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Peri-operative heart-type fatty acid binding protein is associated with acute kidney injury after cardiac surgery

Jennifer A. Schaub, MD¹, Amit X. Garg, MD, PhD², Steven G. Coca, DO, MS¹, Jeffrey M. Testani, MD¹, Michael G. Shlipak, MD, MPH³, John Eikelboom, MBBS⁴, Peter Kavsak, PhD⁵, Eric McArthur, MSc⁶, Colleen Shortt, BSc⁴, Richard Whitlock, MD, MSc⁴, and Chirag R. Parikh, MD, PhD¹ for the TRIBE-AKI Consortium

¹Department of Internal Medicine and Applied Translational Research, Yale University School of Medicine, New Haven, CT, USA

²Division of Nephrology, Department of Medicine, Western University, London, Ontario, Canada

³Division of General Internal Medicine, University of California San Francisco School of Medicine, San Francisco CA

⁴Division of Cardiac Surgery, Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada

⁵Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

⁶Institute for Clinical Evaluative Sciences Western, London, Ontario, Canada

Abstract

Acute Kidney Injury (AKI) is a common complication after cardiac surgery and is associated with worse outcomes. Since heart fatty acid binding protein (H-FABP) is a myocardial protein that detects cardiac injury, we sought to determine if plasma H-FABP was associated with AKI in the TRIBE-AKI cohort; a multi-center cohort of 1219 patients at high risk for AKI who underwent cardiac surgery. The primary outcomes of interest were any AKI (Acute Kidney Injury Network (AKIN) stage 1 or higher) and severe AKI (AKIN stage 2 or higher). The secondary outcome was long-term mortality after discharge. Patients who developed AKI had higher levels of H-FABP pre- and post-operatively than patients who did not have AKI. In analyses adjusted for known AKI risk factors, first post-operative log(H-FABP) was associated with severe AKI (adjusted OR 5.39 [95% CI, 2.87-10.11] per unit increase), while pre-operative log(H-FABP) was associated with any AKI (2.07 [1.48-2.89]) and mortality (1.67 [1.17-2.37]). These relationships persisted after adjustment for change in serum creatinine (for first postoperative log(H-FABP)) and biomarkers of cardiac and kidney injury, including brain natriuretic peptide, cardiac troponin-I, interleukin-18, liver fatty acid binding protein, kidney injury molecule-1, and neutrophil gelatinase associated

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Correspondence: Dr. Chirag R. Parikh, Section of Nephrology, Yale University School of Medicine, 60 Temple Street, Suite 6C, New Haven, CT 06510. chirag.parikh@yale.edu. Telephone: 203-737-2676. Fax: 203-764-8373.

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lipocalin. Thus, peri-operative plasma H-FABP levels may be used for risk-stratification of AKI and mortality following cardiac surgery.

Keywords

Heart-type fatty acid binding protein; Acute Kidney Injury; Mortality; Cardiac Surgery

Introduction

Acute kidney injury (AKI) is a common complication of cardiac surgery and strongly predicts adverse outcomes. Identification and management of AKI remains a troublesome area of clinical practice largely for two reasons. Firstly, the diagnosis of AKI hinges on changes in serum creatinine, which often does not change until two to three days after the initial insult (1). Secondly, serum creatinine can rise for myriad reasons, including true tubular injury, hemodynamic alterations or cardio-renal interactions (1).

Recent biomarker research strives to ameliorate these clinical conundrums. Several urinary proteins have been identified as biomarkers of renal injury, including interleukin 18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid binding protein (L-FABP) and kidney injury molecule-1 (KIM-1) (1-4). These markers detect damage to the proximal and distal tubular cells, and IL-18 and NGAL detect AKI sooner than change in serum creatinine (1). In contrast, cardiac biomarkers, such as serum brain natriuretic peptide (BNP) improves riskstratification for AKI pre-operatively (5). More recent literature has explored phenotyping AKI with a combination of renal and cardiac biomarkers (6).

Fatty Acid Binding Proteins are a family of highly conserved proteins, which are involved in transporting free fatty acid molecules in the cytosol. There are at least 10 variants identified thus far, which are widely expressed in various tissues. One particular member of the protein family, heart fatty acid binding protein (H-FABP), is widely expressed in the cytosol of the myocardium and has limited expression in other tissues, including the distal tubular cells of the kidneys (7, 8). Both animal and human data have demonstrated that H-FABP is released less than 30 minutes after myocardial injury and is mostly renally excreted within 24 hours (9-12). Recent literature has demonstrated that H-FABP has utility in detecting a variety of cardiac derangements, such as myocardial infarction (13), post-operative myocardial injury (14, 15) and ongoing ischemic damage in heart failure (16, 17). One small study recently demonstrated that patients with elevated pre-operative H-FABP undergoing elective coronary artery bypass graft surgery (CABG) were more likely to experience AKI post-operatively (18). H-FABP is additionally strongly associated with mortality in a wide variety of settings (19-25).

Thus, the purpose of our study was three-fold. First, we sought to establish if elevated pre- or post-operative H-FABP levels were associated with any AKI or severe AKI. Second, we explored whether elevated H-FABP levels captured similar information as previously established kidney injury and cardiac biomarkers. Third, we examined the association of H-FABP with long-term mortality for additional risk stratification of patients with AKI.

Results

Patient Characteristics

Baseline characteristics between patients without AKI, any AKI (Acute Injury Network (AKIN) Stage 1 or higher) and severe AKI (AKIN Stage 2 or higher) are presented in Table 1. Overall, 330 patients (34.3%) experienced any AKI and 37 patients (3.9%) had severe AKI during their hospital stay. Only 1.1% of the cohort developed oliguria within the first 24 hours postoperatively, and the median time to creatinine rise was three days. Patients who experienced any AKI were more likely to have a history of diabetes, hypertension, congestive heart failure and lower baseline estimated glomerular filtration rate than patients without AKI (p-value, <0.01 for all comparisons). They were additionally more likely to undergo surgeries that had longer cross-clamp and perfusion time and experience a complicated post-operative course, including more extra-renal complications, longer ventilator time and ICU stays (p-value, <0.001 for all comparisons).

Biomarker Characteristics

Pre-operative plasma H-FABP was associated with pre-operative serum creatinine level ($r=0.50$, p-value <0.001) and pre-operative estimated glomerular filtration rate ($r=-0.55$, p-value <0.001). Patients within the highest tertile of first post-operative H-FABP were more likely to undergo emergency surgery (22.6% in tertile 3 versus 14.5% in tertile 1, p-value 0.018), have longer cross-clamp times (101 minutes versus 56 minutes, p-value <0.001), longer perfusion times (148 minutes versus 80 minutes, p-value <0.001) and less likely to have off-pump surgery (2.5% versus 18.6%, p-value <0.001). The first post-operative values of all cardiac and renal biomarkers, including plasma H-FABP, serum BNP, plasma cardiac troponin-I (cTnI), urinary IL-18, urinary NGAL, urinary KIM-1, urinary L-FABP, were significantly higher in patients who experienced any AKI than patients without AKI (Table 2).

Peri-operative H-FABP Levels in those Without AKI, Any AKI and Severe AKI

Patients who experienced any AKI had higher levels of H-FABP both pre- and post-operatively than patients who did not experience AKI, and patients with severe AKI had the highest levels among the three groups (Figure 1). The first post-operative H-FABP levels in patients who experienced severe AKI increased by about 13-fold (median 77.4 ng/ml, IQR [38.5, 141.0]) (p-value <0.001), whereas they increased by about 8-fold in the patients who experienced any AKI (median 39.6 ng/ml, IQR [25.1, 62.1]) (p-value <0.001). During the subsequent post-operative days, H-FABP levels declined, but at a slower rate in patients who experienced any AKI. By postoperative day three, the H-FABP levels had not returned to baseline in any group.

Correlation between First Post-Operative H-FABP and Other Cardiac and Renal Biomarkers

The first post-operative H-FABP was weakly correlated with other urinary biomarkers of kidney injury, including IL-18, KIM-1, L-FABP, and NGAL. The strongest correlation

between H-FABP and a kidney injury biomarker was with L-FABP ($r=0.31$, p -value <0.001). The association was stronger with cTnI ($r=0.58$, p -value <0.001) (Table 3).

Association of log(H-FABP) with Any AKI and Severe AKI

Pre-operatively, higher log(H-FABP) levels were associated with any AKI in univariate models, and the association persisted after adjusting for clinical covariates and logarithmically transformed individual kidney injury and cardiac biomarkers (Table 4). While pre-operative log(H-FABP) was associated with severe AKI in univariate models, the significance was lost after adjusting for clinical covariates, although the effect size estimate remained similar (Table 5).

Each unit increase in first post-operative log(H-FABP) was independently associated with any AKI (adjusted OR 1.83 [95% CI, 1.41-2.36]) and severe AKI (adjusted OR 5.39 [95% CI, 2.87-10.11]) after adjustment for clinical covariates. The relationship between first post-operative log(H-FABP) and severe AKI (Table 5) persisted after adjustment for change in serum creatinine as well as logarithmically transformed renal and cardiac biomarkers, including IL-18, NGAL, KIM-1, L-FABP, BNP and cTnI. In contrast, the relationship between first post-operative log(H-FABP) and any AKI (Table 4) was attenuated after adjusting for change in serum creatinine, logarithmically transformed renal biomarkers and serum BNP.

The odds ratios between post-operative days 2 and 3 log(H-FABP) and any AKI and severe AKI were all strongly statistically significant and are presented in Supplementary Tables 1 and 2.

Association of log(H-FABP) with Long-Term Mortality

During the follow-up period (median 3 years, IQR [2.2, 3.6]), 10.8% of the entire cohort died. Patients with elevated pre-operative log(H-FABP) were significantly more likely to die, even after adjustment for multiple risk factors (adjusted HR 1.67 [95% CI, 1.17-2.37] per unit increase). This relationship persisted after adjustment for logarithmically transformed renal injury and cardiac biomarkers (Table 6).

Patients with elevated first post-operative log(H-FABP) levels were significantly more likely to die during follow-up after adjustment for multiple risk factors (adjusted HR 1.27 [95% CI, 1.03-1.56]). However, after adjustment for change in serum creatinine, the association became nonsignificant (adjusted HR 1.21 [95% CI, 0.87-1.66], Table 6). Additionally, post-operative days 2 and 3 log(H-FABP) were not consistently associated with mortality after adjustment for change in serum creatinine and logarithmically transformed cardiac and renal biomarkers (Supplementary Table 3).

Diagnostic Ability of log(H-FABP) for Any AKI, Severe AKI and Mortality

The area under the curve and event and non-event net reclassification index (NRI) for log(H-FABP) are presented in Table 7 for pre-operative log(H-FABP) and first post-operative log(H-FABP). Pre-operative log(H-FABP) improved reclassification of non-events for mortality (NRI-0.54) and additionally improved reclassification of AKI and non-

AKI events (NRI=0.16 for both). First post-operative log(H-FABP) improved reclassification of severe AKI events (NRI=0.41) and non-events (NRI=0.46) (Table 7).

Discussion

We have demonstrated that elevated pre-operative H-FABP is associated with any AKI and longterm mortality. Additionally, we have demonstrated for the first time that elevated first postoperative H-FABP levels are associated with severe AKI after cardiac surgery. The relationships between pre-operative H-FABP and any AKI and first post-operative H-FABP and severe AKI persisted after adjustment for both decline in filtration (via change in serum creatinine) and for tubular injury (via urinary IL-18, KIM-1, NGAL, L-FABP). We additionally found that perioperative H-FABP improved reclassification ability over clinical models for AKI and mortality as evidenced by their large NRI in both event and non-event groups.

The association between pre-operative H-FABP and any AKI was recently demonstrated in a small cohort study (18). As our study is larger and includes more AKI events, it adds more credence to the possibility that pre-operative H-FABP might be useful for pre-operative risk stratification of AKI events. We additionally found that pre-operative H-FABP was strongly associated with long-term mortality. H-FABP has been associated with mortality in numerous other settings, including acute coronary syndrome (19-21), out-of-hospital cardiac arrest (22), outpatients from a community setting (23), and sepsis (24). It is likely that patients with an elevated pre-operative H-FABP represent a sicker patient population and hence have higher operative risk. It is notable that another study found that post-operative H-FABP is associated with long-term mortality after cardiac bypass surgery, however the study did not adjust for the occurrence of AKI as we did in our models (25).

To the best of our knowledge, this is the first study to demonstrate that first post-operative H-FABP is strongly associated with severe AKI after adjustment for various cardiac and renal injury biomarkers. Although H-FABP is renally excreted, it is doubtful that the association between elevated first post-operative H-FABP levels and severe AKI is merely due to poor renal excretion of H-FABP during an episode of AKI; although poor renal filtration is likely a contributor to the strong statistical association between post-operative day 2 and 3 H-FABP and AKI events. At the first post-operative time point, which was within six hours after the surgery, the median change in serum creatinine was 0% whereas the median change in H-FABP levels was 600%. Furthermore, the median time until change in serum creatinine was three days and only 1.1% of the cohort developed oliguria within 24 hours, so it is unlikely that the immediate elevation of H-FABP levels post-operatively can be explained by impaired renal filtration. Additionally, the relationship between first post-operative H-FABP and severe AKI persisted even after adjustment for change in serum creatinine in multi-variable analysis.

Despite the strong and consistent association with severe AKI, post-operative H-FABP explained less than 10% of the variability in known kidney injury biomarkers. Thus, it is possible that H-FABP is capturing a different aspect of the pathophysiology of AKI than traditional kidney injury biomarkers. Published literature provides plausible explanations for

why first post-operative H-FABP is strongly associated with severe AKI. First, several studies have demonstrated that H-FABP can be used as a marker of inflammatory injury since H-FABP levels increase postoperatively in patients after on-pump cardiac surgery whereas H-FABP does not increase in patients after off-pump cardiac surgery (15, 26). Thus, it is conceivable that patients who experienced severe myocardial inflammatory injury also experienced severe renal inflammatory injury. Second, H-FABP levels rise post-operatively in patients with a new post-operative myocardial infarction (14, 25, 26). Thus, it is possible that some patients are experiencing pre-renal AKI due to new myocardial infarction. Third, elevated post-operative H-FABP levels could be a marker for hemodynamic changes related to delayed recovery of cardiac tissue after surgery. Fourth, H-FABP is found in the distal tubular cells of the kidney (8) and urinary H-FABP is prognostically useful for intrinsic kidney diseases, such as membranous nephropathy (27). Thus it is possible that there was substantial release of H-FABP from distal renal tubular cells during an AKI event hence strengthening the association between H-FABP and severe AKI. However, expression of H-FABP in the myocardium is about 20 times greater than renal tissue, so it is unlikely that a substantial portion of H-FABP measured in the plasma originated from renal tissue (28). Unfortunately, this cohort does not have hemodynamic data, such as cardiac output or blood pressure measurements, or post-operative EKGs to distinguish between these proposed etiologies.

This is a large, multi-center prospective cohort study in a population of patients who were at high risk for AKI. Since all enrolled patients underwent cardiac bypass surgery, we are able to confidently identify the timing of the renal insult. However, there are important limitations. Statistical power was limited to detect changes in AKI requiring dialysis (n=9, 0.9%), which is an important clinical endpoint. We do not have biopsy data to definitively identify the cause of AKI. We additionally do not have detailed clinical data regarding important cardiac events post-operatively, including post-operative EKGs, occurrence of myocardial infarction, need for inotropes or need for an intra-aortic balloon pump. Additionally, our study population was mostly white, so these findings might not be applicable to a more diverse patient population.

In conclusion, this is the first study to demonstrate that first post-operative H-FABP identifies a cohort of patients after cardiac surgery who experience more post-operative severe AKI. Additionally, we provide further evidence that elevated pre-operative H-FABP is associated with any AKI and long-term mortality. Notably, all of these relationships persisted despite adjustment for cardiac and renal biomarkers. It may be beneficial for future studies to explore using H-FABP to help improve pre-operative risk stratification for both mortality and AKI. Additionally, future studies should obtain more detailed clinical data, such as hemodynamic parameters and occurrence of post-operative myocardial infarction, to elucidate the mechanism behind the relationship between first post-operative H-FABP and severe AKI.

Methods

The Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) cohort was a prospective cohort study of 1219 patients who underwent

cardiac surgery from July 2007 to December 2009. They were at high risk for post-operative AKI, based on the presence of one of the following characteristics prior to surgery: pre-existing renal dysfunction (baseline serum creatinine >2mg/dl), ejection fraction < 35%, age > 65 years, diabetes mellitus, combined CABG and valve surgery or repeat re-vascularization surgery. Patients were excluded if they experienced AKI before the surgery, had undergone kidney transplantation, had a history of ESRD or a baseline serum creatinine >4.5 mg/dL. All the patients provided consent, and the respective institution's review board approved the protocol.

Patients were enrolled from six academic medical centers in North America. The detailed methods have been described previously (1). Briefly, the patients had baseline blood samples collected before their surgery and then for five consecutive days post-operatively. The first post-operative sample was collected zero to six hours post-operatively. Collection of samples was stopped if the patient did not develop an increase in serum creatinine by post-operative day three. We excluded 20 patients who died during their hospitalization. Additionally, we excluded 239 patients who did not have blood and urine samples collected on three consecutive days post-operatively. There were no measurements for H-FABP available for this group of patients. One additional patient was excluded due to measurement errors of H-FABP.

The outcomes of interest were any AKI and severe AKI. Any AKI corresponded to AKIN Stage 1 or higher (serum creatinine increase \geq 0.3 mg/dl or serum creatinine 1.5 times the baseline), while severe AKI corresponded to AKIN Stage 2 or higher (doubling of serum creatinine or AKI requiring dialysis) (29). Thus, the severe AKI outcome included patients who had only experienced AKIN Stage 2 AKI or dialysis, while the any AKI outcome included patients who had experienced any of the following: AKIN Stage 1 AKI, AKIN Stage 2 AKI or dialysis. We additionally evaluated long-term mortality as a secondary outcome.

We collected several covariates on the patients at study enrollment, including demographic characteristics, medical comorbidities and surgical characteristics. To obtain mortality data, we employed several overlapping approaches. For patients from the United States, we called patients' home, searched the National Death Index and reviewed hospital records. For patients from Canada, we used phone calls, as well as data held at the Institute for Clinical Evaluative Sciences (ICES) to acquire vital status. These datasets were linked using unique, encoded identifiers and analyzed at ICES. Death status and date of death were recorded until the last date of follow-up of February 21, 2012.

Biomarker Assays

The EDTA plasma samples were stored frozen (below -70C), and were thawed for the first time for measurement of H-FABP on the Randox Evidence Investigator™ using a Randox developed custom cytokine array (Randox Laboratories Ltd), BNP (Biosite Corporation) and cardiac troponin I (AccuTnI on Access II, Beckman Coulter). The imprecision of the assays were within the manufacturers acceptable range (<20%) and were as follows: H-FABP inter-assay QC level 1 and 2 CV=17%, H-FABP intra-assay QC levels 1 CV=15% and level 2 CV= 8%. Information regarding the biomarker assays for the kidney injury biomarkers and

BNP has been reported previously (1, 2, 5). All laboratory personnel were blinded to clinical outcomes and samples were analyzed according to manufacturer specifications.

Statistical Methods

The distribution of H-FABP was right skewed, so H-FABP was logarithmically transformed and analyzed on a continuous scale. We compared continuous variables with the 2-sample t test or Wilcoxon rank sum test and dichotomous variables with the chi-squared test. We used Kruskal-Wallis test to compare cardiac and renal biomarkers levels between patients without AKI, any AKI and severe AKI. We determined the adjusted odds ratios of AKI with multivariable logistic regression. We adjusted for important clinical covariates, which are included in common clinical prediction scores for AKI after cardiac surgery (30, 31). The first model adjusted for age (per year), sex, race, cardio-pulmonary bypass time >120 minutes, non-elective surgery, pre-operative estimated GFR (in milliliters per minute per 1.73m²), diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin/creatinine ratio and type of surgery. Apart from H-FABP, which was logarithmically transformed, none of the clinical covariates were transformed. The second model adjusted for all of the above, but also included change in serum creatinine (from same time point as H-FABP minus pre-operative value). The third model added other established logarithmically transformed renal and cardiac biomarkers individually into the second model, including IL-18, NGAL, KIM1, L-FABP, BNP, and cTnI. We additionally calculated Spearman correlation coefficients between H-FABP and IL-18, NGAL, KIM1, L-FABP, BNP, and cTnI. We used Cox proportional hazard models to estimate risk of mortality using the same covariates as described for the logistic regression models. We additionally calculated the area under the receiver operating curve and the net reclassification index for events and non-events. All odds ratios and hazard ratios are reported as per log unit increase in H-FABP. Small cell counts are only presented for data collected by TRIBE-AKI and not from ICES data holdings. All analyses were performed in SAS (version 9.2; SAS Institute, Cary, NC) and R 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria) software.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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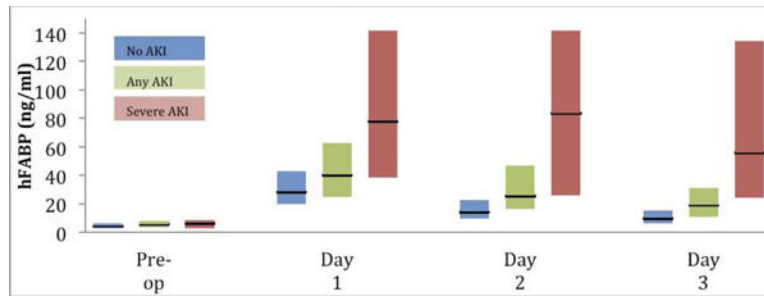


Figure 1. Peri-operative H-FABP Levels by AKI Status

Each bar represents the interquartile range (25th percentile to 75th percentile) and the horizontal black line represents the median. Day 1 represents 0-6 hours after surgery. Day 2 and Day 3 represent 24-48 hours and 48-72 hours, respectively after surgery.

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Table 1

Patient Characteristics by Degree of AKI

Characteristic	No AKI (n=629)	Any AKI (n=330)	Severe AKI (n=37)	Pvalue (No vs. Any)	Pvalue (No vs. Severe)
Demographics					
Age at surgery, mean (SD)	71.3 (10.2)	71.8 (9.5)	70.7 (10.4)	0.480	0.891
Men	417 (66.3%)	238 (72.1%)	27 (73.0%)	0.065	0.402
White race	588 (93.5%)	308 (93.3%)	33 (89.2%)	0.930	0.312
Medical History (time of surgery)					
Diabetes	228 (36.2%)	150 (45.5%)	16 (43.2%)	0.006	0.391
Hypertension	480 (76.3%)	279 (84.5%)	34 (91.9%)	0.003	0.028
Congestive Heart Failure	133 (21.1%)	97 (29.4%)	15 (40.5%)	0.004	0.006
LVEF < 40%	62 (9.9%)	36 (10.9%)	3 (8.1%)	0.609	0.728
Time since myocardial infarction					
7 days	23 (3.7%)	17 (5.2%)	3 (8.1%)	0.592	0.261
7-21 days	23 (3.7%)	14 (4.2%)	0 (0.0%)		
>21 days	112 (17.8%)	58 (17.6%)	8 (21.6%)		
eGFR (mL/min per 1.73 m ²), mean (SD)	69.5 (19.3)	64.4 (19.4)	65.4 (22.9)	<0.001	0.214
Microalbuminuria ²	188 (29.9%)	139 (42.1%)	15 (40.5%)	<0.001	0.500
Surgical Characteristics					
Non-Elective Surgery	102 (16.2%)	85 (25.8%)	10 (27.0%)	<0.001	0.088
Surgery					
CABG or Valve	503 (80.0%)	247 (74.8%)	28 (75.7%)	0.133	0.785
CABG plus Valve	125 (19.9%)	83 (25.2%)	9 (24.3%)		
Off-pump	57 (9.1%)	30 (9.1%)	4 (10.8%)	0.365	0.934
Re-do surgery	14 (2.2%)	4 (1.2%)	1 (2.7%)	0.498	0.536
Perfusion time (minutes), mean (SD)	106.0 (53.0)	124.6 (66.1)	177.4 (101.2)	<0.001	<0.001
Cross-clamp time (minutes), mean (SD)	71.7 (40.2)	86.3 (49.0)	120.9 (67.5)	<0.001	<0.001
Post-operative Complications					
Oliguria in first day, n (%) ³	6 (1.0%)	5 (1.5%)	0 (0.0%)	0.737	0.599
Delta peak serum creatinine (mg/dL), mean (SD)	0.0 (0.1)	0.5 (0.5)	1.3 (0.8)	<0.001	<0.001
# non-renal complications, n(%) ⁴				<0.001	<0.001

Characteristic	No AKI (n=629)	Any AKI (n=330)	Severe AKI (n=37)	Pvalue (No vs. Any)	Pvalue (No vs. Severe)
0	411 (65.3%)	180 (54.5%)	19 (51.4%)		
1-2	184 (29.3%)	104 (31.5%)	6 (16.2%)		
>2	34 (5.4%)	46 (13.9%)	12 (32.4%)		
Ventilator > 48 hours, n(%)	6 (1.0%)	28 (8.5%)	15 (40.5%)	<0.001	<0.001
ICU LOS, median [IQR]	2 (1-3)	2 (1-4)	5 (13-17)	<0.001	<0.001
Hospital LOS, median [IQR]	6 (5-7)	7 (6-10)	17 (8-27)	<0.001	<0.001

Data are presented as the mean (SD), n (%), or median (interquartile range) unless otherwise specified. Any AKI is AKIN Stage 1 or higher. Severe AKI is AKIN Stage 2 or higher. eGFR, estimated GFR; sCr, serum creatinine; LOS, length of stay; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft surgery; H-FABP, plasma heart fatty-acid binding protein. Small cell counts are only presented for data collected by TRIBE-AKI and not from ICES data holdings.

¹To convert serum creatinine values to millimoles per liter, multiply by 88.4.

²Microalbuminuria is defined as a urine albumin to creatinine ratio>30mg/g

³Oliguria is defined as a patient who had less than 125ml or less than 500ml urine output in 6 or 24 hours, respectively.

⁴Non-renal complications are defined as reoperation, infection, neurologic, pulmonary, vascular and other.

Table 2

First Post-operative Cardiac and Renal Biomarkers

Biomarker (median, IQR)	No AKI (n=629)	Any AKI (n=330)	Severe AKI (n=37)	Pvalue ¹ (No vs. Any AKI)	Pvalue (No vs. Severe)
Plasma H-FABP	27.5 (19.5-41.8)	39.6 (25.1-62.1)	77.4 (38.5-141.0)	<0.001	<0.001
Urinary IL-18	10.3 (3.8-29.6)	20.5 (6.3-108.8)	110.1 (31.1-636.0)	<0.001	<0.001
Urinary NGAL	9.0 (3.6-40.6)	15.6 (5.8-102.3)	111.9 (13.5-700.0)	<0.001	<0.001
Urinary KIM-1	0.4 (0.2-0.9)	0.6 (0.2-1.2)	1.0 (0.6-2.5)	<0.001	<0.001
Urinary L-FABP	16.6 (4.0-88.9)	33.4 (6.8-195.2)	72.6 (12.8-400.0)	<0.001	0.001
Serum BNP	47.8 (24.2-103.4)	69.1 (33.9-156.4)	91.5 (53.2-195.2)	<0.001	0.001
Plasma cTnI	1.4 (0.8-2.9)	1.8 (0.9-3.7)	2.7 (1.4-6.9)	0.003	0.001

¹ P-values are calculated from Kruskal-Wallis test.

Any AKI is AKIN Stage 1 or higher. Severe AKI is AKIN Stage 2 or higher. H-FABP, plasma heart fatty acid binding protein; BNP, serum brain-type natriuretic peptide; cTnI, plasma cardiac troponin-I; IL-18, urinary interleukin-18; NGAL, urinary neutrophil gelatinase-associated lipocalin; KIM-1, urinary kidney injury molecule 1; L-FABP, urinary liver fatty-acid binding protein.

Table 3
Correlation Coefficients of First Post-operative H-FABP with Other Kidney and Cardiac Biomarkers

	Urine IL-18	Urine NGAL	Urine KIM-1	Urine LFABP	Plasma cTnI	Serum BNP
Plasma H-FABP	0.28*	0.29*	0.16*	0.31*	0.58*	0.26*
Urine IL-18	...	0.76*	0.58*	0.54*	0.24*	0.13*
Urine NGAL	0.37*	0.61*	0.25*	0.12*
Urine KIM-1	0.11*	0.02	0.19*
Urine LFABP	0.33*	0.04
Plasma cTnI	0.22*

* p-value <0.05

H-FABP, plasma heart fatty-acid binding protein; BNP, serum brain-type natriuretic peptide; cTnI, plasma cardiac troponin-I; IL-18, urinary interleukin-18; NGAL, urinary neutrophil gelatinase-associated lipocalin; KIM-1, urinary kidney injury molecule 1; L-FABP, urinary liver fatty-acid binding protein.

Table 4
Association of Log(H-FABP) with Any AKI

Pre-operative ¹	OR (95% CI)	First Post-Op ²	OR (95% CI)
Log(H-FABP)	2.31 (1.78, 2.99)	Log(H-FABP)	2.27 (1.84, 2.81)
Log(H-FABP)+clinical	2.07 (1.48, 2.89)	Log(H-FABP)+clinical	1.83 (1.41, 2.36)
Log(H-FABP)+clinical + sCr	N/A	Log(H-FABP)+clinical + sCr ³	1.31 (0.97, 1.76)
Log(H-FABP)+clinical+log(IL-18) ⁴	2.09 (1.50, 2.92)	Log(H-FABP)+clinical+ sCr+log(IL-18) ⁴	1.27 (0.94, 1.72)
Log(H-FABP)+clinical+log(NGAL)	2.08 (1.49, 2.90)	Log(H-FABP)+clinical+ sCr+log(NGAL)	1.35 (0.99, 1.82)
Log(H-FABP)+clinical+log(KIM-1)	2.06 (1.47, 2.87)	Log(H-FABP)+clinical+ sCr+log(KIM-1)	1.29 (0.96, 1.74)
Log(H-FABP)+clinical+log(LFABP)	2.04 (1.46, 2.85)	Log(H-FABP)+clinical+ sCr+log(LFABP)	1.30 (0.96, 1.76)
Log(H-FABP)+clinical+log(BNP)	2.01 (1.44, 2.82)	Log(H-FABP)+clinical+ sCr+log(BNP)	1.27 (0.94, 1.71)
Log(H-FABP)+clinical+log(cTnI)	1.98 (1.41, 2.79)	Log(H-FABP)+clinical+ sCr+log(cTnI)	1.71 (1.20, 2.42)

Any AKI is AKIN Stage 1 or higher. Results are shown with continuous log-transformed H-FABP as the predictor variable. All odds ratio expressed as per unit increase in log(H-FABP). H-FABP, plasma heart fatty-acid binding protein; BNP, serum brain-type natriuretic peptide; cTnI, plasma cardiac troponin-I; IL-18, urinary interleukin-18; NGAL, urinary neutrophil gelatinase-associated lipocalin; KIM-1, urinary kidney injury molecule 1; L-FABP, urinary liver fatty-acid binding protein

¹For pre-operative log(H-FABP), the clinical model was adjusted for age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others).

²For first post-operative log(H-FABP), the clinical model was adjusted for age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, pre-op estimated GFR, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others).

³ sCr is change in serum creatinine between pre-operative value and first post-operative value.

⁴ All other biomarkers (IL-18, NGAL, KIM-1, LFABP, cTnI, BNP) are from the same time-point as the H-FABP time-point.

Table 5
Association of Log(H-FABP) with Severe AKI

Pre-operative ¹	OR (95% CI)	First Post-Op ²	OR (95% CI)
Log(H-FABP)	2.12 (1.20, 3.75)	Log(H-FABP)	4.78 (2.90, 7.87)
Log(H-FABP)+clinical	2.13 (0.94, 4.81)	Log(H-FABP)+clinical	5.39 (2.87, 10.11)
Log(H-FABP)+clinical + sCr ³	N/A	Log(H-FABP)+clinical + sCr ³	3.76 (1.91, 7.40)
Log(H-FABP)+clinical+log(IL-18) ⁴	3.98 (2.08, 7.59)	Log(H-FABP)+clinical+ sCr+log(IL-18) ⁴	2.89 (1.44, 5.79)
Log(H-FABP)+clinical+log(NGAL)	2.08 (0.92, 4.70)	Log(H-FABP)+clinical+ sCr+log(NGAL)	3.18 (1.60, 6.32)
Log(H-FABP)+clinical+log(KIM-1)	2.04 (0.89, 4.64)	Log(H-FABP)+clinical+ sCr+log(KIM-1)	3.41 (1.73, 6.71)
Log(H-FABP)+clinical+log(LFABP)	2.04 (0.90, 4.61)	Log(H-FABP)+clinical+ sCr+log(LFABP)	3.60 (1.81, 7.18)
Log(H-FABP)+clinical+log(BNP)	1.94 (0.85, 4.42)	Log(H-FABP)+clinical+ sCr+log(BNP)	3.66 (1.86, 7.21)
Log(H-FABP)+clinical+log(cTnI)	2.07 (0.89, 4.83)	Log(H-FABP)+clinical+ sCr+log(cTnI)	3.95 (1.71, 9.09)

Severe AKI is AKIN Stage 2 or dialysis. Results are shown with continuous log-transformed H-FABP as the predictor variable. All odds ratio expressed as per unit increase in log(H-FABP). H-FABP, plasma heart fatty-acid binding protein; BNP, serum brain-type natriuretic peptide; cTnI, plasma cardiac troponin I; IL-18, urinary interleukin-18; NGAL, urinary neutrophil gelatinase-associated lipocalin; KIM-1, urinary kidney injury molecule 1; L-FABP, urinary liver fatty-acid binding protein.

¹For pre-operative log(H-FABP), the clinical model was adjusted for age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others).

²For first post-operative log(H-FABP), the clinical model was adjusted for age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, pre-op estimated GFR, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others).

³ sCr is change in serum creatinine between pre-operative value and first post-operative value.

⁴ All other biomarkers (IL-18, NGAL, KIM-1, LFABP, cTnI, BNP) are from the same time-point as the H-FABP time-point.

Table 6
Association of Log(H-FABP) with Long-Term Mortality

Pre-operative ¹	HR (95% CI)	First post-op ²	HR (95% CI)
Log(H-FABP)	2.12 (1.60, 2.81)	Log(H-FABP)	1.50 (1.19, 1.89)
Log(H-FABP) + clinical	1.67 (1.17, 2.37)	Log(H-FABP) + clinical	1.27 (1.03, 1.56)
Log(H-FABP) + clinical + sCr	N/A	Log(H-FABP) + clinical + sCr ³	1.21 (0.87, 1.66)
Log(H-FABP)+clinical+log(IL-18) ⁴	1.62 (1.17, 2.23)	Log(H-FABP)+clinical+ sCr+log(IL-18) ⁴	1.17 (0.84, 1.65)
Log(H-FABP)+clinical+log(NGAL)	1.67 (1.17, 2.38)	Log(H-FABP)+clinical+ sCr+log(NGAL)	1.21 (0.86, 1.69)
Log(H-FABP)+clinical+log(KIM-1)	1.65 (1.18, 2.31)	Log(H-FABP)+clinical+ sCr+log(KIM-1)	1.19 (0.84, 1.68)
Log(H-FABP)+clinical+log(L-FABP)	1.68 (1.21, 2.34)	Log(H-FABP)+clinical+ sCr+log(L-FABP)	1.19 (0.86, 1.65)
Log(H-FABP)+clinical+log(BNP)	1.52 (1.10, 2.11)	Log(H-FABP)+clinical+ sCr+log(BNP)	1.16 (0.83, 1.61)
Log(H-FABP)+clinical+log(cTnI)	1.70 (1.29, 2.25)	Log(H-FABP)+clinical+ sCr+log(cTnI)	1.10 (0.79, 1.55)

Results are shown from analysis with continuous, log-transformed as H-FABP as the predictor variable. All hazard ratios expressed per unit increase in log(H-FABP). H-FABP, plasma heart fatty-acid binding protein; BNP, serum brain-type natriuretic peptide; cTnI, plasma cardiac troponin I; IL-18, urinary interleukin-18; NGAL, urinary neutrophil gelatinase-associated lipocalin; KIM-1, urinary kidney injury molecule 1; L-FABP, urinary liver fatty-acid binding protein.

¹For pre-operative log(H-FABP), the clinical model was adjusted for age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others).

²For first post-operative log(H-FABP), the clinical model was adjusted for age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, pre-operative estimated GFR, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others).

³ sCr signifies change in serum creatinine between pre-operative value and first post-operative value.

⁴ All other biomarkers (IL-18, NGAL, KIM-1, LFABP, cTnI, BNP) are from the same time-point as the H-FABP time-point.

Table 7
Area under the ROC Curve and NRI for Pre-operative and First Post-Operative Log(H-FABP)

Pre-operative log(H-FABP)	Any AKI	Severe AKI	Mortality
Area Under ROC (95% CI)			
clinical model ¹	0.69 (0.66, 0.73)	0.76 (0.68, 0.83)	0.74 (0.64, 0.80)
Log(H-FABP)+clinical model	0.71 (0.67, 0.74)	0.78 (0.70, 0.86)	0.75 (0.68, 0.83)
Continuous NRI			
Overall NRI (95% CI)	0.32 (0.19, 0.46)	0.36 (0.02, 0.70)	0.54 (0.21, 0.87)
NRI for events	0.16	0.06	0.00
NRI for non-events	0.16	0.30	0.54
First Post-operative log(H-FABP)			
Area Under ROC (95% CI)			
clinical model ²	0.71 (0.67, 0.74)	0.79 (0.72, 0.86)	0.73 (0.64, 0.80)
Log(H-FABP)+clinical model	0.72 (0.69, 0.76)	0.84 (0.77, 0.92)	0.74 (0.66, 0.81)
Continuous NRI			
Overall NRI (95% CI)	0.24 (0.11, 0.36)	0.87 (0.57, 1.17)	0.39 (0.07, 0.71)
NRI for events	-0.23	0.41	0.03
NRI for non-events	0.47	0.46	0.36

¹Clinical model included age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others)

²Clinical model included for age (per year), sex, white race, cardiopulmonary bypass time > 120 minutes, non-elective surgery, pre-operative estimated GFR, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio, and type of surgery (CABG or valve versus all others).