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Oxygen Saturation Index in Neonates with a Congenital Diaphragmatic Hernia: A Retrospective Cohort Study

Emily J.J. Horn-Oudshoorn[a] Marijn J. Vermeulen[a] Kelly J. Crossley[b, e] Suzan C.M. Cochius-den Otter[c] J. Marco Schnater[c] Irwin K.M. Reiss[a] Philip L.J. DeKoninck[b, d, e]

[a]Division of Neonatology, Department of Pediatrics, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [b]The Ritchie Centre, Hudson Institute of Medical Research, Monash University, Melbourne, VIC, Australia; [c]Intensive Care and Department of Pediatric Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [d]Division of Obstetrics and Fetal Medicine, Department of Obstetrics and Gynecology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [e]The Ritchie Centre, Department of Obstetrics and Gynecology, Monash University, Melbourne, VIC, Australia

Keywords
Congenital diaphragmatic hernia · Pulmonary hypertension · Oxygenation index · Oxygen saturation index · Prediction

Abstract
Introduction: The oxygenation index (OI) is a marker for respiratory disease severity and adverse neonatal outcomes. The oxygen saturation index (OSI) is an alternative that allows for continuous noninvasive monitoring, but evidence for clinical use in critically ill neonates is scarce. The aim of this study was to evaluate the OSI as compared to the OI in term neonates with a congenital diaphragmatic hernia (CDH). ***Methods:*** A single-center retrospective cohort study was conducted including all live-born infants with an isolated CDH between June 2017 and December 2020. Paired values of the OI and OSI in the first 24 h after birth were collected. The relation between OI and OSI measurements was assessed, taking into account arterial pH, body temperature, and preductal versus postductal location of oxygen saturation measurement or arterial blood sampling. The predictive values for pulmonary hypertension, need for extracorporeal membrane oxygenation therapy, and survival at discharge were evaluated. ***Results:*** Of 33 subjects included, 398 paired values of the OI (median 5.8 [3.3–17.2]) and OSI (median 7.3 [3.6–14.4]) were collected. The OI and OSI correlated strongly ($r = 0.77$, $p < 0.001$). The OSI values corresponding to the clinically relevant OI values (10, 15, 20, and 40) were 8.9, 10.9, 12.9, and 20.9, respectively. The predictive values of the OI and OSI were comparable for all adverse neonatal outcomes. No difference was found in the area under the receiver operating characteristic curves for the OI and the OSI for adverse neonatal outcomes. ***Conclusions:*** The OSI could replace the OI in clinical practice in infants with a CDH.

Introduction

Respiratory insufficiency and pulmonary hypertension are common life-threatening complications in neonates born with a congenital diaphragmatic hernia (CDH) [1, 2]. Postnatal management is guided by several factors, such as echocardiography, physiological parameters (e.g.,

karger@karger.com
www.karger.com/neo

Correspondence to:
Philip L.J. DeKoninck, p.dekoninck@erasmusmc.nl

blood pressure), blood gas analyses, and the oxygenation index (OI). The OI is a respiratory parameter used to assess the severity of respiratory failure and to evaluate the efficacy of pulmonary vasodilators (such as inhaled nitric oxide [iNO]). In patients with a CDH, the OI is a leading criterion to administer iNO or to initiate extracorporeal membrane oxygenation (ECMO) therapy [3–6]. In addition, the OI in the first day of life is a predictor for adverse neonatal outcomes, such as mortality and pulmonary morbidity [6–10]. Early identification of infants with a high risk of adverse outcomes could guide treatment and aid parental counseling.

The OI is calculated based on the mean airway pressure (MAP), the fraction of inspired oxygen (FiO_2), and the partial arterial pressure of oxygen (PaO_2) [8]. By combining the oxygen delivery (MAP and FiO_2) and oxygen diffusion (PaO_2), the OI reliably reflects the patient's respiratory status [6]. However, a major disadvantage in using the OI is that it cannot be monitored continuously as it requires arterial blood sampling to determine the PaO_2 [3–5]. In neonates with hypoxemic respiratory failure, the oxygen saturation index (OSI) is proposed as a reliable alternative that uses the oxygen saturation (SpO_2) instead of PaO_2 [3–5, 11]. As such, the OSI could continuously monitor the infant's respiratory status and predict adverse neonatal outcomes [3–5, 11–13]. Continuous bedside monitoring enables tailored therapies (such as respiratory support and the use of pulmonary vasodilators) to the patient's changing individual needs, thereby preventing both hypoxia and hyperoxia.

To date, reports on the clinical use of the OSI in critically ill neonates are scarce. Our study addresses this knowledge gap by evaluating the OSI in neonates with a CDH. We hypothesized that the OI and OSI are related and can be used interchangeably in CDH infants, especially when the SpO_2 and PaO_2 measurements are taken at the same location (preductal or postductal). In addition, we aimed to determine the predictive value of the OSI as an early marker for adverse neonatal outcomes.

Methods

Study Cohort

We performed a single-center retrospective cohort study at Erasmus MC, University Medical Center (Rotterdam, the Netherlands), a tertiary referral center. We included all consecutive live-born cases with an isolated CDH between June 2017 and December 2020. We excluded infants with associated anomalies that would directly influence postnatal outcomes, out-born infants, infants receiving palliative care, infants with bilateral CDH or a diaphragmatic eventration, and infants who were not intubated in the delivery room (shown in Fig. 1). The research protocol was approved by the local medical Ethical Committee, and informed consent was waived.

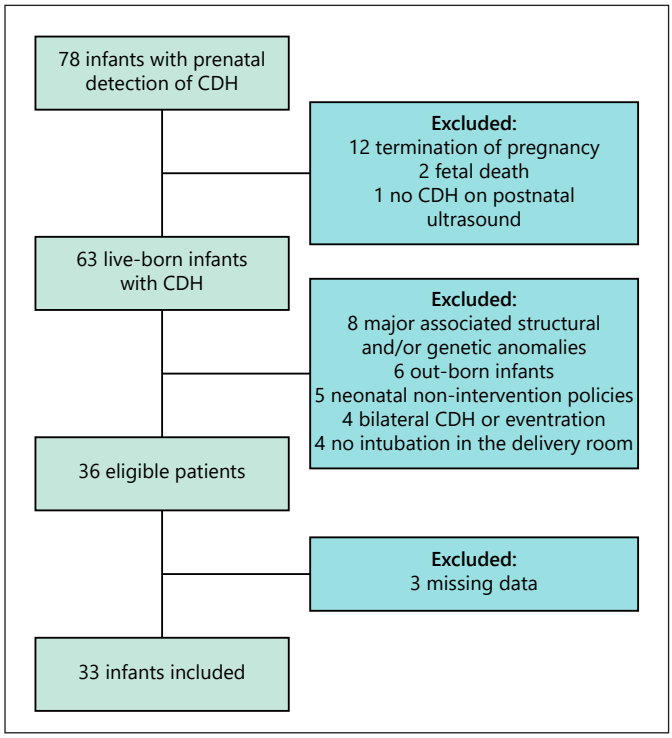

Fig. 1. Flowchart of inclusion. CDH, congenital diaphragmatic hernia.

Data Collection

Baseline characteristics for each patient included gender, gestational age at birth, birth weight, Apgar score at 5 min, umbilical artery pH, prenatal ultrasound measurements of the observed to expected lung-to-head ratio and liver position, side and classification of the diaphragmatic defect, and age at surgical repair [14]. Results from arterial blood samples in the first 24 h after birth were documented together with ventilator settings (i.e., MAP and FiO_2), preductal and postductal SpO_2 levels, and body temperature at the time of arterial blood sampling. The OI was calculated as follows: $OI = FiO_2$ [%] × MAP [cm H_2O]/PaO_2 [mm Hg] [8]. The OSI was calculated as follows: $OSI = FiO_2$ [%] × MAP [cm H_2O]/SpO_2 [%] [11]. Adverse neonatal outcomes included pulmonary hypertension, need for ECMO therapy, and survival at discharge. Pulmonary hypertension was defined as an estimated right-ventricular systolic pressure to systolic blood pressure ratio of ≥2/3 on echocardiography, which required therapy [15].

OI and OSI values were paired taking into consideration a minimal time difference between measurements; for the vast majority, this was within seconds as continuous data were collected. If possible, we combined preductal OI values (preductal PaO_2) with preductal OSI values (preductal SpO_2) and postductal OI values (postductal PaO_2) with postductal OSI values (postductal SpO_2) (*matched* OI-OSI pairs). If we could not match a preductal OI value with a preductal OSI value because of incomplete data, we used the postductal OSI

Table 1. Baseline characteristics

	All subjects (*n* = 33)	
Fetal characteristics	*n*	
o/e LHR, %		44.3±12.0
Gestational age at measurement, weeks^{+days}		26^{+6} [26^{+0}–29^{+3}]
Intrathoracic liver		17 (52)
Left-sided defect		28 (85)
Neonatal characteristics		
Male, *n* (%)		19 (58)
Gestational age at birth, weeks^{+days}		38^{+1} [37^{+5}–38^{+2}]
Birthweight, g		3,000 [2,700–3,200]
Birthweight centile, %		34 [18–61]
Apgar 5′	26	7 [6–8]
Umbilical artery pH	31	7.26±0.08
Age at surgical repair, days	32	6 [5–8]
Defect size, *n* (%)		
A		3 (9)
B		10 (30)
C		8 (24)
D		7 (21)
Unknown		5 (15)

Data are expressed as the median [IQR], mean ± SD, or *N* (%). o/e LHR, observed to expected lung-to-head ratio.

value; if we could not match a postductal OI value with a postductal OSI value because of incomplete data, we used the preductal OSI value (*unmatched* OI-OSI pairs). For each patient, we also determined the OI and OSI values at admission to the intensive care unit (<3 h after birth) and the highest (worst) OI and OSI values in the first 24 h after birth as we expected that these values could be clinically useful in predicting neonatal outcomes [6, 8, 10].

Local Protocol

Our local protocol is based on the CDH EURO Consortium guideline, which recommends to administer iNO in neonates with an OI >20 and to consider ECMO therapy in neonates with an OI ≥40 persisting for ≥3 h [16]. In our center, the OI is, among others, one of the criteria that are used in considering ECMO therapy in infants with a CDH.

Statistical Analysis

Normality of the data was checked with QQ-plots and density distributions combined with the Shapiro-Wilk test. The correlation coefficient of the repeated measurements of the OI and OSI was calculated separately for all pairs, the matched pairs, and the unmatched pairs using the R package "rmcorr." A Spearman correlation coefficient was calculated for the correlation between the OI and OSI values at admission, and the highest OI and OSI values in the first 24 h after birth.

Using linear mixed models, we derived a predictive equation for the association of the OSI with the OI while taking into account the correlation within individuals. Multivariate mixed models were used to correct for both pH and body temperature that affect the oxygen dissociation curve. The best fitting model was determined with ANOVA tests. We used the predictive equation with the best fit and highest clinical relevance to calculate the corresponding OSI cutoff values for relevant OI values. Based on the guidelines, local clinical practice, and other studies assessing the predictive value of the OI, we selected OI values of 10, 15, 20, and 40 [3, 5, 10, 16, 17]. These values and the corresponding OSI values were then used to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the outcomes pulmonary hypertension, ECMO, and mortality. Receiver operator characteristic (ROC) curves and areas under the curve (AUC) further assessed the discriminative ability of the OI and OSI for the adverse neonatal outcomes using the R package "pROC." A sensitivity analysis in 3 subgroups (preductal matched pairs, postductal matched pairs, and unmatched pairs) was performed to evaluate potential bias introduced by combining all data in our mixed model analysis.

Statistical analyses were performed using the computing environment R (v4.0.2; R Core Team [2020], Vienna, Austria). $p < 0.05$ was considered as the level of significance.

Results

Baseline Characteristics

The total study population included 33 neonates with a CDH, of whom 3 infants were diagnosed with minor associated abnormalities (i.e., mosaicism chromosome 7, unilateral renal agenesis, and radial aplasia; the latter two with normal genetic analysis on microarray and whole-exome sequencing). Table 1 provides an overview of the baseline characteristics of all included subjects.

Table 2. Characteristics of data used in statistical analyses

	Total group (n = 398)		Matched pairs (n = 318)		Unmatched pairs (n = 80)	
	n	median [IQR]	n	median [IQR]	n	median [IQR]
pH		7.25 [7.19–7.30]		7.26 [7.20–7.30]		7.24 [7.14–7.32]
PaO_2, mm Hg		85.5 [57.9–130.3]		93.4 [62.3–134.1]		68.6 [47.8–105.0]
FiO_2, %		53 [35–100]		51 [37–99]		88 [25–100]
MAP, cm H_2O		12.7 [10.8–14.8]		12.6 [10.8–14.4]		13.7 [10.9–16.1]
Preductal SpO_2, %	245	97 [93–99]	245	97 [93–99]		
Postductal SpO_2, %	153	94 [79–99]	73	96 [90–99]	80	91 [76–97]
Body temperature, °C		37.0 [36.8–37.4]		37.0 [36.8–37.3]		37.0 [36.8–37.4]
OI		5.8 [3.3–17.2]		5.4 [3.3–13.6]		9.5 [3.6–27.8]
OSI		7.3 [3.6–14.3]		7.1 [3.8–12.6]		12.4 [3.1–21.8]

Data are expressed as median [IQR]. Data on preductal matched pairs and postductal matched pairs separately are shown in online supplementary Table 1. PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; MAP, mean airway pressure; SpO_2, oxygen saturation; OI, oxygenation index; OSI, oxygen saturation index.

Table 3. Mixed models on the OSI in the total group

	Intercept		OI		pH		Temperature	
	β	p value	β	p value	β	p value	β	p value
398 pairs	4.09	<0.001	0.44	<0.001				
33 groups	92.58	<0.001	0.40	<0.001	−12.08	<0.001		
	106.18	<0.001	0.38	<0.001	−15.57	<0.001	0.31	0.36

β reflects the change in the OSI for a one-unit increase in the corresponding predicting variable (i.e., OI, pH, and temperature). OI, oxygenation index; OSI, oxygen saturation index.

Pairs of OI Values and OSI Values

We calculated 406 OI values (327 preductal and 79 postductal) and 700 OSI values (309 preductal and 391 postductal). Preductal OI values were compared to preductal (n = 245, *matched*) or postductal (n = 80, *unmatched*) OSI values; for 2 preductal OI values, this was not possible due to missing SpO_2 values. Postductal OI values were compared to postductal OSI values (n = 73, *matched*); this was not possible for 2 postductal OI values due to missing SpO_2 measurements. Additionally, we excluded 4 unmatched pairs of postductal OI values and preductal OSI values as they only accounted for <1% of the total dataset. This resulted in a total of 398 paired OI and OSI values, with a median OI of 5.8 [3.3–17.2] and a median OSI of 7.3 [3.6–14.4]. Table 2 contains the characteristics of the variables that are used in the statistical analyses, and online supplementary Table 1 (see www.karger.com/doi/10.1159/000520883 for all online suppl. material) contains the characteristics of the *preductal* matched pairs and *postductal* matched pairs.

Correlation of the OI and OSI

OI and OSI values were strongly correlated: all pairs (r = 0.77, p < 0.001), matched pairs (r = 0.73, p < 0.001), and unmatched pairs (r = 0.76, p < 0.001). The correlation of OI and OSI values was also strong at admission (r_s = 0.79, p < 0.001) and was strongest for the highest OI and OSI values in the first 24 h (r_s = 0.93, p < 0.001).

Association between the OI and OSI

Table 3 presents the regression formulas describing the association between OI and OSI values in infants with a CDH. In all analyses, the OI was significantly and strongly associated with the OSI (p < 0.001). Adding pH to the model improved the fit of the model significantly (p < 0.001), but adding body temperature did not (p = 0.35).

OSI Cutoff Values

The multivariate mixed model with the OI and the pH as independent variables fitted the data best. We thus calculated OSI values that correspond with OI values based

Table 4. Predictive values of the OI and OSI

	At admission, %								Highest in first 24 h, %							
	OI				OSI				OI				OSI			
	10	15	20	40	9	11	13	21	10	15	20	40	9	11	13	21
Pulmonary hypertension																
Sensitivity	47	41	41	12	44	44	38	13	77	73	64	32	82	82	64	36
Specificity	70	70	80	100	70	80	90	100	73	73	82	100	73	82	91	100
PPV	73	70	78	100	70	78	86	100	85	84	88	100	86	90	93	100
NPV	44	41	44	40	44	47	47	42	62	57	53	42	67	69	56	44
ECMO																
Sensitivity	71	71	71	29	67	67	67	33	91	91	82	55	91	91	82	64
Specificity	70	75	80	100	70	75	85	100	55	59	68	96	50	55	73	96
PPV	46	50	56	100	40	44	57	100	50	53	56	86	48	50	60	88
NPV	88	88	89	80	88	88	90	83	92	93	88	81	92	92	89	84
Mortality																
Sensitivity	100	100	100	67	100	100	100	50	100	100	100	60	100	100	100	80
Specificity	67	71	75	100	67	71	79	96	46	50	61	86	43	46	64	86
PPV	27	30	33	100	20	22	29	50	25	26	31	43	24	25	33	50
NPV	100	100	100	96	100	100	100	96	100	100	100	92	100	100	100	96

ECMO, extracorporeal membrane oxygenation; NPV, negative predictive value; OI, oxygenation index; OSI, oxygen saturation index; PPV, positive predictive value.

on this model while assuming a mean pH of 7.25 (Table 2). OSI values corresponding with relevant OI values (10, 15, 20, and 40) were 8.9, 10.9, 12.9, and 20.9. For practical use, we rounded these values to 9, 11, 13, and 21.

Adverse Neonatal Outcomes

Of all subjects, 67% developed pulmonary hypertension, 33% required ECMO therapy, and 15% did not survive until discharge. Table 4 shows that the sensitivity, specificity, PPV, and NPV of the OI and OSI values at admission and highest OI and OSI values are comparable. Figure 2 shows the ROC curves for the OI and OSI values at admission and highest OI and OSI values in discrimination for adverse neonatal outcomes. The discriminative ability of the OI and OSI at admission was not different in prediction of pulmonary hypertension (AUC_{OI} = 0.61 vs. AUC_{OSI} = 0.71, p = 0.25), ECMO therapy (AUC_{OI} = 0.78 vs. AUC_{OSI} = 0.82, p = 0.68), and survival at discharge (AUC_{OI} = 0.88 vs. AUC_{OSI} = 0.98, p = 0.35). The discriminative ability of the highest OI and OSI was also not different in the prediction of pulmonary hypertension requiring therapy (AUC_{OI} = 0.83 vs. AUC_{OSI} = 0.90, p = 0.11), ECMO therapy (AUC_{OI} = 0.89 vs. AUC_{OSI} = 0.88, p = 0.85), and survival at discharge (AUC_{OI} = 0.86 vs. AUC_{OSI} = 0.91, p = 0.18).

Sensitivity Analysis

Multivariate mixed models with the OI and the pH as independent variables show a significant association between the OI and OSI in each subgroup (online suppl. Table 2). The effect size and direction of these associations are in line with the results in the total group (Table 3).

Discussion

We found strong correlations between OI and OSI values calculated in the first 24 h after birth in neonates born with a CDH. Based on our models, we have determined that the clinically relevant OI values of 10, 15, 20, and 40 correspond to the OSI values of 9, 11, 13, and 21, respectively. The OI and OSI at admission and the highest OI and OSI in the first 24 h after birth show similar sensitivity, specificity, and predictive values for major adverse neonatal outcomes. These findings highlight that the OSI could replace the OI in clinical practice, thereby enabling continuous real-time noninvasive monitoring of the infant's respiratory status and potentially diminishing the need for arterial blood sampling.

The strong positive correlation between OI values and OSI values is in line with earlier findings in infants with hy-

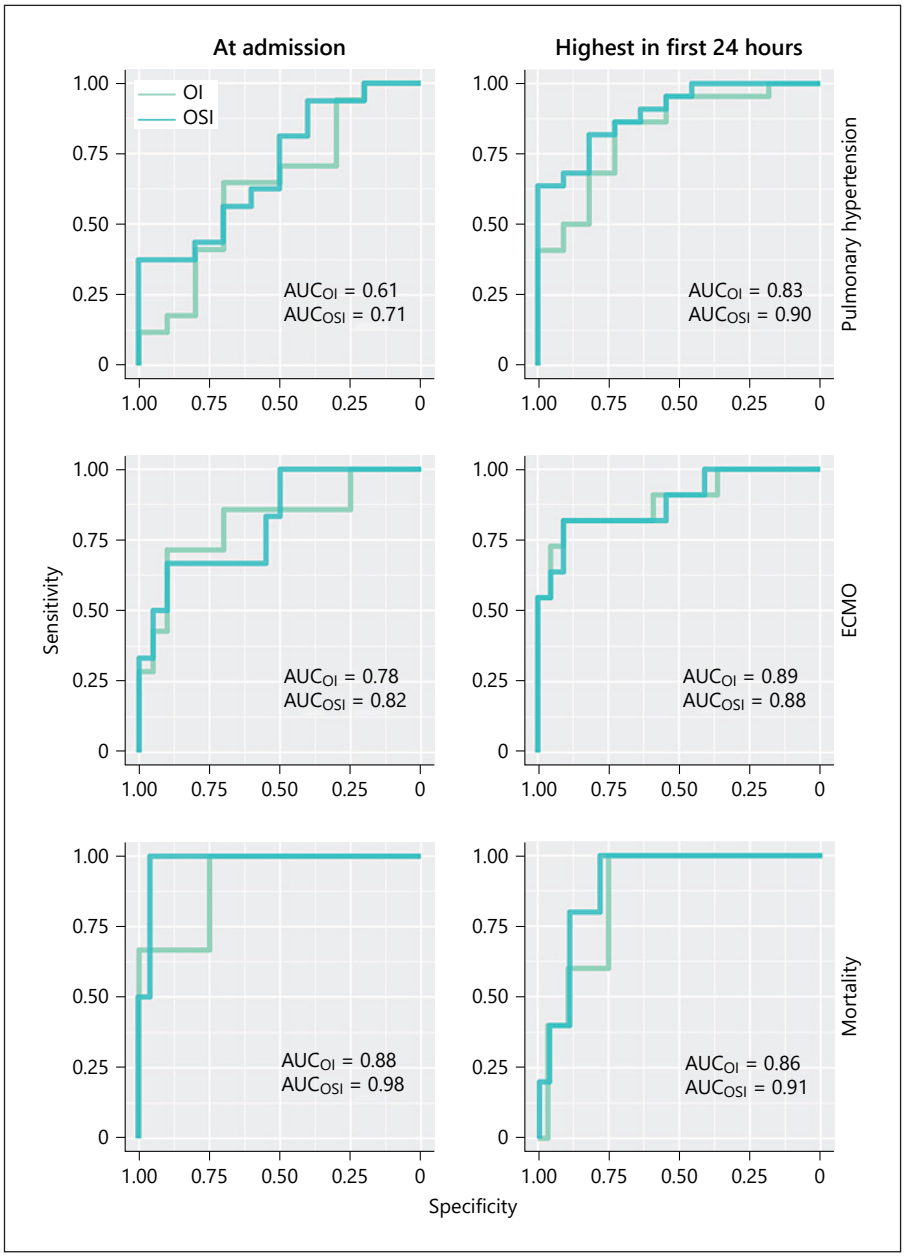

Fig. 2. ROC curves of OI and OSI. ROC, receiver operating characteristic; OI, oxygen index; OSI, oxygenation saturation index; AUC, area under the curve; ECMO, extracorporeal membrane oxygenation.

poxemic respiratory failure [3, 5, 17]. Interestingly, our data suggest that whether the locations of PaO_2 and SpO_2 measurement are identical (pre- or postductal) does not importantly influence the strength of the correlation. In addition, the highest OI and OSI values correlated stronger than the overall OI and OSI values. An explanation for this may be found in SpO_2 and PaO_2 only having a linear relation in the middle part of the oxygen dissociation curve. Hence, at higher SpO_2 values, the correlation may be weaker, as was shown in a previous series in mechanically ventilated neonates in which a stronger correlation was observed when excluding SpO_2 values >98% [17]. This observation was also supported by a more recent study showing that OI and OSI correlated strongest if SpO_2 was 85–95% compared to that with values above 95% [3]. Due to our limited sample size, we refrained from subgroup analyses in those with SpO_2 >95% (present in 53% of the pairs).

The direction and effect size of the linear association between the OI and OSI are comparable to those observed in neonates with hypoxemic respiratory failure [3, 5, 17]. Our data confirm that a two-unit increase of the OI correlates to about a one-unit increase of the OSI.

However, methodological differences, particularly in measurement units, hamper comparison of our exact findings to previous series that reported slightly higher [18] or lower [4, 5, 17] OSI-to-OI ratios. Although we expected an effect on the oxygen dissociation curve, body temperature did not significantly change the OSI values. Lower pH values were associated with higher OSI values, reflecting a left shift in the oxygen dissociation curve [18]. For practical use, we opted for a fixed pH value to determine OSI values that correspond to clinically relevant OI values.

Based on the strong linear relation between the OI and OSI, we speculate that the OSI cutoffs could be used as an alternative to the OI cutoffs used in clinical practice. We propose to use the OSI values of 9, 11, 13, and 21, corresponding to the, respective, OI values of 10, 15, 20, and 40. Prospective validation of these cutoffs in a larger sample size could further increase the clinical relevance and determine potential differences in cutoffs when using either preductal or postductal SpO_2 measurements. Furthermore, a high initial OSI value at admission to the intensive care unit could alert clinicians to an increased risk of a complicated postnatal course.

The OI is a strong predictor of outcomes in neonates with a CDH: the lowest (best) and mean OI in the first 24 h and the highest OI in the first 48 h after birth accurately predict mortality [7–10]. The lowest OI might reflect a transient period of overtreatment instead of overall lung function [6, 7]. Therefore, we did not evaluate the lowest OI but focused on the highest and initial values. The predictive value and discriminative ability of the OI and OSI were comparable in our data; however, specifically, the *highest* OSI showed a slightly higher predictive value for most adverse neonatal outcomes. This trend was consistent in almost all analyses, translating in higher AUCs for most outcomes. Although we did not document significant differences, these observations certainly warrant further investigation in a larger prospective trial.

The sensitivity analysis suggests a low risk of bias due to combining all matched and unmatched pairs. Because of the small sample sizes and the relatively low number of cases with adverse neonatal outcomes, we were not able to determine the sensitivity, specificity, PPV, and NPV for preductal and postductal measurements separately. Further research in a larger sample size could validate whether separate models and predictive values should be conducted.

Calculation of the OSI does not require arterial blood sampling, and, thus, the OSI can be monitored continuously. These serial measurements might predict outcomes more reliably than incidental OI or OSI values. A retrospective cohort study already demonstrated that the *serial* OI had a better sensitivity and specificity than those in the lowest OI [6]. It is likely that changes in the trend of continuously measured OSI values could alert physicians at an early stage of clinical deterioration and, thus, the need for additional therapy. However, whether the OSI could replace the OI or should rather be used as an additional tool in clinical decision-making needs further investigation.

Strengths of our study include the selective use of arterial blood samples and the pairing of OI and OSI values based on preductal or postductal measurements, which has not been described before. Due to the retrospective design, we could not always determine ventilator settings and respiratory parameters exactly at the time point of blood sampling. For the majority of data, this was within seconds, and, thus, we believe that the impact of this was limited. Also, obtaining solely *matched* OI-OSI pairs was not always possible due to the absence of the required SpO_2 value. High-frequency oscillation ventilation uses a higher MAP than conventional mechanical ventilation, thereby potentially falsely increasing the OI and OSI measurements [19]. But, as our local ventilation strategies in CDH only include conventional mechanical ventilation, we could not confirm this hypothesis. Furthermore, as we were limited by our sample size, we could not add additional factors to our model such as (fetal) hemoglobin levels and partial pressure of carbon dioxide, both of which potentially influence the oxygen dissociation curve [18]. Moreover, we recommend that the OSI should be interpreted carefully if SpO_2 is >95%. To capture the most relevant data for early prediction, we only included measurements during the first 24 h after birth. Extrapolation to the period thereafter seems reasonable as we believe that the relation between the OI and OSI does not differ after 24 h.

Conclusion

Our data suggest that OSI measurements could replace OI measurements in infants with a CDH. In the first 24 h after birth, the predictive values and discriminative ability of the OI and OSI are similar for pulmonary hypertension, ECMO therapy, and mortality. Continuously measured OSI values have the potential to offer a real-time guidance on therapy in clinical practice.

Statement of Ethics

This study protocol was reviewed and approved by the Medical Ethics Review Committee of the Erasmus MC University Medical Centre, approval number MEC-2020-0563. Informed consent was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.J.J.H.-O., M.J.V., K.J.C., S.C.M.C.O., J.M.S., I.K.M.R., and P.L.J.D. were all involved in the conception of this paper. E.J.J.H.-O. performed chart reviews and constructed the database for further analysis. E.J.J.H.-O., M.J.V., and P.L.J.D. conceptualized and designed the statistical plan, and contributed to the analysis and the interpretation of the results. E.J.J.H.-O. wrote the first draft, which was critically reviewed by all the authors. All the authors have approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from P.L.J. DeKoninck upon reasonable request.

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