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Intestinal Oxygenation and Survival After Surgery for Necrotizing Enterocolitis

An Observational Cohort Study

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Objective: To assess whether regional intestinal oxygen saturation ($r_{int}SO_2$) and regional cerebral oxygen saturation (r_cSO_2) measurements aid in estimating survival of preterm infants after surgery for NEC.

Summary of Background Data: Predicting survival after surgery for NEC is difficult yet of the utmost importance for counseling parents.

Methods: We retrospectively studied prospectively collected data of preterm infants with surgical NEC who had available $r_{int}SO_2$ and r_cSO_2 values measured via near-infrared spectroscopy 0–24 hours preoperatively. We calculated mean $r_{int}SO_2$ and r_cSO_2 for 60–120 minutes for each infant. We analyzed whether preoperative $r_{int}SO_2$ and r_cSO_2 differed between survivors and non-survivors, determined cut-off points, and assessed the added value to clinical variables.

Results: We included 22 infants, median gestational age 26.9 weeks [interquartile range (IQR): 26.3–28.4], median birth weight 1088 g [IQR: 730–1178]. Eleven infants died postoperatively. Preoperative $r_{int}SO_2$, but not r_cSO_2, was higher in survivors than in non-survivors [median: 63% (IQR: 42–68) vs 29% (IQR: 21–43), $P < 0.01$), with odds ratio for survival 4.1 (95% confidence interval, 1.2–13.9, $P = 0.02$) per 10% higher $r_{int}SO_2$. All infants with $r_{int}SO_2$ values of >53% survived, whereas all infants with $r_{int}SO_2$ <35% died. Median C-reactive protein [138 mg/L (IQR: 83–179) vs 73 mg/L (IQR: 12–98), $P < 0.01$), lactate [1.1 mmol/L (IQR: 1.0–1.6) vs 4.6 mmol/L (IQR: 2.8–8.0), $P < 0.01$], and fraction of inspired oxygen [25% (IQR: 21–31) vs 42% (IQR: 30–80), $P < 0.01$] differed between survivors and non-survivors. Only $r_{int}SO_2$ remained significant in the multiple regression model.

Conclusions: Measuring $r_{int}SO_2$, but not r_cSO_2, seems of added value to clinical variables in estimating survival of preterm infants after surgery for NEC. This may help clinicians in deciding whether surgery is feasible and to better counsel parents about their infants' chances of survival.

Keywords: cerebral oxygen saturation, intestinal oxygen saturation, near-infrared spectroscopy, necrotizing enterocolitis, preterm infants, surgery, survival

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Necrotizing enterocolitis (NEC) is a severe intestinal inflammatory disease that particularly affects preterm infants.[1–5] Surgical intervention to resect ischemic and/or perforated bowel is necessary in approximately 40% of the cases.[1,6] Nevertheless, approximately 50% of the infants who require surgical intervention succumb.[5,7–9] To date, clinical assessments of the severity of illness and additional comorbidities are used to estimate whether affected infants have a chance to survive surgical intervention.[8,10,11] Conventionally, the severity of illness is based on several clinical and biochemical variables representing the infant's intestinal and systemic condition, whereby the patient characteristics and the comorbidities of interest include postmenstrual age, weight, presence of severe cerebral hemorrhage, and additional respiratory and circulatory diseases caused by prematurity.[10,11] At this moment, there is no measurement available that can aid in the prediction of survival when surgical intervention has become necessary in preterm infants with NEC (ie, deterioration despite maximal medical treatment or perforation). Such a measurement could also be of help when counseling parents.[4,8]

A noninvasive tool used to identify preterm infants at risk of developing NEC or progression to complicated NEC is near-infrared spectroscopy (NIRS).[6,9,12–14] This technique measures regional tissue oxygen saturation (rSO_2) to assess end-organ perfusion.[15–17] As fulminant NEC is frequently accompanied by intestinal ischemia and necrosis, intestinal rSO_2 measurements ($r_{int}SO_2$) might be indicative of the local severity of illness. In addition, fulminant NEC might be accompanied by systemic inflammatory response syndrome, resulting in compromised organ perfusion or multi-organ failure.[3,6,14,17–21] As a consequence, cerebral rSO_2 (r_cSO_2) measurements might contribute towards assessing the presence of a compromised systemic circulation as indicator for the overall severity of the disease. Hence, preoperative $r_{int}SO_2$ and r_cSO_2 measurements might contribute towards estimating more accurately the outcomes of infants with severe NEC who require surgical intervention. We therefore aimed to determine whether preoperative $r_{int}SO_2$ and r_cSO_2 measurements are of added value to conventional clinical assessment in identifying which preterm infants with NEC will survive after surgery.

METHODS

Study Design

We performed an observational cohort pilot study consisting of a retrospective analysis of prospectively collected data. All

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A part of the included infants participated in one of our prospective online registered NEC studies (NaNEC-Trial, Dutch Trial Registry NTR4816).

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preterm infants (gestational age (GA) <37 weeks) admitted to our tertiary NEC referral neonatal intensive care unit (NICU) with proven NEC (Bell classification Stage ≥2) and who required laparotomy were eligible for inclusion between January 2015 and January 2019.[22] We excluded infants with no NIRS values, congenital heart disease (as these infants may have a different pathophysiology regarding the development of NEC)[23] – with the exception of a patent ductus arteriosus – large chromosomal and syndromal defects, and congenital abdominal malformations, such as omphalocele, gastroschisis, and intestinal atresia. We excluded r_cSO_2 data from infants diagnosed with a major cerebral hemorrhage (≥ Grade 3) before NEC onset, as this affects r_cSO_2 values.[24,25] Indications to perform a laparotomy were signs of intestinal perforation or a deteriorating clinical condition despite maximal conservative treatment, potentially in combination with a fixed bowel loop suggesting ongoing peritonitis. The final decision to operate was made by a multidisciplinary team including neonatologists, pediatric surgeons, pediatric anesthetists, and the infant's parents. This study was approved by the local ethical review board. Approximately one-half of the included infants participated in one of our prospective online registered NEC studies (NaNEC-Trial, Dutch Trial Registry NTR4816).

NIRS

For the purpose of routine clinical monitoring of the infants at our NICU we used an INVOS 5100C near-infrared spectrometer in combination with neonatal SomaSensors (Medtronic, Dublin, Ireland). The INVOS measures rSO_2 every 5 seconds (0.2 Hz.). The intestinal sensor was placed infraumbilically on the central abdomen and the cerebral sensor on the left or right frontoparietal side. Mepitel film (Mölnlycke, Sweden) was used below each sensor for skin protection.[17] Routinely, NIRS monitoring was performed in infants at risk of cerebral hypoperfusion and/or at risk of intestinal hypoperfusion, according to the local hospital protocol.[9,26] Sensor placement was checked and documented several times a day by the NIRS research team and a nurse. We used routinely measured $r_{int}SO_2$ and r_cSO_2 values that had been obtained within 24 hours before surgery. These data were stored in an off-line database. Next, we calculated mean values of 60–120 minutes of continuously measured $r_{int}SO_2$ and r_cSO_2 values closest to the time of surgery, with at least 75% of data showing no visual artifacts. Artifacts were defined as documented sensor displacements and/or sudden nonphysiological changes of the rSO_2 values within seconds, which suggest incorrect measurements.

Clinical, Biochemical, and Demographical Variables

We retrospectively collected data on clinical and biochemical variables, and comorbidities from the infant's medical files. Clinical and biochemical variables included transcutaneous arterial oxygen saturation (SpO_2) (Nellcor, Medtronic) and blood pressure, both measured simultaneously with the NIRS measurements, urine output (mL/kg/h) during the last 24 hours before surgery, need for inotropes, and maximum fraction of inspired oxygen (FiO_2) during the 24 hours before surgery. The FiO_2 was manually controlled to keep SpO_2 within the target range of 90%–92%, according to our local hospital protocol. Furthermore, we collected laboratory findings from the last blood test before surgery within 24 hours before surgery. Data on comorbidities included the presence of a hemodynamically significant patent ductus arteriosus (needed treatment according to the attending neonatologist and pediatric cardiologist on clinical and echocardiographic grounds), respiratory support before NEC onset, blood culture proven sepsis during NEC. Furthermore, we collected data on postnatal characteristics and data regarding the development of NEC.[22,27]

Statistical Analysis

We used SPSS 23.0 (IBM Corp., Armonk, NY) for statistical analysis. Patient characteristics and clinical and biochemical variables were described as median [interquartile range (IQR)], and preoperative $r_{int}SO_2$ and r_cSO_2 values as median [IQR] of the calculated means. Differences in preoperative $r_{int}SO_2$ and r_cSO_2 values, clinical and biochemical variables, presence of comorbidities, and other patient characteristics between survivors and infants who died were determined by the Mann-Whitney test. To determine whether NIRS measurements were of added value to conventional assessments, we first determined whether $r_{int}SO_2$ and r_cSO_2 values could estimate survival and mortality after surgery, using univariate logistic regression analysis. Mortality after surgery was defined as death because of NEC within 14 days after surgery. When the $r_{int}SO_2$ and/or r_cSO_2 values turned out to be significant, we determined cut-off points by generating receiver operating characteristic curves for survival with a 100% specificity and for mortality with a 100% sensitivity. Next, we performed a Kaplan-Meier survival analysis based on the cut-off points for survival.

The added value of $r_{int}SO_2$ and r_cSO_2 values to current clinical and biochemical variables and the presence of comorbidities was determined with multiple regression models, using LR forward logistic regression analysis. Variables that significantly differed between survivors and non-survivors were included in the multiple model. Each multiple model consisted of one rSO_2 variable with one of the clinical/biochemical variables or comorbidities, thus avoiding multicollinearity between clinical/biochemical variables. Because of the explorative nature of our study we chose not to correct for multiple testing, confidence intervals (CIs) will be displayed for certainty assessment. A P value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

We identified 43 preterm infants who required surgical treatment for NEC (Fig. 1). We excluded 21 infants, 8 of whom (19%) were offered comfort care because of an inoperable general clinical condition with eminent demise (n = 5) or surgery was not performed given the expected poor neurological outcome of these extremely preterm born infants (n = 3). We offered comfort care in consultation with the parents. Our final study population consisted of 22 preterm infants with a median GA of 26.9 weeks [IQR 26.3–28.4] and birth weight (BW) of 1088 g [IQR 730–1178]. Median postnatal age at time of NEC onset was 9 days [IQR 6–12], with a median time between NEC onset and surgery of 27 hours [IQR 16–61]. Median time between the NIRS measurements and surgery was 3.2 hours [IQR 1.2–6.9]. In the case of 2 infants we only used the $r_{int}SO_2$ values, because they were diagnosed with a major cerebral hemorrhage (≥ Grade 3) before NEC onset. Patient characteristics are depicted in Table 1. Patient characteristics of the 11 infants who were excluded because of lacking rSO_2 values did not differ significantly from the characteristics of the included infants regarding GA, BW, and the percentage of survival after surgery. Infants who were excluded because surgery was not performed had a significant lower GA and tended to have a lower BW compared to infants who had undergone surgery.

Mortality and Cause of Death

Out of the 22 included infants, 11 infants (50%) died shortly after surgery with a median time between surgery and demise of 10.1 hours [IQR 4.9–48.0]. The cause of death consisted of the sequelae of massive intestinal necrosis including fulminant sepsis

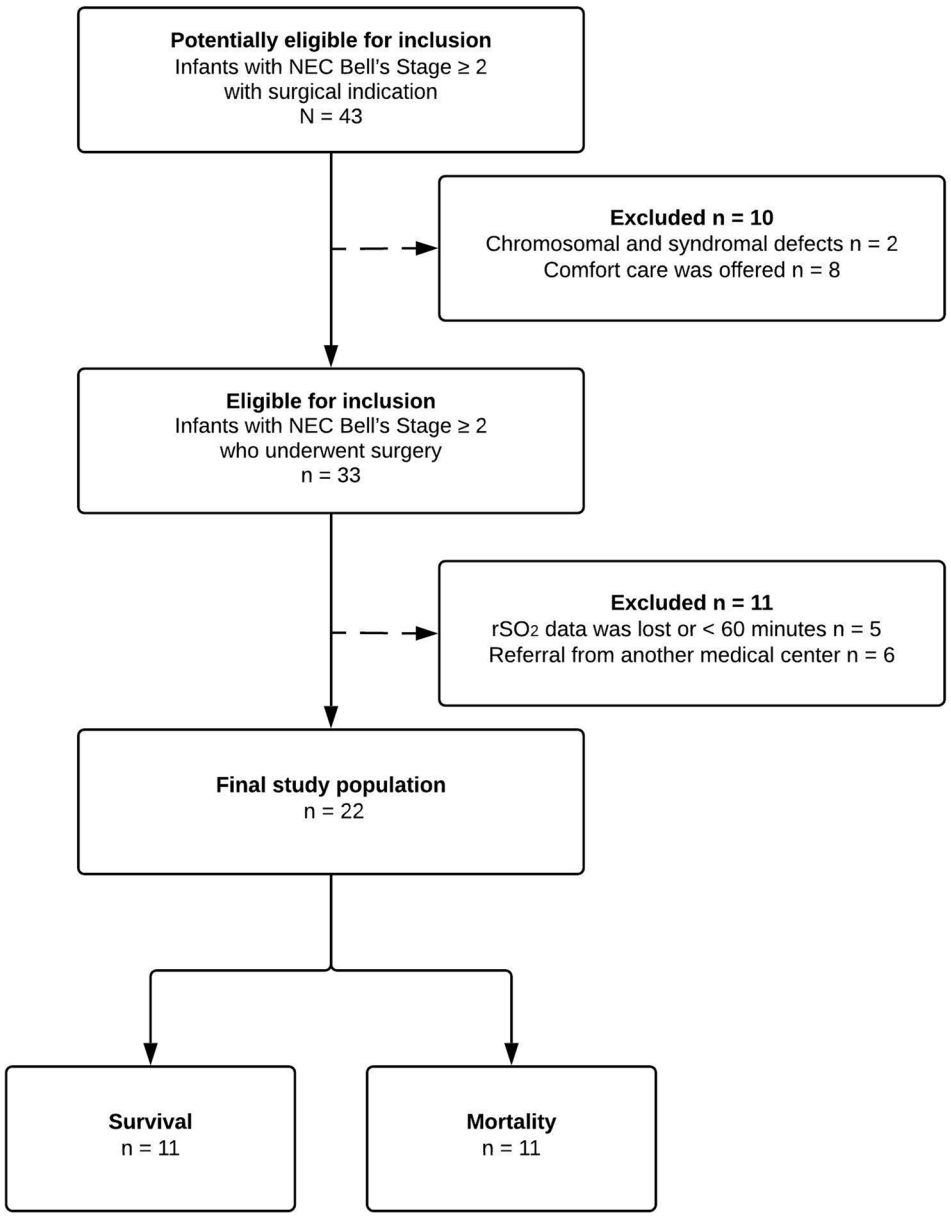


FIGURE 1. Flow diagram of the study population.

and multi-organ failure, which was observed during primary surgery (n = 8) or relaparotomy (n = 3) leading to an open/close procedure in 6 out of the 11 infants. Of the surviving infants 2 infants died 54 and 72 days, respectively, after NEC onset, on account of recurrent NEC and sepsis.

Intestinal Oxygenation and Postoperative Outcome

Preoperative $r_{int}SO_2$ values were higher in infants who survived surgery compared to infants who died after surgery [median (IQR): 63% (42–68) vs 29% (21–43), $P = < 0.01$, n = 9 vs 9] (Fig. 2). For every 10% higher preoperative $r_{int}SO_2$ value, the infants were 4 times more likely to survive after surgery [odds ratio (OR) 4.1, CI, 1.2–13.9, $R^2 = 0.64$, $P = 0.02$). The receiver operating characteristic curve for the $r_{int}SO_2$ values showed an area under the curve of 0.92 (95% CI, 0.80–1.00, $P < 0.01$). First, we found that all infants who had a preoperative mean $r_{int}SO_2$ value of 53% or higher survived after surgery. Six (67%) out of the 9 infants who survived actually had a $r_{int}SO_2$ value above this threshold (specificity 100%, sensitivity 67%, positive predictive value 100%, negative predictive value 86%) (Fig. 3). Second, we found that all infants with a preoperative mean $r_{int}SO_2$ value of <35% died despite surgery. Six (67%) out of the 9 infants who died had a $r_{int}SO_2$ value below this threshold (specificity 77%, sensitivity 100%, positive predictive value 72%, negative predictive value 100%). Out of the 6 infants with a $r_{int}SO_2$ value between 35% and 53%, 3 infants survived. Infants who were inoperable and were offered comfort care had a median $r_{int}SO_2$ value of 20% [IQR: 18–34] (n = 5).

Cerebral Oxygenation and Postoperative Outcome

Preoperatively, the r_cSO_2 value tended to be higher in infants who survived after surgery compared to infants who died despite surgery [median (IQR): 70% [54–73] vs 55% (46–66), $P = 0.08$, n =

TABLE 1. Patient Characteristics

N = 22	Survived n = 11	Deceased n = 11
Baseline characteristics		
Gestational age (wk)	26.9 [26.3–29.3]	27.0 [26.1–28.3]
Birth weight (g)	900 [750–1250]	1105 [670–1170]
Small for gestational age[†]	2 (18%)	2 (18%)
Male	6 (55%)	6 (55%)
Apgar score		
1 min	5 [2–7]	5 [3–8]
5 min	7 [6–8]	7 [5–9]
Administration of antenatal steroids	10 (91%)	10 (91%)
Administration of antenatal antibiotics	4 (36%)	4 (36%)
Antibiotics administration <48 h after birth	7 (64%)	7 (64%)
HsPDA before NEC onset	5 (46%)	6 (55%)
Characteristics regarding the development of NEC		
Postmenstrual age at NEC onset (wk)	28.57 [28.3–30.4]	28.1 [27.3–29.6]
Weight at NEC onset (g)	1000 [800–1300]	1075 [1000–1200]
Time between NEC onset and surgery (h)	47.1 [27.1–125.2][*]	17.5 [10.6–27.3][*]
Time between NEC onset and death (h)	—	48.5 [27.0–71.8][*]
Time between surgery and death (h)	—	10.1 [4.9–48.0][*]
Time of death (postnatal day)	—	12 [8–18][*]
Laparotomy procedure		
End-to-end anastomosis	5 (46%)[*]	—
Stoma	4 (36%)	4 (36%)
Primary anastomosis with protective stoma	2 (18)	1 (9%)
Relaparotomy	2 (18%)	3 (27%)
Open/close procedure[‡]	—	6 (55%)[*]
NEC Bell Stage 3B	6 (55%)	8 (73%)
Development of complications		
Recurrent NEC	2 (18%)	—
Post-NEC stenosis	1 (9%)	—
Short Bowel[§]	2 (18%)	—

Data are expressed as numbers (percentages) or median [interquartile range] unless otherwise specified.

[*] $P < 0.05$.

[†] Based on Kloosterman curves with a birth weight cut-off at p10.[27]

[‡] Open/close procedure was performed in case of massive intestinal necrosis (NEC totalis), with <20 cm of vital bowel length left, according to the local hospital protocol.

[§] Short bowel is defined as resection of ≥70% of the total intestine or <50 cm intestinal length remaining when measured from the ligament of Treitz, according to the local hospital protocol.[36]

HsPDA indicates hemodynamically significant patent ductus; NEC, necrotizing enterocolitis.

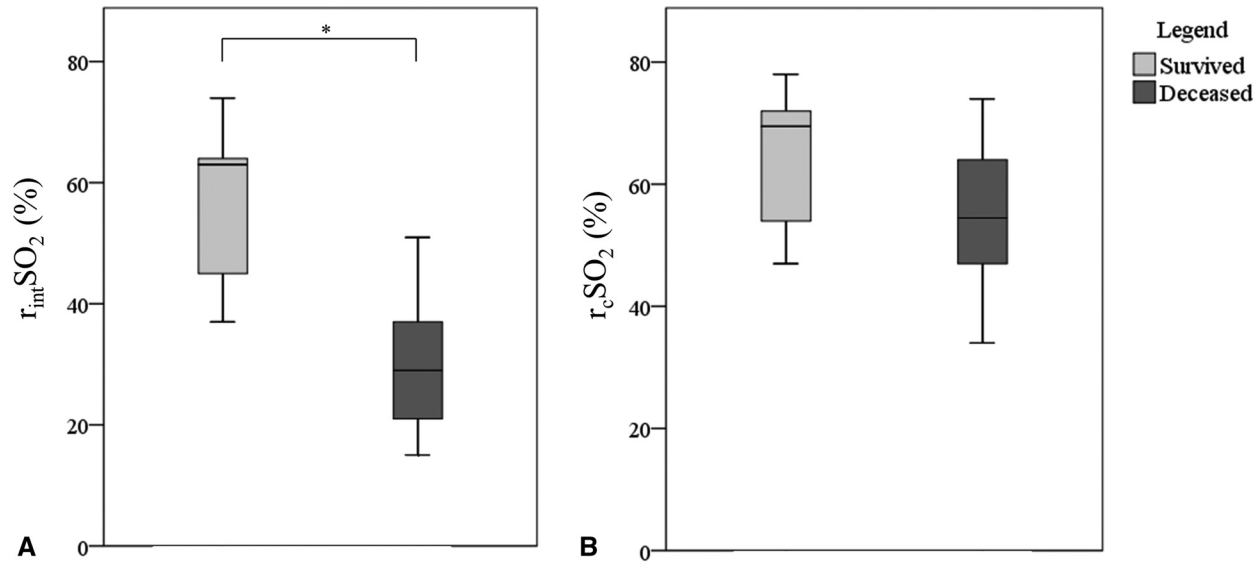
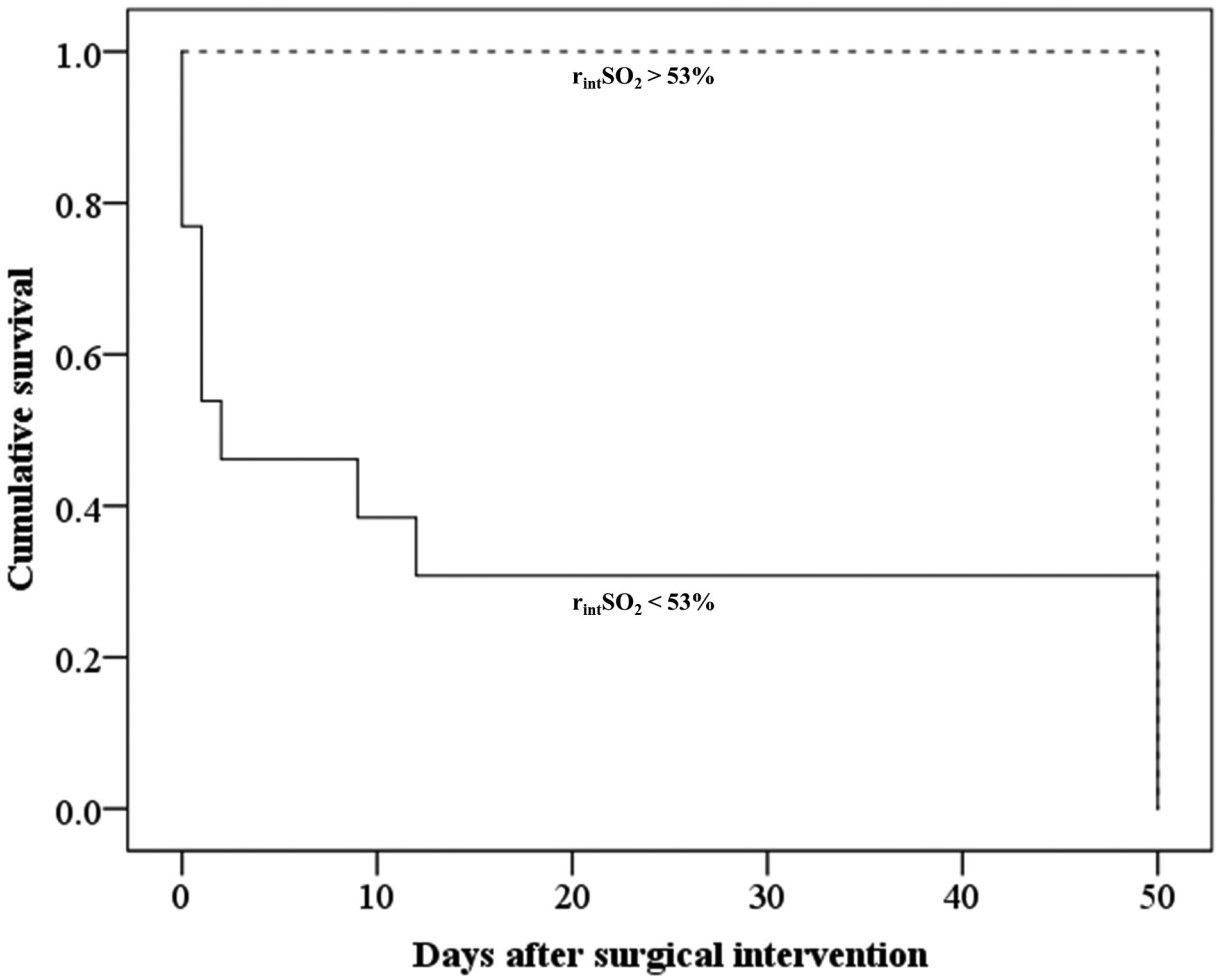


FIGURE 2. Preoperative $r_{int}SO_2$ and r_cSO_2 measurements and surgical outcome. The boxes represent individual $r_{int}SO_2$ (A) and r_cSO_2 (B) values between the 25th and 75th centiles (interquartile range); the whiskers represent the range with exception of outliers between 1.5 and 3 interquartile ranges from the end of a box. $^*P < 0.05$. r_cSO_2, regional cerebral oxygen saturation; $r_{int}SO_2$, regional intestinal oxygen saturation.



No. at risk

$r_{int}SO_2 > 53\%$	6	6	6	6	6	6
$r_{int}SO_2 < 53\%$	13	5	3	3	3	3

FIGURE 3. Kaplan-Meier plot illustrating the survival of preterm infants with NEC during the first 50 d after surgical intervention with $r_{int}SO_2$ values above (- - -) and below (—) the cut-off value of 53%. $r_{int}SO_2$ indicates regional intestinal oxygen saturation.

10 vs 10] (Fig. 2), but the OR was not significant (OR 1.6, 95% CI, 0.8–3.3, $P = 0.21$). Infants who were inoperable and were offered comfort care had a median r_cSO_2 value of 51% [IQR: 46–71] (n = 5).

The Added Value of Intestinal Oxygenation Values to Clinical and Biochemical Assessments

A complete overview of all the clinical and biochemical variables we assessed, and the comorbidities, is presented in Table 2. Only the biochemical variables C-reactive protein (CRP), lactate, and the clinical variable FiO_2 turned out to be significantly different between infants who survived and infants who died after surgery (Table 2). None of the comorbidities were different between survivors and non-survivors (Table 2). We found that in all 3 multiple regression models only the preoperative $r_{int}SO_2$ value remained a significant estimator of surgical outcome, in contrast to CRP, lactate, and FiO_2. Table 3 provides a complete overview of the results of these 3 regression models with the corresponding ORs and 95% CIs.

DISCUSSION

This study indicated that preoperative $r_{int}SO_2$ measurements contribute towards achieving an accurate estimate of the chances of survival of preterm infants with severe NEC after surgical intervention. We showed that preoperative intestinal oxygen saturation values are significantly higher in infants who survived and lower in infants who died despite surgical intervention. The $r_{int}SO_2$ cut-off value for survival was >53% and for mortality the $r_{int}SO_2$ cut-off value was <35%. Furthermore, we demonstrated that cerebral oxygen saturation did not contribute toward accurately estimating survival after surgery for severe NEC.

TABLE 2. Clinical and Biochemical Variables and Comorbidities

N = 22	Survived n = 11	Deceased n = 11
Clinical variables (0–24 h before surgery)		
Endotracheal intubation after NEC onset	10 (91%)	11 (100%)
Maximum FiO_2 (%)	25 [21–31]*	42 [30–80]*
Mean arterial blood pressure (mm Hg)	39 [34–42]	34 [25–39]
Diuresis (mL/kg/h)	4.0 [3.6–4.6]	2.8 [2.1–7.3]
Circulatory failure preoperative		
Fluid resuscitation	6 (55%)	9 (82%)
Inotrope administration	5 (46%)	8 (73%)
Biochemical variables (last blood test before surgery)		
Hemoglobin (mmol/L)	7.8 [6.7–8.6]	7.6 [7.2–8.8]
Thrombocytes (∗10^9/L)	87 [62–233]	116 [73–165]
Leucocytes (∗10^9/L)	10.5 [6.1–19.4]	8.6 [4.8–12.6]
C-reactive protein (mg/L)	138 [83–179]*	73 [12–98]*
Lactate (mmol/L)	1.1 [1.0–1.6]*	4.6 [2.8–8.0]*
Glucose (mmol/L)	5.8 [4.1–9.7]	6.3 [4.9–7.4]
pH	7.24 [7.18–7.30]	7.26 [7.19–7.30]
pCO_2 (kPa)	6.4 [5.2–8.0]	6.2 [4.6–6.5]
Comorbidities		
Endotracheal intubation before NEC onset	3 (27%)	3 (27%)
Sepsis during NEC (blood culture proven)	5 (46%)	3 (37%)
HS PDA during NEC	3 (27%)	3 (27%)

Data are expressed as numbers (percentages) or median [interquartile range] unless otherwise specified.
*$P < 0.05$
FiO_2 indicates fraction of inspired oxygen; HS PDA, hemodynamically significant patent ductus arteriosus; NEC, necrotizing enterocolitis; pCO_2, partial pressure of carbon dioxide.

We aimed to determine whether preoperative $r_{int}SO_2$ and r_cSO_2 measurements are of added value to conventional clinical assessment in identifying which preterm infants with NEC will survive surgery. After validation in a larger cohort, this will help clinicians in the shared decision making process by identifying preterm infants with severe NEC who are likely to survive surgery, to be better able to estimate whether surgical intervention is in the infant's best interest, and to better counsel the parents about their infant's chance of survival.

Remarkably, the median $r_{int}SO_2$ values of the infants who survived surgery were relatively high (63%).[16] As the GA and postmenstrual age did not differ between infants who survived and infants who did not, we cannot clearly attribute the higher $r_{int}SO_2$ values to an age-dependent effect. We hypothesize that the infants who survived might have had intestinal hyperemia as a result of intense intestinal inflammation with concomitant higher CRP values (as opposed to the flow that is present when necrosis has developed).[6] In line with our findings, several studies found higher intestinal oxygen saturation values using NIRS or larger blood flow velocities of the superior mesenteric artery using Dopplers in infants with NEC (Bell Stage 2) who survived, compared to infants who did not suffer from NEC.[6,28,29]

A higher intestinal perfusion in survivors may also be the result of a smaller part of the intestines being affected.[6,14] This is supported by our finding that the infants who survived had higher preoperative $r_{int}SO_2$ values and smaller parts of ischemic resected intestine compared to infants who died (Table 1). Moreover, 9 of the 11 infants who did not survive died because of massive intestinal necrosis, whereas only 2 infants died as a result of circulatory failure.

The $r_{int}SO_2$ was not related to FiO_2, indicating that FiO_2 represents hypoxemia and illness severity, as FiO_2 is manually increased when SpO_2 drops below 90%. When the FiO_2 was high to keep the infants' systemic saturation within the target range, the

TABLE 3. Preoperative $r_{int}SO_2$ and Clinical Variables to Estimate Survival After Surgery, Using Multiple Regression Analyses in 3 Separate Models (Method FORWARD)

Outcome Survival	Univariate Regression Models			Multiple Regression Models		
	OR (95% CI)	R^2	*P* value	OR (95% CI)	R^2	*P* value
Model 1						
rintSO2 (per 10%)	4.09 (1.21–13.85)	0.64	0.02	6.70 (1.02–44.2)	0.74	0.048
C-reactive protein (per 10 mg/L)	1.32 (1.02–1.71)	0.45	0.03			
Model 2						
$r_{int}SO_2$ (per 10%)	4.09 (1.21–13.85)	0.64	0.02	3.61 (1.08–12.09)	0.58	0.04
Lactate (per mmol/L)	0.55 (0.32–0.97)	0.48	0.04			
Model 3						
$r_{int}SO_2$ (per 10%)	4.09 (1.21–13.85)	0.64	0.02	3.76 (1.15–12.23)	0.63	0.03
Inspired FiO_2 (per 5%)	0.27 (0.07–1.03)	0.65	0.05			

CI indicates confidence interval; FiO_2, fraction of inspired oxygen; OR, odds ratio; r_cSO_2, regional cerebral oxygen saturation; $r_{int}SO_2$, regional intestinal oxygen saturation.

infants who did not survive were possibly unable to increase their intestinal saturation, due to massive intestinal necrosis.

Although the preoperative $r_{int}SO_2$ was higher in survivors than in non-survivors the r_cSO_2 did not differ between NEC survivors and non-survivors after surgical intervention. This suggests that the chance of postoperative survival of a preterm infant with severe NEC is predominantly determined by how severe the intestines are affected, and less by the overall systemic severity of the disease. As the conventional clinical assessment predominantly consists of clinical variables addressing the overall severity of illness, this might explain why $r_{int}SO_2$ measurements add important value to the conventional assessment.

Although the systemic circulation did not seem to differ between infants who survived and infants who died, as there was no difference in cerebral oxygen saturation, we did show that infants who survived after surgery had a median r_cSO_2 of >60%, whereas infants who died had a median of <60%. Recently, our research group reported that infants with complicated NEC had median r_cSO_2 values below 60% between 8 and 48 hours after NEC onset.[6] These relatively low r_cSO_2 values in non-survivors may be explained as a result of systemic inflammatory response syndrome as a result of progressive NEC,[3,6] or that these infants are more vulnerable to develop an impaired cerebrovascular autoregulation, which in turn results in compromised cerebral perfusion.[21,30–32]

All infants included in this study underwent a laparotomy. It would be of interest to evaluate whether peritoneal drainage would offer the infants with low preoperative $r_{int}SO_2$ values a better chance to survive than by performing a laparotomy. As peritoneal drainage in our hospital is very uncommon we were unable to address this issue.[33]

We excluded preterm infants with NEC who had an indication for surgical intervention but who were offered comfort care instead, in line with parental preferences. These infants had $r_{int}SO_2$ and r_cSO_2 values comparable to the included infants who died after surgery. Based on our findings, we speculate that the infants in whom comfort care was offered might have had severe intestinal necrosis.

The strength of this study is that as far as we are aware it is first study to demonstrate that intestinal NIRS measurements can be used to estimate survival after surgery in preterm infants with severe NEC. Nevertheless, we acknowledge several limitations. First, we conducted a retrospective cohort study with a small sample. For this reason we could not correct for all potential confounders. As only half of the infants eligible for inclusion had preoperative NIRS data and were included, this might also have induced some bias. Furthermore, the validity for NIRS in assessing intestinal oxygenation is still under debate, and it is unclear exactly which part of the intestine is being measured on account of changing gas-fluid surfaces, intraluminal fecal content, and intestinal peristalsis and gut movements.[6,16,17] Even so, strong correlations between $r_{int}SO_2$ measurements and Doppler flow measurements of the mesenteric artery have previously been demonstrated.[34,35] Ultimately, although we firmly believe in the concept of shared decision making regarding end-of-life decisions, we realize that decisions about treatments and interventions in very sick preterm infants are ethically complex and approaches differ between and even within countries. The value of predictive tools like the ones we suggest should therefore be interpreted within the clinical and social context of the preterm infant with NEC.

In conclusion, we demonstrated that intestinal oxygen saturation measured via NIRS just before surgery adds to the value of current conventional clinical and biochemical assessments to help clinicians to accurately estimate which preterm infants with severe NEC are likely to survive surgery. This may aid clinicians and parents in the shared decision making process to decide whether surgery is in the best interest for the infant.

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