

Table S1: Distributions of candidate clinical variables for multivariable regression

	All (N = 400)	No AKI or Stage 1 (N = 386)	Stage 2 or 3 (N = 14)	P-value
Age (years)				0.04
mean (sd)	65.8 (12.7)	66.1 (12.7)	59.1 (12.8)	
median	67	67	59	
IQR	23 , 92	58 , 75	51.2 , 69	
Female	131 (33%)	125 (32%)	6 (43%)	0.40
Medical history				
CHF	163 (40.8%)	156 (40.4%)	7 (50.0%)	0.58
Current smoker	67 (16.8%)	66 (17.1%)	1 (7.1%)	0.48
Diabetes mellitus	123 (30.8%)	120 (31.1%)	3 (21.4%)	0.56
Cardiac surgery	74 (18.5%)	69 (17.9%)	5 (35.7%)	0.15
Cardiac catheterization*	148 (37.0%)	144 (37.3%)	4 (28.6%)	0.59
BMI (kg/m ²) [†]				0.10
mean (sd)	28.5 (6.1)	28.4 (5.9)	33.2 (9.9)	
Median	27.4	27.3	31.7	
IQR	15.2 , 54.1	24.7 , 31	23.9 , 39.3	
Charlson index				0.12
mean (sd)	2.4 (1.9)	2.4 (1.9)	3.1 (2)	
median	2	2	4	
IQR	0 , 9	1 , 4	1 , 4.8	
Baseline SCr				0.14
mean (sd)	1.1 (0.5)	1.1 (0.4)	1.8 (1.2)	
Median	1	1	1.4	
IQR	0.5 , 4.4	0.8 , 1.2	0.8 , 2.8	
Baseline eGFR [§]				0.08
mean (sd)	70.2 (22.8)	70.7 (22)	56.6 (37.1)	
median	72.3	72.9	45.8	
IQR	11.6 , 123.2	54.3 , 87.9	22.9 , 83.2	
CKD stage				0.07
mean (sd)	2.2 (0.8)	2.2 (0.8)	2.6 (1.2)	
median	2	2	3	
IQR	1 , 4	2 , 3	2 , 3.8	
Thakar score [†]				<0.001
mean (sd)	1.9 (1.3)	1.9 (1.2)	3.7 (2)	
Median	1	1	3	
IQR	1 , 6	1 , 3	3 , 6	
Baseline hematocrit [†]				<0.001
mean (sd)	39.3 (5)	39.5 (4.9)	34 (5.8)	
median	40	40	33.5	
IQR	26 , 52	37 , 43	31 , 36.8	
Procedure				
Isolated CABG	131 (32.8%)	127 (32.9%)	4 (28.6%)	0.74
Isolated valve	168 (42.0%)	165 (42.7%)	3 (1.4%)	0.11
CABG/valve	61 (15.3%)	58 (15.0%)	3 (21.4%)	0.51
Aorta	40 (10.0%)	36 (9.3%)	4 (28.6%)	0.04
CPB use	283 (70.8%)	272 (70.5%)	11 (78.6%)	0.77

*Within 10 days of surgery; [†]Selected by LASSO regression for multivariable modeling; [§]Calculated by CKD-EPI equation; IQR, interquartile range; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease;

Table S2: Perioperative 10th, 25th, 50th (median), 75th, and 90th percentiles of [TIMP-2]•[IGFBP7] and percentages of patients greater than the 0.3 and 2.0 thresholds. P-values represent [TIMP-2]•[IGFBP7] distribution comparisons against No AKI patients using the Conover test.

AKI	Timepoint	N	10%	25%	50%	75%	90%	% > 0.3	% > 2.0	P-value
No AKI	Induction of anesthesia	309	0.02	0.04	0.11	0.28	0.58	24%	3%	
No AKI	30 min after start of CPB or OpCAB	309	0.02	0.06	0.17	0.41	0.86	33%	3%	
No AKI	Immediately after end of CPB or OpCAB	309	0.04	0.08	0.20	0.57	1.50	37%	6%	
No AKI	ICU admission	309	0.02	0.04	0.10	0.23	0.51	20%	3%	
No AKI	Six hours after ICU admission	309	0.03	0.09	0.18	0.38	0.68	33%	1%	
No AKI	Post-op day 1	309	0.02	0.05	0.18	0.42	1.18	31%	5%	
No AKI	Post-op day 2	309	0.03	0.05	0.13	0.31	0.81	29%	2%	
No AKI	Post-op day 3	309	0.03	0.05	0.12	0.29	0.53	24%	1%	
Stage 1 AKI	Induction of anesthesia	77	0.02	0.03	0.11	0.26	0.74	21%	3%	1.00
Stage 1 AKI	30 min after start of CPB or OpCAB	77	0.02	0.06	0.17	0.35	1.32	33%	6%	1.00
Stage 1 AKI	Immediately after end of CPB or OpCAB	77	0.06	0.10	0.26	0.58	1.79	43%	10%	0.17
Stage 1 AKI	ICU admission	77	0.03	0.06	0.12	0.43	0.83	28%	6%	0.09
Stage 1 AKI	Six hours after ICU admission	77	0.04	0.17	0.32	0.62	1.16	51%	7%	0.01
Stage 1 AKI	Post-op day 1	77	0.02	0.05	0.18	0.82	1.97	43%	10%	0.35
Stage 1 AKI	Post-op day 2	77	0.02	0.05	0.14	0.46	1.24	35%	6%	0.40
Stage 1 AKI	Post-op day 3	77	0.03	0.05	0.10	0.28	0.58	24%	2%	0.97
Stage 2-3 AKI	Induction of anesthesia	14	0.02	0.04	0.12	0.28	3.84	21%	14%	1.00
Stage 2-3 AKI	30 min after start of CPB or OpCAB	14	0.03	0.07	0.14	0.24	1.28	21%	7%	1.00
Stage 2-3 AKI	Immediately after end of CPB or OpCAB	14	0.18	0.42	0.45	0.87	3.66	85%	15%	0.02
Stage 2-3 AKI	ICU admission	14	0.08	0.12	0.26	0.33	1.03	31%	8%	0.06
Stage 2-3 AKI	Six hours after ICU admission	14	0.11	0.56	1.45	2.20	10.08	73%	27%	0.002
Stage 2-3 AKI	Post-op day 1	14	0.05	0.21	1.58	2.13	9.13	67%	33%	0.006
Stage 2-3 AKI	Post-op day 2	14	0.07	0.09	0.20	1.83	9.29	46%	23%	0.19
Stage 2-3 AKI	Post-op day 3	14	0.05	0.06	0.57	1.33	13.49	56%	11%	0.37

Kruskal-Wallis test was performed at each timepoint to test for global differences of [TIMP-2]•[IGFBP7] concentrations among the three groups. Conover test was employed for pairwise multiple comparisons when appropriate. P values for pairwise multiple comparisons were adjusted by the Holm method.

Table S3. Effect of atorvastatin administration on $\log_{10}([\text{TIMP-2}] \cdot [\text{IGFBP7}])$ levels at each timepoint. Estimates calculated by linear regression. P-values represent the affect of atorvastatin treatment on $[\text{TIMP-2}] \cdot [\text{IGFBP7}]$ at each timepoint.

Timepoint	Estimate (95% CI)	P-value
Induction of anesthesia (baseline)	0.06 (-0.06-0.18)	0.34
30 min after start of CPB or OpCAB	0.05 (-0.08-0.17)	0.47
Immediately after end of CPB or OpCAB	-0.05 (-0.17-0.07)	0.43
ICU admission	-0.05 (-0.17-0.07)	0.41
Six hours after ICU admission	0.03 (-0.09-0.13)	0.57
Postoperative day 1	-0.09 (-0.23-0.05)	0.23
Postoperative day 2	0.09 (-0.04-0.22)	0.17
Postoperative day 3	0.03 (-0.10-0.16)	0.64

CPB, cardiopulmonary bypass; OpCAB, off-pump coronary artery bypass; ICU, intensive care unit

Table S4. In-hospital outcomes in all patients and those with [TIMP-2]•[IGFBP7] concentrations ≤ 0.3 , >0.3 to ≤ 2.0 , and >2.0 (ng/mL)²/1000 at induction of anesthesia, immediately after end of CPB or OpCAB, at ICU admission, and 6 hours after ICU admission. Continuous variables are represented as median (25th-75th percentiles), and categorical variables as number (percent). P-values compare outcome distributions among patients grouped by [TIMP-2]•[IGFBP7] categories and represent Kruskal-Wallis test for continuous variables and Chi-squared test for categorical variables.

Induction of anesthesia	[TIMP-2]•[IGFBP7]				P-value
	All	≤ 0.3	>0.3 to ≤ 2.0	>2.0	
N	390	299	78	13	--
ICU LOS, days	3 (2-24)	3 (2-5)	3 (2-5)	4 (3-6.5)	0.31
Hospital LOS, days	8 (4-38)	7 (6-9)	8 (6-9)	8.5 (6.8-9)	0.61
ICU readmission	16 (4.0%)	13 (4.3%)	3 (3.8%)	0 (0%)	1.00
Stage 2 or 3 AKI*	14 (3.5%)	11 (3.7%)	1 (1.3%)	2 (15.4%)	0.06
Dialysis	7 (1.8%)	4 (1.3%)	1 (1.3%)	2 (15.4%)	0.03
Death	5 (1.2%)	3 (1%)	0 (0%)	2 (15.4%)	0.01
Immediately after end of CPB or OpCAB	[TIMP-2]•[IGFBP7]				P-value
	All	≤ 0.3	>0.3 to ≤ 2.0	>2.0	
N	382	231	123	28	--
ICU LOS, days	3 (2-24)	3 (2-5)	3 (2-5)	4 (2.8-5)	0.84
Hospital LOS, days	7 (4-38)	8 (6-10)	7 (6-9)	7 (6-8.2)	0.41
ICU readmission	16 (4%)	10 (4.3%)	4 (3.3%)	1 (3.6%)	0.91
Stage 2 or 3 AKI*	14 (3.5%)	2 (0.9%)	9 (7.3%)	2 (7.1%)	0.002
Dialysis	7 (1.8%)	1 (0.4%)	4 (3.3%)	1 (3.6%)	0.05
Death	5 (1.2%)	1 (0.4%)	1 (0.8%)	1 (3.6%)	0.24
ICU admission	[TIMP-2]•[IGFBP7]				P-value
	All	≤ 0.3	>0.3 to ≤ 2.0	>2.0	
N	391	305	73	13	--
ICU LOS, days	3 (2-24)	3 (2-5)	4 (2-5)	3 (3-5)	0.65
Hospital LOS, days	7 (4-38)	8 (6-9)	7 (6-9)	8 (7-9)	0.86
ICU readmission	16 (4.0%)	14 (4.6%)	2 (2.7%)	0 (0.0%)	0.85
Stage 2 or 3 AKI*	14 (3.5%)	9 (3%)	3 (4.1%)	1 (7.7%)	0.37
Dialysis	7 (1.8%)	3 (1%)	1 (1.4%)	1 (7.7%)	0.14
Death	5 (1.2%)	2 (0.7%)	0 (0%)	1 (7.7%)	0.10
Six hours after ICU admission	[TIMP-2]•[IGFBP7]				P-value
	All	≤ 0.3	>0.3 to ≤ 2.0	>2.0	
N	357	223	124	10	--
ICU LOS, days	3 (2-21)	3 (2-4.8)	4 (3-5)	5 (4.2-6.8)	0.006
Hospital LOS, days	7.5 (4-38)	7 (6-9)	8 (6-9)	8.5 (7-11.8)	0.18
ICU readmission	16 (4.0%)	10 (4.5%)	3 (2.4%)	0 (0%)	0.58
Stage 2 or 3 AKI*	14 (3.5%)	3 (1.3%)	5 (4.0%)	3 (30.0%)	<0.001
Dialysis	7 (1.8%)	3 (1.3%)	0 (0%)	3 (30.0%)	<0.001
Death	5 (1.2%)	1 (0.4%)	1 (0.8%)	1 (10.0%)	0.08

*Within 48 hours of surgery. LOS, length of stay

Table S5. AUROC, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of [TIMP-2]•[IGFBP7] with corresponding 95% CI at each timepoint for prediction of stage 2 or 3 AKI within 48 hours of surgery with 0.3 and 2.0 thresholds.

Timepoint	AUROC	cutoff of 0.3 [TIMP-]•[IGFBP7]				cutoff of 2.0 [TIMP-]•[IGFBP7]			
		sens	spec	ppv	npv	sens	spec	ppv	npv
Induction of anesthesia	0.53 (0.37-0.69)	0.21 (0.05-0.51)	0.77 (0.72-0.81)	0.03 (0.01-0.09)	0.96 (0.94-0.98)	0.14 (0.02-0.43)	0.97 (0.95-0.99)	0.15 (0.02-0.45)	0.97 (0.95-0.98)
30 min after start of CPB or OpCAB	0.52 (0.36-0.68)	0.21 (0.05-0.51)	0.67 (0.62-0.72)	0.02 (0.00-0.07)	0.96 (0.92-0.98)	0.07 (0.00-0.34)	0.97 (0.94-0.98)	0.08 (0.00-0.36)	0.96 (0.94-0.98)
Immediately after end of CPB or OpCAB	0.71 (0.58-0.82)	0.85 (0.55-0.98)	0.62 (0.57-0.67)	0.07 (0.04-0.13)	0.99 (0.97-1.00)	0.15 (0.02-0.45)	0.93 (0.90-0.95)	0.07 (0.01-0.24)	0.97 (0.95-0.98)
ICU admission	0.68 (0.54-0.81)	0.31 (0.09-0.61)	0.78 (0.74-0.82)	0.05 (0.01-0.11)	0.97 (0.94-0.99)	0.08 (0.00-0.36)	0.97 (0.95-0.98)	0.08 (0.00-0.36)	0.97 (0.95-0.98)
Six hours after ICU admission	0.78 (0.58-0.93)	0.73 (0.39-0.94)	0.64 (0.58-0.69)	0.06 (0.03-0.11)	0.99 (0.96-1.00)	0.27 (0.06-0.61)	0.98 (0.96-0.99)	0.30 (0.07-0.65)	0.98 (0.96-0.99)
Post-op day 1	0.75 (0.59-0.90)	0.67 (0.35-0.90)	0.67 (0.62-0.71)	0.06 (0.03-0.12)	0.98 (0.96-1.00)	0.33 (0.10-0.65)	0.94 (0.91-0.96)	0.15 (0.04-0.35)	0.98 (0.96-0.99)
Post-op day 2	0.65 (0.48-0.81)	0.46 (0.19-0.75)	0.70 (0.65-0.75)	0.06 (0.02-0.12)	0.97 (0.94-0.99)	0.23 (0.05-0.54)	0.97 (0.95-0.99)	0.23 (0.05-0.54)	0.97 (0.95-0.99)
Post-op day 3	0.65 (0.42-0.89)	0.56 (0.21-0.86)	0.76 (0.71-0.81)	0.07 (0.02-0.15)	0.98 (0.95-1.00)	0.11 (0.00-0.48)	0.99 (0.96-1.00)	0.20 (0.01-0.72)	0.97 (0.95-0.99)
Sum of Post CPB/OpCAB and six hours after ICU admission	0.81 (0.74-0.90)	0.93 (0.66-1.00)	0.56 (0.51-0.61)	0.07 (0.04-0.12)	1.00 (0.97-1.00)	0.21 (0.05-0.51)	0.95 (0.92-0.97)	0.13 (0.03-0.34)	0.97 (0.95-0.99)
Product of Post CPB/OpCAB and six hours after ICU admission	0.81 (0.71-0.89)	0.86 (0.57-0.98)	0.65 (0.60-0.70)	0.08 (0.04-0.14)	0.99 (0.97-1.00)	0.21 (0.05-0.51)	0.98 (0.96-0.99)	0.25 (0.05-0.57)	0.97 (0.95-0.99)
Maximum of Post CPB/OpCAB and six hours after ICU admission	0.82 (0.73-0.90)	1.00 (0.77-1.00)	0.44 (0.39-0.49)	0.06 (0.03-0.10)	1.00 (0.98-1.00)	0.29 (0.08-0.58)	0.92 (0.88-0.94)	0.11 (0.03-0.26)	0.97 (0.95-0.99)
Sum of all timepoints	0.82 (0.71-0.91)	0.93 (0.66-1.00)	0.59 (0.54-0.64)	0.08 (0.04-0.13)	1.00 (0.98-1.00)	0.14 (0.02-0.43)	0.99 (0.97-1.00)	0.29 (0.04-0.71)	0.97 (0.95-0.98)
Maximum of all timepoints	0.82 (0.72-0.91)	1.00 (0.77-1.00)	0.18 (0.15-0.23)	0.04 (0.02-0.07)	1.00 (0.95-1.00)	0.57 (0.29-0.82)	0.81 (0.77-0.85)	0.10 (0.04-0.19)	0.98 (0.96-0.99)

Figure S1. Area under the receiver operating characteristic (AUROC) curves for the baseline clinical model (AUROC [95% CI] = 0.86 [0.77-0.94]) and the model that includes the maximum of the post cardiopulmonary bypass/OpCAB timepoint and the six-hours after ICU admission timepoint, in addition to baseline clinical factors (AUROC = 0.90 [0.82-0.96]).

