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Continuous oxygen saturation and risk of retinopathy of prematurity in a Japanese cohort

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ABSTRACT

Background/aims We assessed the associations between retinopathy of prematurity (ROP) and continuous measurements of oxygen saturation (SpO_2), and developed a risk prediction model for severe ROP using birth data and SpO_2 data.

Methods This retrospective study included infants who were born before 30 weeks of gestation between August 2009 and January 2019 and who were screened for ROP at a single hospital in Japan. We extracted data on birth weight (BW), birth length, gestational age (GA) and minute-by-minute SpO_2 during the first 20 days from the medical records. We defined four SpO_2 variables using sequential measurements. Multivariate logistic regression was used to develop a model that combined birth data and SpO_2 data to predict treatment-requiring ROP (TR-ROP). The model's performance was evaluated using the area under the receiver operating characteristic curve (AUC).

Results Among 350 infants, 83 (23.7%) required ROP treatment. The SpO_2 variables in infants with TR-ROP differed significantly from those with non-TR-ROP. The average SpO_2 and high SpO_2 showed strong associations with GA (r=0.73 and r=0.70, respectively). The model incorporating birth data and the four SpO_2 variables demonstrated good discriminative ability (AUC=0.83), but it did not outperform the model incorporating BW and GA (AUC=0.82).

Conclusion Data obtained by continuous SpO_2 monitoring demonstrated valuable associations with severe ROP, as well as with GA. Differences in the distribution of average SpO_2 and high SpO_2 between infants with TR-ROP and non-TR-ROP could be used to establish efficient cut-off values for risk determination.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Oxygen supplementation, oxygen saturation (SpO_2) and SpO_2 targets affect retinopathy of prematurity (ROP). Recent studies have reported that a lower average SpO_2 and larger SpO_2 fluctuation increase the risk of ROP severity.

WHAT THIS STUDY ADDS

⇒ Being outside of the target SpO_2 range is associated with ROP severity. Average SpO_2 and high SpO_2 were both strongly positively associated with gestational age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Differences in the distribution of average SpO_2 and high SpO_2 between infants with treatment-requiring ROP (TR-ROP) and non-TR-ROP could help to set efficient cut-off values for risk determination.

INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness, though it is largely avoidable. The number of infants who develop severe ROP varies considerably depending on the population and the level of neonatal care provided.[1 2] Short gestation and low birth weight (BW) (or prematurity) pose the highest risk for developing ROP, regardless of the level of neonatal care. In contrast, neonatal management affects many systemic diseases and related interventions, which have been demonstrated to cause severe ROP, including infection, necrotising enterocolitis, respiratory distress syndrome, late circulatory failure, blood transfusion and oxygen supplementation.[3–5] In particular, since oxygen supplementation was first identified as a cause of severe ROP,[6] several studies have attempted to achieve appropriate oxygen supplementation for premature infants.[5 7–10]

During postnatal early life, premature infants often receive respiratory support. Oxygen supplementation is a pivotal component of intensive neonatal care for preterm infants. Ideally, oxygen administration provides adequate oxygenation to meet the metabolic demands of premature infants while avoiding the consequences of both hypoxaemia and hyperoxia. One of the problems with oxygen treatment is that there is a trade-off between reducing the incidence of severe ROP and chronic lung disease with low oxygenation and achieving low mortality with high oxygenation.[4 9 10] Although the associations of ROP with oxygen delivery, monitoring and mechanical ventilation have been evaluated, no key parameters or thresholds to reduce ROP have been established. Differences in the monitoring interval and monitoring period of oxygen saturation (SpO_2) and differences in the delivery setting have led to inconsistent results. Therefore, it still remains clinically challenging to define the optimal target levels of oxygen for both low ROP treatment and low motility rate in preterm infants.

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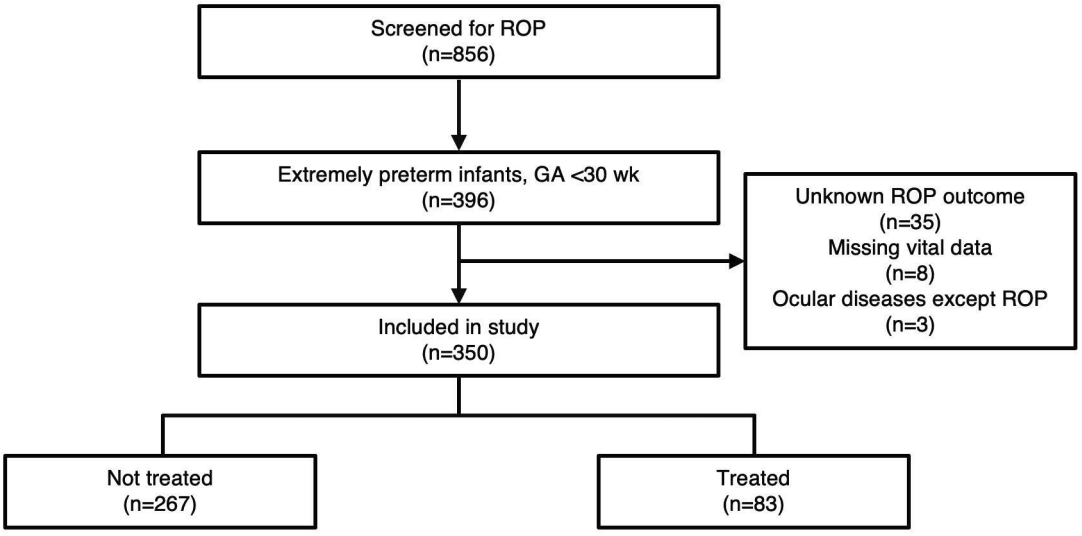

Figure 1 Participant flow diagram. GA, gestational age; ROP, retinopathy of prematurity.

Recently, several studies have demonstrated that the minute-by-minute fluctuations in SpO_2 measured by pulse oximetry are strongly associated with ROP in extremely preterm infants.[11 12] Non-invasive continuous monitoring of SpO_2 for optimal oxygen delivery has become almost universal in the neonatal intensive care unit (NICU).[13] The use of non-invasive and continuous monitoring of SpO_2 is now common in the NICU. Large numerical datasets from bedside SpO_2 monitoring of premature infants have been incorporated into electronic medical records, allowing for objective analysis of continuous SpO_2 measurements. In this study, we evaluated the correlation between birth prematurity and early postnatal SpO_2, as well as the association between ROP severity and early postnatal SpO_2. We also attempted to determine the risk of severe ROP using birth data and continuous early postnatal SpO_2 data.

MATERIALS AND METHODS

Study population

This study was conducted at the NICU of a single institution in Japan. We included infants born before 30 weeks of gestation between August 2009 and January 2019 at Osaka Women's and Children's Hospital. We excluded infants without a known ROP outcome, those without sequential measurements of SpO_2, and those with ocular diseases other than ROP. A flow chart of patient enrolment is shown in figure 1.

ROP screening

All infants included in the study underwent ROP examination. We performed the initial ROP examination at 29 or 30 weeks of postmenstrual age (PMA) or 3 weeks after birth, whichever came later unless there was a reason not to conduct this examination. The diagnosis of ROP and the indication for ROP treatment followed the International Classification of ROP Revisited[14] and the Early Treatment for ROP (ETROP) study,[15] respectively.

Data collection

We retrospectively collected birth data, ROP data and SpO_2 data from the electronic medical records of the infants. Birth data included sex, BW, birth length (BL) and gestational age (GA). ROP data included the dates of retinal examinations, ROP stages and zone at each fundus examination and treatments for ROP. SpO_2 data included all SpO_2 measurements during the first 20 days after birth. Specifically, we continuously monitored SpO_2 in all infants with a probe and pulse oximeter (TL-535U, Nihon Kohden, Tokyo, Japan) at both NICUs. We averaged the acquired sequential SpO_2 measurements over 1 min, and the values were recorded using a biomedical information system (PRM-7400, Nihon Kohden). We extracted all measurements during the period from the system. If measurements were continuously recorded for 20 postnatal days (28 800 min), with no missing measurements, the number of measurements was recorded as 28 800 counts. Subsequently, we removed times with 0% SpO_2 owing to artefacts and times with missing SpO_2 values. We did not conduct data imputation in this study.

Definition of SpO_2 variables

We defined four SpO_2 variables: SpO_2 average, SpO_2 fluctuation, high SpO_2 and low SpO_2. SpO_2 average was obtained by dividing the total SpO_2 measurements by the total valid recording time. SpO_2 fluctuation was obtained by dividing the total difference between two consecutive SpO_2 measurements by the total valid time (figure 2).

From July 2009 to June 2013, neonatologists used a target SpO_2 range of 85%–95% for infants. From July 2013, the target SpO_2 range for infants was 90%–95% for infants within the first week of life and 88%–95% for infants through a PMA of 36 weeks. In cases where an infant was over the target range without respiratory support, additional oxygen supplementation was not administrated.[12] To evaluate the impact of being outside of the target SpO_2 range, we calculated high SpO_2 and low SpO_2 as the proportion of cumulative time spent over 95% and below 80%, respectively (figure 2).

Outcome and statistical analysis

First, we compared the birth data and SpO_2 variables of patients with non-TR-ROP with those of patients with TR-ROP. Second, we analysed the correlations between SpO_2 variables and GA. Finally, we developed the prediction model using the above variables. After univariate screening to identify potentially important variables, we selected all potential predictive variables with $p<0.05$ for further analysis. We then analysed the selected variables by multivariate logistic regression. We measured the accuracy, precision and F-measure of the model, and we evaluated the model's performance in terms of discrimination and

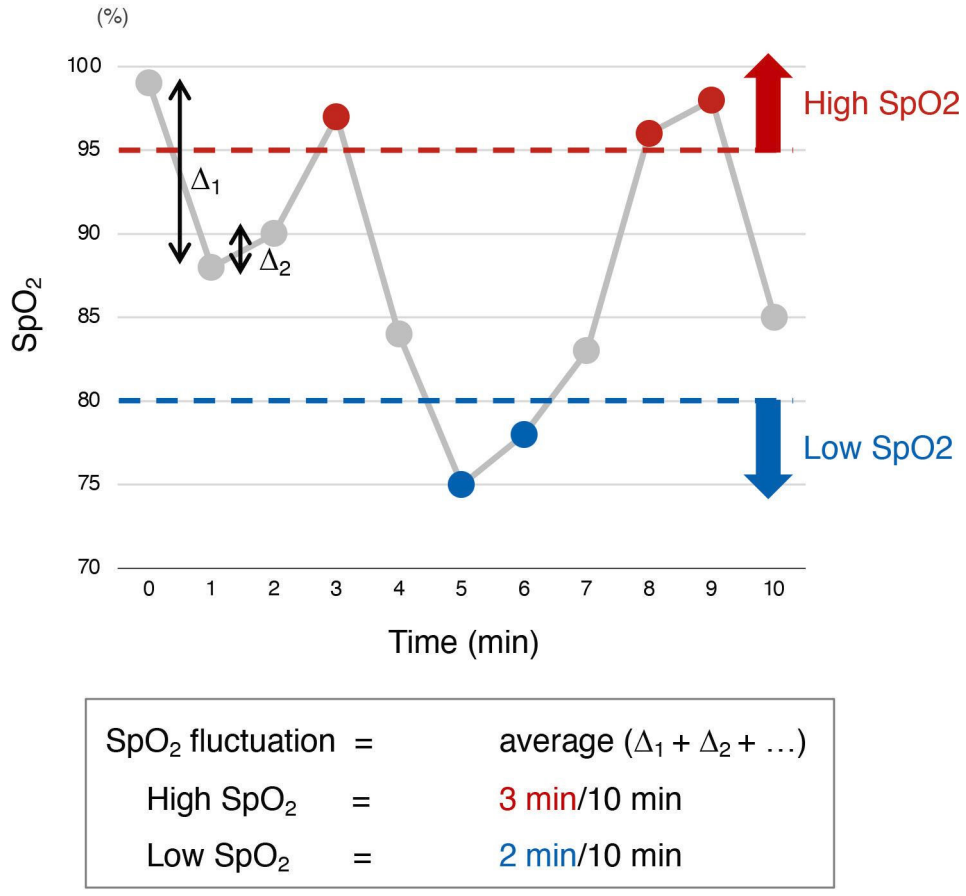

Figure 2 Schematic diagram representing SpO_2 fluctuation, high SpO_2 and low SpO_2. SpO_2 fluctuation is defined as the average value of the differences between two consecutive SpO_2 measurements during the entire study period. High SpO_2 and low SpO_2 are cumulative rates; >95% SpO_2 and<80% SpO_2, respectively. SpO_2, oxygen saturation.

calibration using the area under the receiver operating characteristic curve (AUC). In addition to the model with all selected variables, we constructed two other rigorous models by removing the initially included variables while maintaining the predictive power. We compared the performance of the models based on the AUC.

Continuous variables are presented as the mean and range. For comparisons between the two groups, we used Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Values of $p<0.05$ were considered statistically significant. Correlations were calculated with Pearson's correlation coefficient. We performed linear regression analysis and tested if the two regression lines of non-TR-ROP and TR-ROP had an equal slope. All analyses were performed by using JMP Pro statistical software, V.16 (SAS Institute).

RESULTS

Among 350 infants (mean BW, 839 g; mean GA, 26.5 weeks), 293 infants (83.7%) developed any ROP. Of these infants, 83 (23.7%) required treatment for ROP. The average BW, BL and GA values in TR-ROP infants were lower than those in non-TR-ROP infants (table 1).

The average count of SpO2 measurements for all infants was 27 235, which is equivalent to 18.9 days. More than 95% of the maximum of 28 800 counts were valid measurements in 262 infants; values were less than 90% in 20 infants. While the SpO_2 average and low SpO_2 in TR-ROP infants were significantly lower than in non-TR-ROP infants, SpO_2 fluctuation and high SpO_2 in TR-ROP infants were significantly higher than in non-TR-ROP infants (table 1).

We identified significant correlations between all SpO_2 variables and GA. The average SpO_2 and high SpO_2 had strong positive correlations with GA (r=0.73 (0.68–0.78) and r=0.70 (0.65–0.75), respectively), while SpO_2 fluctuation and low SpO_2 had negative correlations with GA (r=−0.30 (−0.20 to −0.39) and r=−0.52 (−0.44 to −0.59), respectively). Figure 3 shows the distributions of the SpO_2 variables by GA for non-TR-ROP and TR-ROP infants. All four SpO_2 variables had weaker associations with GA in TR-ROP infants than in non-TR-ROP infants. The regression line slopes of the average SpO_2-GA and the high SpO_2-GA were statistically unequal between non-TR-ROP and TR-ROP infants. Notably, the high SpO_2-GA slope differed by approximately two times between non-TR-ROP and TR-ROP infants.

Table 2 summarises the performance of the three models. We first constructed a full prediction model incorporating the following seven variables: BW, BL, GA, SpO_2 average, SpO_2 fluctuation, high SpO_2 and low SpO_2. The model had moderate predictive performance, with an AUC of 0.83. Subsequently, we constructed a rigorous model that removed all four SpO_2 variables and a minimal model incorporating only BW and GA. Both models demonstrated similar performance to the full model. Ultimately, although the F-measure of the full model was the highest among the three models, its model performance according to the AUC was not superior to the other models (p=0.58).

Table 1 Birth characteristics of the study population

	Non-TR-ROP	TR-ROP	P value
No. of patients	267	83	
Male sex, no. (%)	140 (52.4)	33 (39.7)	0.17
Birth weight, g			
Mean	898	649	<0.001
Range	422–1724	394–1024	
Birth length, cm			
Mean	33.3	29.8	<0.001
Range	22.2–44.5	25.0–36.0	
Gestational age, weeks			
Mean	27.1	24.8	<0.001
Range	22.2–29.8	22.2–27.5	
SpO_2 average, %			
Mean	94.2	92.4	<0.001
Range	86.5–98.2	88.2–95.1	
SpO_2 fluctuation, %			
Mean	1.6	1.7	0.03
Range	0.9–3.6	0.9–3.2	
High SpO_2 ($\times 10^{-2}$)			
Mean	46.7	28.2	<0.001
Range	1.1–93.3	7.0–56.5	
Low SpO_2 ($\times 10^{-2}$)			
Mean	1.1	2.1	<0.001
Range	0.0–8.1	0.1–9.2	

ROP, retinopathy of prematurity; SpO_2, oxygen saturation; TR-ROP, treatment-requiring ROP.

DISCUSSION

Since the first clinical report of ROP in premature infants who received 100% oxygen administration in the 1950s,[16] numerous studies have been conducted to determine appropriate oxygen supplementation and respiratory support to reduce ROP severity by analysing factors related to oxygen, such as the fraction of inspired oxygen (FiO_2), SpO_2 and partial pressure of oxygen.[4 17 18] Recent technological advances have enabled the analysis of continuous SpO_2 data from infants in the NICU. However, the raw data from continuous SpO_2 monitoring, before being compressed and processed, have rarely been used for ROP risk determination and prediction. In this study, we shed light on how the minute-by-minute SpO_2 levels in early life influenced ROP severity. Although all four SpO_2 variables differed between infants with and without treatment, these differences did not improve the predictive performance for severe ROP. Eventually, GA and BW, which are well-known risk factors for ROP, contributed the most to predicting ROP severity. Moreover, the performance of our model was poorer than several existing models.[19–22] One possible explanation could be that we targeted all infants born before 30 weeks of gestation, without setting a lower limit for GA when developing the model to avoid overly optimistic performance with unbalanced data.[23]

We demonstrated previously that the SpO_2 average and SpO_2 fluctuation differed between non-TR-ROP and TR-ROP infants.[12] In this study, we further investigated the association between SpO_2 variables and GA. Among the four SpO_2 variables, both SpO_2 average and high SpO_2 showed a strong association with GA, despite the target oxygen level remaining constant across GAs. Although no infants had an average SpO_2 below the target during the study period, some infants with a longer GA had average SpO_2 levels exceeding the target range. This observation may be explained by the fact that premature infants were able to exceed the upper limit of the target SpO_2 (SpO_2>95%) without

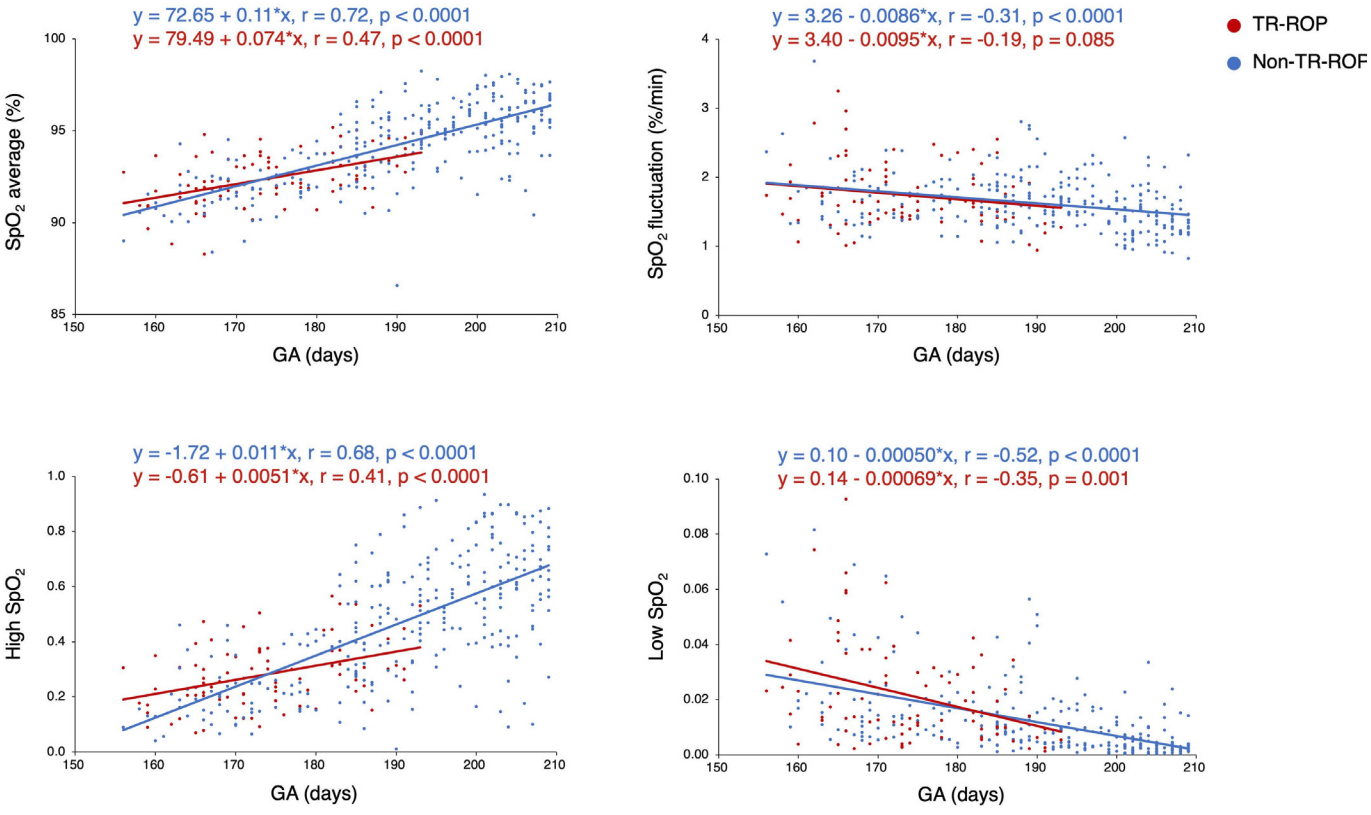

Figure 3 Associations between SpO_2 variables and GA by group. Scatter plots and linear regression lines of four SpO_2 variables and GA in non-TR-ROP (blue) and TR-ROP (red) infants. The equation, correlation coefficient and statistical significance are provided for non-TR-ROP (blue) and TR-ROP (red) red and blue in the plots. GA, gestational age; SpO_2, oxygen saturation; TR-ROP, treatment-requiring retinopathy of prematurity.

Table 2 Model performance for predicting ROP severity

Model	Variables	Accuracy	Precision	F-measure	AUC (95% CI)
Full	BW, BL, GA, SpO_2 average, SpO_2 fluctuation, high SpO_2, low SpO_2	0.76	0.51	0.43	0.83 (0.78 to 0.86)
Rigorous	BW, BL, GA	0.75	0.48	0.40	0.82 (0.78 to 0.86)
Minimal	BW, GA	0.76	0.50	0.41	0.82 (0.78 to 0.86)

AUC, area under the curve; BL, birth length; BW, birth weight; GA, gestational age; ROP, retinopathy of prematurity; SpO_2, oxygen saturation; TR-ROP, treatment-requiring ROP.

receiving supplemental oxygen as they matured postnatally.[24 25] Consequently, infants can surpass the target SpO_2 range without requiring oxygen supplementation. Although we did not include information on oxygen treatment in this study, the decreasing trend in low SpO_2 with a longer GA supports this explanation. Regarding ROP severity, these strong associations did not lead to refinements in the prediction model. However, we observed an increasing gap in the regression line slope of high SpO_2 and GA between non-TR-ROP and TR-ROP, suggesting the potential to set an effective cut-off value for high SpO_2. In particular, if we had defined infants with high SpO_2<0.6 as a high-risk TR-ROP group, the estimated number of infants requiring screening would have decreased to 88 (25.1%), with 100% sensitivity. This promissing cut-off value must be validated in the future studies.

As for one of the other oxygen-related factors, FiO_2 data remain controversial in terms of its ability to determine ROP risk. Recent studies have reported that although incorporating daily FiO_2 into the screening criteria proposed in the Postnatal Growth and ROP Study improved both the sensitivity and specificity of type 1 ROP risk determination,[26] weekly FiO_2 measurement did not improve the predictive performance of GA for TR-ROP.[27] With titration of FiO_2 to SpO_2, FiO2 might demonstrate a correlation with GA. When oxygen-related factors, such as SpO_2 and FiO_2, are incorporated into the risk determination of ROP, the relationship between GA and oxygen-related factors should be considered. In addition, it would be necessary to properly set the starting point, the time period and the data collection interval of oxygen-related factor analysis when incorporating oxygen-related factors into the predictive model. In view of technological advances in big data analysis, using machine learning would make it possible to explore the best application of continuous data, including SpO_2 and FiO_2, for ROP risk determination. Using the data-driven approach, we aim to identify novel trends over time or specific points at which SpO_2 and FiO_2 predict severe ROP. In the future, a real-time analysis system for ROP risk prediction might be implemented using monitoring devices powered by artificial intelligence.

There are several limitations to consider in this study. First, the study included a small cohort of Japanese patients in a single NICU. Because the rates of infants treated for ROP in our study were comparable to those in the Neonatal Research Network of Japan database, our cohort can be considered a group of standard Japanese infants. However, our results may not be generalisable to other populations.[2] Second, we have concerns about the SpO_2 data, such as SpO_2 measurement. For example, oximeter inaccuracy and failure owing to motion artefact may have decreased the valid recording duration of SpO_2.[28] An increase in the invalid recording duration or low accuracy may have affected the SpO_2 variables, resulting in difficulties in setting the cut-off values. Another concern is the target SpO_2 range, which has been changed as a result of some clinical trials over the years.[7–10] With further optimisation of the target range, it may be necessary to revise the definitions of SpO_2 variables, such as high SpO_2 and low SpO_2. Finally, we did not compare our model with other predictive models.

Conclusion

In conclusion, this study demonstrated that SpO_2 variables, which were obtained by continuous data monitoring, were associated with severe ROP and GA. Of note, different distributions of average SpO_2 and high SpO_2 between non-TR-ROP and TR-ROP could help to set efficient cut-off values for risk determination. Future ROP research should be directed at data-driven analysis of continuous data monitoring using artificial intelligence, which could help to discover novel risk determination models for ROP.

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Competing interests None declared. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethics review board of Osaka Women's and Children's Hospital (the approved number, 888-2). The study protocol did not require that each patient provide written informed consent (based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese government). We instead posted the protocol on the hospital organisation website to notify study guardians of all infants.

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