**Supplemental Data**

**Near-infrared-based cerebral oximetry for prediction of severe acute kidney injury in critically ill children after cardiac surgery**

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**eMethods.**

**Acute kidney injury definition**

Severe AKI was defined as serum creatinine (SCr) level ≥ 2 times the baseline level, or urine output (UO) < 0.5 ml/kg/hour for ≥ 12 hours, or provision of dialysis (AKI stage 2 or 3) according to the Kidney Disease: Improving Global Outcome criteria (1). Baseline SCr was determined as the lowest level in the 3 months before admission or calculated using the Schwarz formula (2) with estimated glomerular filtration rate dependent on age (3) . SCr was measured daily and UO several times a day for all patients. At least 1 SCr measurement or at least 12 hours of UO in the first 7 days were required to assess AKI. The maximum AKI stage was used when the SCr and UO criteria resulted in different stages.

**Observation window**

For development of the prediction models for acute kidney injury (AKI), data were retrieved during the observation window, which lasted from admission until prediction time (eFigure 4a-b). For patients with AKI, the observation window lasted until 6 hours before AKI onset. To reduce possible bias from monitoring duration, for patients without AKI, the observation window was determined by fitting a similar distribution of observation windows than for the patients with AKI (eFigure4c).

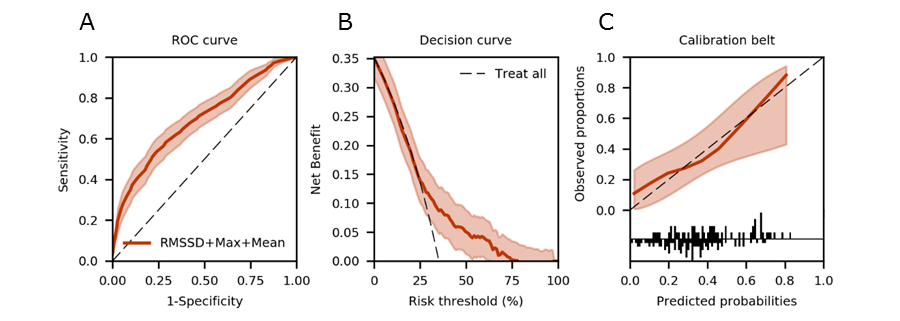
**eFigure 1. Performance of individual NIRS predictors**

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*Top row*. Performance of maximum NIRS signal, a. ROC curve (AUROC, 0.59; 95% CI 0.59-0.59), b. Decision curve (clinical usefulness in ranges 32-58%), c. Calibration belts (P=0.59). *Middle row*. Performance of mean NIRS signal, d. ROC curve (AUROC, 0.59; 95% CI 0.58-0.59), e. Decision curve (clinical usefulness in ranges 34-72%), f. Calibration belt (P=0.60). *Bottom row*. Performance of RMSSD of NIRS signal, g. ROC curve (AUROC 0.68; 95% CI 0.67-0.68). h. Decision curve (clinical usefulness in ranges 27-94%). i. Calibration belt (P=0.61).

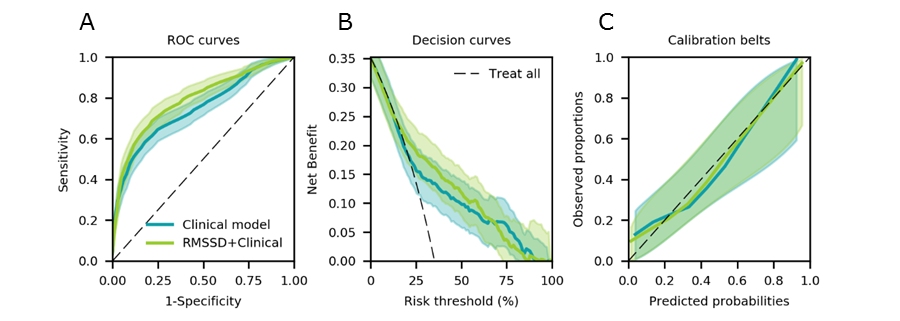
Abbreviations: AUROC, area under the ROC curve; NIRS, near-infrared spectroscopy; RMSSD, root mean square of successive differences; ROC, receiver-operating characteristic

**eFigure 2. Performance of combined NIRS predictors**

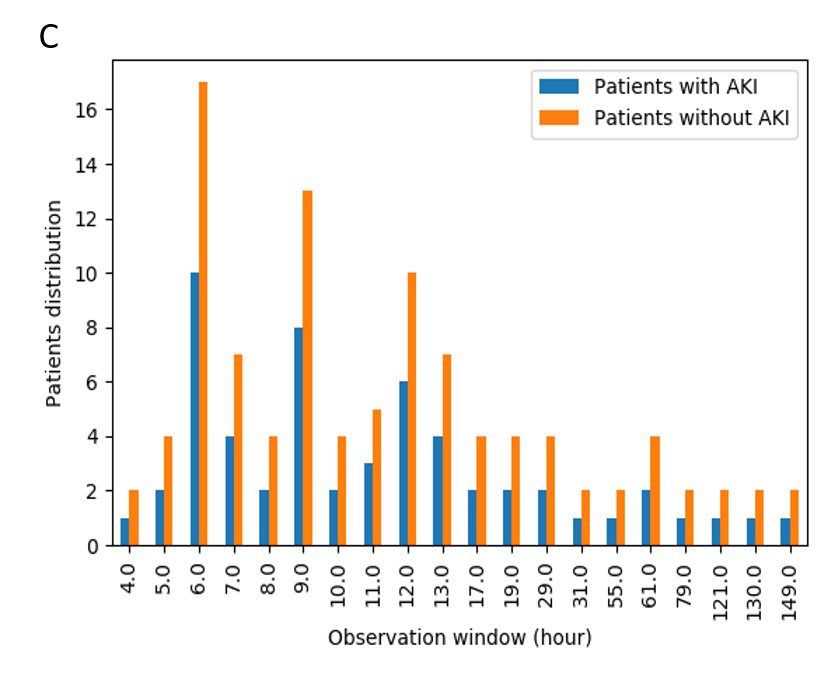
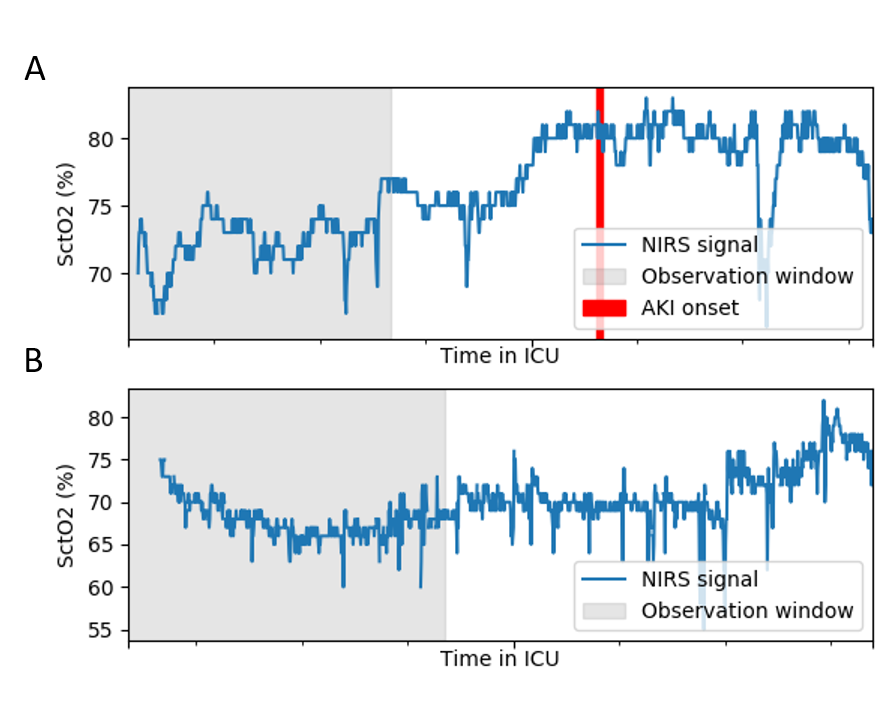


A. ROC curve of model combining maximum, mean and RMSSD of NIRS signal (AUROC 0.69; 95% CI 0.69-0.70). B. Decision curve (clinical usefulness in ranges 25-79%). C. Calibration belt (P=0.59).  
Abbreviations: AUROC, area under the ROC curve; NIRS, near-infrared spectroscopy; RMSSD, root mean square of successive differences; ROC, receiver-operating characteristic

**eFigure 3. Comparison of performance of clinical model and combined NIRS + clinical model**

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A. Comparison of ROC curves of clinical model (AUROC 0.75; 95% CI 0.75-0.75) and of combined NIRS RMSSD + clinical model (AUROC 0.79; 95% CI 0.79-0.80). B. Decision curve of clinical model (clinical usefulness in ranges 22-94%) and of combined NIRS RMSSD + clinical model (clinical usefulness in ranges 16-97%). Clinical benefit of combined model is improved by 2.2% as compared to only using the clinical model at a risk threshold of 20%; 2.4% at a risk threshold of 40%, and 1.3% at a risk threshold of 60% C. Calibration belt of clinical model (P=0.57) and of combined NIRS RMSSD + clinical model (P=0.56).  
Abbreviations: AUROC, area under the ROC curve; NIRS, near-infrared spectroscopy; RMSSD, root mean square of successive differences; ROC, receiver-operating characteristic

**eFigure 4. Distribution of observation windows**

Example of the observation window for a patient who (A) developed AKI during ICU stay, (B) did not develop AKI. For patient with AKI, the observation window corresponds to the time between admission and 6 hours prior to AKI onset. To reduce bias due to monitoring duration, the duration of the observation window for the non-AKI patients was chosen to match that of the AKI cases. (C) Bar chart of the distribution of observation windows for the patients with AKI together with the fitted distribution of observation windows for the patients without AKI.

**eTable 1. NIRS predictors**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All patients** (n=156) | **AKI patients** (n=55) | **No AKI patients** (n=101) | **P-value** |
| **Value-based metrics** |  |  |  |  |
| Mean | 70.2 (64.6-74.8) | 69.8 (60.2-73.8) | 70.4 (66.7-75.1) | 0.007 |
| Minimum | 61 (53-66) | 60 (51-67) | 61 (54-66) | 0.20 |
| Maximum | 78 (72-82) | 76 (68-82) | 79 (73-83) | 0.01 |
| **Variability metrics** |  |  |  |  |
| Maximum-minimum | 16 (12-21) | 15 (11-19) | 16 (12-21) | 0.29 |
| SD | 2.9 (2.0-3.7) | 3.2 (2.0-3.8) | 2.9 (2.0-3.6) | 0.69 |
| SD-s | 2.8 (1.8-3.6) | 3.0 (1.8-3.7) | 2.7 (1.8-2.8) | 0.48 |
| RMSSD | 0.78 (0.63-0.95) | 0.68 (0.56-0.87) | 0.83 (0.69-0.98) | <0.0001 |
| Slope | 0.002 (-0.007-0.011) | 0.005 (-0.006-0.014) | 0.001 (-0.008-0.008) | 0.28 |
| **Dose** |  |  |  |  |
| Dose < patient-specific 25 percentile | 0.4 (0.3-0.6) | 0.4 (0.2-0.6) | 0.4 (0.3-0.6) | 0.98 |
| Dose < 50% | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 0.03 |
| Dose < 60% | 0.0 (0.0-0.2) | 0.0 (0.0-0.7) | 0.0 (0.0 -0.0) | 0.001 |
| Dose > patient-specific 75 percentile | 14.2 (10.7-16.5) | 13.4 (10.5-15.8) | 14.4 (11.3-16.7) | 0.13 |
| Dose > 80% | 0.0 (0.0-0.9) | 0.0 (0.0-0.5) | 0.0 (0.0-1.1) | 0.97 |
| **Time** |  |  |  |  |
| Time < patient-specific 25 percentile | 20.0 (15.5-23.2) | 20.0 (13.5-23.3) | 20.0 (16.1-22.9) | 0.41 |
| Time < 50% | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 0.01 |
| Time < 60% | 0.0 (0.0-4.7) | 0.0 (0.0-33.3) | 0.0 (0.0-0.9) | 0.001 |
| Time > patient-specific 75 percentile | 19.6 (16.0-22.4) | 20.2 (15.8-21.7) | 19.1 (16.2-23.2) | 0.49 |
| Time > 80% | 0.0 (0.0-1.4) | 0.0 (0.0-1.0) | 0.0 (0.0-1.4) | 0.95 |
| **Frequency components** |  |  |  |  |
| Magnitude of first largest frequency component | 37277 (24816-58793) | 39889 (20301-57287) | 36063 (25421-59083) | 0.93 |
| Frequency of first largest frequency component, Hz | 632 (420-1020) | 625 (404-886) | 660 (420-1020) | 0.82 |
| Magnitude of second largest frequency component | 208 (114-469) | 225 (125-537) | 191 (110-464) | 0.25 |
| Frequency of second largest frequency component, Hz | 225 (151-334) | 203 (134-327) | 225 (156-334) | 0.81 |
| Magnitude of third largest frequency component | 208 (114-469) | 225 (125-537) | 191 (110-464) | 0.25 |
| Frequency of third largest frequency component, Hz | 214 (132-347) | 212 (127-301) | 223 (132-347) | 0.83 |

Data are reported as median (IQR). Time and dose predictors are reported as time-weighted metrics. P-value is shown for differences between patients with and without AKI. Abbreviations: FFT, fast-Fourier transform; RMSSD, root-mean square of successive differences; SD, standard deviation; SD-s, standard deviation of smoothed signal

**eTable 2. Performance of combined NIRS predictors**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **AUROC (95%CI)** | **OR (95%CI)** | **P-value** |
| **Combined model** | 0.69 (0.69-0.70) |  |  |
| RMSSD |  | 0.041 (0.007-0.234) | <0.001 |
| Maximum |  | 1.107 (0.984-1.245) | 0.17 |
| Mean |  | 0.871 (0.773-0.982) | 0.07 |

Abbreviations: AUROC, area under the ROC curve; CI, confidence interval; OR, odds ratio; RMSSD, root mean square of successive differences; ROC, receiver-operating characteristic

**eTable 3. Interaction analysis between NIRS predictors and mean blood pressure**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **AUROC (95%CI)** | **OR (95%CI)** | **P-value** |
| **NIRS RMSSD** | 0.77 (0.77-0.77) |  |  |
| RMSSD |  | 2.28 (0->999999) | 0.86 |
| Blood pressure |  | 0.08 (0-19979) | 0.47 |
| RMSSD\*blood pressure |  | 1662928 (4.03->999999) | 0.57 |
| **NIRS mean** | 0.69 (0.69-0.69) |  |  |
| Mean |  | 0.81 (0.58-1.12) | 0.24 |
| Blood pressure |  | 1270723 (0->999999) | 0.19 |
| Mean\*blood pressure |  | 1.3 (0.82-2.06) | 0.32 |
| **NIRS max** | 0.68 (0.68-0.69) |  |  |
| Max |  | 0.69 (0.49-0.97) | 0.07 |
| Blood pressure |  | 0.13 (0.00->999999) | 0.05 |
| Max\*blood pressure |  | 1.66 (1.03-2.68) | 0.09 |

Abbreviations: AUROC, area under the ROC curve; CI, confidence interval; OR, odds ratio; RMSSD, root mean square of successive differences; ROC, receiver-operating characteristic  
Blood pressure has been standardized by dividing by maximum value.

**eTable 4. Interaction analysis between NIRS predictors and arterial carbon dioxide**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **AUROC (95%CI)** | **OR (95%CI)** | **P-value** |
| **NIRS RMSSD** | 0.72 (0.72-0.73) |  |  |
| RMSSD |  | 14.93 (0->999999) | 0.92 |
| CO2 |  | 96.26 (0->999999) | 0.77 |
| RMSSD\*CO2 |  | 0.01 (0->999999) | 0.58 |
| **NIRS mean** | 0.63 (0.63-0.64) |  |  |
| Mean |  | 0.89 (0.63-1.27) | 0.45 |
| CO2 |  | >999999 (50442->999999) | 0.47 |
| Mean\*CO2 |  | 1.12 (0.67-1.87) | 0.58 |
| **NIRS max** | 0.63 (0.63-0.64) |  |  |
| Max |  | 0.88 (0.62-1.25) | 0.43 |
| CO2 |  | >999999 (52.47->999999) | 0.43 |
| Max\* CO2 |  | 1.16 (0.7-1.92) | 0.53 |

Abbreviations: AUROC, area under the ROC curve; CI, confidence interval; CO2, carbon dioxide; OR, odds ratio; RMSSD, root mean square of successive differences; ROC, receiver-operating characteristic  
CO2 has been standardized by dividing by maximum value.

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