

Near-Infrared–Based Cerebral Oximetry for Prediction of Severe Acute Kidney Injury in Critically Ill Children After Cardiac Surgery

Marine Flechet, PhD; Fabian Güiza, PhD; Isabelle Scharlaeken, MD; Dirk Vlasselaers, PhD; Lars Desmet, MD; Greet Van den Berghe, PhD; Geert Meyfroidt, PhD

Objectives: Cerebral oximetry by near-infrared spectroscopy is used frequently in critically ill children but guidelines on its use for decision making in the PICU are lacking. We investigated cerebral near-infrared spectroscopy oximetry in its ability to predict severe acute kidney injury after pediatric cardiac surgery and assessed its additional predictive value to routinely collected data.

Design: Prospective observational study. The cerebral oximeter was blinded to clinicians.

Setting: Twelve-bed tertiary PICU, University Hospitals Leuven, Belgium, between October 2012 and November 2015.

Patients: Critically ill children with congenital heart disease, younger than 12 years old, were monitored with cerebral near-infrared spectroscopy oximetry from PICU admission until they were successfully weaned off mechanical ventilation.

All authors: Clinical Division and Laboratory of Intensive Care Medicine, Academic Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium.

Supplemental digital content is available for this article. Direct URL citations appear in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccejournal>).

Dr. Flechet received funding from the Research Foundation, Flanders (FWO) as a PhD fellow (11Y1118N). Dr. Van den Berghe received funding from Methusalem program of the Flemish Government (Belgium) and the European Research Council advanced grant AdvG-2012–321670. Dr. Meyfroidt received funding from FWO as senior clinical investigator (1843118N). The remaining authors have disclosed that they do not have any potential conflicts of interest.

The FORESIGHT monitors and sensors used in the study were supplied partially by CAS Medical Systems. CAS Medical Systems has not been involved in the data analysis or data interpretation.

Trial registration: ClinicalTrials.gov NCT01706497.

For information regarding this article, E-mail: geert.meyfroidt@uzleuven.be

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Crit Care Expl 2019; 1:e0063

DOI: 10.1097/CCE.000000000000063

Interventions: None.

Measurements and Main Results: The primary outcome was prediction of severe acute kidney injury 6 hours before its occurrence during the first week of intensive care. Near-infrared spectroscopy-derived predictors and routinely collected clinical data were compared and combined to assess added predictive value. Of the 156 children included in the analysis, 55 (35%) developed severe acute kidney injury. The most discriminant near-infrared spectroscopy-derived predictor was near-infrared spectroscopy variability (area under the receiver operating characteristic curve, 0.68; 95% CI, 0.67–0.68), but was outperformed by a clinical model including baseline serum creatinine, cyanotic cardiopathy pre-surgery, blood pressure, and heart frequency (area under the receiver operating characteristic curve, 0.75; 95% CI, 0.75–0.75; $p < 0.001$). Combining clinical and near-infrared spectroscopy information improved model performance (area under the receiver operating characteristic curve, 0.79; 95% CI, 0.79–0.80; $p < 0.001$).

Conclusions: After pediatric cardiac surgery, near-infrared spectroscopy variability combined with clinical information improved discrimination for acute kidney injury. Future studies are required to identify whether supplementary, timely clinical interventions at the bedside, based on near-infrared spectroscopy variability analysis, could improve outcome.

Key Words: acute kidney injury; cerebral oximetry; intensive care; near-infrared spectroscopy; pediatrics; predictive modeling

Near-infrared spectroscopy (NIRS) has gained popularity in the PICU, as it allows for continuous and noninvasive assessment of cerebral or somatic tissue oxygenation at the bedside (1–4). NIRS-detected cerebral hypoxia has been validated in relation to venous oximetry and anaerobic metabolism (3, 5, 6). Therefore, cerebral NIRS monitoring is used as a hemodynamic monitor for early recognition of an inadequate global oxygen supply/demand relationship, and to adapt interventions to minimize the risk of secondary organ dysfunction.

Evidence on the usefulness of NIRS monitoring both for prognosis and to guide management decisions in pediatrics is limited

and has focused on cardiac surgery settings. A single study (7) suggests that NIRS-guided early detection of decreased tissue perfusion and oxygenation could allow initiation of prompt therapies to avoid organ damage and hence improve patient outcome. However, there is currently no consensus on which critical NIRS thresholds could guide patient care, trigger interventions, or be used for prognostication (8–10). Given the relatively high cost of the monitoring sensors, it is crucial to determine specific settings in which NIRS monitoring could improve patient care.

One such setting, to which impaired global perfusion contributes significantly, is acute kidney injury (AKI). AKI affects approximately 40% of children after pediatric cardiac surgery (11, 12), and is associated with prolonged duration of ICU and hospital stay and increased mortality (11–15). A reduced systemic oxygen delivery or its variability may be correlated with reduction in renal substrate delivery and AKI. Indeed, a prior study has shown that decreased renal NIRS oxygen saturation was predictive of AKI after adult cardiac surgery (16). Whether the more common cerebral site of NIRS monitoring is equally predictive of AKI is unclear.

In this study, we hypothesized that cerebral NIRS oximetry could adequately discriminate the risk of severe AKI in children following cardiac surgery and could be combined with routinely collected patient information to improve predictive performance.

MATERIALS AND METHODS

Study Design

This prospective blinded observational study (ClinicalTrials.gov NCT01706497) was performed between October 2012 and November 2015, in the PICU of the Leuven University Hospitals, Leuven, Belgium. The study aimed at evaluating associations between NIRS and ICU short- and long-term outcomes (17) and hemodynamic instabilities, including AKI. Patient enrollment and clinical data collection protocol, including a waiver of parental consent for study participation, were approved by the Institutional Review Board.

Study Population

Children after cardiac surgery, younger than 12 years old, with an arterial line in place, mechanically ventilated upon PICU admission or intubated after admission, and expected to stay at least 24 hours in the PICU, were eligible for the study. Patients were excluded if they had actual or potential brain damage, or if they had a condition or a wound that prohibited the placement of the forehead NIRS sensors. In addition, we excluded patients who developed AKI within 6 hours after admission and patients in whom NIRS monitoring was initiated after AKI onset.

Near-Infrared Spectroscopy Monitoring

The cerebral oxygen saturation was continuously measured with NIRS in all eligible patients from PICU admission until they were weaned off mechanical ventilation, using the FORESIGHT cerebral oximeter (CAS Medical Systems, Branford, CT). The monitor screens were blinded to the bedside clinicians with a sealed screen-cover in order not to influence the predictive value of the signal.

Prediction of Acute Kidney Injury

The primary outcome was prediction of severe AKI 6 hours before its occurrence during the first week of ICU stay. Severe AKI was defined according to stage 2 and 3 of the Kidney Disease: Improving Global Outcome criteria (18), as described in the **supplemental data** (Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>).

Prediction of severe AKI was performed, first using the signal from the cerebral NIRS oximeter (NIRS signal), second using routinely collected clinical data, and third by combining NIRS and clinical information. Data were retrieved during the observation window, which lasted from admission until prediction (supplemental data, Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>).

NIRS Model. A NIRS model was developed using the minute-by-minute NIRS signal after preprocessing, as described in (17), and transformation to relevant predictors (for complete list, see **eTable 1**, Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>), including value-based metrics, variability metrics, frequency components, time and dose below and above various hypoxic and hyperoxic thresholds (19, 20). Variability metrics included root mean square of successive differences (RMSSD), SD, and smoothed SD (SD-s) (17). It is important to note that up-to-date cerebral oximeters only display value-based metrics and the dose below a user-defined threshold. For the most predictive NIRS predictors, interaction analyses were conducted with mean blood pressure and arterial carbon dioxide (CO_2) independently, as they may influence the NIRS signal.

Clinical Model. A clinical prediction model was developed based on patient demographics and prospectively collected clinical information recorded during surgery and ICU stay (**Table 1**). Monitoring information included minute-by-minute heart rate and systolic blood pressure, daily lactate levels, hemoglobin levels, arterial oxygen saturation, and central venous oxygen saturation measured using intermittent blood sampling and treatment with extracorporeal membrane oxygenation. The median values and variability metrics of minute-by-minute monitoring signals were used as clinical predictors.

Combination of NIRS and Clinical Models. Predictors included in the NIRS model and in the clinical model were combined to assess the added predictive value of the NIRS signal as compared with routinely collected data.

Statistical Analysis

Data are presented as means and SD, medians and interquartile ranges, and numbers and proportions, where appropriate. Differences between characteristics of patients with and without AKI were compared with one-way analysis of variance for continuous variables and Fisher exact test for categorical variables. Statistical significance was set at p value of less than 0.05. All analyses were performed using Python Version 3.7 (Python Software Foundation, <http://www.python.org>), Scipy Version 1.3 (SciPy.org).

Reporting of the study was performed using the Strengthening of Reporting of Observational Studies in Epidemiology guidelines (21).

Prediction Model Development. Prediction models were developed using logistic regression. For each model, predictors with a univariable p value of less than 0.05 were included in the models. To reduce overfitting and optimize model generalizability,

TABLE 1. Patient Characteristics

Characteristics	All Patients (n = 156)	Patients With AKI (n = 55)	Patients Without AKI (n = 101)	p
Demographics				
Age, mo	4.0 (1.8–14.3)	2.0 (0.0–8.0)	6.0 (3.0–16.0)	0.35
Weight, kg	5.6 (3.8–8.7)	4.1 (3.3–7.4)	6.5 (4.5–8.8)	0.20
Height, cm	61.0 (53.0–74.5)	54.0 (50.0–68.0)	63.0 (57.0–76.0)	0.12
Male gender, n (%)	97 (62.2)	37 (67.3)	60 (59.4)	0.33
Surgery data				
Univentricular circulation, n (%)	40 (25.6)	15 (27.3)	25 (24.8)	0.85
Cardiopulmonary bypass, n (%)	140 (89.7)	51 (92.7)	89 (88.1)	0.42
Deep hypothermic cardiac arrest, n (%)	8 (5.1)	5 (9.1)	3 (3.0)	0.09
Cyanotic heart defect pre-surgery, n (%)	99 (63.5)	45 (81.8)	54 (53.5)	0.0004
Cardiopulmonary bypass duration, min	77.0 (48.5–105.0)	88.0 (55.5–111.5)	75.0 (45.0–98.0)	0.01
Aortic clamp duration, min	53.2 (36.0–72.3)	58.0 (45.5–78.5)	53.2 (34.0–68.0)	0.04
Minimum temperature, °C	34.6 (33.5–35.3)	34.4 (33.5–35.4)	34.6 (33.5–35.3)	0.14
Maximum lactate, mmol/L	2.2 (1.5–2.5)	2.5 (1.6–3.5)	2.0 (1.5–2.5)	0.0008
ICU admission data				
Pediatric Index of Mortality 2 probability of death, %	10.3 (3.5–22.0)	18.1 (5.1–33.2)	7.2 (3.2–15.5)	< 0.0001
Baseline serum creatinine, mg/dL ^a	0.31 (0.25–0.42)	0.39 (0.29–0.51)	0.29 (0.24–0.37)	< 0.0001
Elective admission, n (%)	138 (88.5)	46 (83.6)	92 (91.1)	0.19
Cyanotic heart defect post-surgery, n (%)	58 (37.2)	22 (40.0)	36 (35.6)	0.60
Risk Adjustment in Congenital Heart Surgery-1 score, n (%)				0.01
1	9 (5.8)	0 (0.0)	9 (8.9)	
2	67 (42.9)	19 (34.5)	48 (47.5)	
3	52 (33.3)	21 (38.2)	31 (30.7)	
4	19 (12.2)	12 (21.8)	7 (6.9)	
5	0 (0.0)	0 (0.0)	0	
6	9 (5.8)	3 (5.5)	6 (5.9)	
ECMO upon admission, n (%)	6 (3.8)	5 (9.1)	1 (1.0)	0.02
Monitoring data				
ECMO during ICU stay, n (%)	7 (4.5)	5 (9.1)	2 (2.0)	0.09
Heart frequency, beat/min	132 (118–145)	142 (131–150)	129 (116–139)	< 0.0001
RMSSD of heart frequency, beat/min	2.61 (1.88–4.22)	2.69 (1.93–5.36)	2.60 (1.85–4.06)	0.10
Hemoglobin, g/dL	11.5 (10.2–12.4)	11.5 (10.4–12.6)	11.5 (10.2–12.3)	0.44
Systolic blood pressure, mm Hg	81.00 (70.75–90.00)	72.00 (60.50–84.00)	85.00 (75.00–93.00)	< 0.0001
RMSSD of systolic blood pressure, mm Hg	3.30 (2.41–4.46)	3.07 (2.04–3.74)	3.52 (2.57–4.80)	0.005
Mean blood pressure, mm Hg	59.5 (54.0–66.2)	54.9 (48.7–63.4)	62.3 (57.4–62.6)	< 0.0001
Lactate, mmol/L	1.2 (0.9–1.8)	1.6 (1.0–3.0)	1.1 (0.9–1.5)	< 0.0001
Maximum lactate, mmol/L	2.1 (1.5–3.1)	3.0 (1.8–3.8)	1.8 (1.4–2.6)	< 0.0001
Arterial oxygen saturation, %, mean (sd)	93.6 (8.7)	93.7 (8.7)	93.6 (8.7)	0.93
Arterial carbon dioxide, mm Hg	37.0 (33.5–40.0)	35.6 (32.6–38.5)	37.6 (34.2–40.8)	0.007

(Continued)

TABLE 1. (Continued). Patient Characteristics

Characteristics	All Patients (n = 156)	Patients With AKI (n = 55)	Patients Without AKI (n = 101)	p
Kidney function, n (%)				
Severe AKI	55 (35.3)	55	0	—
Severe AKI				
Urine output criterion	54 (34.6)	54 (98.2)	0 (—)	—
Serum creatinine criterion	15 (9.6)	15 (27.3)	0 (—)	—
Dialysis				
Both criteria	14 (9.0)	14 (25.5)	0 (—)	—
Maximum AKI				
Urine output criterion	53 (34.0)	53 (96.4)	0 (—)	—
Serum creatinine criterion	15 (9.6)	15 (3, 27)	0 (—)	—
Dialysis	3 (1.9)	3 (5.5)	0 (—)	—
Both criteria	13 (8.3)	13 (23.6)	0 (—)	—
Outcomes				
PICU LOS, d	4.0 (3.0–7.0)	7.0 (4.0–16.5)	3.0 (2.0–5.0)	0.0004
Hospital LOS, d	9.0 (6.0–18.0)	13.0 (8.0–31.5)	8.0 (6.0–14.0)	0.0003
Duration of mechanical ventilation, hr	97.7 (67.7–167.0)	164.2 (97.7–393.3)	74.7 (48.1–120.9)	0.0004
PICU mortality, n (%)	6 (3.8)	5 (9.1)	1 (1.0)	0.02
90-d mortality, n (%)	5 (3.2)	4 (7.3)	1 (1.0)	0.05

AKI = acute kidney injury, ECMO = extracorporeal membrane oxygenation, LOS = length of stay, RMSSD = root mean square of successive differences.

*Baseline serum creatinine was available in 154 patients and calculated in two patients.

Data are summarized using median (interquartile range) except where stated otherwise. p value is shown for comparison between patients with and without AKI.

Dashes indicate no value was calculated.

backward feature selection was used to identify the smallest and most accurate model. Model performance and stability were internally validated using 1,000 bootstrap replicas (22).

Diagnostic Accuracy Assessment. Model performance was reported using discrimination, calibration, and net benefit (23). Discrimination between patients with and without AKI was evaluated with the receiver operating characteristics (ROCs) curve and the area under the ROC curve (AUROC). Calibration refers to the agreement between the observed frequency of AKI in the population and the model predictions. Calibration was assessed using calibration belts together with the distribution of patient numbers (24). A statistically significant difference from perfect calibration is reported by a calibration test p value of less than 0.05 (24). Finally, the net benefit of the model was assessed by the difference between the expected benefit and the expected harm associated with model classification of AKI. Net benefit was visualized using decision curves and reported using ranges above “treat-all” and “treat-none” curves (25, 26).

RESULTS

Study Population

A total of 177 patients met inclusion criteria. Twenty-one patients were excluded (Fig. 1): four had AKI within 6 hours after admission, 16 were monitored with NIRS after AKI onset, and one had

NIRS monitoring initiated later than 72 hours, which prevented the fit of prediction time for this patient. The remaining 156 patients were included in the analysis.

Demographics and outcomes of study participants are reported in Table 1. Fifty-five patients (35.3 %) developed severe AKI. Compared with patients without AKI, patients with AKI had a higher PICU and 90-day mortality risk ($p = 0.02$ and $p = 0.05$, respectively), longer PICU and hospital stay ($p < 0.001$) and longer duration of mechanical ventilation ($p < 0.001$).

Performance of NIRS Model

Compared to patients without AKI, patients with AKI had a lower maximum value of NIRS signal (eTable 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>) ($p = 0.01$), lower mean ($p = 0.007$), lower RMSSD ($p < 0.001$), and increased time and dose below 50% ($p = 0.01$, $p = 0.03$, respectively) and 60% ($p = 0.001$). These predictors were calculated 6 hours prior to AKI diagnosis, suggesting that the NIRS signal carries meaningful information for severe AKI prediction. However, given the low occurrence rate of saturations below 50% and 60%, the robustness of these predictors could not be assessed with the bootstrapping approach.

Performance of each significant NIRS predictor for severe AKI is reported in eFigure 1 (Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>) and Table 2. Overall, the RMSSD

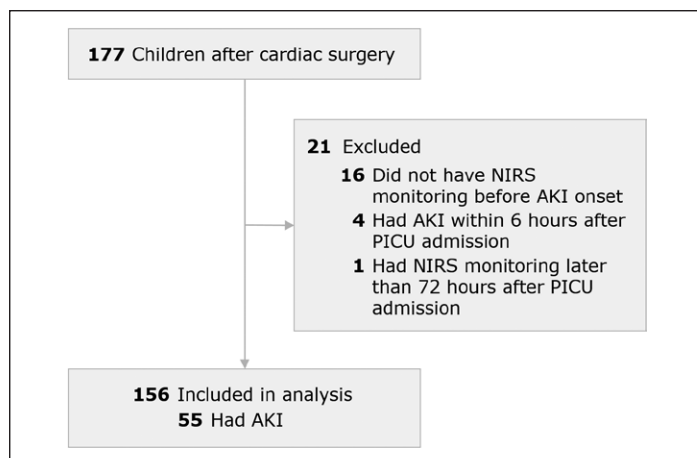


Figure 1. Flow diagram. AKI = acute kidney injury, NIRS = near-infrared spectroscopy.

(Fig. 2), a measure of NIRS variability, was more discriminant than the mean and the maximum values of NIRS (AUROC, 0.68; 95% CI, 0.67–0.68; $p < 0.001$), had wider (25–92%) and higher ranges of net benefit, and was well calibrated ($p = 0.6$). A patient with low NIRS RMSSD (e.g., 0.56, 25th percentile) (eTable 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>) had a 28% larger probability of developing AKI than a patient with high NIRS RMSSD (e.g., 0.98, 75th percentile) (eTable 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>). Difference was 17% between low (68) and high (83) maximum NIRS value, and 20% between low (60.2) and high (75.1) mean value.

Combining the NIRS predictors slightly improved discrimination (eFig. 2 and eTable 2, Supplemental Digital Content 1,

<http://links.lww.com/CCX/A126>) (AUROC, 0.69; 95% CI, 0.69–0.70; $p < 0.001$). However, only the RMSSD remained in the NIRS model after backward feature selection.

Finally, no interaction effect was found between NIRS predictors and mean blood pressure and arterial CO_2 (eTables 3 and 4, Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>).

Performance of Clinical Model

Table 1 reports univariable differences in clinical variables between patients with and without AKI. After backward feature selection, the remaining significant predictors were baseline serum creatinine, cyanotic heart defect prior to surgery, and median blood pressure and heart frequency ($p < 0.001$ for all). The multivariable clinical model achieved good discrimination (Fig. 3A–C and Table 2; AUROC, 0.75; 95% CI, 0.75–0.75), a wide range of net benefit (22–93%) and was well calibrated ($p = 0.56$).

Comparison of NIRS and Clinical Models

The NIRS RMSSD was less discriminant for severe AKI than the clinical model ($p < 0.001$). However, combining them improved model sensitivity which translated in significantly higher discrimination (Fig. 3D–F and Table 2; AUROC, 0.79; 95% CI, 0.79–0.80; $p < 0.001$), wider ranges of net benefit (14–100%), and larger benefit in the 14–68% range compared with the clinical model (eFig. 3, Supplemental Digital Content 1, <http://links.lww.com/CCX/A126>). For risk thresholds lower than 14%, the highest net benefit is achieved by considering that all patients have AKI. For risk thresholds comprised between 14% and 68%, the highest net benefit is achieved by combining NIRS RMSSD with the clinical model. Finally, above 68%, the highest net benefit is achieved by

TABLE 2. Individual Predictors and Models Performance

Model	Area Under the Receiver Operating Characteristic Curve (95% CI)	OR (95% CI)	<i>p</i>
Individual near-infrared spectroscopy predictors			
RMSSD	0.68 (0.67–0.68)	0.058 (0.013–0.272)	< 0.001
Maximum	0.59 (0.59–0.59)	0.951 (0.912–0.991)	0.06
Mean	0.59 (0.58–0.59)	0.943 (0.902–0.986)	0.04
Clinical model			
Baseline SCr		559.86 (9.48–40326.18)	0.05
Cyanotic heart defect pre-surgery		2.64 (1.05–6.7)	0.12
Heart frequency		1.02 (1.00–1.05)	0.12
Blood pressure		0.97 (0.94–1.00)	0.12
Combined model			
Baseline SCr	0.79 (0.79–0.80)	171.06 (2.39–20799.26)	0.12
Cyanotic heart defect pre-surgery		1.90 (0.72–5.13)	0.30
Heart frequency		1.02 (1.00–1.05)	0.15
Blood pressure		0.96 (0.92–1.00)	0.05
RMSSD		0.08 (0.01–0.46)	0.01

OR = odds ratio, RMSSD = root mean square of successive differences, SCr = serum creatinine.

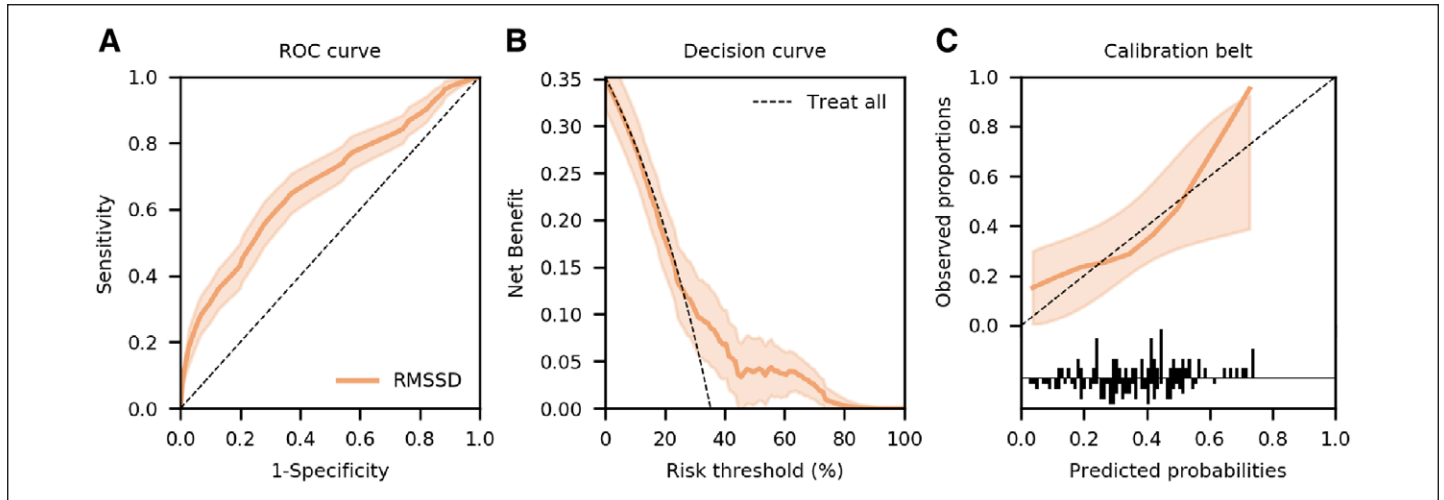


Figure 2. Performance of root mean square of successive differences (RMSSD) of near-infrared spectroscopy signal. **A**, Receiver operating characteristic (ROC) curve (area under the receiver operating characteristic curve, 0.68; 95% CI, 0.67–0.68). **B**, Decision curve (clinical usefulness in ranges 27–94%). **C**, Calibration belt ($p = 0.61$).

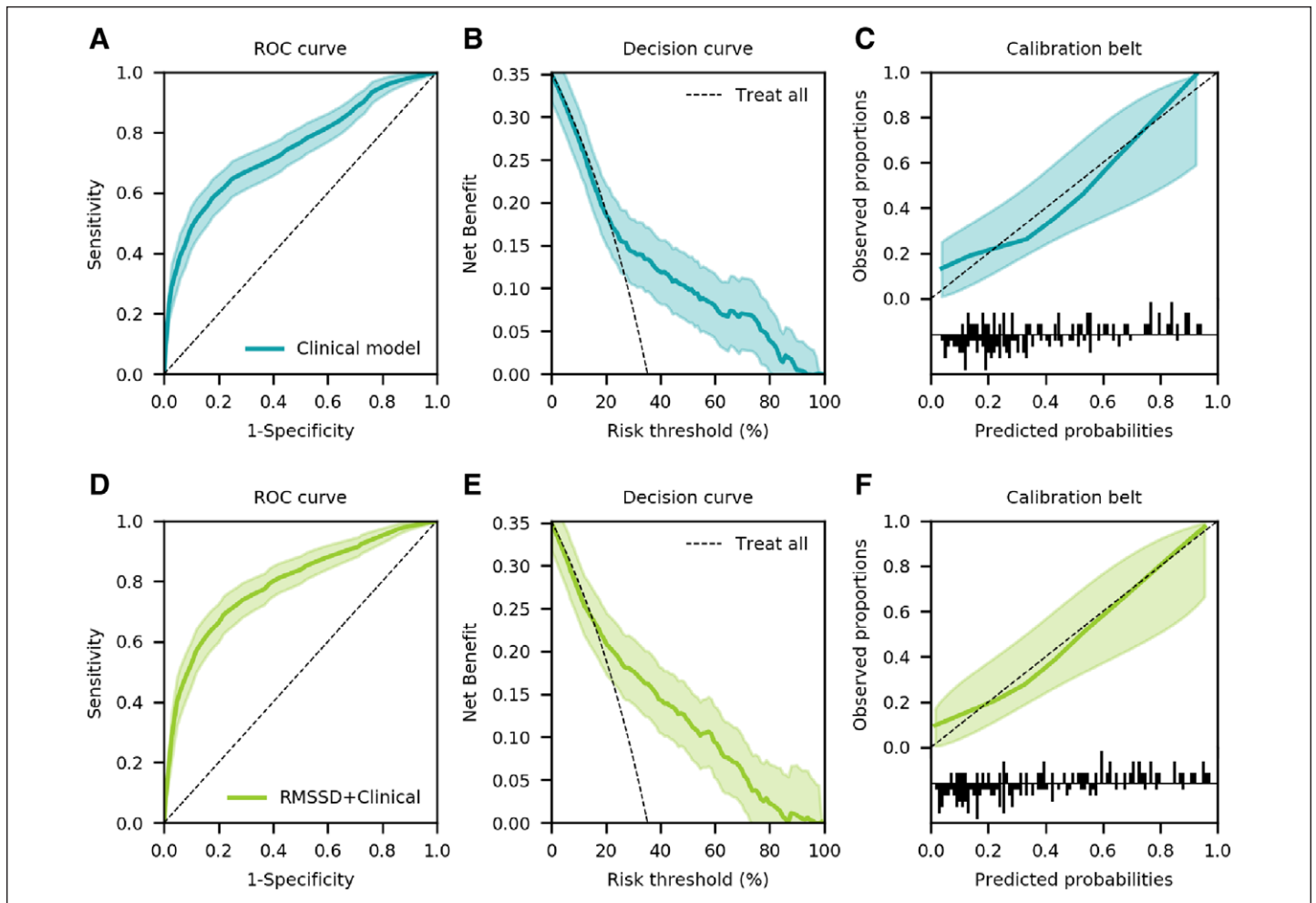


Figure 3. Performance of clinical models. *Top row:* Performance of clinical model including baseline serum creatinine, cyanotic heart defect prior to surgery, heart rate, and blood pressure. **A**, Receiver operating characteristic (ROC) curve (area under the receiver operating characteristic [AUROC] curve, 0.75; 95% CI, 0.75–0.75). **B**, Decision curve (clinical usefulness in ranges 22–94%). **C**, Calibration belt ($p = 0.57$). *Bottom row:* Performance of model combining root mean square of successive differences (RMSSD) of near-infrared spectroscopy signal with clinical model. **D**, ROC curve (AUROC, 0.79; 95% CI, 0.79–0.80). **E**, Decision curve (clinical usefulness in ranges 16–97%). **F**, Calibration belt ($p = 0.56$).

using the clinical model only. Crucially, at the prevalence of AKI in this cohort and for prevalence reported in the literature (11, 12), NIRS would provide benefit. These are the risk thresholds for which the tool is likely to have clinical impact. Depending on the intended use of the predictions, only if one would need a more sensitive model, would NIRS monitoring provide additional value.

DISCUSSION

Currently, there is little evidence available to support the use of cerebral NIRS oximetry after pediatric cardiac surgery. In this study, we aimed to determine the potential of this cerebral oximeter to predict AKI by prospectively monitoring children after surgery for correction of a congenital heart disease. Overall, we found that the data currently displayed in cerebral oximeters have only fair discrimination for 6-hour-ahead prediction of severe AKI. Retrospective calculation of NIRS variability with RMSSD achieved better performance, although not sufficient to outperform a clinical model based on routinely collected patient information. However, combining NIRS variability with the clinical model significantly improved predictive capabilities, suggesting that the NIRS signal carries independent relevant information in addition to routinely collected clinical data.

Cerebral NIRS oximetry is appealing as it allows measuring brain oxygen levels noninvasively and continuously. In a pediatric perioperative setting where the use of invasive catheters is not feasible or available, such a monitor has high potential provided its clinical value is proven. Currently, there is little evidence to support the use of cerebral oximetry at the pediatric patient bedside. Two randomized trials (7, 27) in coronary artery bypass patients and preterm infants used an active NIRS display and treatment intervention protocol based on NIRS desaturation. They showed that NIRS monitoring avoided profound cerebral desaturation but were not powered to detect differences on mortality and morbidity. Other observational and retrospective studies have reported an association between (dose of) NIRS desaturation and worse (neurodevelopmental) outcomes (4, 28, 29). A single study has investigated the use of NIRS oximetry for AKI prediction in adults. The authors found that decreased renal NIRS oxygen saturation was predictive for AKI development after cardiac surgery (16). In accordance with these studies, we found that NIRS-detected low oxygen saturation was predictive for severe AKI. However, the mean and maximum NIRS values were only fair predictors of AKI, and although the time and dose of desaturation below 50% and 60% were predictive, they did not occur frequently enough for inclusion in the predictive model. When cerebral autoregulation is intact, blood flow and oxygen delivery to the brain may be preserved in low cardiac output states. Therefore, the cerebral NIRS values might not represent the perfusion to the other organs during low cardiac output and could partially explain the lack of predictive value for AKI.

Interestingly, we found that decreased NIRS variability had more discriminative power than the NIRS value currently displayed at the patient bedside. Spaeder et al (30) investigated NIRS variability previously and found that decreased NIRS RMSSD, a notion of high frequency variability, was associated with poor neurodevelopmental outcomes in neonatal survivors of congenital

heart disease surgery. In a previous study (17), we found that the low frequency variability ($SD-s$) was associated with prolonged ICU stay and prolonged duration of mechanical ventilation. Here, as patients developed AKI early during ICU stay, the monitoring period before prediction was short which could have explain the lack of predictive capability from the $SD-s$. To our knowledge, this is the first study investigating the use of NIRS variability for acute clinical events, such as severe AKI. This study supports displaying such a metric at the patient bedside, as it may improve the predictive value of NIRS-based cerebral oximeters.

The current study not only reports an added predictive value of cerebral NIRS monitoring but also highlights the predictive performance of routinely collected patient information to predict severe AKI after pediatric cardiac surgery. AKI is an increasingly recognized concern in pediatric patients (31). Therefore, it is essential to identify children whose kidney function will deteriorate to provide appropriate intervention to mitigate AKI (31). For that purpose, several biomarkers have shown great diagnostic and predictive abilities (32, 33). However, due to their high cost, serial measurements is not always applicable (34). The model developed in the current study could be used continuously at the patient bedside, after translation to an online predictor such as similar models for adults (35) or encoded in electronic health records.

Our study has several strengths: its prospective and blinded design that excludes treatment bias, its large sample size as compared with other studies investigating NIRS oximetry (3, 5, 6, 27, 30), and the thorough statistical analysis of the cerebral NIRS oxygen saturation which included not only value-based metrics and dose below hypoxic and above hyperoxic thresholds as previous studies (6, 19), but also measures of variability and frequency.

Our study has several limitations. First, as no precise information on the cause of AKI was available, the clinical model did not include this information, nor did it include medication, while both could have influenced model performance. However, the clinical model included relevant surgical data that were associated with AKI. Second, it is unclear how the findings are affected by cerebral autoregulation. Indeed, in case of decreased systemic perfusion and intact cerebral autoregulation, the cerebral blood flow would initially remain unchanged. Therefore, the NIRS signal would not change. On the other side, in case of impaired cerebral autoregulation, disturbances in systemic perfusion would be reflected by cerebral perfusion and by the NIRS signal. Therefore, the lack of predictive power of cerebral NIRS oximetry might be explained by a late indication of reduced systemic oxygen delivery. However, we did not find any interaction effect between NIRS and mean blood pressure or arterial CO_2 . Third, we could not compare or combine the performance of the models with renal NIRS oximetry, which might be a more sensitive marker of kidney perfusion than cerebral NIRS oximetry, in particular in case of deficient autoregulation (6, 16, 36). However, major drawbacks limit the use of renal NIRS oximetry (37, 38). First, renal oxygen saturation is influenced by the distance between the body surface and the kidney, which largely varies between patients. Additionally, the presence of subcutaneous fat alters the measurement of light absorption by hemoglobin. These limitations explain why the most common clinical application of the NIRS technology has

been in assessing cerebral oxygen saturation, unaffected by these limitations. Fourth, as a single-center study, our findings might not generalize to other centers or to different (noncardiac) populations. Although we performed internal validation via bootstrapping to improve generalizability, validation in external centers is required. Fifth, the lack of standardization between NIRS monitors additionally contributes to the difficulty of identifying NIRS critical thresholds in previous studies, and it is well known that the different devices have discordant values in certain ranges (39); therefore, the findings of our study might not generalize to different cerebral oximeters. Finally, prospective validation of the models developed in this study is warranted to identify potential clinical benefit for their use at the patient bedside.

CONCLUSIONS

The predictive value of cerebral NIRS oximetry as displayed in the current monitors, without monitoring cerebral autoregulation, is limited for prediction of severe AKI after pediatric cardiac surgery. However, NIRS variability, in particular combined with routinely collected patient information, showed improved discrimination. Future studies are required to validate these findings as compared with renal NIRS and to identify whether implementation of NIRS variability at the bedside could help identify children whose kidney function will deteriorate early enough to initiate mitigating interventions.

ACKNOWLEDGMENTS

We are grateful to the PICU nurses and residents for the patient care and setting up the near-infrared spectroscopy monitoring, in particular to Stoffel Lamote, MD, Heidi Delrue, MD, and Marc Beckers, MD, for patient management and data collection; to Pieter Wouters, MSc, for database exports; to Koen Vanhonsbrouck, PICU head nurse, for the assistance in coordinating the monitoring setup; to Tom Fivez, MD, for patient management and signaling eventual technical problems; to Marc Denturck, Fredrik Hermans, and Jan Lauwers (biotechnology department UZ Leuven) for blinding the FORESIGHT monitors.

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