Recalibrating the Cardiac Renal Angina Index in Children Following Cardiac Surgery

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Background

- Acute kidney injury (AKI) is common in children after cardiac surgery and associated with poor outcomes yet remains challenging to predict.

- The cardiac Renal Angina Index (cRAI) is a calculable bedside prediction tool to identify children at risk for developing severe AKI and related adverse outcomes in the early post-operative period.

- Urine neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of kidney tubular injury, may enhance cRAI performance.

Objectives

1. Recalibrate the cRAI to identify new risk and injury strategies for the composite outcome of **Postoperative Day 2-4 serum creatinine-defined AKI or mechanical ventilation (MV) ≥3 days.**

2. Determine if the addition of NGAL enhances the performance of the recalibrated cRAI.

Methods

- **Study Design:** Two-center prospective observational study conducted at Cincinnati Children's Hospital Medical Center and Children's Hospital Colorado.

- **Inclusion:** Children aged 0-18 years with congenital heart disease admitted to the Cardiac Intensive Care Unit (CICU) with NGAL measured 8-12 hours after cardiac surgery.

- After cRAI recalibration, clinical variables and outcomes were compared for patients with and without the composite outcome, and test characteristics were compared after the addition of NGAL to the analysis.

Results

Table 1: Univariable Regression for the Composite Outcome

Characteristic	N	OR	95% CI	p-value
Age <1 year	476	3.31	2.02, 5.67	<0.001
VIS ≥10	476	4.23	2.77, 6.50	<0.001
CPB >150 mins	444	3.10	2.00, 4.87	<0.001
STAT score ≥4	466	5.98	3.83, 9.51	<0.001
Daily Fluid Balance on POD1, Hours 0-12 (ml/kg)	475			
<5		—	—	
5 - <10		1.79	0.84, 3.65	0.12
10 - <20		2.62	1.45, 4.72	0.001
≥20		3.67	2.23, 6.13	<0.001
NGAL (ng/ml)	476			
<50		—	—	
50 - <100		4.75	2.37, 9.39	<0.001
100 - <150		7.01	2.96, 16.5	<0.001
≥150		16.9	9.80, 29.8	<0.001

Note: STAT = Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery category; CPB = cardiopulmonary bypass; VIS = Vasoactive Ionotropic Score

Significant variables identified on univariate analysis that are known to be associated with AKI were used to generate the recalibrated cRAI for prediction of the new composite outcome (Figure 1).

Figure 1: Recalibrated Cardiac Renal Angina Index

Risk Score	
Post-Operative CICU Admission	1
Age <1 year	2
CPB Time > 150 minutes	4
STAT Score ≥4	6
VIS ≥10 at 8 hours	8

X

Injury Score: Cumulative Fluid Balance, POD 0	
<5 mL/kg	1
5 - <10 mL/kg	2
10 - <20 mL/kg	4
≥20 mL/kg	8

As calculated in the original cRAI, the highest applicable risk and injury scores are multiplied 8-12 hours after CICU admission to obtain a value 0-64. Scores ≥6 denoted a positive test in the recalibrated model (Youden's Index= 0.35).

Reference: Gist KM, et al. Modifying the Renal Angina Index for Predicting AKI and Related Adverse Outcomes in Pediatric Heart Surgery. World J Pediatr Congenit Heart Surg. 2022;13(2):196-202.

Table 2: Characteristics and Outcomes for Children After Cardiac Surgery by the Presence or Absence of the Composite Outcome

Variable	Overall (n=476)	No Composite Endpoint (n=347)	Composite Endpoint (n=129)	p-value
Age, years	0.40 (0.12, 2.53)	0.48 (0.26, 3.22)	0.10 (0.02, 0.41)	<0.001
Age <1	319 (67%)	211 (61%)	108 (84%)	<0.001
Sex				0.52
Female	185 (39%)	139 (40%)	46 (37%)	
Male	286 (61%)	206 (60%)	80 (63%)	
Unknown	5	2	3	
Single Ventricle	151 (32%)	97 (28%)	54 (42%)	0.005
STAT Score				<0.001
1	80 (17%)	76 (22%)	4 (3.2%)	
2	133 (29%)	116 (34%)	17 (13%)	
3	59 (13%)	45 (13%)	14 (11%)	
4	146 (31%)	91 (27%)	55 (44%)	
5	48 (10%)	12 (3.5%)	36 (29%)	
Unknown	10	7	3	
CPB	439 (93%)	321 (93%)	118 (94%)	0.55
CPB Duration, min	148 (107.75, 201.25)	139.5 (102, 186.25)	179.5 (139, 231)	
Crossclamp Time, min	78 (38.25, 127.5)	73 (32, 119)	87 (64, 154)	<0.001
Delayed Sternal Closure	77 (16%)	19 (5.5%)	58 (46%)	<0.001
8 Hour VIS	7.50 (5, 12)	7 (5, 10)	11 (7.50, 16)	<0.001
8 Hour Urine Output, ml/kg/hr	1.65 (1.21, 2.34)	1.61 (1.23, 2.20)	1.86 (1.14, 2.74)	0.16
POD 0 Fluid Balance, ml/kg	77 (3, 187.25)	74 (-7.35, 189)	81 (22, 165)	0.46
POD 0 AKI	23 (5)	17 (5)	6 (5)	0.91
cRAI+	341 (72)	215 (62)	125 (97)	<0.001
cRAI Score	8 (4-24)	6 (4-18)	24 (8-32)	<0.001
NGAL, ng/ml	26 (10-110.5)	16.4 (10-42)	159 (49-567)	<0.001
NGAL ≥125 ng/ml	111 (23)	39 (11)	72 (56)	<0.001
Day 2-4 AKI	44 (9.2%)	0 (0%)	44 (34%)	--
MV ≥3 days	101 (21%)	0 (0%)	101 (78%)	--
MV Duration, days	1 (0.15-2.8)	0.68 (0-1.09)	4 (3-8)	<0.001
ICU Length of Stay, days	4.16 (2, 12)	3 (1.95, 6)	15 (9, 23)	<0.001
ICU Mortality	23 (4.8%)	8 (2.3%)	15 (12%)	<0.001

Of 476 patients, 27% suffered the composite outcome, with 78% of this cohort experiencing MV ≥3 days and fewer patients (34%) experiencing Day 2-4 AKI. The cRAI was positive in 72% of all patients, while NGAL ≥125 ng/ml was less common (23%).

Results (Cont)

- Patients who suffered the composite outcome were younger, had higher surgical complexity and longer CPB durations, and suffered worse outcomes including longer CICU stays and higher mortality (Table 2).

- Urine output and presence of POD 0 serum creatinine-defined AKI were not significantly different between those who did and did not suffer the composite outcome.

Table 3: Comparison of Test Characteristics for Prediction of the Composite Outcome by cRAI, NGAL, and cRAI+NGAL+

	cRAI+	NGAL+	cRAI+ & NGAL+
AUROC	0.74 (0.69-0.78)*	0.81 (0.76-0.85)*	--
Sensitivity	0.97	0.79	0.54
Specificity	0.38	0.74	0.89
PPV	0.37	0.57	0.65
NPV	0.97	0.89	0.84

cRAI+: ≥6; NGAL+: ≥125 ng/ml; * Delong's Test *p*=0.012. The NGAL cutoff of 125ng/mL was used based on the FDA-approved value.

Figure 2: Area Under the Curve (AUC) for cRAI vs NGAL

AUC: 0.807
AUC: 0.736
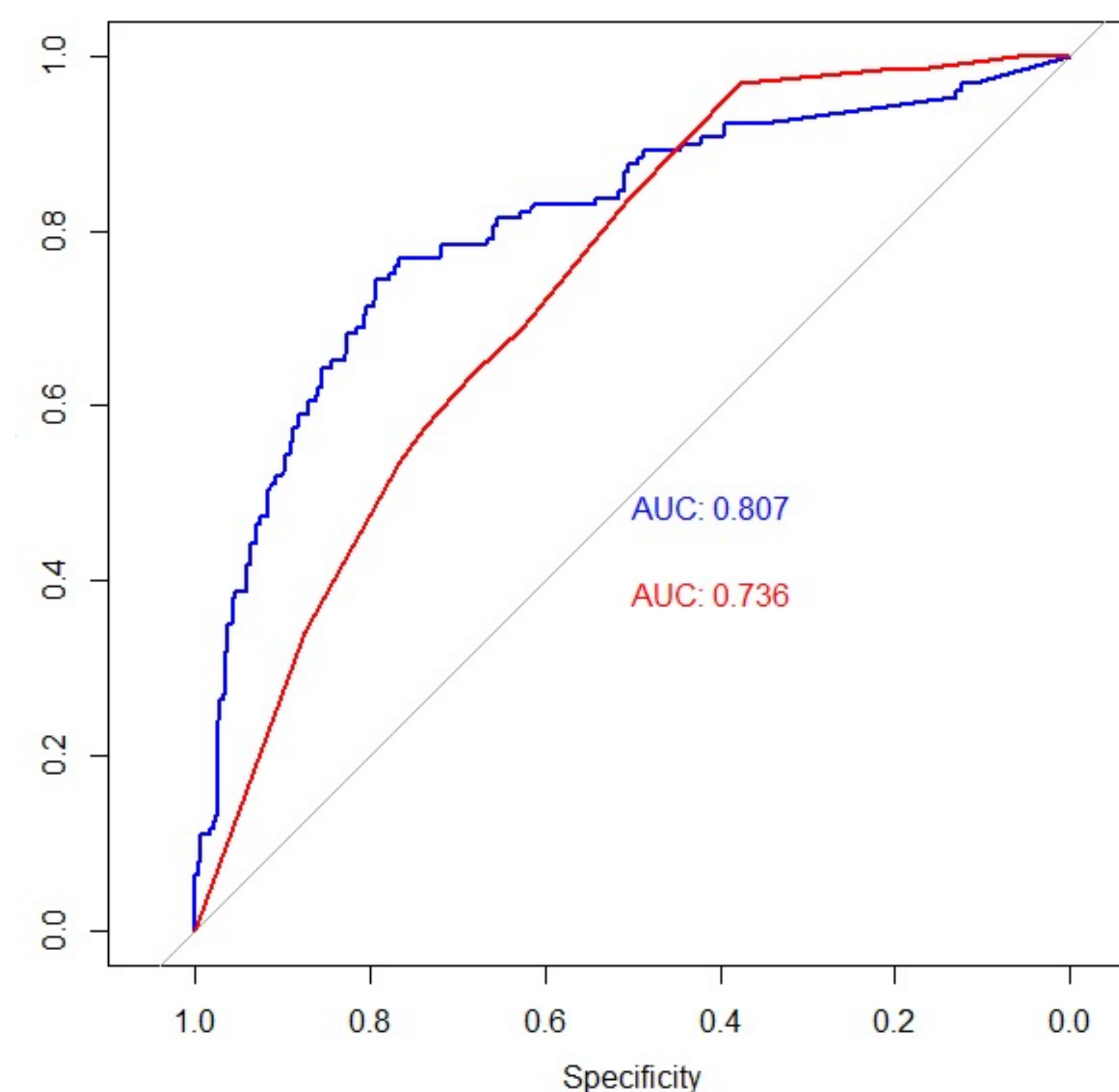
NGAL (blue) as a continuous variable predicts the composite outcome with a superior AUC compared to cRAI (red).

Analysis

- Univariate analysis was used to generate the recalibrated cRAI and the optimal cutoff was determined using Youden's Index.

- A Receiver Operating Characteristic Curve was generated and AUCs were compared for cRAI+ and NGAL ≥125 ng/ml prediction using DeLong's Test.

- Sensitivity, specificity, positive predictive values and negative predictive values were compared for cRAI+, NGAL+, and cRAI+NGAL+.

Conclusions

- Critically ill children who experience Day 2-4 AKI and/or MV ≥3 days after cardiac surgery suffer worse outcomes.

- Early serum creatinine-defined AKI and urine output were not associated with the composite outcome, further confirming the need for post-operative predictive tools.

- The recalibrated cRAI, when calculated 8 hours after cardiac surgery, has modest predictive performance for the composite outcome.

- While NGAL alone outperformed the cRAI, the addition of NGAL ≥125ng/mL to cRAI+ improved test specificity and PPV for the composite outcome.

- Targeted NGAL evaluation in cRAI+ patients should be considered and tested to determine if it aids in clinical decision support.

Acknowledgements