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The Oxygen Saturation Index as Early Predictor of Outcomes in Congenital Diaphragmatic Hernia

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

Abstract
Objective: The aim of the study was to evaluate the oxygen saturation index (OSI) as an early predictor of clinical deterioration in infants with congenital diaphragmatic hernia (CDH). ***Methods:*** A single-center retrospective cohort study was conducted in consecutive infants with isolated CDH with continuous OSI measurements collected in the first 24 h after birth between June 2017 and July 2021. Outcomes of interest were pulmonary hypertension, extracorporeal membrane oxygenation (ECMO)-therapy, and mortality. We evaluated the discriminative values of the maximum OSI value and of mean OSI values with receiver operator characteristic (ROC) analysis and the area under the ROC curve. ***Results:*** In 42 infants with 49,473 OSI measurements, the median OSI was 5.0 (interquartile range 3.1–10.6). Twenty-seven infants developed pulmonary hypertension on a median of day 1 (1-1), of which 15 infants had an indication for ECMO-therapy, and 6 infants died. Maximum OSI values were associated with pulmonary hypertension, ECMO-therapy, and mortality. Mean OSI values had an acceptable discriminative ability for pulmonary hypertension and an excellent discriminative ability for ECMO-therapy and mortality. Although OSI measurements were not always present in the first hours after birth, we determined discriminative cut-offs for mean OSI values already in these first hours for pulmonary hypertension, the need for ECMO-therapy, and mortality. ***Conclusions:*** Continuous OSI evaluation is a promising modality to identify those infants at highest risk for clinical deterioration already in the first hours after birth. This provides an opportunity to tailor postnatal management based on the individual patient's needs.

Introduction

Congenital diaphragmatic hernia (CDH) is a birth defect that is associated with postnatal cardiopulmonary insufficiency and pulmonary hypertension (PH) [1, 2]. Consequently, affected infants commonly need mechanical ventilation, pulmonary vasodilators, and/or extracorporeal membrane oxygenation (ECMO)-therapy. Around 30% of all affected infants do not survive [3]. Early iden-

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tification of those infants at risk for a complicated postnatal course could alert physicians and refine individualized treatment strategies. Ideally, risk stratification is done within the first hours after birth as early clinical deterioration due to PH is not uncommon, yet this is not feasible with most of the currently available prediction models [4–6].

Given that the severity of lung disease (i.e., pulmonary hypoplasia and PH) has the largest influence on postnatal outcomes, it is reasonable to revert to markers that are a composite of elements determining the efficiency of gas exchange within the lungs. Such markers are the oxygenation index (OI) and oxygen saturation index (OSI), based on partial pressure of oxygen (pO_2) and on oxygen saturation (SpO_2), respectively. Both indices combine oxygen delivery (defined by mean airway pressure [MAP] and fraction of inspired oxygen [FiO_2]) and oxygen diffusion (pO_2 or SpO_2) into a ratio [7, 8]. As the OSI could be monitored *continuously* and *transcutaneously*, in contrast to the commonly used OI that requires blood sampling, the OSI might be used for real-time and bedside guidance during the crucial first hours of life. We have recently demonstrated that both the OI and OSI predict adverse outcomes in infants with CDH, but up until now, studies have focused on either the predictive value of OSI measurements at pre-specified time points or the comparability of paired OI and OSI measurements [9–15]. Hence, studies on the predictive value of continuous OSI measurements are scarce, especially in infants with CDH [16].

In this study, we hypothesized that continuous OSI measurements in the first 24 h after birth can discriminate which infants are at highest risk for a complicated postnatal course. The OSI's discriminative value was assessed for clinically relevant outcomes: PH, ECMO-therapy, and mortality.

Methods

Study Design

We conducted a single-center retrospective cohort study at the Erasmus MC, University Medical Center (Rotterdam, The Netherlands). Eligible cases were added to an existing database that was used in a recent study [14]. All consecutive infants born with a prenatally detected isolated left-sided or right-sided CDH between June 2017 and July 2021 were included. We excluded infants with a diaphragmatic eventration, infants that were out-born, infants receiving palliative care immediately after birth, infants that deceased in the delivery room, infants with confirmed syndromes that would influence the postnatal course, and infants with less than 1 h of OSI measurements. The research protocol was approved by the Local Medical Ethical Committee (MEC-2020-0563), and informed consent was waived.

Postnatal Management

Local postnatal management is based on the CDH EURO Consortium Guideline that recommends, among others, to (1) adapt respiratory support to reach a preductal SpO_2 between 80 and 95% and a postductal SpO_2 >70%, and (2) consider ECMO-therapy in infants with an OI ≥ 40 for at least 3 consecutive hours [17].

Data Collection

The following baseline characteristics were collected from clinical charts for each patient: prenatal observed to expected lung-to-head ratio, side of the diaphragmatic defect (left or right), liver position (intra-abdominal or intra-thoracic), gestational age at birth, birthweight, umbilical artery pH, age at surgical repair, occurrence of sepsis confirmed by a positive blood culture, number of days on mechanical ventilation, need for supplemental oxygen on day 28, and number of days of hospital admission. OSI values were calculated for the first 24 h after birth (FiO_2 [%]*MAP [cmH_2O]/SpO_2 [%]) by combining FiO_2, MAP, and SpO_2 measurements [7]. The respiratory settings (i.e., FiO_2 and MAP) and physiological measurements (i.e., SpO_2) are locally stored each minute, however not synchronized, as these measurements are collected by different devices. Therefore, we pre-specified a maximum time difference of 120 s between respiratory settings and physiological measurements. In CDH infants, both the preductal and postductal SpO_2 are commonly collected, but we aimed at collecting *preductal* SpO_2 measurements. Based on historical cohorts, OSI > 8 is highly discriminative in the assessment of respiratory failure severity and the OSI's value is generally equal to half of the OI's value [7, 9, 18, 19].

Outcomes of interest were the presence of PH, defined as an estimated right ventricular systolic pressure to systolic blood pressure ratio of ≥2/3 on echocardiography that required therapy; the need for ECMO-therapy, defined as a clinical decision for ECMO-requirement irrespective of actual ECMO-initiation; and all-cause mortality before hospital discharge [20]. For each infant, OSI measurements were excluded after the time point at which the particular outcome of interest was observed.

Statistical Analysis

Normality of the data was checked with QQ plots and density distributions combined with the Shapiro-Wilk test. Continuous variables were described using mean ± standard deviation in case of a normal distribution and median [interquartile range] in case of a non-normal distribution. Categorical data are reported as number (percentage).

For each infant, we collected (1) the mean OSI for the first 1, 2, 3, 6, 12, and 24 h after birth; and (2) the maximum (worst) OSI measurement during the first 12 h and 24 h after birth. A receiver operator characteristic analysis and the area under the receiver operator characteristic curve (AUROC) assessed the discriminative ability of these parameters for the abovementioned outcomes of interest using the R package "cutpointr." Optimal cut-offs and corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with the Youden index, which gives equal weight to the sensitivity and the specificity and optimizes the differentiating ability. Differences in maximum OSI measurement between infants with and without

Table 1. Patient characteristics

	All subjects (n = 42)	
	n	
Observed to expected lung-to-head-ratio, %		43.6±12.7
Intra-thoracic liver		20 (48)
Left-sided defect		36 (86)
Gestational age at birth, weeks^{+days}		38^{+1} [37^{+4}–38^{+3}]
Birthweight, g		3,000 [2,725–3,168]
Umbilical artery pH	39	7.29 [7.23–7.33]
Age at surgical repair, days	40	5 [4–7]
Culture proven sepsis		13 (31)
Days on mechanical ventilation		10 [7–21]
Supplemental oxygen on day 28	37	19 (51)
Days of neonatal admission		35 [22–63]
Pulmonary hypertension		27 (64)
Age at onset pulmonary hypertension, days		1 [1-1]
Need for ECMO-therapy		15 (36)
Mortality		6 (14)
Age at mortality, days		19 [7–21]

Data are expressed as median [IQR], mean ± SD, or *N* (%). ECMO, extracorporeal membrane oxygenation.

one of the outcomes of interest were assessed with the Mann-Whitney test. Due to measurement errors, our dataset contains outliers such as FiO_2 values <21%, whereas hypoxic ventilation in CDH infants is not performed in our center. To assess the risk on bias by including all data in our analysis, we performed a sensitivity analysis in which FiO_2 values <21% were set to 21% and MAP values <4 cmH_2O were removed. Statistical analyses were performed using the computing environment R (R Core Team [2020], Vienna, Austria). $p < 0.05$ was considered statistically significant for all tests.

Results

Baseline Characteristics

The total study population consisted of 42 infants with CDH with a median gestational age at birth of 38^{+1} [37^{+4}–38^{+3}] weeks. Five infants were diagnosed with minor genetic or additional anatomical abnormalities. The baseline characteristics of all patients are depicted in Table 1. A total of 49,473 OSI measurements were collected with a median number per patient of 1,258 [1,064–1,335]. Minimum and maximum values of the respective parameters were FiO_2 20.5–100%, MAP 0.1–28.9 cmH_2O, and SpO_2 13–100%. Median OSI was 5.0 [3.1–10.6], and the first OSI measurement was collected at 0.5 h after birth. Figure 1 depicts the OSI measurements of one specific patient. The majority of infants (n = 27, 64%) developed PH after birth; in 22 cases, this presented within the first 24 h. Seven of the infants with PH required ECMO-therapy already within the first 24 h because of therapy-resistant PH. In one case, ECMO-therapy was not initiated on parental request and palliative care was given instead. Eight infants required ECMO-therapy after the first 24 h, seven of them because of therapy-resistant PH and one

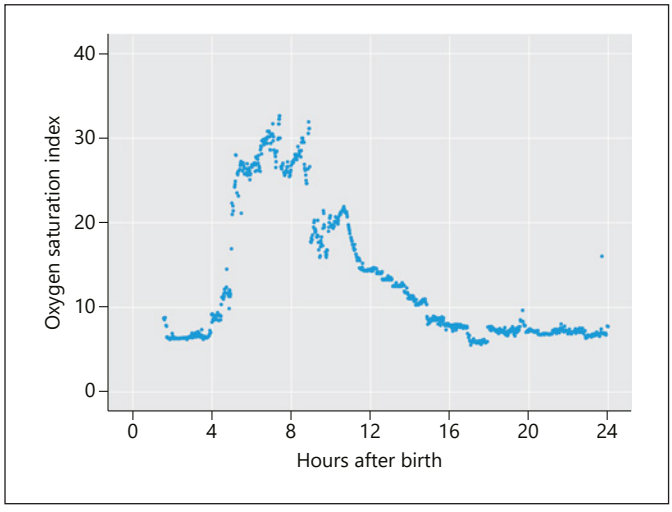

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Fig. 1. Oxygen saturation index over the first 24 h for 1 patient with a left-sided diaphragmatic defect, an observed to expected lung-to-head ratio of 51%, and intra-abdominal liver position. This patient developed severe pulmonary hypertension on the first day, did not require extracorporeal membrane oxygenation, and survived until discharge.

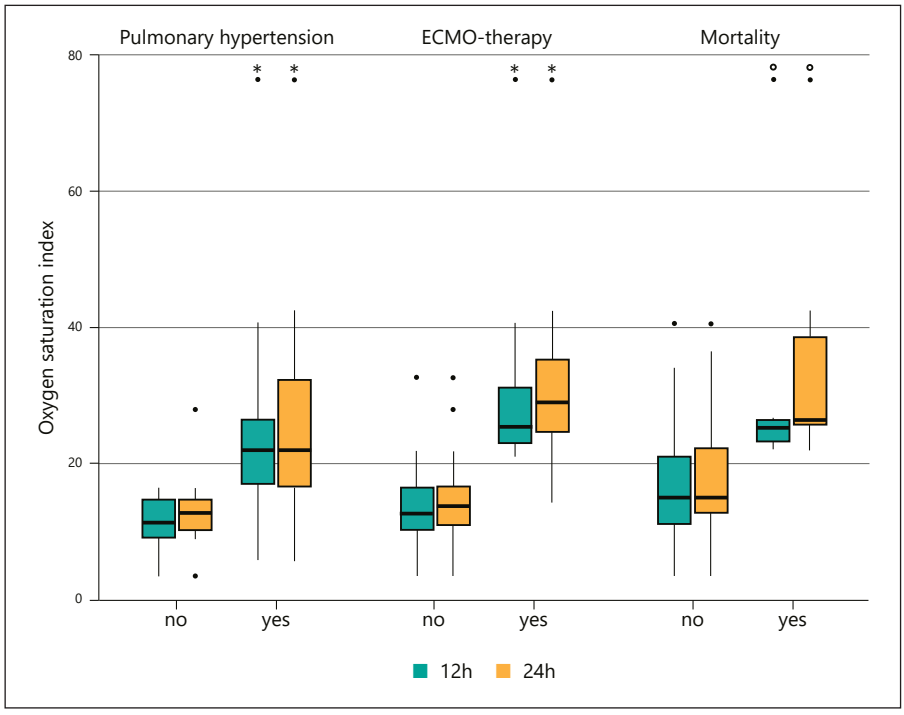

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Fig. 2. Maximum oxygen saturation index in the first 12 h and 24 h after birth. *p < 0.001, °p < 0.01.

because of severe left-sided cardiac failure. Six infants (14%) died before hospital discharge.

Early Prediction of Adverse Outcomes

The discriminative ability of the mean OSI was acceptable for the occurrence of PH and excellent for ECMO-therapy and mortality (Table 2). Optimal cut-offs, defined by highest sensitivity and specificity, for mean OSI values varied between 3 and 20 for the different time periods and outcomes. Already in the first hour after birth, mean OSI predicts outcomes: mean OSI ≥ 15 predicts both the occurrence of PH (AUC 0.76; sensitivity 56%; specificity 100%; PPV 100%; NPV 56%) and need for ECMO-therapy (AUC 0.96; sensitivity 83%; specificity 100%; PPV 100%; NPV 89%). Furthermore, mean OSI ≥ 17.3 predicts mortality (AUC 0.94; sensitivity 100%; specificity 91%; PPV 75%; NPV 100%).

Maximum OSI

The maximum OSI values in the first 12 and 24 h after birth were significantly higher in infants who developed PH, required ECMO-therapy, or died before discharge, as compared to those who did not (Fig. 2). Also, the maximum OSI measurement was a reliable predictor for adverse outcomes. OSI ≥ 12.5 in the first 12 h predicts the development of clinically relevant PH (AUC 0.70; sensitivity 75%; specificity 67%; PPV 55%; NPV 83%). OSI ≥ 22 within the first 12 h in infants with PH predicts the need for ECMO-therapy >12 h (AUC 0.83; sensitivity 88%; specificity 83%; PPV 88%; NPV 83%). OSI ≥ 24 within the first 24 h in infants with PH predicts the need for ECMO-therapy >24 h (AUC 0.84; sensitivity 86%; specificity 88%; PPV 86%; NPV 88%). OSI ≥ 22 in the first 12 h and 24 h predicts mortality before discharge (AUC 0.85; sensitivity 100%; specificity 75–80%; PPV 40–46%; NPV 100%). In other words, all infants that died had an OSI measurement ≥22 within the first day and all infants with a maximum OSI measurement <22 survived.

Sensitivity Analysis

The sensitivity analysis did not show differences in the cut-off levels and corresponding sensitivity, specificity, PPV, NPV, and AUROC values for any of the combinations of mean OSI and adverse outcomes.

Discussion

In this retrospective cohort study, we have assessed the predictive value of continuous OSI measurements for clinically relevant outcomes in infants born with an isolated CDH. Our results confirm that implementing con-

Table 2. Prediction of adverse outcomes

n	*n*	PH	*n*	ECMO	*n*	Mortality
Mean 0–1 h						
AUROC	14	0.76	14	0.96	14	0.94
OSI cut-off		15.0		15.0		17.3
Sensitivity, %		56		83		100
Specificity, %		100		100		91
PPV, %		100		100		75
NPV, %		56		89		100
Mean 0–2 h						
AUROC	28	0.66	30	0.93	30	0.96
OSI cut-off		9.1		13.8		20.0
Sensitivity, %		38		78		100
Specificity, %		67		100		96
PPV, %		60		100		75
NPV, %		44		91		100
Mean 0–3 h						
AUROC	27	0.68	33	0.93	33	0.96
OSI cut-off		12.2		13.2		17.8
Sensitivity, %		36		80		100
Specificity, %		100		100		93
PPV, %		100		100		67
NPV, %		59		92		100
Mean 0–6 h						
AUROC	27	0.66	37	0.94	38	0.85
OSI cut-off		3.5		12.5		14.9
Sensitivity, %		100		82		80
Specificity, %		36		96		85
PPV, %		59		90		44
NPV, %		100		93		97
Mean 0–12 h						
AUROC	23	0.64	37	0.92	41	0.89
OSI cut-off		3.6		12.2		12.4
Sensitivity, %		100		90		100
Specificity, %		33		93		80
PPV, %		44		82		46
NPV, %		100		96		100
Mean 0–24 h						
AUROC	20	0.56	35	0.90	42	0.85
OSI cut-off		3.2		9.9		8.6
Sensitivity, %		100		88		100
Specificity, %		40		93		64
PPV, %		36		78		32
NPV, %		100		96		100

AUROC, area under the receiver operator characteristic curve; ECMO, extracorporeal membrane oxygenation; OSI, oxygen saturation index; NPV, negative predictive value; PH, pulmonary hypertension; PPV, positive predictive value.

tinuous OSI evaluation may aid in the early prediction of PH, need for ECMO-therapy, and mortality. Hence, maximum and mean OSI values may be used to detect clinical deterioration at a very early stage.

Deterioration of a patient's cardiorespiratory status (e.g., PH) often results in an increase in OSI – through intensified respiratory support and/or decreased SpO_2 – and consequently an increase in the mean of continuous OSI measurements during a set period. Mean OSI is calculated during a set period of time; thus, it may be a better reflection of the patient's respiratory status than single measurements that can easily be influenced by outliers, such as maximum OSI. We confirmed that already in the first hour, reliable cut-offs for mean OSI could be estab-

lished for all outcomes of interest. Only infants that developed PH reached a mean OSI ≥ 15 in the first hour after birth. The same cut-off identifies infants at risk for ECMO-therapy, with a specificity and PPV of 100%; this translates to all infants with a mean OSI ≥ 15 requiring ECMO-therapy. Mean OSI in the first hour also proved to be a reliable marker to identify infants with a high risk of mortality: infants that ultimately survived to discharge had lower OSI values, and a corresponding mean value of <17.3 identified all survivors. As only 14 infants had OSI measurements in the first hour, our results have to be confirmed in a larger population.

We observed a decreasing trend in the established cut-offs for mean OSI values during the first 24 h after birth. A potential explanation is the censoring of data by excluding infants that had already developed PH or required ECMO-therapy at a certain time point; those infants likely have the highest mean OSI values. Also, supportive therapy (e.g., fluid therapy or inotropic and vasopressor support) is often initiated during the first day of life, as cardiopulmonary problems regularly arise in these hours, potentially improving the infant's cardiorespiratory status and with that the OSI. Although the discriminative ability of mean OSI for PH was still *acceptable*, it was not as good as the *excellent* discriminative ability for ECMO-therapy and mortality. This might be the result of our retrospective study design and the challenge in determining the exact time point of developing PH.

In our cohort, maximum OSI values in the first 12 and 24 h were associated with all outcomes of interest and they reliably predicted these outcomes. Infants with any OSI value ≥12.5 are at high risk for the occurrence of PH, and in these infants, additional or prophylactic therapies could be considered (e.g., pulmonary vasodilators). An OSI value ≥22 is strongly associated with both the need for ECMO-therapy and mortality, both of which are in accordance with previous findings. We speculate that individualizing and intensifying therapy in the OSI range between 12.5 and 22 might avoid further clinical deterioration [14]. However, more evaluation of this concept is warranted.

We have previously shown comparable predictive values of OSI values equivalent to the OI values that are currently used to decide on upscaling therapy such as ECMO [12, 14]. However, the main advantage of continuous OSI measurements is that it may provide early warnings of clinical deterioration, thus allowing for preventive measures rather than adjusting treatment at the moment that clinical deterioration has already occurred. Although we did not assess this, real-time OSI measurements may provide an opportunity to evaluate treatment effectiveness without the necessity of repeated blood sampling, for instance when pharmaceutically managing PH, given the considerable individual variability in treatment response.

Another consideration is that ineffective ventilation, evaluated by partial pressure of carbon dioxide (CO_2), is equally as important as inadequate oxygenation when it comes to CDH-related mortality [21–23]. In that respect, recent advances in developing transcutaneous CO_2 monitoring devices are encouraging and combining this with OSI may provide a more complete evaluation of the infant's respiratory status and may potentially optimize our prediction model even further.

There has been growing interest in the association between markers of cardiac function and disease severity with consequent adverse outcomes in infants with CDH [24]. Markers such as left ventricular dysfunction, pro-b-type natriuretic peptide levels, lactate, and echocardiographic measures have been established as early predictors of outcomes [24–29]. Combining early cardiac markers with early markers of respiratory function, such as the OSI, might provide a more thorough prediction model that could identify a population at high risk for adverse outcomes. An advantage of this combination over currently used prediction models, such as the Brindle scoring model, Wilford Hall/Santa Rosa prediction model, and Score for Neonatal Acute Physiology-II, is the use of continuous measurements instead of either only the worst value in a set time period or binary outcomes at baseline [4–6, 21, 30, 31].

A limitation of using physiological data is the issue of measurement errors. In this study, we have deliberately not removed any outliers from the dataset to provide an accurate reflection of continuous OSI monitoring in day-to-day clinical practice. Anticipating on the development of monitoring equipment with algorithms that can filter between clinically valid and invalid values, we carried out a sensitivity analysis using a clean dataset. The sensitivity analysis did not show significant differences in the predictive capacity of the parameters that we have evaluated; consequently, data collected at the patient's bedside could be used without further data cleaning. Although we are confident to have collected mainly preductal SpO_2 measurements due to the standard-of-care in our center, we acknowledge that our dataset might contain a limited number of postductal SpO_2 measurements, which we were unable to exclude due to the retrospective study design. Further evaluation of continuous OSI monitoring

using solely preductal SpO_2 measurements could validate our results. Another limitation is that SpO_2 is considered a suboptimal reflection of oxygenation when compared to pO_2, as its accuracy is relatively low and patients show a variable response on increasing FiO_2 levels [32–35]. As such, we do not recommend to replace OI measurements with OSI measurements at this stage, but we propose to add continuous OSI measurements as early indication of a complicated course.

We considered but did not use a combined outcome as main outcome, as the outcomes of interest are inherently associated with each other and may compete if mutually exclusive. However, all infants who died completed the triad of PH, ECMO-requirement, and mortality. Therefore, a combined outcome would not have increased the validity of our results. The high incidence of the main outcomes and availability of nearly 50,000 OSI measurements allowed us to run multiple analyses and explore different time periods in a relatively small study population. We support validation of our findings in a larger multicenter cohort and expansion to lower risk patient groups. To make OSI values available in other centers, real-time OSI values, mean values, and maximum values need to be calculated, which are based on parameters (e.g., FiO_2, MAP, and SpO_2) that are readily available. Implementation in day-to-day practice of these non-invasive continuous OSI measurements requires confirmation of the clinical value of OSI as a real-time bedside measure in prospective clinical studies.

Conclusion

Continuous OSI measurements are a reliable predictor of outcomes in infants with CDH. We now propose continuous OSI evaluation as a promising modality allowing early identification of infants with CDH with the highest risk of developing PH, needing ECMO-therapy, or postnatal death. Already in the first hours after birth, continuous OSI measurements could provide the opportunity to adjust postnatal therapy to the individual patient's needs.

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 report no conflicts of interest.

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Author Contributions

Emily J.J. Horn-Oudshoorn, Marijn J. Vermeulen, Ronny Knol, Arjan B. te Pas, Suzan C.M. Cochius-den Otter, J. Marco Schnater, Irwin K.M. Reiss, and Philip L.J. DeKoninck were all involved in the conception of this paper. Emily J.J. Horn-Oudshoorn performed chart reviews, constructed the database for further analysis, and wrote the first draft, which was critically reviewed by all authors. Emily J.J. Horn-Oudshoorn, Marijn J. Vermeulen, and Philip L.J. DeKoninck conceptualized and designed the statistical plan, and contributed to the analysis and the interpretation of the results. All authors have approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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