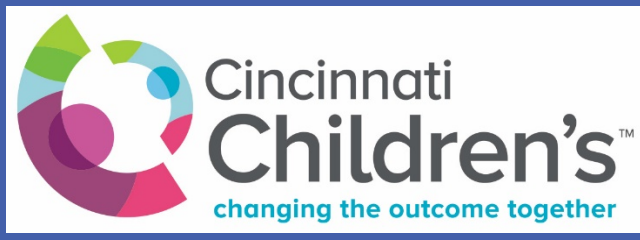


PERSEVERE Biomarkers Predict Severe Acute Kidney Injury and Renal Recovery in Children with Septic Shock

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Purpose

- Acute kidney injury is a common complication of sepsis that is associated with substantial morbidity and mortality
 - SPROUT (Fitzgerald et al, Crit Care Med, 2016):
 - 21% of children with severe sepsis develop severe acute kidney injury
 - Adjusted OR of 3.1 (p <0.001) for mortality in those who develop severe sepsis-associated AKI (SA-AKI)
- Despite the known consequences, there have been no successful disease modifying therapies for SA-AKI established to date. The mainstays of therapy remain renal protective strategies and supportive care, both of which are likely to be more effective if implemented early. Therefore, the ability to predict early and accurately who might develop severe, persistent SA-AKI is important.
- PERSEVERE-II is a validated, biomarker-based tool for estimating baseline 28-day mortality risk in pediatric septic shock in the first 24 hours of admission (Wong et al, Science and Translational Med, 2019)
 - Includes 5 serum biomarkers (C-C chemokine ligand 3 (CCL3), heat shock protein 70 kDa 1B (HSPA1B), IL-8, granzyme B (GZMB) and matrix metalloproteinase-8 (MMP8)) and platelet count
 - The calculated mortality probability places patients into one of 3 risk categories: Low Risk: 0-0.019, Intermediate Risk: 0.167-0.189 or High Risk: 0.3-0.571

Hypothesis

PERSEVERE-II mortality probability calculated in the first 24 hours of PICU admission can predict the severity of sepsis-associated AKI at day 3 of septic shock. Furthermore, values of the individual PERSEVERE biomarkers themselves can be utilized to develop a model for the prediction of severe Day 3 SA-AKI.

Methods

Design:

- Secondary analysis of a prospective study of children admitted with septic shock to 14 pediatric intensive care units (PICUs) in the US from 2015-2018
- 379 total included patients after exclusion criteria applied (ages 1 week to 18 years)
 - Exclusion Criteria: known pre-existing renal disease, missing Day 1 or Day 3 creatinine data

Patient Demographics:

	No Severe D3 AKI	Severe Day 3 AKI	P value
N(%)	314 (83)	65 (17)	--
Age, years	6.5 (2.5-12.4)	5.1 (1.3-13.5)	0.32
Gender (% male)	162 (52)	33 (51)	0.99
PRISM III	10 (6-14)	14 (10-20.5)	<0.001
PERSEVERE-II Mortality Risk	0.007 (0.007-0.167)	0.189 (0.019-0.33)	<0.001
Organism, n (%)			
Gram positive	68 (22)	13 (20)	0.9
Gram negative	77 (25)	19 (29)	0.52
Viral	23 (7)	6 (9)	0.79
Fungal	6 (2)	4 (6)	0.13
None	140 (45)	23 (35)	0.22
Mortality, n (%)	18 (6)	24 (37)	<0.001
PICU LOS, days	6 (3-12)	10 (7-21)	<0.001
PICU-Free days	22 (14-25)	5 (0-19)	<0.001

Outcomes of Interest:

- Incidence of Severe Day 3 SA-AKI (defined as KDIGO stage 2 or higher)
- Renal replacement therapy use
- Incidence of Day 3 Renal Recovery (defined as improvement in early AKI by day 3 of septic shock)

Potential Confounders Considered:

- Age
- Severity of illness (PRISM III)

Statistical Methods:

- Utilized regression analyses to assess for outcomes of interest after consideration of confounders
- Utilized Classification and Regression Tree analysis incorporating the PERSEVERE biomarkers and Day 1 AKI KDIGO stage to develop a prediction tool for Severe Day 3 SA-AKI

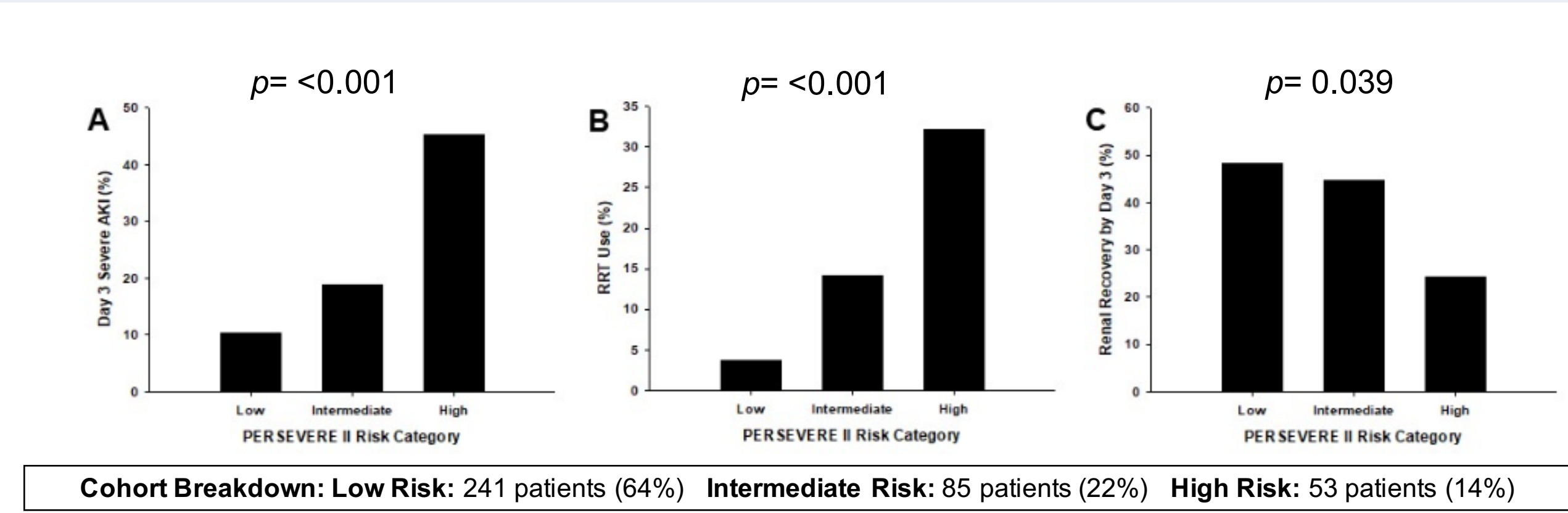
Results

Increasing PERSEVERE-II is independently associated with poor outcomes.

Outcome	Variable	N	O.R. (95% CI, p-value)
Severe Day 3 AKI	PERSEVERE-II	379	1.4 (1.2-1.7, <0.001)
	PRISM III		1.1 (1.0-1.1, <0.001)
	Age (years)		1.0 (0.9-1.0, 0.972)
RRT Use	PERSEVERE-II	379	1.6 (1.3-2.0, <0.001)
	PRISM III		1.1 (1.0-1.1, 0.003)
	Age (years)		1.0 (1.0-1.1, 0.581)
Day 3 Renal Recovery	PERSEVERE-II*	131	1.3 (1.0-1.6, 0.047)
	PRISM III		1.0 (0.9-1.1, 0.745)
	Age (years)		1.0 (0.9-1.1, 0.962)

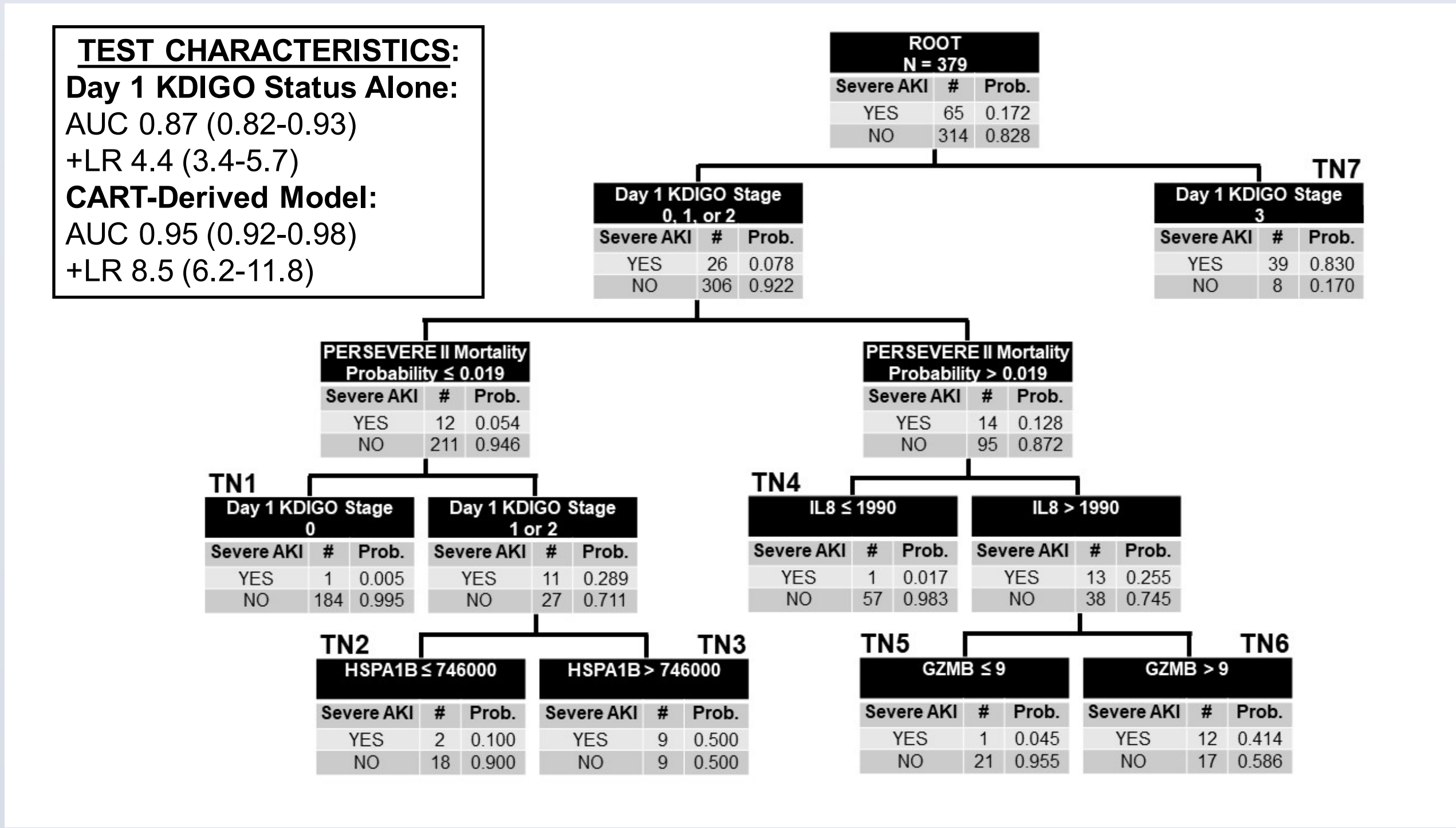
* Lower PERSEVERE-II mortality probability associated with increased odds of renal recovery

There is a stepwise worsening of outcomes with increasing PERSEVERE-II risk category.



Stanski et al, Am Journal Resp and Crit Care Med, 2020 (In Press)

A new model utilizing the PERSEVERE biomarkers and Day 1 KDIGO stage predicts severe Day 3 SA-AKI.



Conclusions and Future Directions

Conclusions:

- Among children with septic shock, PERSEVERE-II and the PERSEVERE biomarkers predict severe D3 SA-AKI and identify patients with early SA-AKI likely to have renal recovery.
- Risk stratification of patients using this strategy may allow for:
 - Proactive intervention in patients at high risk for SA-AKI, potentially mitigating its progression.
 - A precision medicine approach to clinical trial enrollment

Future Directions:

- Prospective validation of the model in a prospective cohort, including attempts to enhance the current model with AKI biomarkers
- Assessment of prediction tool in murine sepsis model (are these biomarkers potentially linked to SA-AKI pathogenesis?)
- If validated, utilization of prediction model for interventional trial