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Association of Cardiac Biomarkers with Acute Kidney Injury after Cardiac Surgery: A Multicenter Cohort Study

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Abstract

Background—Acute kidney injury (AKI) is common after cardiac surgery and is associated with post-operative mortality. Perioperative cardiac biomarkers may predict AKI and mortality.

Objective—We evaluated whether cardiac biomarkers were associated with severe AKI, defined as a doubling in serum creatinine or requiring renal replacement therapy during hospital stay after surgery, and mortality.

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Disclosures

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Methods—In a prospective multicenter cohort of adults undergoing cardiac surgery, we measured the following biomarkers in pre- and post-operative banked plasma: high-sensitivity troponin T (hs-cTnT), troponin I (cTnI), CK-MB and NT-proBNP.

Results—In the patients who were discharged alive, severe AKI occurred in 37/960 (3.9%) and 43/960 (4.5%) died within 1 year of follow-up. NT-proBNP was the only pre-operative biomarker that was independently associated with severe AKI (with log transformation, adjusted OR=1.4, 95% CI (1.0, 1.9)). Biomarkers measured within 6 hours of surgery (Day 1) were all associated with severe AKI. Pre-operative NT-proBNP was also independently associated with 1-year mortality (with log transformation, adjusted OR=1.7, 95% CI (1.2–2.2)). Patients in the highest tertile for NT-proBNP pre-operatively (>1006.4 ng/L) had marked increases in their risk for 1-year mortality (adjusted OR=27.2, 95%CI (3.5–213.5)). Day 1 NT-proBNP was associated with mortality independently of change in serum creatinine from pre-operative baseline.

Conclusion—Of the studied biomarkers, NT-proBNP was the only pre-operative biomarker independently associated with severe AKI and mortality. Early increases in post-operative cardiac biomarkers were associated with severe AKI after cardiac surgery. Future research should focus on whether interventions that lower NT-proBNP can impact upon post-operative outcomes.

Ultramini-abstract

Acute kidney injury (AKI) is common after cardiac surgery and is associated with post-operative mortality. In a prospective cohort of adults undergoing cardiac surgery, early increases in post-operative cardiac biomarkers were associated with severe AKI after cardiac surgery. Pre-operative NT-proBNP levels were independently associated with post-operative severe AKI and mortality.

Keywords

Biomarkers; Cardiac Surgery; Acute Kidney Injury; Mortality; Troponin; BNP

Introduction

Acute kidney injury (AKI) is a frequent complication after cardiac surgery. In the CORONARY trial, when defined as an increase of 50% or more in baseline serum creatinine, AKI occurs in 21% of patients undergoing cardiac surgery with cardiopulmonary bypass.(1) Dialysis is required in 1–2% of patients undergoing cardiac surgery.(2, 3) The development of post-operative AKI is associated with an increased mortality.(4, 5) Pre-operative and intraoperative risk factors for AKI have been identified and include age, congestive heart failure, proteinuria, longer cardiopulmonary bypass time and post-operative low output state.(3, 5–7) Validated pre-operative risk prediction models for dialysis requiring AKI exist.(8, 9) However, less severe AKI is also associated with morbidity and mortality.(2, 5, 6, 10–12) On an individual patient level, the identification of patients at high risk for AKI could lead to modifications in therapeutic decisions or to a more informed consent before cardiac surgery. For the medical community, it means the possibility of evaluating therapies in a high risk, high response population, thereby increasing the chance to identify potentially promising therapies without large trials. Perioperative cardiac biomarkers, such as CK-MB, cardiac troponin (cTn) and NT-proBNP, are associated with an increased mortality risk after cardiac surgery.(13–15) Higher perioperative NT-proBNP levels have been associated with

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post-operative AKI, independently of EuroSCORE.(16, 17) With the imminent move towards high-sensitivity cardiac troponin assays, the prognostic value of this biomarker needs to be clarified in patients undergoing cardiac surgery.(18) In a prospective multicenter cohort of adults undergoing cardiac surgery, we aimed to evaluate whether pre- and post-operative cardiac biomarkers, including high-sensitivity cardiac troponin T (hs-cTnT), are associated with the development of severe AKI within the hospital stay, 1-year and long-term mortality after cardiac surgery.

Methods

Study design, setting and patient selection

Detailed methods of the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) cardiac surgery cohort (NCT00774137) have been described previously.(19) In summary, following research ethics board approval and informed consent, 1219 patients undergoing cardiac surgery (coronary artery bypass grafting (CABG) or valve) who were at high risk for AKI at six academic medical centers in North America were prospectively enrolled between July 2007 and December 2009. The inclusion and exclusion criteria were designed to capture high-risk patients undergoing cardiac surgery to increase the event rates for AKI. High risk for AKI was defined by the presence of one or more of the following: emergency surgery, preoperative serum creatinine > 2 mg/dl (>177 μmol/L), ejection fraction ≤35% or grade 3 or 4 left ventricular dysfunction, age > 70 years, diabetes mellitus, concomitant CABG and valve surgery, or repeat revascularization surgery. The evaluation of cardiac biomarkers was a pre-specified substudy of the TRIBE-AKI main study. Samples were collected with the a priori defined goal of conducting these analyses.

Clinical and Laboratory Data Collection

Prior to surgery, we recorded demographic and patient history data. Information regarding the surgical procedure was obtained from the medical record using the standardized definitions of the Society of Thoracic Surgeons (STS) data collection tool (www.sts.org).

Following informed consent, samples were collected pre-operatively (less than 60 days before surgery), on day 1 (within 6 hours after surgery), and daily for a maximum of 5 days. The highest measured value was the highest value measured post-operatively. Sample collection was stopped on day 3 in participants transferred out of the intensive care unit (ICU) who did not meet our severe AKI definition. Samples were collected in EDTA tubes, centrifuged to separate plasma and subsequently stored at −80°C.

We obtained vital status after discharge through various mechanisms that allowed complete follow up at one year. For those living in the United States, we phoned to the patients' homes, 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 to acquire vital status. These datasets were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

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Biomarker Measurements

Following one freeze-thaw (storage at −80°C), bioma rker measurements were conducted in batches with an Elecsys 2010 analyzer, Roche Diagnostics for NT-proBNP (**ng/L**) and hs-cTnT (ng/L), and Beckman Coulter's Access II instrument for cTnI (ug/L; AccuTnI assay) and CK-MB (ug/L). The imprecision of the assays were within the manufacturers acceptable range and were as follows: NTproBNP inter-assay quality control (QC) level 1 (n=148, mean= 15.7pmol/L) coefficient of variation (CV)=5% and level 2 (n=147, mean= 4423 ng/L) CV=4%, cTnI inter-assay QC level 1 (n= 165, mean= 0.04ug/L) CV=22% and level 3 (n= 167, mean= 3.2ug/L) CV= 6%, CK-MB inter-assay QC level 1 (n= 164, mean= 3.8ug/L) CV=6% and level 3 (n=169, mean= 69.1ug/L) CV= 4% and hs-cTnT inter-assay QC level 1 (n= 135, mean= 25.8ng/L) CV=10% and QC level 2 (n=134, mean= 1993.3ng/L) CV=3%. Samples were analyzed according to the manufacturer's specifications and laboratory staff were blinded to clinical outcomes. For NTproBNP, the analyzer automatically calculated the concentration in pmol/L; however, to be consistent with the literature preference for this analyte (i.e., mass units) the results were converted to ng/L by the following conversion factor: pmol/L × 8.457 = ng/L. Pre-operative and post-operative serum creatinine was measured as part of routine clinical care in hospital laboratories.

Statistical Analysis

Patient characteristics were compared between groups of patients with and without primary outcomes (severe AKI defined as a doubling in serum creatinine from baseline or requiring renal replacement therapy during hospital stay, and mortality at one year and on long-term follow-up) using two-sample t-test or Wilcoxon-Mann-Whitney rank sum test for continuous variables and chi-squared test for categorical and binary variables. For each biomarker at each time point, we divided the cohort into tertiles to evaluate the association of each specific biomarker at each specific time point with severe AKI and 1-year mortality. After continuous log-transformation of the biomarkers, logistic regression models were used to determine the unadjusted and adjusted odds ratios for severe AKI and 1-year mortality. Cox regression models were used to determine the unadjusted and adjusted hazard ratios for long term mortality (median follow-up of 3 years). Adjustments were made using covariates that predict severe AKI and mortality age (per year), sex, white race, cardiopulmonary bypass (CBP) time > 120 minutes, non-elective surgery, pre-op estimated glomerular filtration rate (eGFR), diabetes, hypertension, center, congestive heart failure (CHF), myocardial infarction (MI), pre-operative urine albumin to creatinine ratio, and type of surgery CABG or valve versus all others)].(5, 6, 8, 9) Each time point was handled as an independent event and analyzed separately.

Receiver operator characteristic (ROC) curves were constructed to find the optimal cut-point of the ROC curve (i.e. the Youden index) for the prediction of severe AKI and 1-year mortality for each biomarker at each time point. We also identified the cut-points corresponding to the lower value of each tertile range.

We stratified the highest measured biomarker values in tertiles and built Kaplan Meier curves in order to visually show the potential association between highest measured biomarker values and long-term mortality.

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All two-sided p-values less than 0.05 were considered statistically significant. Statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, North Carolina). Small cell counts are only presented for data collected by TRIBE-AKI and not from ICES data holdings.

Results

Between July 2007 and December 2009, 1238 eligible patients undergoing cardiac surgery in participating centers consented to participate. Of those, 239 were excluded because samples were insufficient to measure all cardiac biomarkers on three consecutive post-operative days, 19 for various other reasons and 20 additional patients were excluded after they died in hospital (see Figure 1). Of the 960 patients included in our analyses, 37 (3.9%) developed severe AKI, 43 (4.5%) died at 1 year and 104 (10.8%) died on long-term follow-up (Table 1 and Appendix 1). AKI occurred after a median of 3 days (IQR 2–4) after surgery.

Patients who developed severe AKI were more likely to have a history of hypertension and congestive heart failure. They had longer cardiopulmonary bypass and cross clamp times. Congestive heart failure and post-operative severe AKI were significantly more common in patients who died at one year.

Nine patients (0.9%) required acute dialysis (Table 2 and Appendix 2). Non-renal complications occurred more frequently in the patients who developed severe AKI. Mechanical ventilation duration, ICU and hospital stay were longer for the patients with severe AKI and those who died at 1 year and on long-term follow-up.

Both highest measured hs-cTnT and cTnI were on day 2 (Appendix 3) whereas highest measured CK-MB was on day 1 and NT-pro-BNP was at its highest on day 3 (Appendix 3). All post-operative biomarkers were higher in the group that developed severe AKI.

Kaplan-Meier curves showing the association between highest measured biomarkers divided in tertiles and long-term mortality are presented in Appendix 9.

Severe Acute Kidney Injury

Associations of continuous log transformed values of biomarkers at different time peri-operative points with severe AKI are presented in Table 3. NT-proBNP was the only pre-operative biomarker associated with severe AKI and remained statistically significant after adjustment for age, sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, CPB time >120 minutes, pre-op eGFR, and type of surgery. Patients in the highest tertile pre-operatively (NT-proBNP ≥1009.7ng/L) had a more than fourfold increase in severe AKI (adjusted OR=4.5, 95% CI (1.3, 15.1), p = 0.02). First post-operative biomarkers (measured within 6 hours of surgery) including NT-proBNP, hs-cTnT, cTnI and CK-MB were all associated with severe AKI on both univariable and multivariable analyses. On day 1, patients in the third tertile of NT-proBNP (≥ 828.8ng/L) and hs-cTnT (≥591.4 ng/L) had the highest increase in risk of severe AKI (respectively, adjusted OR=4.0, 95%CI (1.2, 13.4),

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p=0.02 and adjusted OR=4.6, 95%CI (1.5, 14.4), p<0.01) (Appendix 4). The highest measured concentrations of these biomarkers were also associated with severe AKI. However, the highest measured concentration occurred concurrently with the occurrence of AKI. Despite their association with severe AKI, the discriminatory properties of the cardiac biomarkers, as assessed by ROC curve analyses, were modest (Appendix 5).

1-Year Mortality

Table 4 presents the association between the biomarkers and 1-year mortality. Pre-operative NT-proBNP and hs-cTnT were associated with 1-year mortality and remained significant after adjustment for age, 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.

Patients in the highest tertile for NT-proBNP (range: > 1009.8ng/ L) and hs-cTnT (range: >19.4 ng/L) pre-operatively had marked increases in their risk for 1-year mortality (respectively, adjusted OR=27.2, 95%CI (3.5, 213.5), p<0.01 and adjusted OR=4.2, 95%CI (1.3, 13.7), p=0.02). Day 1 hs-cTnT and cTnI were associated with mortality univariately but not after adjustment for patient characteristics, surgical factors and change in serum creatinine day 1 from baseline. Day 1 NT-proBNP was associated with 1-year mortality independent of clinical characteristics and change in serum creatinine from pre-operative level. The risk increased with higher NT-proBNP concentrations (Appendix 6): the adjusted OR was 15.1 ((95% CI 1.9, 117.9), p<0.01) in the second tertile (265.6–827.9 ng/L) and 25.7 ((95% CI 3.3, 201.2), p<0.01) in the third tertile (≥828.8 ng/L). Highest measured hs-cTnT and cTnI were not associated with 1-year mortality after adjustment whereas highest measured NT-proBNP remained significantly associated with mortality. Highest measured hs-cTnT and NT-proBNP have similar AUC for predicting 1-year mortality (Appendix 7).

Long-Term Mortality

The median follow-up of the cohort was 3 years (2.2 to 3.5 years). The association between log transformed biomarkers and long-term mortality is presented in Appendix 8. Pre-operative hs-cTnT, CK-MB and NT-proBNP were associated with long-term mortality after multivariable analysis. After surgery, no association between mortality and CK-MB was observed. Day 1 and highest measured values of hs-cTnT and NT-pro-BNP were associated with long-term mortality. For NT-proBNP, the risk increased with higher values at all time points.

Discussion

Key Results

NT-proBNP seems to be the most promising of the studied cardiac biomarkers. Higher pre-operative and day-1 post-operative concentrations of NT-proBNP were associated with an increased risk for severe AKI. Mortality at one year and on long-term follow-up was associated with NT-proBNP concentrations at all time points and was independent of increases in serum creatinine after cardiac surgery. All cardiac biomarkers on day 1 were associated with severe AKI. Pre-operative and highest measured hs-cTnT concentrations

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were associated with 1-year mortality, though after multivariate adjustment only the pre-operative concentration was significant. However, hs-cTnT levels at all time points were independently associated with long-term mortality. cTnI were not associated with 1-year and long-term mortality. CK-MB were not associated with 1-year mortality but the pre-operative level was associated with long-term mortality.

Existing Studies

NT-proBNP is thought to be a predictor of complications after cardiac surgery. A systematic review published in 2012 evaluated the role of pre-operative BNP and NT-proBNP in predicting mortality (4 studies, 1101 patients). The summary AUC was 0.61 (95% CI 0.51, 0.70), suggesting a moderate association.(13) In another observational study of 365 intermediate-risk patients undergoing CABG surgery, pre-operative NT-proBNP was associated with morbidity (including renal failure) and mortality.(16) A prospective cohort including 1,559 patients undergoing on-pump cardiac surgery reported that a post-operative (day 1 and 2) BNP value >790 ng/L was associated with an adjusted HR for mortality of 2.44 (95% CI 1.65–3.62).(17) In that study, post-operative BNP had additional predictive value for 1-year mortality when combined with the logistic EuroSCORE.(17) In another study that included only valvular surgery patients, pre-operative BNP levels were found to be predictive of post-operative inotrope duration (OR=5.9, 95% CI 1.2, 29.68) and ventilation time (OR= 4.7, 95% CI 1.74,17.21).(20) BNP and NT-proBNP levels reflect cardiac filling pressures.(21) These biomarkers therefore provide a surrogate for hemodynamic status, which explains their association with severe AKI and mortality after cardiac surgery. Our results confirm the results of previous smaller studies. However, we have the advantage of a larger sample size that enables adjustment for more variables and greater generalizability. Moreover, the simultaneous measurement of CK-MB, cTnI, hs360 cTnT and NT-proBNP allows head to head comparisons between these biomarkers.

The type of procedure performed and the cross-clamp time affect post-operative CK-MB and cTnI release(22) and have both been shown to predict both AKI and 1-year mortality.(5) Therefore, the association of day 1 biomarkers with severe AKI does not come as a surprise. However, the absence of association between the widely used biomarkers (CK-MB and cTnI) and mortality warrants further discussion. Arbitrarily, a cardiac biomarker value > 10 times the upper limit of normal is used in the Third Universal definition of myocardial infarction for patients who have undergone CABG surgery.(23) A clinically relevant post cardiac surgery myocardial infarction definition should be associated with increased mortality and morbidity. It is of concern that the biomarkers that are currently available in most centers failed to predict 1-year and long-term mortality. The exclusion of patients with very early mortality and the adjustment for other known risk factors might explain this unexpected finding. The inclusion of patients who underwent isolated valvular or aortic procedures could also be in cause. A recent study of patients who underwent isolated valvular surgery found no association between CK-MB and cTnI and short-term morbidity. (20)

Often, clinicians use high-sensitivity cardiac troponin assays interchangeably with sensitive cardiac troponin assays. However, these biomarkers behaved differently in our study. Pre-

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operative hs-cTnT was associated with 1-year and long-term mortality, whereas cTnI was not. The increased analytical sensitivity of these assays accounts for their capacity to identify high risk patients and their predictive value in cardiac surgery mirrors what was seen in other non acute coronary syndrome populations. (21–25) Interestingly, the cut-point for highest measured hs-cTnT identified on our ROC curve for 1-year mortality was approximately 40 times the upper limit of normal (i.e., 40 × 99th percentile) suggesting the currently used MI definition (10 × 99th percentile) may fail to identify patients at higher mortality risk. The transition towards hs-cTn assays means that understanding their perioperative predictive value is crucial. The VISION (Vascular events In Surgery patIents cOhort evaluatioN) Cardiac Surgery Study (NCT01842568), a 15,000-patient cohort that is currently recruiting will inform on the predictors of complications after cardiac surgery, including hs-cTn.

Strengths and Limitations

The included patients are representative of a high-risk North American cardiac surgery population. We minimized the variation in biomarker measurement by centralizing the analyses. This study is the largest prospective cohort evaluating the association of multiple pre and post-operative cardiac biomarkers with severe AKI and mortality in cardiac surgery. However, despite including high-risk patients, relatively few events occurred and our model might be over-fitted. The exclusion of patients needing emergent surgery may have contributed to the low event rate. It would be interesting to evaluate the association of cardiac biomarkers with other cardiovascular events in order to increase the power and number of possible analyses. Moreover, patients may see stroke and myocardial infarction, given the associated morbidity, as being more important than a doubling in serum creatinine. Combining a doubling in serum creatinine with the need for acute dialysis may be questioned but aims to use the RIFLE criteria for injury while accounting for patients needing temporary renal replacement therapy.(24) The association of cardiac biomarkers with in-hospital mortality, probably the highest risk group, also warrants further research.

Future Directions

The integration of biomarkers to pre-operative risk prediction tools could refine their predictive value and help patients and clinicians weight the surgical procedure associated risks and benefits. Given the proven benefit to BNP-guided therapy in congestive heart failure,(25, 26) NT-proBNP modulation to prevent post-operative AKI and mortality warrants further investigation.

Conclusions

NT-proBNP is the most promising of the biomarkers we studied for the prediction of post-operative severe AKI and mortality. The commonly used CK-MB and cTnI did not appear to provide prognostic information in addition to clinical characteristics, while pre-operative hs-cTn did have prognostic utility for mortality beyond such parameters. Widespread update of hs-cTn should help physicians better inform patients and their families of risk.

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List of abbreviations

AKI	Acute kidney injury
CABG	Coronary artery bypass grafting
CHF	Congestive heart failure
CK-MB	Creatinine kinase-MB
CBP	Cardiopulmonary bypass
CV	Coefficient of variation
cTnI	Troponin I
eGFR	Estimated glomerular filtration rate
hs-cTnT	High-sensitivity troponin T
ICES	Institute for Clinical Evaluative Sciences
ICU	Intensive care unit
MI	Myocardial infarction
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OR	Odds ratio

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QC	Quality control
ROC	Receiver operator characteristic
STS	Society of Thoracic Surgeons
TRIBE-AKI	Translational Research Investigating Biomarker Endpoints in AKI
VISION	Vascular events In Surgery patIents cOhort evaluatioN

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Appendix 1

Baseline Patient Characteristics by 1-Year Mortality

Characteristics	Dead at 1 year	Alive at 1 year	P-value
N (%)	43 (4.5)	917 (95.5)	
Age, (years) mean (SD)	74 (10)	71 (10)	0.1
Male, n (%)	29 (67.4)	626 (68.3)	0.9

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Characteristics	Dead at 1 year	Alive at 1 year	P-value
Caucasian, n (%)	39 (90.7)	858 (93.6)	0.5
Previous history, n (%)			
Diabetes	20 (46.5)	359 (39.1)	0.3
Hypertension	36 (83.7)	723 (78.8)	0.4
Congestive Heart Failure	18 (41.9)	212 (23.1)	0.005
LVEF<40%	5 (11.6)	93 (10.1)	0.8
eGFR, n (%)			
>60 mL/min per 1.73 m^2	25 (58.1)	608 (66.3)	0.3
30–60 mL/min per 1.73 m^2	15 (34.9)	281 (30.6)	
< 30 mL/min per 1.73 m2	3 (7.0)	28 (3.1)	
Urine albumin/creatinine, n (%)			
<10	5 (11.6)	331 (36.1)	0.01
10–30	19 (44.2)	266 (29.0)	
30–300	13 (30.2)	254 (27.7)	
>300	5 (11.6)	56 (6.1)	
Non-elective surgery, n (%)	8 (18.6)	179 (19.5)	0.9
Surgery, n (%)			
Isolated CABG or valve	15 (34.9)	193 (21.0)	0.1
CABG + valve	28 (65.1)	724 (78.0)	
Off-pump surgery, n (%)	3 (7.0)	84 (9.2)	0.5
Re-do surgery, n (%)	0 (0.0)	18 (2)	0.4
CBP time (minutes), mean (SD)	138 (56)	111 (58)	0.004
Cross-clamp time (minutes), mean (SD)	99 (46)	76 (44)	<0.001

Appendix 2

Post-Operative Complications During Hospitalization for Cardiac Surgery by 1-Year Mortality

Complications	Dead at 1 year	Alive at 1 year	P-value
Clinical AKI, n (%)			
Increase > 50% or >0.3 mg/dL	20 (46.5)	310 (33.8)	0.09
Acute dialysis	2 (4.7)	7 (0.8)	0.01
Non-renal complications, n (%)			

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Complications	Dead at 1 year	Alive at 1 year	P-value
none	20 (46.5)	571 (62.3)	0.02
1 or 2	15 (34.9)	274 (29.9)	
>2	8 (18.6)	72 (7.9)	
Oliguria on post-operative day 1, n (%)	0 (0.0)	11 (1.2)	0.5
Mechanical ventilation > 48 hours, n (%)	4 (9.3)	30 (3.3)	0.04
ICU length of stay **(days)**, median (IQR)	4 (2–5)	2 (1–3)	<0.001
Hospital length of stay **(days)**, median (IQR)	8 (6–13)	6 (5–8)	<0.001

Appendix 3

Boxplots of the Peri-operative Cardiac Biomarkers According to Severe AKI

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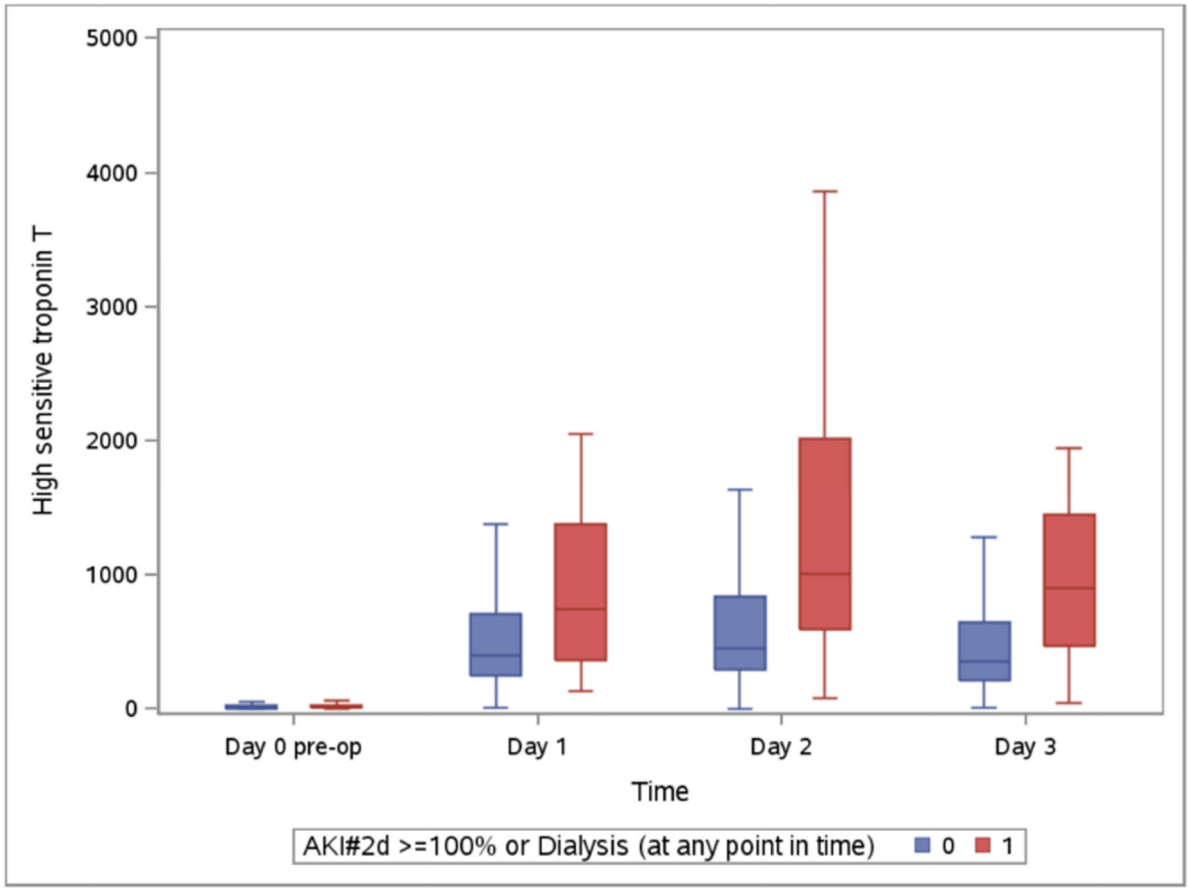
A. hs-cTnT



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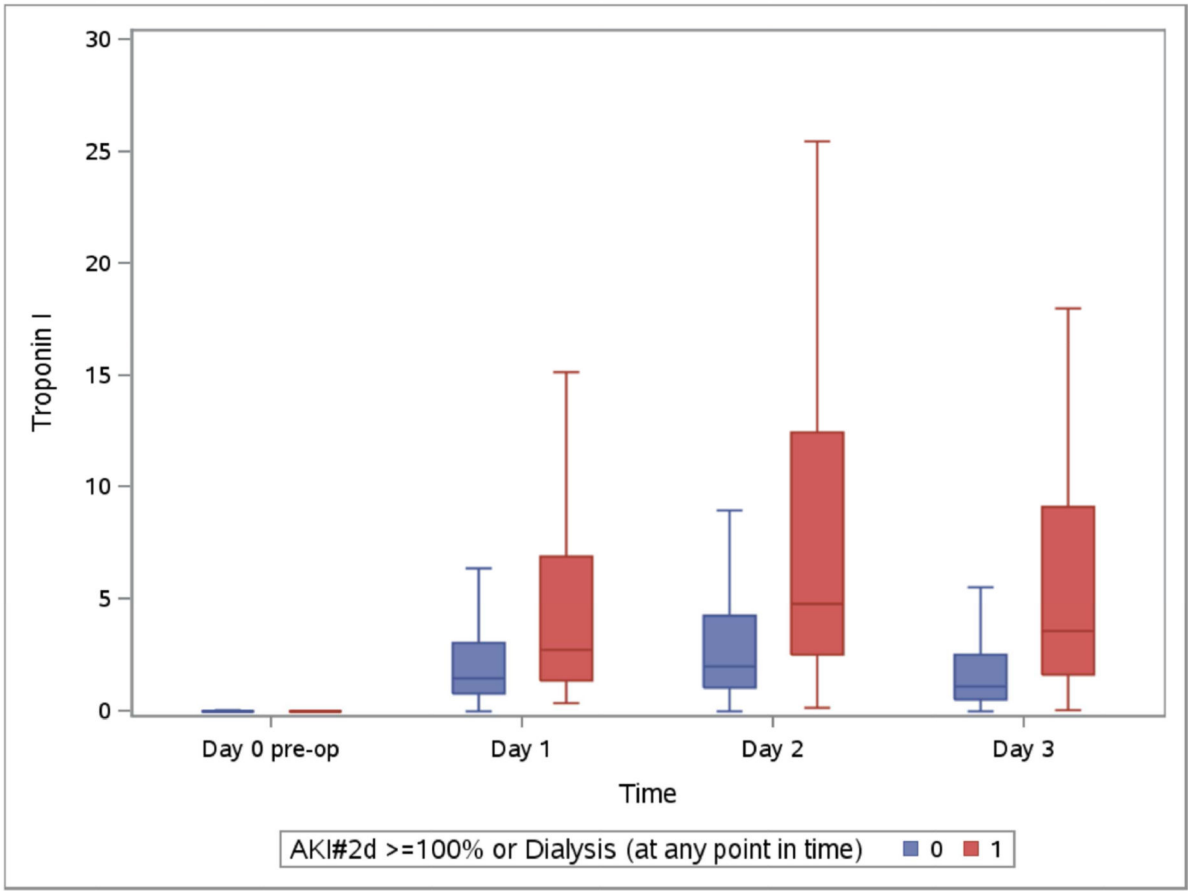
B. cTnI



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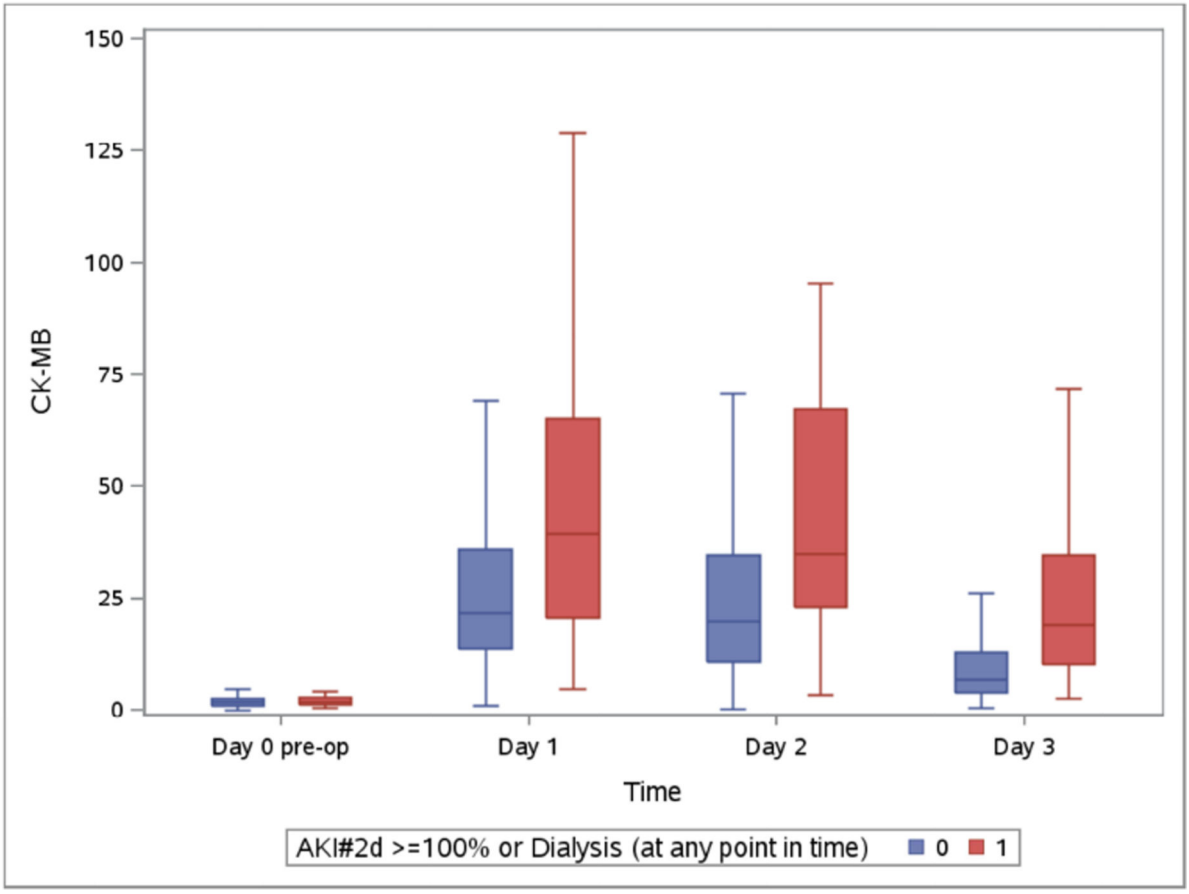
C. CK-MB



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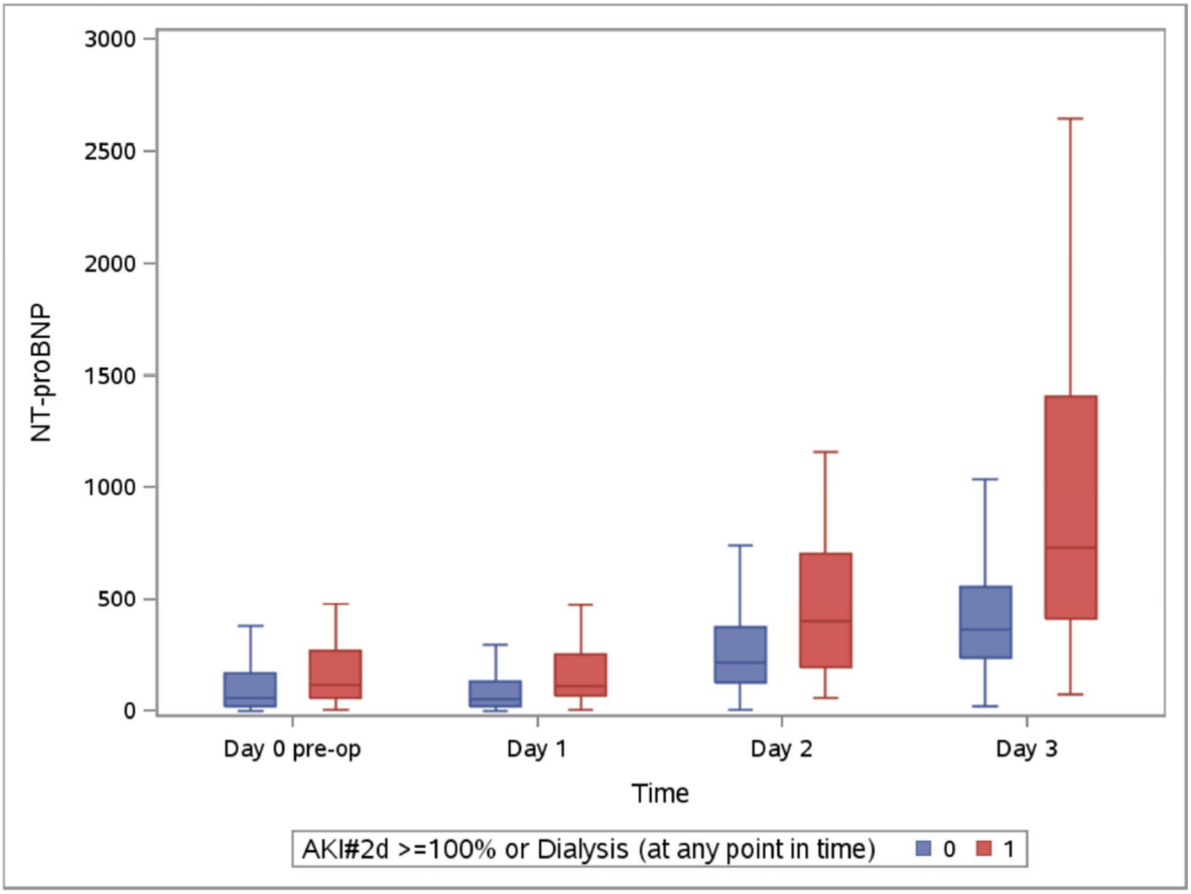

The patients who developed the events are represented in blue. The patients free events are in green. Day 1 samples were collected within 6 hours of surgery. Horizontal line is the median, box encourages the 25th to 75th percentile.

Appendix 4

Biomarkers as Predictors of Severe AKI Divided by Tertiles

	Time point	Tertile	Range	Adjusted OR* (95% CI)	p-value
hs-cTnT (ng/L)	Pre-op	T1	3.0 – 7.9	1.0	
		T2	8–19.3	0.93 (0.36, 2.41)	0.9
		T3	>19.4	1.54 (0.60, 3.99)	0.4
	Day 1	T1	8.0–291.0	1.0	
		T2	291.1–588.0	1.67 (0.51, 5.45)	0.4
		T3	>591.0	4.57 (1.46, 14.36)	0.009

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	Time point	Tertile	Range	Adjusted OR* (95% CI)	p-value
NT-proBNP (ng/L)	Pre-op	T1	6.77–287.5	1.0	
		T2	288.4 – 1006.4	4.13 (1.30, 13.06)	0.02
		T3	>1007.2	4.48 (1.33, 15.07)	0.02
	Day 1	T1	15.2–264.7	1.0	
		T2	265.6–827.9	2.52 (0.77, 8.28)	0.1
		T3	≥828.8	4.02 (1.21, 13.38)	0.02

*Adjusted for Age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, and type of surgery

Appendix 5

Association Between Biomarkers and Severe Acute Kidney Injury

Biomarkers	Time point	n	AUC (SE)	cut point	Sensitivity	Specificity
hs-cTnT (ng/L)	Day 1	949	0.68 (0.05)	714.4	0.59	0.8
cTnI (ug/L)	Day 1	959	0.65 (0.05)	1.8	0.70	0.6
CK-MB (ug/L)	Pre-op	958	0.57 (0.05)	1.9	0.59	0.5
	Day 1	959	0.67 (0.05)	39.5	0.51	0.8
NT-proBNP (ng/L)	Pre-op	931	0.64 (0.04)	504.0	0.78	0.5
	Day 1	947	0.68 (0.04)	556.5	0.81	0.6

AUC: Area Under the Receiver Operative Curve
Pre-op: Pre-operative
SE: Standard Error
hs-cTnT: High sensitive troponin T
cTnI: Troponin I

Appendix 6

Biomarkers as Predictors of 1-Year Mortality Divided by Tertiles

	Time point	Tertile	Range	OR* (95% CI)	p-value
h-cTnT (ng/L)	Pre-op	T1	3.0–7.9	1.0	
		T2	8.0–19.3	3.78 (1.21, 11.77)	0.02
		T3	>19.4	4.18 (1.27, 13.74)	0.02
	Day 1	T1	8.0–290.8	1.0	
		T2	291.1–587.8	1.04 (0.40, 2.68)	0.9
		T3	≥591.4	1.66 (0.62, 4.42)	0.3

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	Time point	Tertile	Range	OR* (95% CI)	p-value
	Highest measured	T1	9.1–393.7	1.0	
		T2	393.9–802.6	2.23 (0.76, 6.52)	0.1
		T3	>804	2.95 (0.96, 9.06)	0.1
NT-proBNP (ng/L)	Pre-op	T1	6.8–287.5	1.0	
		T2	288.4–1006.4	15.24 (1.95, 118.91)	0.009
		T3	≥1009.8	27.20 (3.46, 213.50)	0.002
	Day 1	T1	15.2–264.7	1.0	
		T2	265.6–827.9	15.10 (1.93, 117.94)	0.01
		T3	≥828.8	25.74 (3.29, 201.18)	0.002
	Highest measured	T1	70.2–2462.7	1.0	
		T2	2468.6–4260.6	9.83 (2.18, 44.24)	0.003
		T3	≥8263.2	11.68 (2.50, 54.55)	0.002

*For pre-op biomarkers: Adjusted for Age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, and type of surgery

For day 1 and highest measured biomarkers: Adjusted for Age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, and type of surgery and change in serum creatinine day 1 0–6 hours from pre-op.

Appendix 7

Association Between Biomarkers and 1-Year Mortality

	Time point	n	AUC (SE)	cut point	Sensitivity	Specificity
hs-cTnT (ng/L)	Pre-op	928	0.64 (0.04)	9.0	0.88	0.39
	Day 1	949	0.59 (0.05)	912.6	0.38	0.82
	Highest measured	952	0.64 (0.04)	542.9	0.74	0.51
cTnI (ug/L)	Pre-op	956	0.59 (0.04)	<0.01	0.64	0.53
	Day 1	959	0.59 (0.05)	5.0	0.35	0.85
	Highest measured	959	0.63 (0.04)	4.9	0.49	0.74
CK-MB (ug/L)	Pre-op	958	0.51 (0.04)	3.2	0.98	0.17
	Day 1	959	0.55 (0.05)	38.3	0.40	0.77
NT-proBNP (ng/L)	Pre-op	931	0.72 (0.03)	843.6	0.81	0.56
	Day 1	947	0.71 (0.03)	751.8	0.71	0.64
	Highest measured	956	0.68 (0.04)	2940.5	0.84	0.47

AUC: Area Under the Receiver Operative Curve
SE: Standard Error
Pre-op: Pre-operative

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hs-cTnT: High sensitive troponin T
cTnI: Troponin I

Appendix 8

Log Transformed Biomarkers as Predictors of Long-Term Mortality, Median Follow-up of 3 Years

	Time point	HR* (95% CI)
hs-cTnT	Pre-op	1.31 (1.14, 1.51)
	Day 1	1.28 (1.03, 1.58)
	Highest measured	1.25 (1.05, 1.47)
cTnI	Pre-op	1.04 (0.9, 1.21)
	Day 1	1.14 (0.98, 1.31)
	Highest measured	1.12 (0.96, 1.32)
CK-MB	Pre-op	1.17 (1.02, 1.33)
	Day 1	1.1 (0.91, 1.32)
	Highest measured	1.02 (0.84, 1.23)
NT-proBNP	Pre-op	1.44 (1.30, 1.59)
	Day 1	1.37 (1.26, 1.49)
	Highest measured	1.93 (1.42, 2.62)

HR: Hazard Ratio
CI: Confidence Interval
Pre-op: Pre-operative
hs-cTnT: High sensitive troponin T
cTnI: Troponin I
*For pre-op biomarkers: Adjusted for Age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, and type of surgery

For day 1 and highest measured biomarkers : Adjusted for Age (per year), sex, white race, non-elective surgery, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, and type of surgery and change in serum creatinine day 1 0–6 hours from pre-op.

Appendix 9

Kaplan-Meier Curve – Association between highest measured hs-cTnT tertiles and long-term mortality

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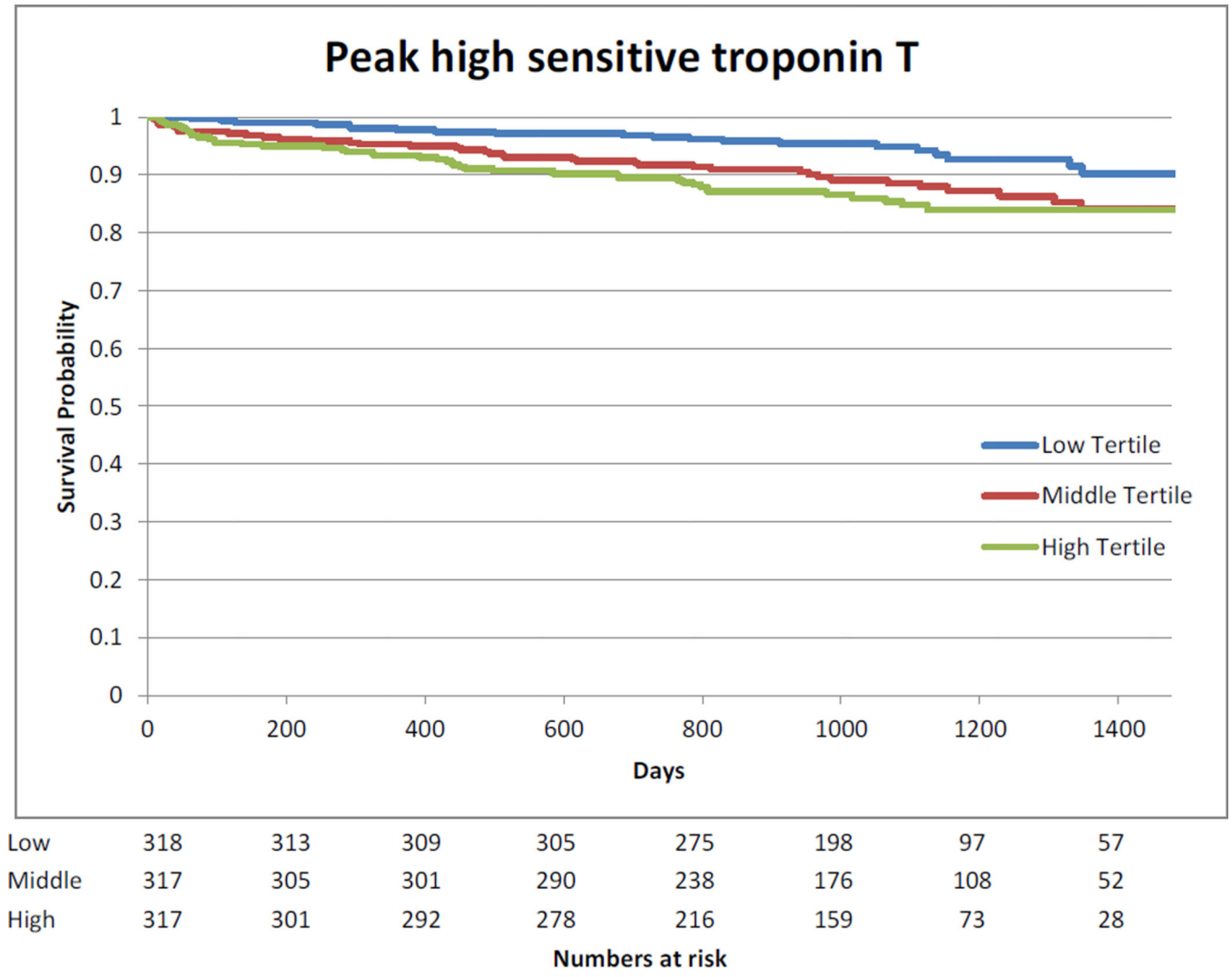

Kaplan-Meier Curve – Association between highest measured cTnI tertiles and long-term mortality

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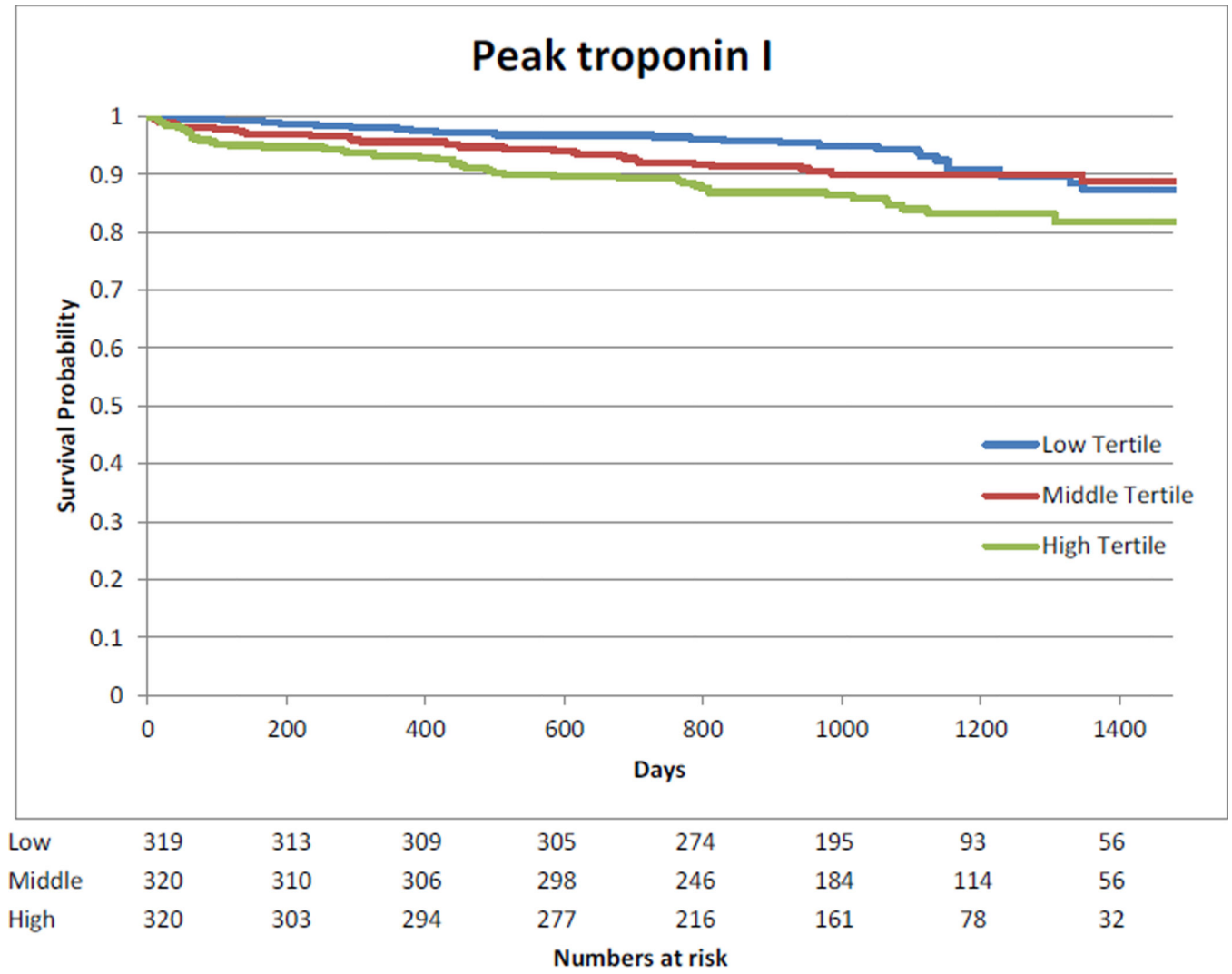

Kaplan-Meier Curve – Association between highest measured CK-MB tertiles and long-term mortality

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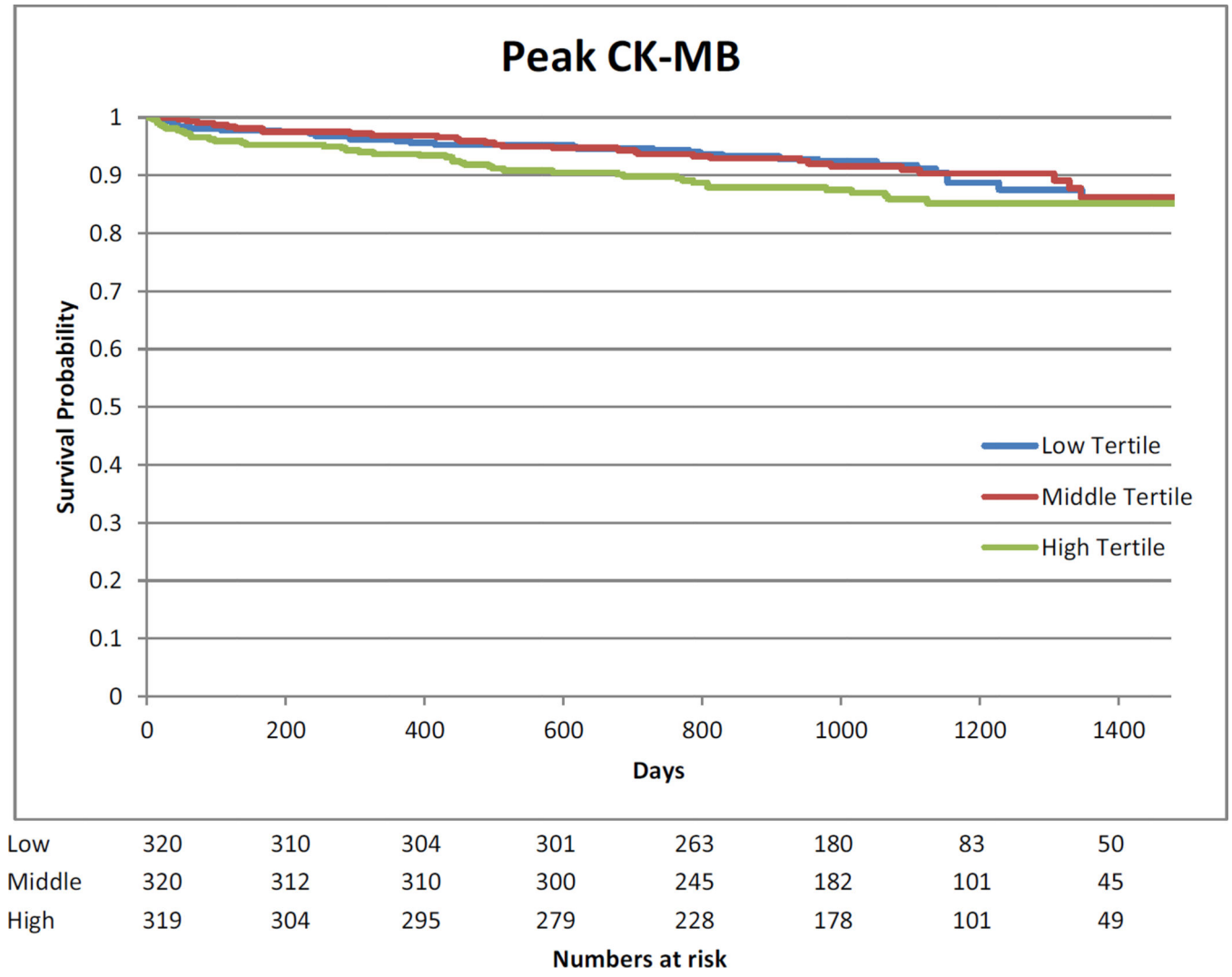

Kaplan-Meier Curve – Association between highest measured NT-proBNP tertiles and long-term mortality

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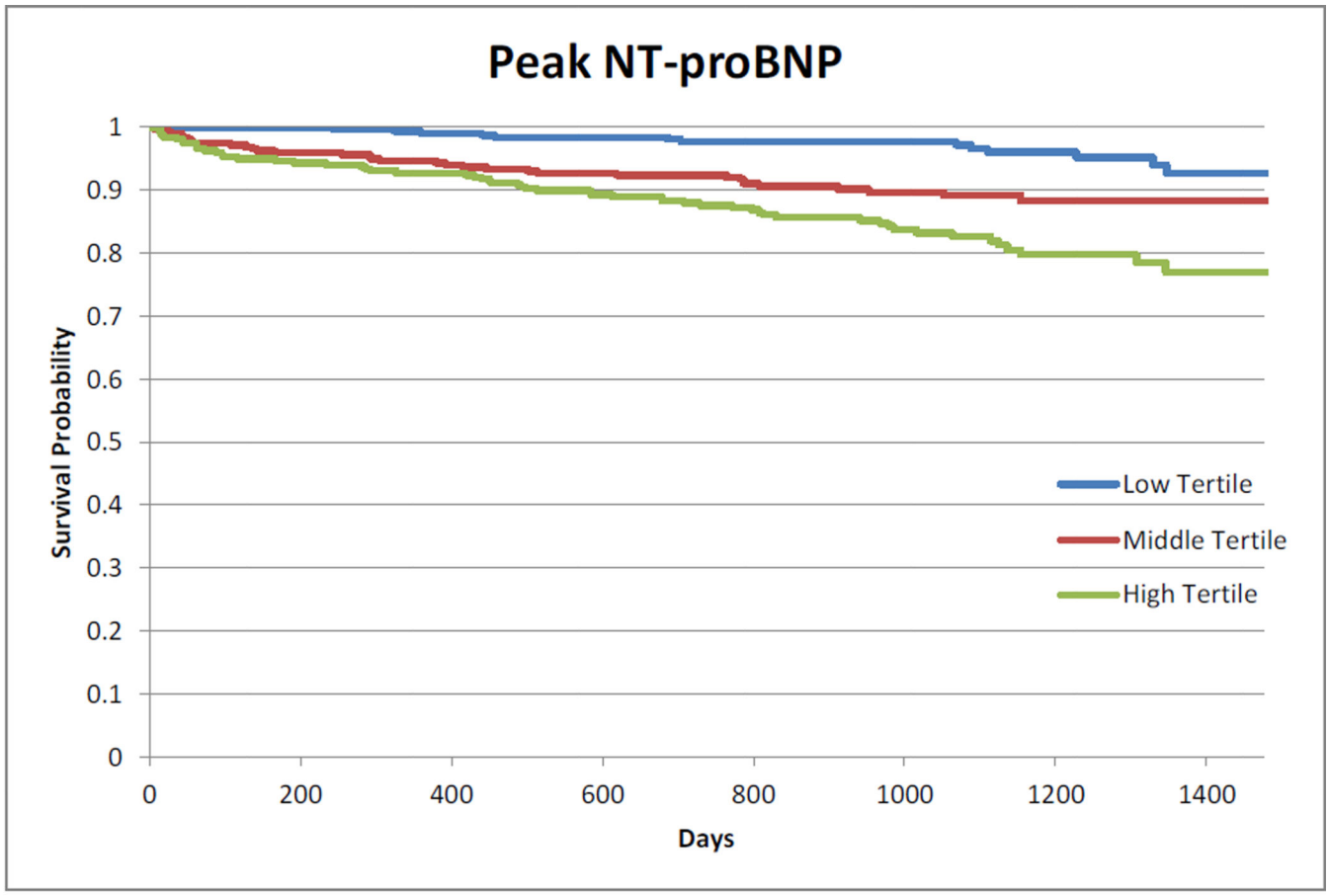

Low	318	318	315	309	261	196	110	57
Middle	319	305	296	290	248	181	88	44
High	319	300	295	278	224	160	84	41

Numbers at risk

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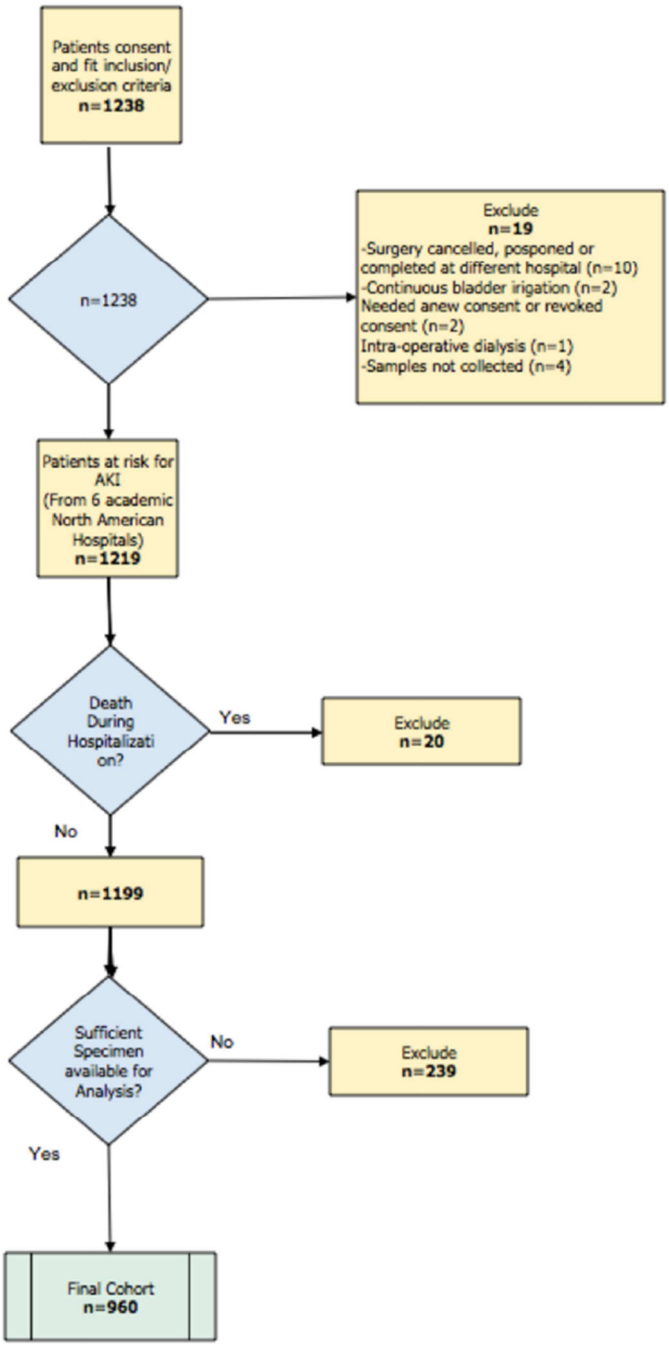

Figure 1.
Study Flow Diagram

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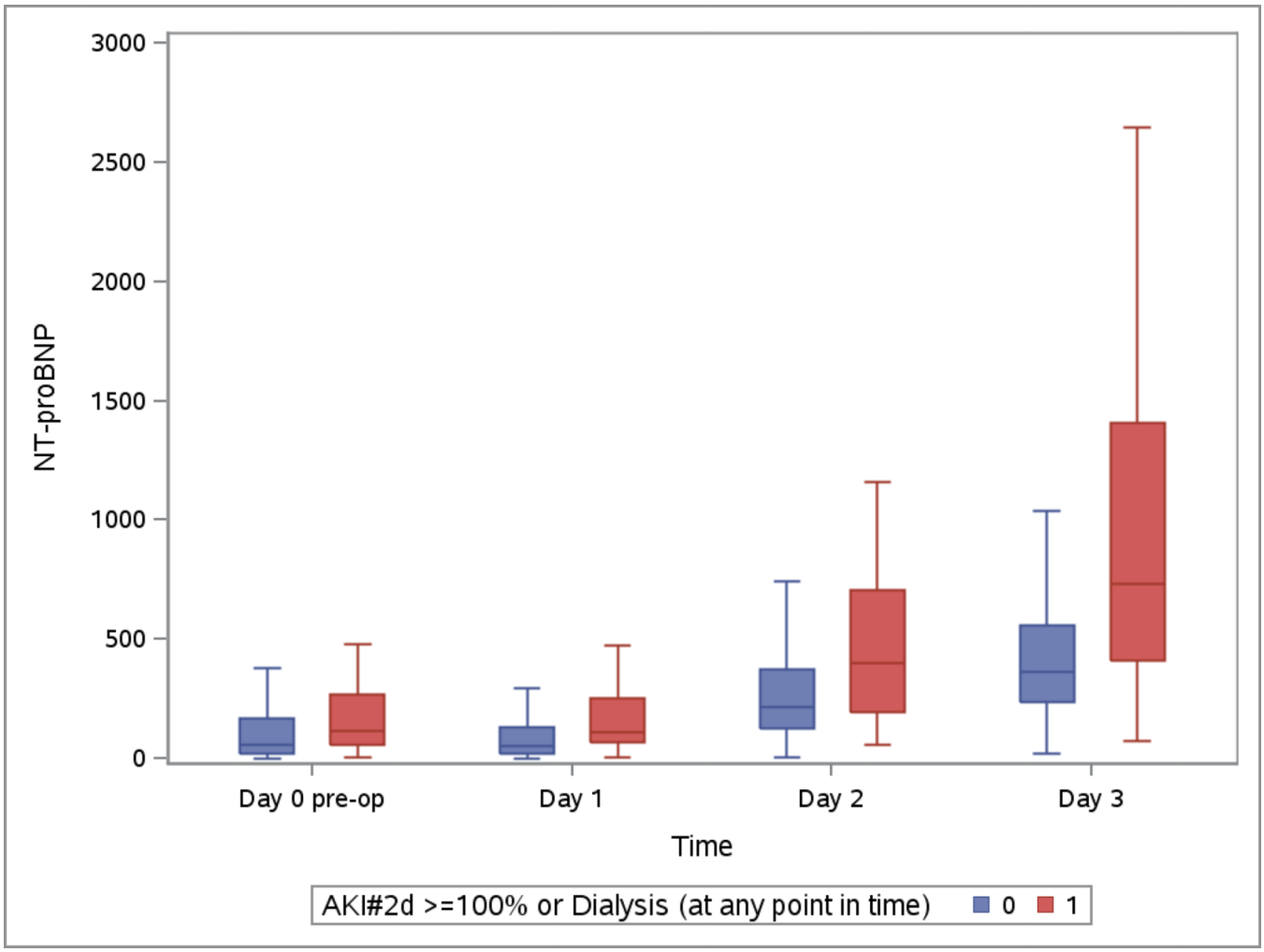

Figure 2.

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Table 1

Baseline Patient Characteristics by Severe AKI

Characteristics	Severe AKI	No Severe AKI	P-value
N (%)	37 (3.9)	923 (96.1)	
Age, (years) mean (SD)	70.7 (10.4)	71.53 (10)	0.6
Male, n (%)	27 (73)	628 (68)	0.5
Caucasian, n (%)	33 (89.2)	864 (93.6)	0.3
Previous history, n (%)			
Diabetes	16 (43.2)	363 (39.3)	0.6
Hypertension	34 (91.9)	725 (78.5)	0.05
Congestive Heart Failure	15(40.5)	215 (23.3)	0.02
LVEF<40%	3 (8.1)	95 (10.3)	0.7
eGFR, n (%)			
>60 mL/min per 1.73 m^2	22 (59.5)	611 (66.2)	0.2
30–60 mL/min per 1.73 m^2	12 (32.4)	284 (30.8)	
< 30 mL/min per 1.73 m^2	3 (8.1)	28 (3)	
Urine albumin/creatinine, n (%)			
<10	10 (27)	326 (35.3)	0.8
10–30	12 (32.4)	273 (29.6)	
30–300	12 (32.4)	255 (27.6)	
>300	3 (8.1)	58 (6.3)	
Non-elective surgery, n (%)	10 (27)	177 (19.2)	0.2
Surgery, n (%)			
Isolated CABG or valve	28 (75.7)	724 (78.4)	0.7
CABG + valve	9 (24.3)	199 (21.6)	0.9
Off-pump surgery, n (%)	4 (10.8)	83 (9.0)	0.9
Re-do surgery, n (%)	1 (2.7)	17 (1.8)	0.5
CBP time (minutes), mean (SD)	177 (101)	110 (55)	<0.001
Cross-clamp time (minutes), mean (SD)	121(67)	75 (42)	<0.001

n: Number
SD: Standard Deviation
CPB: Cardiopulmonary Bypass
LVEF: Left Ventricular Ejection Fraction
eGFR: Estimated Glomerular Filtration Rate
CABG: Coronary Artery Bypass Graft

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Table 2

Post-Operative Complications During Hospitalization for Cardiac Surgery by Severe AKI

Complications	**Severe AKI**	**No Severe AKI**	**P-value**
Clinical AKI, n (%)			
Increase > 50% or >0.3 mg/dL	37 (100.0)	293 (31.7)	<0.001
Acute dialysis	9 (24.3)	0 (0.0)	<0.001
Non-renal complications, n (%)			
none	19 (51.4)	572 (62.0)	<0.001
1 or 2	6 (16.2)	283 (30.7)	
>2	12 (32.4)	68 (7.4)	
Oliguria on post-operative day 1, n (%)	0 (0.0)	11 (1.2)	0.6
Mechanical ventilation > 48 hours, n (%)	15 (40.5)	19 (2.1)	<0.001
ICU length of stay **(days)**, median (IQR)	5 (3–17)	2 (1–3)	<0.001
Hospital length of stay **(days)**, median (IQR)	17 (8–27)	6 (5–8)	<0.001

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Table 3

Log Transformed Biomarkers and Association With Severe Acute Kidney Injury

	Time point	n	Unadjusted OR (95% CI)	P-value	Adjusted OR* (95% CI)	P-value
hs-cTnT	Pre-op	928	1.11 (0.88, 1.40)	0.3671	1.17 (0.84, 1.61)	0.4
	Day 1	949	1.96 (1.40, 2.75)	<0.0001	2.10 (1.32, 3.34)	0.002
cTnI	Pre-op	956	1.10 (0.88, 1.37)	0.4185	1.22 (0.92, 1.63)	0.2
	Day 1	959	1.56 (1.20, 2.02)	0.0009	1.59 (1.10, 2.28)	<0.0001
CK-MB	Pre-op	958	1.44 (0.95, 2.19)	0.0862	1.55 (0.94, 2.58)	0.1
	Day 1	959	2.09 (1.42, 3.06)	0.0002	2.19 (1.31, 3.66)	0.003
NT-ProBNP	Pre-op	931	1.37 (1.08, 1.74)	0.0113	1.39 (1.03, 1.88)	0.03
	Day 1	947	1.54 (1.19, 2.00)	0.0009	1.46 (1.05, 2.03)	0.02

OR: Odds Ratio
CI: Confidence Interval
Pre-op: Pre-operative
hs-cTnT: High sensitive troponin T
cTnI: Troponin I
Day 1 samples were collected within 6 hours of surgery

*Adjusted for age, sex, white race, CPB time > 120 minutes, non-elective surgery, pre-op eGFR, diabetes, hypertension, center, congestive heart failure, myocardial infarction, pre-operative urine albumin to creatinine ratio and type of surgery.

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Table 4

Log Transformed Biomarkers as Predictors of 1-Year Mortality

	Time point	n	OR (95% CI)	P-value	OR* (95% CI)	P-value
hs-cTnT	Pre-op	928	1.30 (1.08, 1.58)	0.0065		
	Day 1	949	1.45 (1.05, 2.01)	0.023	1.38 (0.90, 2.12)	0.1
	Highest measured	952	1.64 (1.18, 2.28)	0.0035	1.50 (0.98, 2.29)	0.1
cTnI	Pre-op	956	1.16 (0.96, 1.41)	0.1285		
	Day 1	959	1.30 (1.02, 1.67)	0.0353	1.25 (0.89, 1.74)	0.2
	Highest measured	959	1.43 (1.11, 1.85)	0.006	1.29 (0.93, 1.79)	0.1
CK-MB	Pre-op	958	0.92 (0.58, 1.47)	0.7305		
	Day 1	959	1.24 (0.87, 1.78)	0.2405	1.11 (0.71, 1.75)	0.7
	Highest measured	959	1.19 (0.82, 1.73)	0.3499	1.01 (0.64, 1.59)	1
NT-proBNP	Pre-op	931	1.70 (1.35, 2.14)	<0.0001		
	Day 1	947	1.68 (1.32, 2.14)	<0.0001	1.65 (1.21, 2.23)	0.001
	Highest measured	956	1.99 (1.37, 2.88)	0.0003	1.99 (1.22, 3.26)	0.006

OR: Odds Ratio
CI: Confidence Interval
Pre-op: Pre-operative
hs-cTnT: High sensitive troponin T
cTnI: Troponin I

*Adjusted for age, sex, white race, CPB time > 120 minutes, non-elective surgery, pre-op eGFR, diabetes, hypertension, centre, congestive heart failure, myocardial infarction, pre-operative urine albumin and change in creatinine from baseline.

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