Post-Operative Biomarkers and Risk of Chronic Kidney Disease After Cardiac Surgery: the TRIBE-AKI Study

SUPPLEMENTAL MATERIAL

Steven Menez, MD, MHS[1]; Dennis G. Moledina, MBBS, PhD[2,3]; Amit X. Garg, MD, PhD[4,5,6]; Heather Thiessen-Philbrook, MMath[1]; Eric McArthur, MSc[6]; Yaqi Jia, MPH[1]; Caroline Liu, MHS[1]; Wassim Obeid, PhD[1]; Sherry G. Mansour, DO, MS[2,3]; Jay L. Koyner, MD[7]; Michael G. Shlipak, MD, MPH[8]; Francis P. Wilson, MD, MSCE[2,3]; Steven G. Coca, DO, MS[9]; Chirag R. Parikh, MD, PhD[1]

CONTENTS

Table S1: Comparison of Baseline Demographics in Patients with Vs. without Follow-up Serum Creatinine Measurements

Label	Value	ALL (N=753)	SCr not available (N=140)	SCr available (N=613)	P**
Age at the time of surgery		71.52 (9)	71.52 (9.77)	71.52 (8.82)	0.559
Sex	F	204 (27%)	36 (26%)	168 (27%)	0.684
	M	549 (73%)	104 (74%)	445 (73%)	
Diabetes (yes/no)	No	435 (58%)	78 (56%)	357 (58%)	0.585
	Yes	318 (42%)	62 (44%)	256 (42%)	
Ejection fraction <35% or grade 3 or 4 left ventricular function	No	687 (91%)	122 (87%)	565 (92%)	0.058
	Yes	66 (9%)	18 (13%)	48 (8%)	
Myocardial Infarction	No	542 (72%)	102 (73%)	440 (72%)	0.798
	Yes	211 (28%)	38 (27%)	173 (28%)	
Pre-Op Serum Creatinine #1 (last level drawn before time zero)		1.03 (0.31)	1.04 (0.28)	1.03 (0.31)	0.481
CKD-EPI GFR Pre-op		70.97 (18.28)	70.84 (18.55)	71 (18.23)	0.958
Pre-op CKD Stages (based on CKD-EPI egfr)	1	111 (15%)	19 (14%)	92 (15%)	0.919
	2	439 (58%)	83 (59%)	356 (58%)	
	3	188 (25%)	36 (26%)	152 (25%)	
	4/5	15 (2%)	2 (1%)	13 (2%)	
Congestive Heart Failure	No	680 (90%)	129 (92%)	551 (90%)	0.415
	Yes	73 (10%)	11 (8%)	62 (10%)	
Perfusion Time		108.05 (58.12)	112.31 (59.16)	107.09 (57.89)	0.490
Cross Clamp time (min)		71.77 (43.48)	72.74 (42.04)	71.55 (43.84)	0.741
Length of ICU stay (days)		3.34 (9.85)	4.56 (10.68)	3.06 (9.63)	0.321
Length of hospital stay (days)		9.99 (13.26)	10.75 (14.78)	9.82 (12.89)	0.057

Mean (SD) and frequency (%) are presented for the continuous and categorical variables, respectively

Table S2: Risk of CKD Incidence or Progression by Post-operative Biomarker Tertiles					
Biomarker	**Tertile (range)**	**N**	**Event Rate (per 1000 person-years)**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**
bFGF (pg/mL)	1st Tertile (1.37-5.97)	206	37.1	1 (ref)	1 (ref)
	2nd Tertile (5.98-9.85)	202	51.9	1.40 (0.94, 2.08)	1.32 (0.87, 1.99)
	3rd Tertile (9.90-121.8)	204	72.2	1.99 (1.36, 2.91)	1.89 (1.26, 2.82)
KIM-1 (pg/mL)	1st Tertile (78.4-177.0)	204	39.4	1 (ref)	1 (ref)
	2nd Tertile (177.2-238.2)	204	60.0	1.53 (1.05, 2.25)	1.42 (0.96, 2.11)
	3rd Tertile (238.6-6849.8)	204	60.3	1.55 (1.06, 2.29)	1.29 (0.85, 1.97)
NT pro-BNP (pmol/L)	1st Tertile (2.0-28.5)	129	41.3	1 (ref)	1 (ref)
	2nd Tertile (28.7-80.7)	129	56.9	1.39 (0.87, 2.21)	1.35 (0.83, 2.20)
	3rd Tertile (81.5-2684.0)	129	73.6	1.81 (1.16, 2.83)	1.56 (0.95, 2.58)
TNF-r1 (pg/mL)	1st Tertile (1779-5403)	204	44.0	1 (ref)	1 (ref)
	2nd Tertile (5409-7922)	204	49.4	1.14 (0.77, 1.68)	1.12 (0.75, 1.67)
	3rd Tertile (7932-23596)	204	66.7	1.53 (1.06, 2.21)	1.41 (0.94, 2.12)

* Adjusted for age, sex, AKI stage, pre-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine

Table S3: Risk of CKD Incidence or Progression by Post-operative Biomarker Level, Adjusted for Pre-operative Level

Biomarkers (natural log-transformed)	Adjusted Hazard Ratio (95% CI)*
bFGF	1.56 (1.21, 2.00)
KIM-1	0.81 (0.36, 1.83)
Pro-BNP	1.21 (0.81, 1.80)
TNF-r1	1.45 (0.96, 2.21)

n=613

*adjusted for age, sex, AKI stage, pre-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine

Table S4: Baseline Demographics, Replication Cohort				
Variable		**ALL**	**No primary outcome**	**Developed primary outcome**	**P-value**
		(N=310)	(N=191)	(N=119)	
Age at the time of surgery		71.97 (9.63)	72.23 (10.05)	71.55 (8.94)	0.36
Sex (female, %)		101 (33%)	63 (33%)	38 (32%)	0.85
Race (white, %)		301 (97%)	185 (97%)	116 (97%)	0.75
Diabetes		111 (36%)	56 (29%)	55 (46%)	0.003
Hypertension		242 (78%)	149 (78%)	93 (78%)	0.98
Congestive Heart Failure		59 (19%)	31 (16%)	28 (24%)	0.11
Left ventricular ejection fraction <40%		26 (8%)	14 (7%)	12 (10%)	0.40
Previous myocardial infarction		61 (21%)	28 (15%)	33 (29%)	0.004
eGFR, mL/min per 1.73m^2		65.75 (17.84)	65.4 (18.7)	66.33 (16.41)	0.43
eGFR, mL/min per 1.73m^2	>60	188 (61%)	107 (56%)	81 (68%)	0.11
	<60	122 (39%)	84 (44%)	38 (32%)	
Serum creatinine, mg/dL		1.09 (0.29)	1.1 (0.29)	1.09 (0.3)	0.58
Urine Microalbumin, pre-operative (>30 mg/g)		76.05 (190.29)	65.84 (166.15)	94.22 (226.84)	0.047
STS Score		9.64 (3.68)	9.47 (3.61)	9.92 (3.8)	0.19
Elective surgery		269 (87%)	167 (87%)	102 (86%)	0.66
Isolated CABG or valve surgery		236 (76%)	146 (76%)	90 (76%)	0.87
Off-pump		40 (13%)	21 (11%)	19 (16%)	0.19
Reoperation		0 (0%)	NA	NA	NA
Perfusion time, min		110.07 (46.76)	113.43 (44.76)	104.56 (49.58)	0.10
Crossclamp time, min		84.34 (36.8)	85.78 (34.03)	81.95 (41.04)	0.22
AKIN Stage	0	228 (74%)	146 (76%)	82 (69%)	0.54
	1	78 (25%)	43 (23%)	35 (29%)	
	2 or 3	4 (2%)	2 (1%)	2 (2%)	
AKI Duration (days)	1 to 2	228 (74%)	146 (76%)	82 (69%)	0.54
	3 to 6	78 (25%)	43 (23%)	35 (29%)	
	>6	4 (1%)	2 (1%)	2 (1%)	
Last serum Creatinine before discharge		1.03 (0.3)	1.02 (0.28)	1.05 (0.33)	0.43

eGFR: estimated glomerular filtration rate. STS: Society of Thoracic Surgeons. CABG: coronary artery bypass graft.
AKI: acute kidney injury. AKIN: acute kidney injury network
CKD incidence (pre-operative eGFR ≥60): 25% reduction in eGFR and a fall below 60 mL/min/1.73m^2
CKD progression (pre-operative eGFR <60):50% reduction in eGFR or a fall below 15 mL/min/1.73m^2
- Mean (SD) and frequency (%) are presented for the continuous and categorical variables, respectively

Table S5: Risk of CKD Incidence or Progression by Post-operative Biomarker Level, Replication Cohort

Biomarker	Tertile (range)	Event Rate (per 1000 person-years)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
bFGF (pg/mL)	Continuous	N/A	1.25 (1.02, 1.53)	1.24 (1.00, 1.52)
	1st Tertile (1.9-7.8)	40.2	1 (ref)	1 (ref)
	2nd Tertile (8-19.9)	61.8	2.00 (1.15, 3.48)	1.86 (1.05, 3.29)
	3rd Tertile (20.6-231.4)	55.2	2.00 (1.12, 3.6)	1.98 (1.09, 3.62)
KIM-1 (pg/mL)	Continuous	N/A	1.69 (1.18, 2.41)	1.51 (1.02, 2.23)
	1st Tertile (125.4-163.69)	42.1	1 (ref)	1 (ref)
	2nd Tertile (197.34-231.72)	55.6	1.67 (0.94, 2.97)	1.56 (0.87, 2.79)
	3rd Tertile (281.73-377.77)	68.5	2.23 (1.28, 3.89)	2.03 (1.14, 3.61)
NT pro-BNP (pmol/L)	Continuous	N/A	1.32 (1.1, 1.6)	1.35 (1.07, 1.70)
	1st Tertile (1.8-24)	40.5	1 (ref)	1 (ref)
	2nd Tertile (24-89)	56.1	1.45 (0.79, 2.65)	1.53 (0.81, 2.86)
	3rd Tertile (90-2287)	67.6	2.09 (1.13, 3.87)	2.09 (1.02, 4.28)
TNF-r1 (pg/mL)	Continuous	N/A	1.97 (1.18, 3.28)	1.73 (0.94, 3.18)
	1st Tertile (1721-4400)	34.6	1 (ref)	1 (ref)
	2nd Tertile (4405-6399)	62.0	2.04 (1.15, 3.60)	2.02 (1.12, 3.64)
	3rd Tertile (6399-16817)	61.5	2.16 (1.21, 3.87)	1.95 (0.99, 3.82)

* Adjusted for age, sex, AKI stage, pre-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine

Table S6: Risk of CKD Incidence or Progression by Post-operative Biomarker Level Using Sub-distribution Hazard Model, Primary Cohort

Biomarkers (natural log-transformed)	Sub-distribution Hazard Ratio (95% CI)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
bFGF	1.47 (1.18, 1.83)	1.48 (1.16, 1.89) *
NT pro-BNP	1.17 (1.02, 1.34)	1.17 (0.99, 1.37)
TNF-r1	1.62 (1.16, 2.27)	1.66 (1.12, 2.48) *
IL-10	1.14 (1.01, 1.27)	1.11 (0.98, 1.25)
IL-2	1.15 (0.98, 1.34)	1.06 (0.91, 1.25)
KIM-1	1.42 (1.02, 1.98)	1.41 (0.91, 2.19)
VEGFr1	1.29 (1.06, 1.57)	1.20 (0.96, 1.49)
YKL-40	1.21 (0.98, 1.50)	1.07 (0.85, 1.35)

n=613
* $p<0.05$
Adjusted for age, sex, AKI stage, pre-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine

Table S7: Evaluation for Interactions Between Biomarker Level and Pre-Operative CKD on the Risk of CKD Incidence or Progression

Biomarker (natural log-transformed)	Adjusted Hazard Ratio (95% CI)		
	No baseline CKD	Baseline CKD	Interaction P-value
bFGF	1.79 (0.86, 3.71)	1.42 (1.10, 1.83)	0.74
KIM-1	1.70 (0.79, 3.70)	1.82 (1.18, 2.82)	0.69
NT pro-BNP	1.83 (1.20, 2.81)	1.18 (0.97, 1.42)	0.22
TNFr1	6.58 (1.74, 24.95)	1.77 (1.18, 2.68)	0.08

Adjusted for age, sex, AKI stage, pre-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine

Table S8: Model Performance using Net Reclassification Index*				
Biomarker	**Cohort**	**Continuous NRI at 6 years follow-up**		
		Overall	**Events**	**Non Events**
Plasma bFGF	Primary	0.19	0.03	0.16
	Replication	0.19	0.08	0.11
Plasma KIM-1	Primary	0.06	-0.04	0.10
	Replication	0.06	-0.23	0.29
Plasma NT pro-BNP	Primary	0.21	0.00	0.21
	Replication	0.43	0.33	0.10
Plasma TNFr1	Primary	0.03	-0.05	0.08
	Replication	0.01	-0.19	0.20

*Clinical parameters include age, sex, AKI stage, per-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine. Biomarkers are natural log-transformed.

Table S9: Risk of CKD Incidence or Progression by Peak Biomarker Level, Primary Cohort

Peak blood biomarker (natural log transformed)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
bFGF	1.55 (1.24, 1.93) *	1.58 (1.24, 2.00)*
KIM-1	1.53 (1.04, 2.27) *	1.34 (0.77, 2.32)
NT pro-BNP	1.29 (1.04, 1.60) *	1.27 (0.96, 1.70)
TNFr1	1.81 (1.28, 2.56) *	1.81 (1.20, 2.72) *
IL-10	1.13 (1.00, 1.29) *	1.10 (0.95, 1.26)
Il-2	1.21 (1.03, 1.43) *	1.11 (0.94, 1.31)
VEGFr1	1.30 (1.07, 1.58) *	1.20 (0.97, 1.48)
YKL-40	2.60 (0.60, 11.18)	2.85 (0.59, 13.72)

* $p < 0.05$

Adjusted for age, sex, AKI stage, pre-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine

Table S10: Risk of CKD Incidence or Progression by Mean Biomarker Level, Primary Cohort

Mean blood biomarker (natural log transformed)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
bFGF	1.53 (1.20, 1.95)*	1.55 (1.20, 2.01) *
KIM-1	1.59 (1.12, 2.28) *	1.49 (0.88, 2.53)
NT pro-BNP	1.35 (1.09, 1.67) *	1.39 (1.06, 1.83) *
TNFr1	2.13 (1.48, 3.09) *	2.61 (1.60, 4.28) *
IL-10	1.15 (1.00, 1.32) *	1.10 (0.94, 1.27)
Il-2	1.21 (1.02, 1.45) *	1.10 (0.91, 1.32)
VEGFr1	1.31 (1.06, 1.62) *	1.18 (0.93, 1.49)
YKL-40	2.82 (1.37, 5.84) *	1.88 (0.88, 4.02)

* $p<0.05$

Adjusted for age, sex, AKI stage, pre-operative albuminuria, pre-operative serum creatinine, discharge serum creatinine

Table S11: Biomarker Measurement Details

| Sample Type	Biomarker	Biomarker Name	Assay	Units
Blood	bFGF	basic fibroblast growth factor	MSD (Ang.)	pg/mL
	CK-MB	creatine kinase-MB	Coulter Access	ug/L
	EGF	epidermal growth factor	Biochip	pg/mL
	Gal3	Galectin-3	MSD(Custom)	pg/mL
	hFABP	heart-type fatty acid-binding protein	Biochip	pg/mL
	hsTnT	high-sensitivity Troponin T	Coulter Access	ng/L
	IFN	interferon gamma	MSD (Pro-inf.)	pg/mL
	IL-1	interleukin 1b	MSD (Custom)	pg/mL
	IL-2	interleukin 2	MSD (Pro-inf.)	pg/mL
	IL-4	interleukin 4	MSD (Pro-inf.)	pg/mL
	IL-6	interleukin 6	MSD (Pro-inf.)	pg/mL
	IL-8	interleukin 8	MSD (Pro-inf.)	pg/mL
	IL-10	interleukin 10	MSD (Pro-inf.)	pg/mL
	IL-12	interleukin 12	MSD (Pro-inf.)	pg/mL
	IL-13	interleukin 13	MSD (Pro-inf.)	pg/mL
	IL-18	interleukin 18	MSD (Custom)	pg/mL
	KIM-1	kidney injury molecule-1	MSD (Custom)	pg/mL
	MCP-1	monocyte chemotactic protein 1	MSD (Custom)	pg/mL
	NGAL	neutrophil gelatinase-associated lipocalin	Abbott Architect	pg/mL
	NT pro-BNP	N-terminal prohormone of brain natriuretic peptide	Coulter Access	pmol/L
	PIGF	placental Growth Factor	MSD (Ang.)	pg/mL
	ST2	Soluble suppression of tumorigenicity	MSD(Custom)	pg/mL
	Tie2	angiopoietin-1 receptor	MSD (Ang.)	pg/mL
	TNF-r1	Tumor necrosis factor receptor 1	MSD (Custom)	pg/mL
	TNF-r2	Tumor necrosis factor receptor 2	MSD (Custom)	pg/mL
	TNFα	tumor necrosis factor alpha	MSD (Pro-inf.)	pg/mL
	TnI	troponin I3	Coulter Access	ug/L
	VEGF	vascular endhotehlial growth factor	MSD (Ang.)	pg/mL
	VEGFc	vascular endothelial growth factor C	MSD (Ang.)	pg/mL
	VEGFd	vascular endothelial growth factor D	MSD (Ang.)	pg/mL
	VEGFR1	anti-angiogenic vascular endothelial growth factor receptor 1	MSD (Ang.)	
	YKL-40	chitinase-3-like protein 1	MSD (Custom)	pg/mL
Urine	Albumin	NA	ELISA	mg/L
	Creatinine	NA	Clinical Autoanalyzer	mg/dL
	Cystatin-C	NA	Genz. Virotech	mg/L
	IL-18	interleukin 18	Abbott Architect	ng/mL
	KIM-1	kidney injury molecule-1	Genz. Virotech	ng/mL
	L-FABP	liver-type fatty acid-binding protein	Genz. Virotech	ng/mL
	NGAL	neutrophil gelatinase-associated lipocalin	Abbott Architect	ng/mL
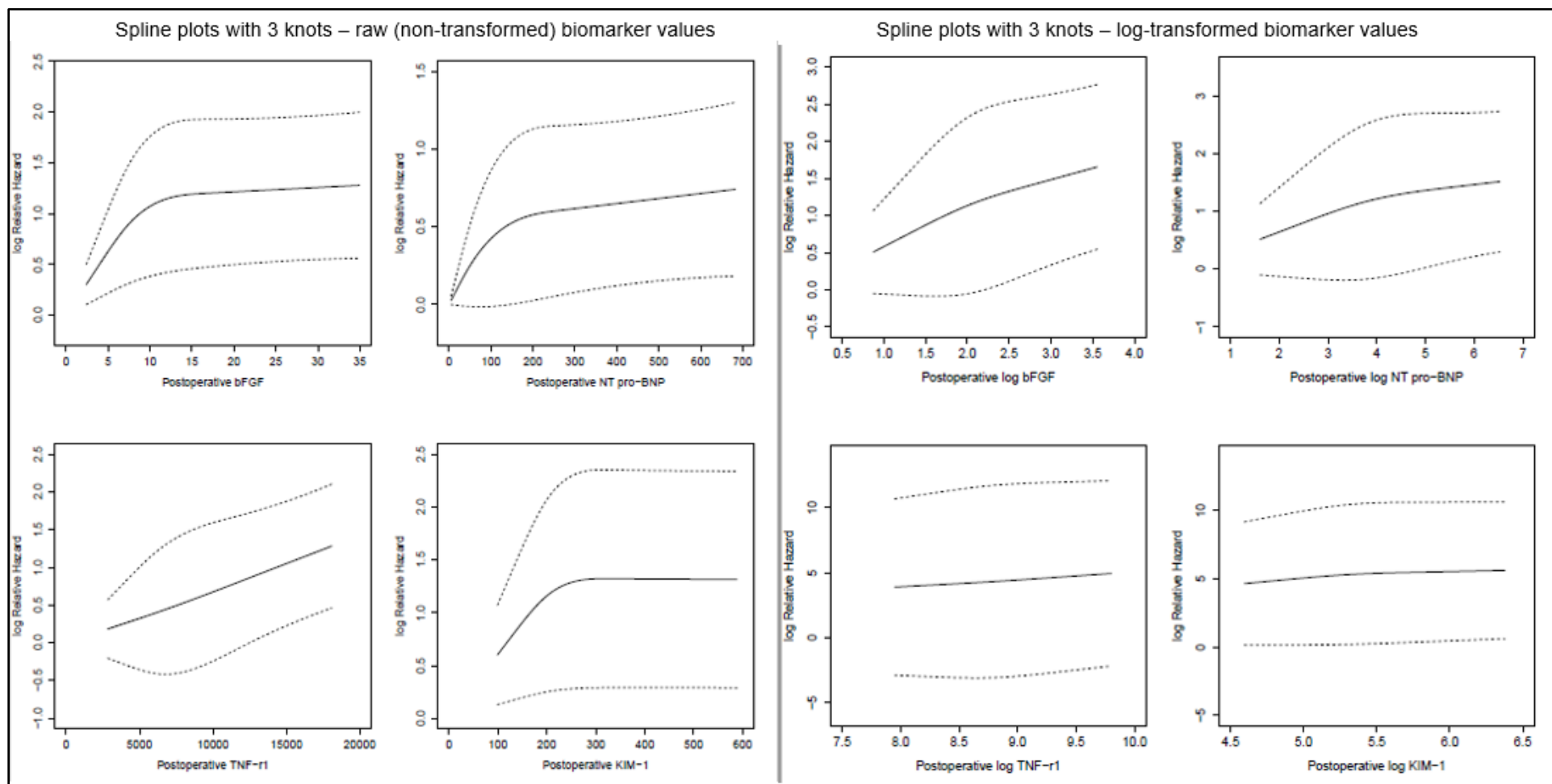
Figure S1: Post-operative biomarker spline plots using 3 cubic spline knots