SUPPLEMENTARY MATERIAL

**Use of minimally invasive surgery and therapies mitigating pulmonary arterial pressure and intraoperative blood loss may offer protection against cardiac surgery-associated acute kidney injury**

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This supplementary material has been provided by the authors to give readers additional information about their work.

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# SUPPLEMENTAL METHODS

## Study design

Heart failure was diagnosed according to current guidelines [11]. The following criteria were applied: i) minimum one symptom typical of heart failure: positive physical examination (e.g., bilateral edema, increased jugular pressure) or positive clinical history (e.g., orthopnea, history of coronary vascular disease, history of arterial hypertension, exposition to cardiotoxic drug/radiation, diuretic use); b-type natriuretic peptide (BNP) levels ≥35 pg/mL; and iii) classification as New York Heart Association (NYHA) functional class 2 or 3. There was no prespecified inclusion criterion with respect to left ventricular ejection fraction. In case of left ventricular ejection fraction (LVEF) equal or greater than 50 %, an additional functional (E/e′ ≥13 and a mean e’ septal and lateral wall <9 cm/s) abnormality was required.

# ONLINE FIGURES



|  |  |
| --- | --- |
|  |  |

## Figure S1: Receiver operating characteristic curves of preoperative, intraoperative, and combined pre- and intraoperative variables for detection of cardiac surgery-associated acute kidney injury

Receiver operating characteristic analyses showed that preoperative variables predicted AKI with an AUC of 0.688 (Akaike information criterion = 475.27; goodness of fit p = 0.707; correctly classified 80.81%; sensitivity 15.53%; specificity 97.96%) **(a)**, and intraoperative variables predicted AKI with an AUC of 0.7575 (Akaike information criterion = 446.08; goodness of fit p = 0.038; correctly classified 80.40%; sensitivity 21.36%; specificity 95.92%) **(b)**, while combined pre- and intraoperative variables predicted AKI with an AUC of 0.7652 (Akaike information criterion = 445.69; goodness of fit p = 0.0305; correctly classified 80.81%; sensitivity 22.33%; specificity 96.17%) **(c)**. Diagonal segments are produced by ties.

AKI = acute kidney injury; AUC = area under the curve.

# ONLINE TABLES

## *Table S1: Additional data on patient characteristics*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** **(n = 495)** | **Non-AKI group**†**(n = 392)** | **AKI group**†**(n = 103)** | **p-value\*** |
| **Comorbidities** |  |  |  |  |
| Chronic obstructive pulmonary disease [yes] | 35 (7.1%) | 23 (5.9%) | 12 (11.7%) | 0.0421 |
| Previous cardiac surgery [yes] | 22 (4.4%) | 16 (4.1%) | 6 (5.8%) | 0.234 |
| **Baseline clinical data** |  |  |  |  |
| Sodium (mmol/L) | 141±2 | 141.2±2.2 | 141.11±2.3 | 0.752 |
| Potassium (mmol/L) | 3.9±0.3 | 3.95±0.3 | 3.95±0.3 | 0.6680 |
| **Surgical clinical data** |  |  |  |  |
| Urgency |  |  |  |  |
|  *Elective* | 399 (80.6%) | 315 (80.4%) | 84 (81.6%) | 0.76 |
|  *Urgent* | 56 (11.3%) | 45 (11.5%) | 11 (10.7%) | 0.76 |
|  *Emergency* | 40 (8.1%) | 32 (8.2%) | 8 (7.8%) | 0.76 |
| Intraoperative ultrafiltration (mL)a | 43.74±320.3 | 48.6±344.2 | 25.2±205.2 | 0.6229 |
| Intraoperative furosemide (mg) | 1.3±5.9 | 1.3±5.1 | 1.5±5.9 | 0.811 |
| Intraoperative colloids (mL) | 62.1±173.5 | 53.4±160.8 | 95.1±212.8 | 0.0192 |
| Intraoperative mannitol (mL) | 214.8±89.6 | 217.7±86.7 | 203.7±100.8 | 0.302 |
| Intraoperative contrast media [yes] | 15 (3.0%) | 7 (46.7%) | 8 (53.3%) |  |
| Highest systolic arterial pressure (mm Hg) | 139.7±19.2 | 138.6±18.3 | 143.78±21.7 | 0.075 |
| Lowest systolic arterial pressure (mm Hg) | 91.7±11.6 | 91.7±11.8 | 91.7±10.6 | 0.991 |
| Highest diastolic arterial pressure (mm Hg) | 71.1±9.1 | 70.8±8.8 | 72.33±10.1 | 0.168 |
| Lowest diastolic arterial pressure (mm Hg) | 51.7±9.1 | 52.0±5.8 | 50.6±7.1 | 0.033 |
| Base excessat beginning of surgery (mmol/L)b | 0.6±2.2 | 0.6±2.1 | 0.61±2.3 | 0.856 |
| Base excessat end of surgery (mmol/L)b | –1.9±2.9 | –2.01±2.81 | –1.31±3.1 | 0.0292 |
| HCO3– at beginning of surgery (mmol/L)b | 24.4±9.3 | 24.5±10.4 | 24.2±2.4 | 0.773 |
| HCO3– at end of surgery (mmol/L)b | 22.6±2.5 | 22.4±2.3 | 23.1±2.9 | 0.0113 |
| Serum lactateat beginning of surgery (mmol/L)b | 1.1±0.4 | 1.1±0.3 | 1.2±0.5 | 0.213 |
| Serum lactate at end of surgery (mmol/L)b | 1.8±0.8 | 1.8±0.7 | 1.9±1.1 | 0.0874 |
| Lowest hemoglobin (g/dL) | 9.6±1.6 | 9.6±1.5 | 9.4±1.8 | 0.107 |
| **ICU clinical data** |  |  |  |  |
| Myocardial infarction [yes] | 1 (0.2%) | 1 (0.3%) | 0 (0%) | 0.608 |
| Stroke [yes] | 8 (1.62%) | 5 (1.3%) | 3 (3.0%) | 0.063 |
| Arrythmia [yes] | 80 (16.2%) | 61 (15.6%) | 19 (18.4%) | 0.284 |
| Cardiac arrest [yes] | 9 (1.8%) | 4 (1.0%) | 5 (4.9%) | 0.0220 |
| Use of ACEi or ARB during ICU stay [yes] | 121 (24.4%) | 95 (24.2%) | 26 (25.2%) | 0.462 |
| Use of spironolactone or eplerenone during ICU stay [yes] | 91 (18.4%) | 61 (15.6%) | 30 (29.1%) | 0.0018 |
| Vancomycin use during ICU stay [yes] | 81 (16.4%) | 53 (13.5%) | 28 (27.2%) | 0.0012 |
| NSAID use during ICU stay [yes] | 13 (2.%) | 10 (2.6%) | 3 (2.9%) | 0.860 |
| Mean arterial pressure <65 mmHg within the first 24 h [yes] | 206 (41.6%) | 147 (37.5%) | 59 (57.3%) | 0.0002 |
| Use of inotropesc |  |  |  | <0.0001 |
|  *None upon ICU arrival* | 302 (61.0%) | 259 (66.1%) | 43 (41.7%) |  |
|  *<24 h after ICU arrival* | 135 (27.3%) | 105 (26.8%) | 30 (29.1%) |  |
|  *>24 h after ICU arrival* | 58 (11.7%) | 28 (7.1%) | 30 (29.1%) |  |
| Use of vasopressorsc |  |  |  |  |
|  *None upon ICU arrival* | 443 (89.4%) | 360 (91.8%) | 83 (80.6%) | <0.0001 |
|  *<24 h after ICU arrival* | 37 (7.5%) | 26 (6.6%) | 10 (9.7%) |  |
|  *>24 h after ICU arrival* | 16 (3.3%) | 6 (1.5%) | 10 (9.7%) |  |
| Use of vasodilatorsc |  |  |  |  |
|  *None upon ICU arrival* | 486 (98.2%) | 384 (98.0%) | 1 (1.0%) | 0.738 |
|  *<24 h after ICU arrival* | 8 (1.6%) | 7 (1.8%) | 0 (0%) |  |
|  *>24 h after ICU arrival* | 1 (0.2%) | 1 (0.3%) | 1 (1.0%) |  |

Summaries of quantitative variables are the mean ± standard deviation. For categorical variables, the absolute and relative frequencies (as %, in parentheses) for the categories are presented. For dichotomous variables, the respective category is presented in square brackets.

\*After application of the Bonferroni correction, p<0.001 was considered significant.

aUltrafiltration was done *via* a heart–lung machine.

bSampling of arterial blood gas.

cAdrenaline, dopamine, dobutamine, and isoprenaline were labeled as inotropes.

cNoradrenaline and vasopressin were labeled as vasopressors.

cNitroglycerin was labeled as vasodilators.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HCO3– = bicarbonate; ICU = intensive care unit; NSAID = non-steroidal anti-inflammatory drug.

## *Table S2: Comparison of staging of acute kidney injury with and without correction of serum creatinine for fluid balance*

|  |  |
| --- | --- |
|  | **AKI stages with serum creatinine corrected for fluid balance** |
| **AKI stages** | ***0*** | ***1*** | ***2*** | ***3*** | Total |
| ***0*** | 389 | 3 | 0 | 0 | 392 |
| ***1*** | 2 | 74 | 0 | 0 | 76 |
| ***2*** | 0 | 0 | 17 | 1 | 18 |
| ***3*** | 0 | 0 | 0 | 9 | 9 |
|  |  |  |  |  |  |
| Total | 391 | 77 | 17 | 10 | 495 |

Correction of AKI diagnosis and staging for fluid balance was performed as previously described [9].

AKI = acute kidney injury.

## *Table S3: Preoperative predictors of cardiac surgery-associated acute kidney injury by the univariate logistic regression analysis*

|  |  |
| --- | --- |
|  | **Univariate** |
| **Predictor** | **OR (95% CI)** | **p value** |
| Age | 1.51 (1.24−1.87) | <0.0001 |
| Male sex | 0.66 (0.42−1.03) | 0.069 |
| Peripheral vasculopathy | 2.88 (1.72−4.81) | <0.0001 |
| Coronary heart disease | 2.52 (1.61−3.97) | <0.0001 |
| Diabetes mellitus | 2.92 (1.65−5.15) | <0.0001 |
| Dyslipidemia | 2.33 (1.49−3.64) | <0.0001 |
| Acute decompensated heart failure | 5.27 (1.91−14.50) | 0.001 |
| Chronic obstructive pulmonary disease | 2.12 (1.01−4.41) | 0.046 |
| Carotid stenosis | 2.43 (1.18−5.01) | 0.016 |
| NYHA classification | 1.79 (1.29−2.48) | <0.0001 |
| EuroSCORE II for operative riska | 2.30 (1.46−3.63) | 0.0002 |
| Statin | 2.22 (1.43−3.45) | <0.001 |
| Antiplatelet | 1.74 (1.10−2.74) | 0.018 |
| Beta-blocker | 1.61 (1.03−2.50) | 0.035 |
| Hemoglobin | 0.78 (0.64−0.96) | 0.016 |
| Urea | 1.89 (1.21−2.96) | 0.005 |
| Preoperative intra-aortic balloon pump | 7.88 (1.42−43.63) | 0.018 |
| Preoperative intravenous contrast media | 1.58 (1.14−2.18) | 0.006 |
| Preoperative systolic pulmonary arterial pressure | 3.62 (1.28−10.27) | 0.016 |

All available study variables were included in the univariate analysis, but only variables that were significant in the univariate analysis are presented here.

aThe EuroSCORE score is calculated by means of a logistic-regression equation and ranges from 0% to 100%, with higher scores indicating greater risk.

EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association; OR = odds ratio.

## *Table S4:Intraoperative predictors of cardiac surgery-associated acute kidney injury by the univariate logistic regression analysis*

|  |  |
| --- | --- |
|  | **Univariate** |
| **Predictor** | **OR (95% CI)** | **p value** |
| Male sex | 0.66 (0.42−1.03) | 0.060 |
| Age | 1.52 (1.24−1.87) | <0.0001 |
| Urgency of surgery | 7.03 (3.36−14.69) | <0.0001 |
| HCO3– level at end of surgery | 1.83 (1.18−2.83) | 0.007 |
| Base excess at end of surgery | 1.63 (1.05−2.53) | 0.029 |
| Intraoperative intravenous contrast media | 4.63 (1.62−13.24) | 0.002 |
| Intraoperative colloids | 2.01 (1.12−3.60) | 0.019 |
| Red blood cell volume transfused | 4.41 (2.52−7.73) | <0.0001 |
| Duration of cardiopulmonary bypass  | 1.31 (1.07−1.59) | 0.008 |
| Minimally invasive surgery | 0.21 (0.13−0.33) | <0.0001 |
| Mitral valve surgery | 0.28 (0.17−0.45) | <0.0001 |
| Aortic valve surgery | 3.70 (2.32−5.91) | <0.0001 |
| Tricuspid valve surgery | 0.096 (0.13−0.73) | 0.005 |
| Valve replacement | 2.99 (1.95−4.58) | <0.0001 |
| Coronary artery bypass graft | 2.69 (1.63−4.42) | 0.0001 |
| Number of coronary artery bypass grafts | 1.45 (1.15−1.82) | 0.003 |
| Replacement of the ascending aorta | 1.84 (1.04−3.24) | 0.034 |
| Surgery of atrial septal defects | 0.23 (0.08−0.66) | 0.003 |

All available study variables were included in the univariate analysis, but only variables that were significant in the univariate analysis are presented here.

HCO3–, = bicarbonate; OR = odds ratio.