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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 (SpO₂), and developed a risk prediction model for severe ROP using birth data and SpO₂ 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 SpO₂ during the first 20 days from the medical records. We defined four SpO₂ variables using sequential measurements. Multivariate logistic regression was used to develop a model that combined birth data and SpO₂ 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 SpO₂ variables in infants with TR-ROP differed significantly from those with non-TR-ROP. The average SpO₂ and high SpO₂ showed strong associations with GA ($r=0.73$ and $r=0.70$, respectively). The model incorporating birth data and the four SpO₂ 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 SpO₂ monitoring demonstrated valuable associations with severe ROP, as well as with GA. Differences in the distribution of average SpO₂ and high SpO₂ 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 (SpO₂) and SpO₂ targets affect retinopathy of prematurity (ROP). Recent studies have reported that a lower average SpO₂ and larger SpO₂ fluctuation increase the risk of ROP severity.

WHAT THIS STUDY ADDS

⇒ Being outside of the target SpO₂ range is associated with ROP severity. Average SpO₂ and high SpO₂ were both strongly positively associated with gestational age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Differences in the distribution of average SpO₂ and high SpO₂ between infants with treatment-requiring ROP (TR-ROP) and non-TR-ROP could help to set efficient cut-off values for risk determination.

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.^{5–10}

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 (SpO₂) 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.

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



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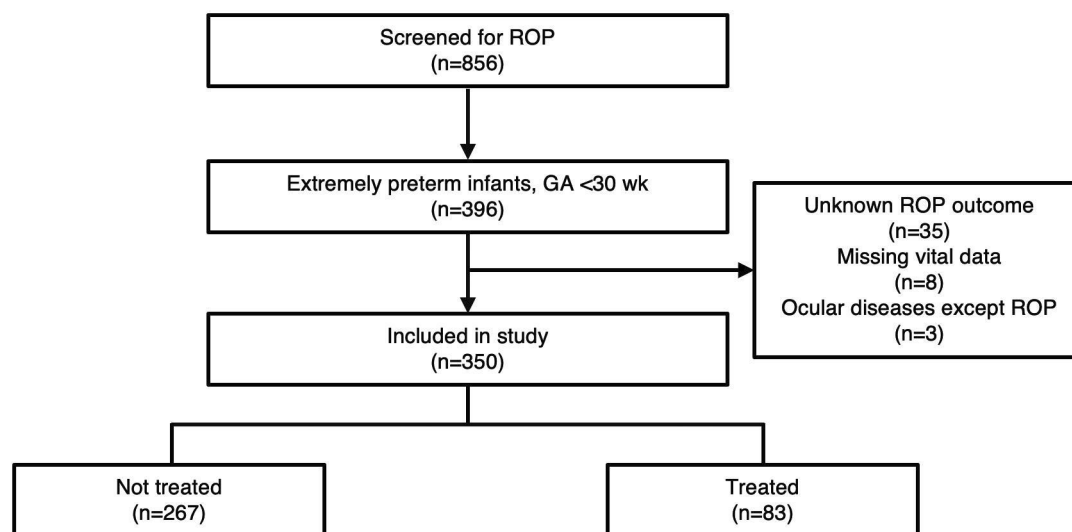


Figure 1 Participant flow diagram. GA, gestational age; ROP, retinopathy of prematurity.

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 Revisited¹⁴ 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

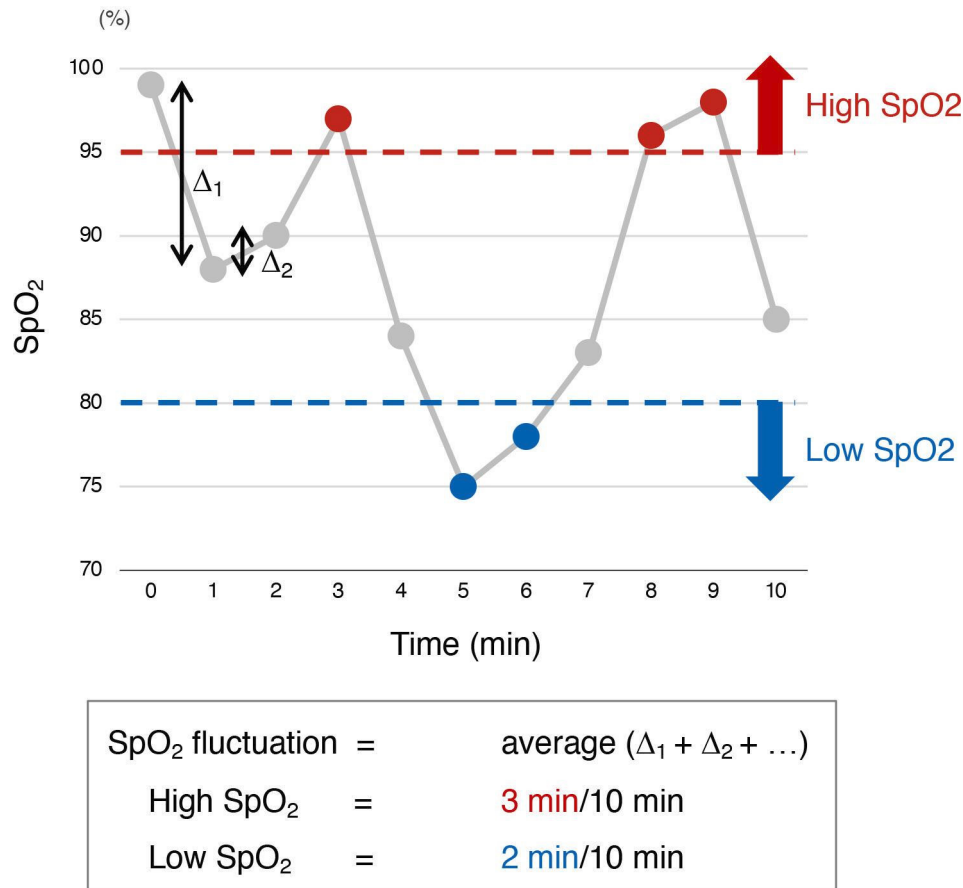


Figure 2 Schematic diagram representing SpO₂ fluctuation, high SpO₂ and low SpO₂. SpO₂ fluctuation is defined as the average value of the differences between two consecutive SpO₂ measurements during the entire study period. High SpO₂ and low SpO₂ are cumulative rates; >95% SpO₂ and <80% SpO₂, respectively. SpO₂, 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 SpO₂ average and low SpO₂ in TR-ROP infants were significantly lower than in non-TR-ROP infants, SpO₂ fluctuation and high

SpO₂ in TR-ROP infants were significantly higher than in non-TR-ROP infants (table 1).

We identified significant correlations between all SpO₂ variables and GA. The average SpO₂ and high SpO₂ had strong positive correlations with GA ($r = 0.73$ (0.68–0.78) and $r = 0.70$ (0.65–0.75), respectively), while SpO₂ fluctuation and low SpO₂ 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 SpO₂ variables by GA for non-TR-ROP and TR-ROP infants. All four SpO₂ variables had weaker associations with GA in TR-ROP infants than in non-TR-ROP infants. The regression line slopes of the average SpO₂-GA and the high SpO₂-GA were statistically unequal between non-TR-ROP and TR-ROP infants. Notably, the high SpO₂-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, SpO₂ average, SpO₂ fluctuation, high SpO₂ and low SpO₂. The model had moderate predictive performance, with an AUC of 0.83. Subsequently, we constructed a rigorous model that removed all four SpO₂ 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; SpO₂, 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 (FiO₂), SpO₂ and partial pressure of oxygen.^{4 17 18} Recent technological advances have enabled the analysis of continuous SpO₂ data from infants in the NICU. However, the raw data from continuous SpO₂ 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 SpO₂ levels in early life influenced ROP severity. Although all four SpO₂ 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 SpO₂ average and SpO₂ fluctuation differed between non-TR-ROP and TR-ROP infants.¹² In this study, we further investigated the association between SpO₂ variables and GA. Among the four SpO₂ variables, both SpO₂ average and high SpO₂ showed a strong association with GA, despite the target oxygen level remaining constant across GAs. Although no infants had an average SpO₂ below the target during the study period, some infants with a longer GA had average SpO₂ 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 SpO₂ (SpO₂>95%) without

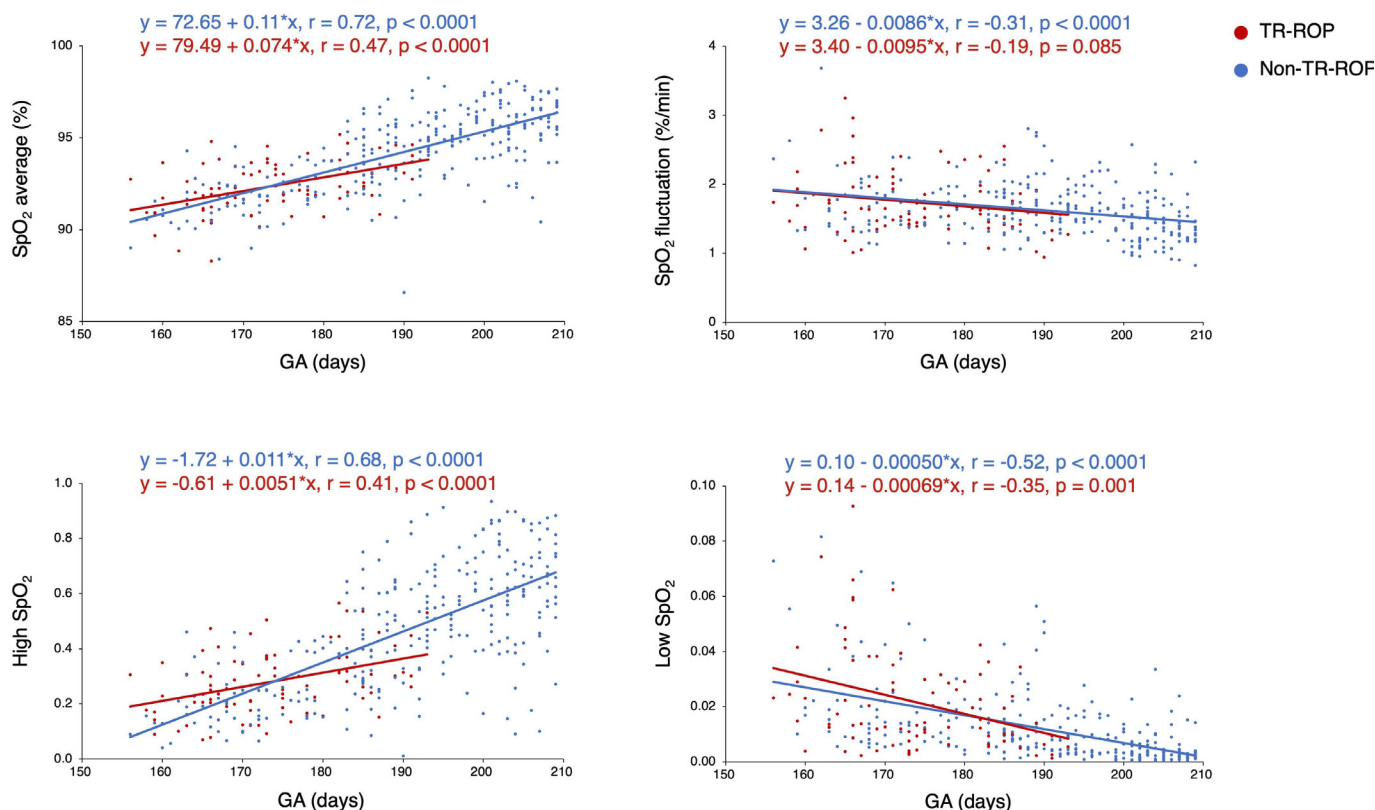


Figure 3 Associations between SpO₂ variables and GA by group. Scatter plots and linear regression lines of four SpO₂ variables and GA in non-TR-ROP (blue) and TR-ROP (red) infants. The equation, correlation coefficient and statistical significance are provided for non-TR-ROP (blue) and TR-ROP (red) red and blue in the plots. GA, gestational age; SpO₂, 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; SpO₂, oxygen saturation; TR-ROP, treatment-requiring ROP.

receiving supplemental oxygen as they matured postnatally.^{24 25} Consequently, infants can surpass the target SpO₂ range without requiring oxygen supplementation. Although we did not include information on oxygen treatment in this study, the decreasing trend in low SpO₂ 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 SpO₂ and GA between non-TR-ROP and TR-ROP, suggesting the potential to set an effective cut-off value for high SpO₂. In particular, if we had defined infants with high SpO₂ < 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 promising cut-off value must be validated in the future studies.

As for one of the other oxygen-related factors, FiO₂ data remain controversial in terms of its ability to determine ROP risk. Recent studies have reported that although incorporating daily FiO₂ 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 FiO₂ measurement did not improve the predictive performance of GA for TR-ROP.²⁷ With titration of FiO₂ to SpO₂, FiO₂ might demonstrate a correlation with GA. When oxygen-related factors, such as SpO₂ and FiO₂, 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 SpO₂ and FiO₂, for ROP risk determination. Using the data-driven approach, we aim to identify novel trends over time or specific points at which SpO₂ and FiO₂ 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 SpO₂ data, such as SpO₂ measurement. For example, oximeter inaccuracy and failure owing to motion artefact may have decreased the valid recording duration of SpO₂.²⁸ An increase in the invalid recording duration or low accuracy may have affected the SpO₂ variables, resulting in difficulties in setting the cut-off values. Another concern is the target SpO₂ 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 SpO₂ variables, such as high SpO₂ and

low SpO₂. Finally, we did not compare our model with other predictive models.

Conclusion

In conclusion, this study demonstrated that SpO₂ variables, which were obtained by continuous data monitoring, were associated with severe ROP and GA. Of note, different distributions of average SpO₂ and high SpO₂ 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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Data availability statement Data are available on reasonable request.

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