SUPPLEMENTAL MATERIAL

Supplement A. Derivation of the renal angina index

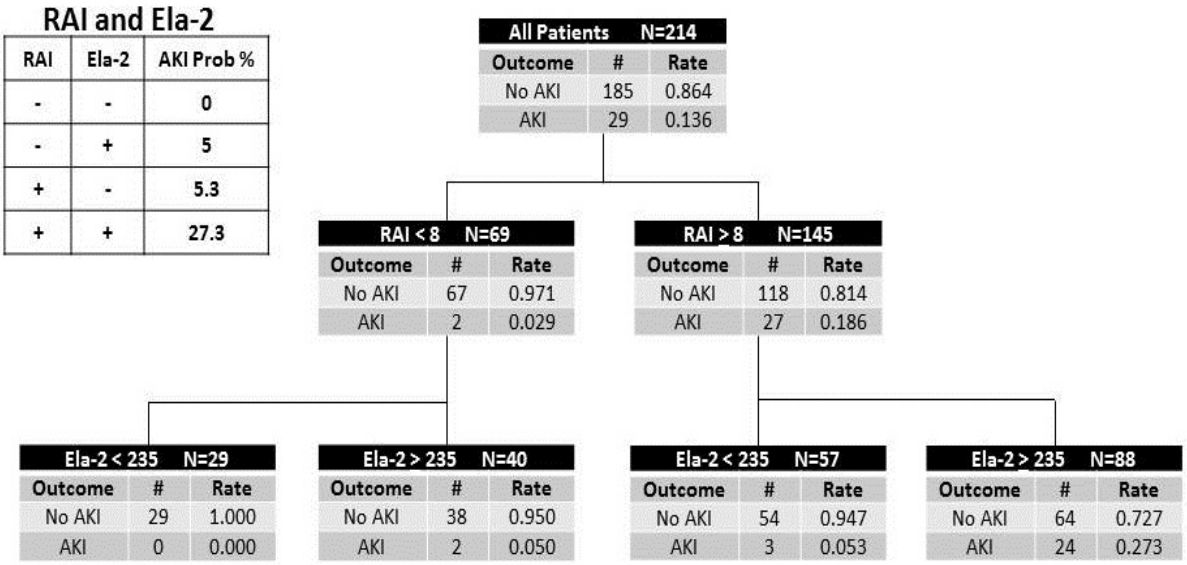
In order to operationalize renal angina, we developed the renal angina index (RAI). RAI was derived as a composite of risk factors and clinical signs of AKI. The logic behind the equation dictates that as a patient achieves higher risk they require less "clinical sign of AKI" early on to fulfill renal angina. Similarly, if a patient has less risk but shows more overt signs of clinical AKI signs, renal angina would also be fulfilled. Per the epidemiology of AKI, the risk of AKI increases in multiplicative fashion with increased risk factors. The incidence of AKI demonstrates fold-increases (5 to 10 to 50%) for higher risk patients. This same increase is seen retrospectively in the case of fluid overload. Risk of mortality in patients with AKI demonstrates similar fold-increases for increasing AKI severity. Thus, the creation of the renal angina index was done by a multiplicative index (instead of sum). We felt this more accurately mirrored the fold-increases seen with the epidemiology of pediatric AKI. The RAI score is a composite of risk strata and clinical signs. Risk strata were given point values that were essentially the epidemiologic risk compared to general pediatric risk divided by 10: 5 (very high risk), 3 (high risk), and 1 (moderate risk). Clinical signs of injury are based on changes in estimated creatinine clearance (Δ eCCl) or % fluid overload (% FO). The assigned point values are: 1 (ICU status and no decrease in eCCl or <5% FO), 2 ($\geq$ 5% FO or eCCl decrease of 0-25%), 4 ($\geq$10% FO or eCCl decrease of 25-50%), or 8 ($\geq$15% FO or eCCl decrease of $\geq$ 50%). The composite range of the RAI is therefore: 1, 2, 3, 4, 5, 6, 8, 10, 12, 20, 24, and 40.

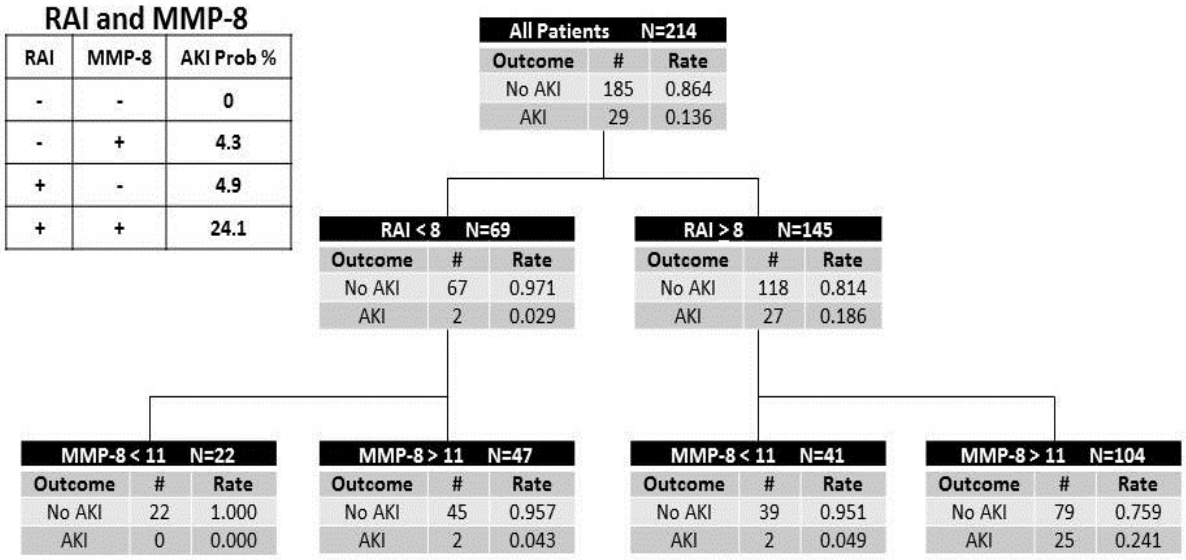
Sensitivity analysis was performed on Cohort 1 and the RAI in our original angina manuscript (Basu, et al. *Kidney International* 2013). The table depicts the RAI cut-off scores in increasing order and associated predictive performance and Youden's index (J-statistic). Based on the most optimal Youden's index and highest negative predictive value (important for a clinician to rule OUT the likelihood of subsequent AKI), an RAI $\geq$ 8 was indicative of fulfilling renal angina.

RAI	#	# Day 3 - AKI	Sens	Spec	PPV	NPV	J-statistic
≥ 1	144	28	1	0	0.19	n/c	0
≥ 2	109	28	1	0.30	0.26	1	0.30
≥ 3	100	26	0.93	0.36	0.26	0.95	0.29
≥ 4	88	24	0.86	0.45	0.27	0.93	0.31
≥ 5	69	22	0.79	0.59	0.32	0.92	0.38
≥ 6	56	21	0.75	0.69	0.38	0.92	0.45
≥ 8	51	21	0.75	0.74	0.41	0.92	0.49
≥ 10	36	14	0.5	0.81	0.39	0.87	0.31
≥ 12	31	14	0.5	0.85	0.45	0.88	0.35
≥ 20	22	9	0.32	0.89	0.41	0.84	0.21
≥ 24	9	6	0.21	0.97	0.67	0.84	0.19
≥ 40	3	2	0.07	0.99	0.67	0.82	0.06

Supplement B

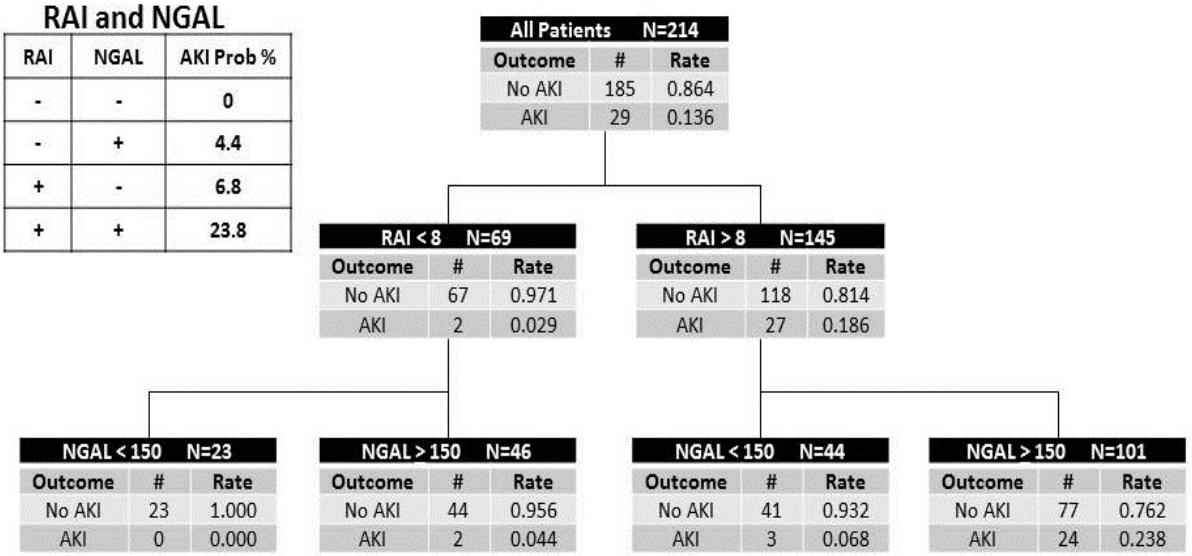
AKI probability after the incorporation of biomarkers into the renal angina index model. The following four trees classify patients for the outcome of acute kidney injury (AKI) by a profile of renal angina index (RAI) and biomarker positivity or negativity using cut-offs as branch points. Elastase-2 (Ela-2), matrix metalloproteinase-8 (MMP-8), and neutrophil gelatinase associated lipocalin (NGAL) are shown independently incorporated with RAI. The final tree incorporates both Ela-2 and MMP-8 into the model. The probability of AKI (AKI prob%) is listed for each subset of patients with a certain RAI and biomarker 'profile'.





RAI and NGAL

RAI	NGAL	AKI Prob %
-	-	0
-	+	4.4
+	-	6.8
+	+	23.8



RAI, Ela-2, & MMP-8

RAI	Ela-2	MMP-8	AKI Prob %
-	-	-	0
-	-	+	0
-	+	-	0
-	+	+	7.4
+	-	-	0
+	-	+	8.8
+	+	-	11.1
+	+	+	31.4