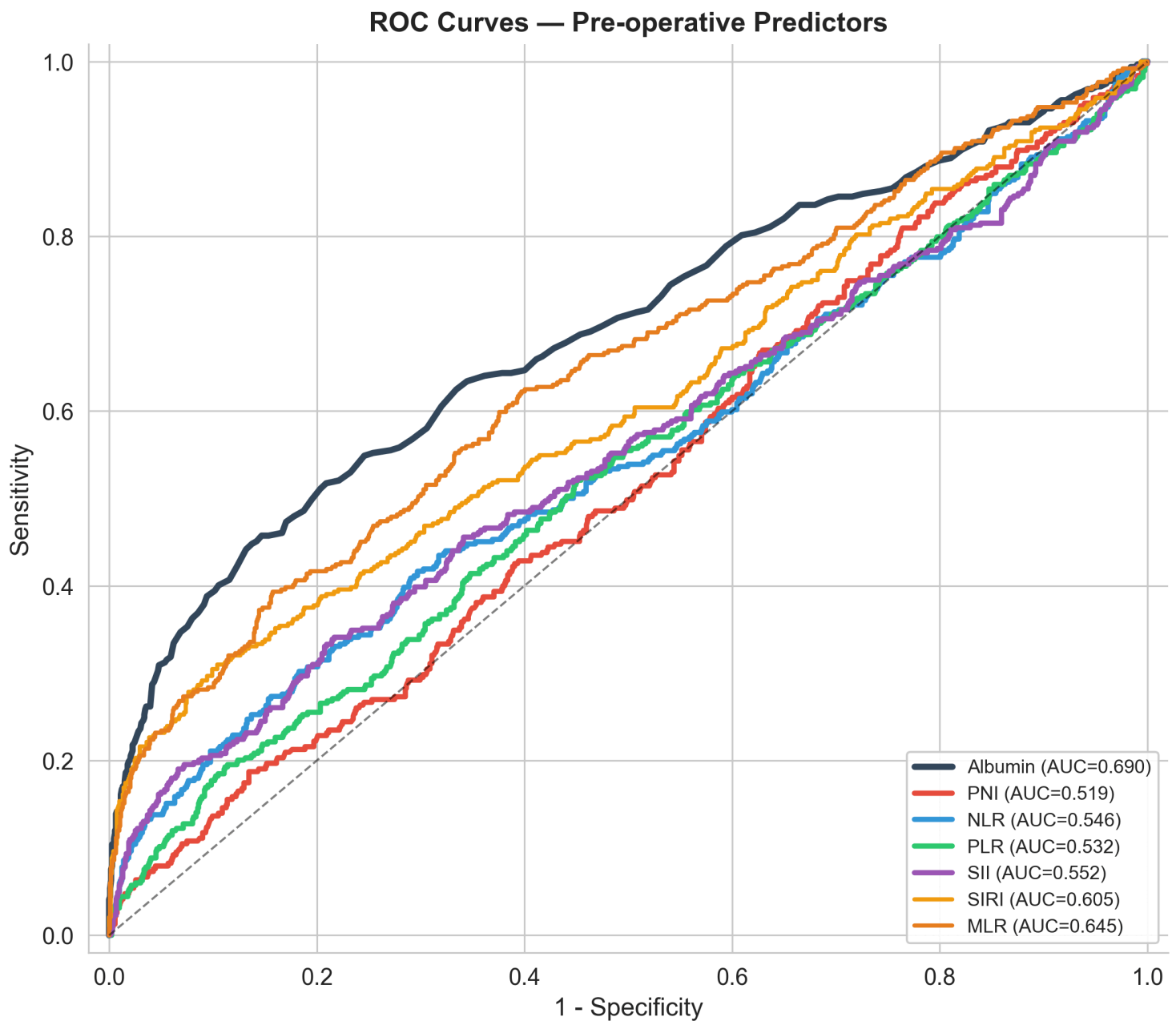


Figure 2

Receiver operating characteristic (ROC) curves comparing individual pre-operative predictors for composite adverse outcomes after pediatric CHD surgery. Albumin (AUC=0.690) outperforms all NHANES-derived composite indices.

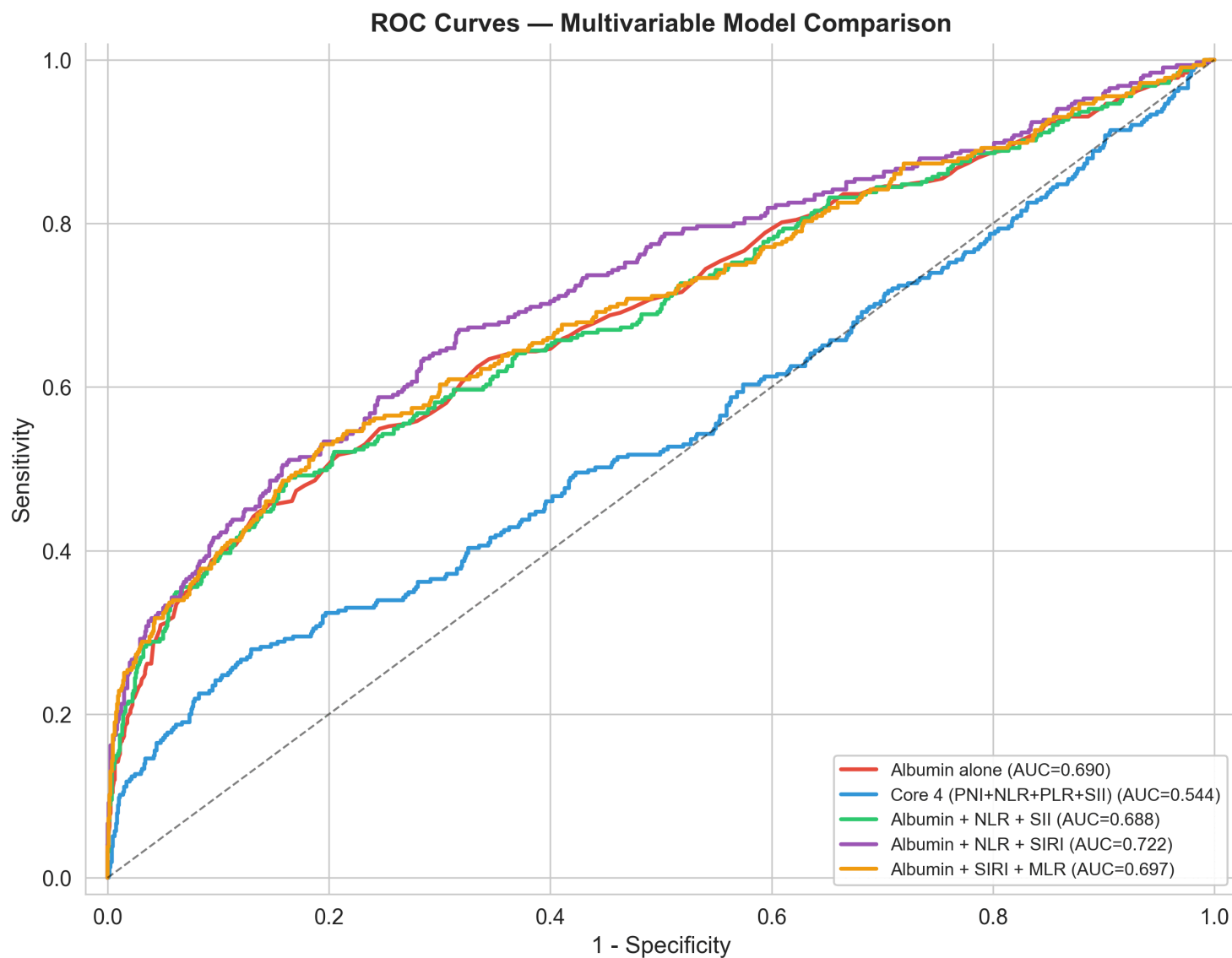


Figure 3

ROC curves comparing multivariable logistic regression models. The albumin+NLR+SIRI model achieves the highest AUC (0.722).

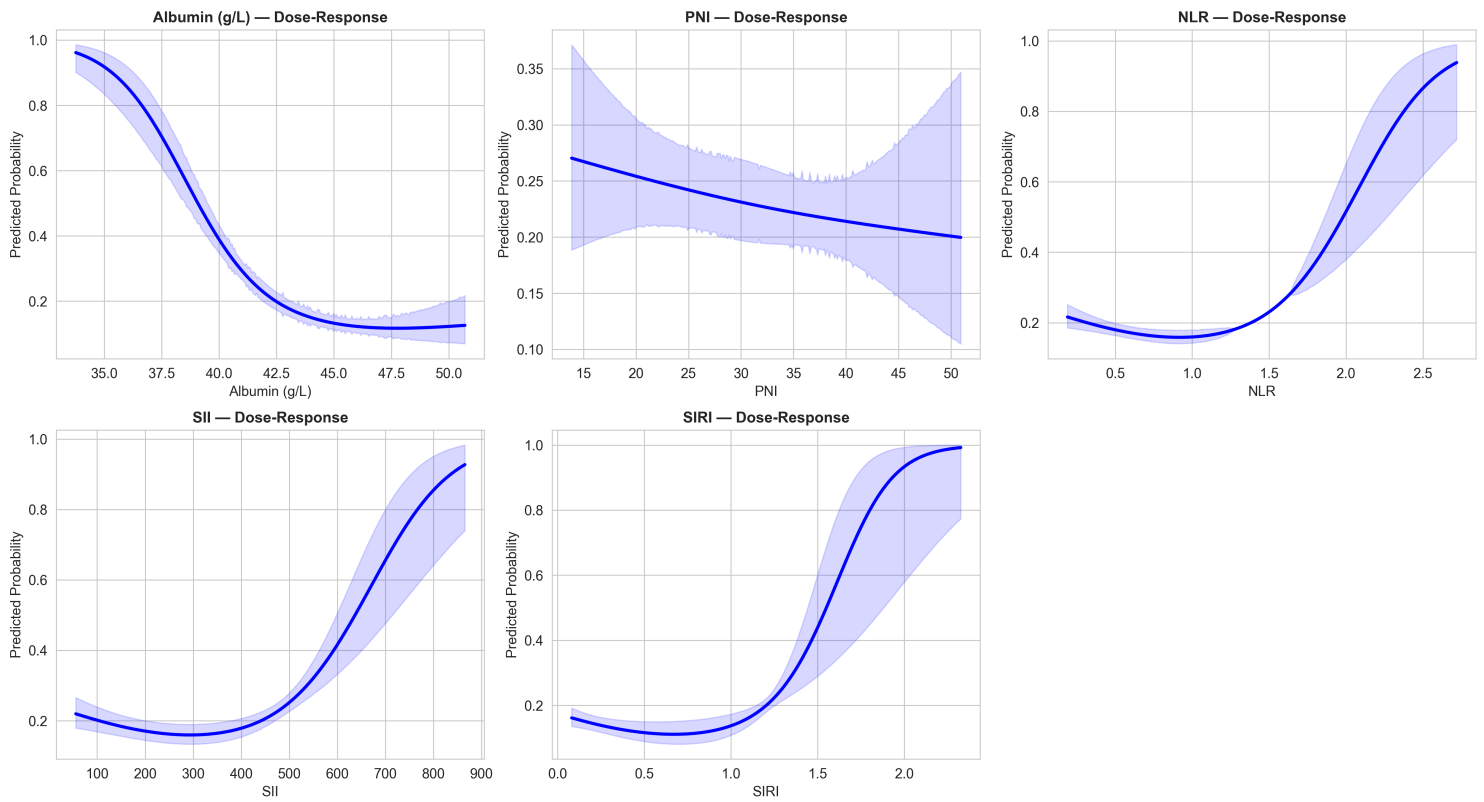


Figure 4

Restricted cubic spline analysis showing dose-response relationships between pre-operative biomarkers and adverse outcomes. Solid lines represent odds ratios; shaded areas represent 95% confidence intervals.

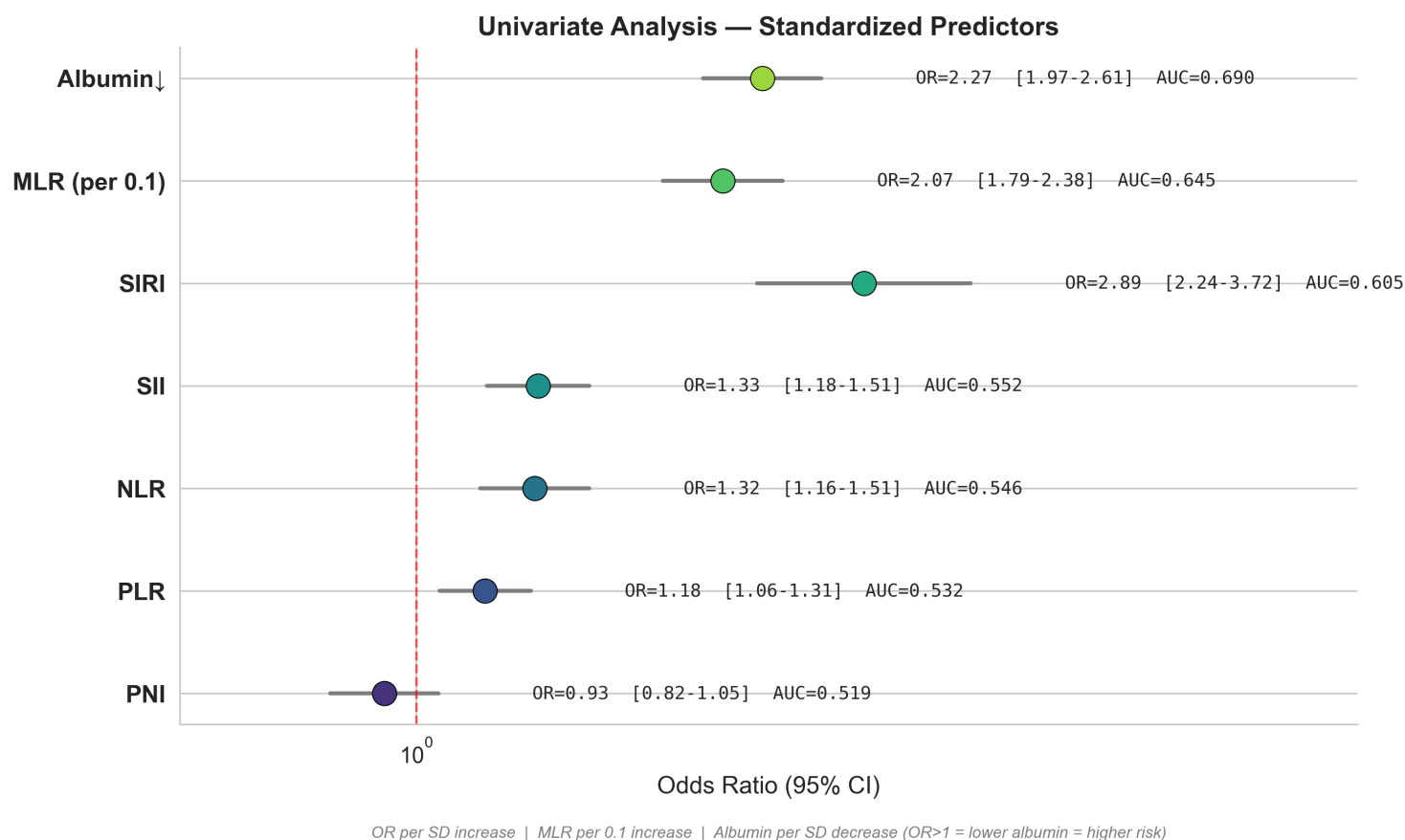


Figure 5

Standardized forest plot of univariate logistic regression results for all pre-operative predictors. Points represent odds ratios with 95% confidence intervals.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFigureS1Flow.pdf](#)
- [SupplementaryFigureS2MIMIC3validation.tif](#)
- [SupplementaryTableS1InternalValidation.docx](#)
- [SupplementaryTableS2SensitivityAnalyses.docx](#)
- [SupplementaryTableS3YoudenCutoffs.docx](#)
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