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Assessing the risk of retinopathy of prematurity in preterm neonates using the expanded Apgar score

Zastosowanie rozszerzonej skali Apgar do oceny ryzyka wystąpienia retinopatii wcześniaków

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Abstract

Aim: Using the expanded Apgar score, it was determined whether interventions performed in the ward could reliably predict the occurrence of retinopathy of prematurity (ROP). **Materials and methods:** A single-centre study based on a retrospective analysis of medical records of 287 children with a gestational age of ≤32 weeks. Artificial intelligence algorithms and chi-square automatic interaction detection (CHAID) were used to analyse the Apgar score, and the course of resuscitation was documented according to the expanded Apgar score. The CHAID classification tree creates a transparent knowledge system based on decision rules. **Results:** The mean gestational age of newborns with severe ROP (sROP) was 25.6 weeks, compared to 28.7 weeks ($p < 0.001$). No significant sex-related differences in sROP occurrence were observed in the study group. Analysis of the expanded Apgar score parameters showed that the fraction of inspired oxygen – oxygen concentration in the gas mixture (FiO_2) – received by the newborn at 10 minutes was a statistically significant parameter. The cut-off point was a FiO_2 of 0.8. Of the newborns with sROP, 29.6% had FiO_2 above this concentration, compared to only 6.5% below it ($p < 0.001$). The analysis also showed that 15.1% of babies requiring intubation within 3 minutes of life developed sROP, indicating a significant effect of this expanded Apgar score parameter. Only 3.7% of non-intubated newborns had sROP ($p = 0.001$). Chest compression and epinephrine administration showed no significant effect on sROP occurrence. **Conclusions:** Considering intubation and oxygen concentration supplied during resuscitation significantly improves the prognosis of retinopathy of prematurity compared to using the Apgar score alone.

Keywords: algorithm, Apgar score, expanded Apgar score, chi-square automatic interaction detection, retinopathy of prematurity

Streszczenie

Wprowadzenie i cel: W niniejszym badaniu, wykorzystując rozszerzoną skalę Apgar, oceniano, czy interwencje po urodzeniu na sali porodowej mogą wiarygodnie przewidywać wystąpienie retinopatii wcześniaków (*retinopathy of prematurity*, ROP). **Materiał i metody:** Wykonano analizę oceny wg skali Apgar i udokumentowania przebiegu resuscytacji według rozszerzonej skali Apgar u 696 noworodków urodzonych przedwcześnie w latach 2009–2011 w Klinice Neonatologii i Intensywnej Terapii Noworodka Warszawskiego Uniwersytetu Medycznego. Do analizy wykorzystano metodę automatycznej detekcji interakcji chi-kwadrat. **Wyniki:** Średni wiek ciążowy noworodków z ciężką ROP wynosi 25,6 tygodnia ciąży, natomiast dla grupy bez niej – 28,7 ($p < 0{,}001$). W grupie badanej nie stwierdzono istotnej różnicy między płciami w zakresie występowania ciężkiej ROP. Analizując parametry rozszerzonej skali Apgar, wykazano, że stężenie tlenu w mieszaninie oddechowej stosowane u noworodka w 10. minucie jest parametrem istotnym statystycznie. Punkt odcięcia stanowi tutaj stężenie tlenu w mieszaninie oddechowej wynoszące 0,6, przy czym ciężką ROP powyżej tego stężenia rozpoznaje się u 26,3% noworodków, a poniżej – tylko u 6,9% ($p = 0{,}005$). Przeprowadzona analiza wykazała istotność statystyczną również w zakresie intubacji na sali porodowej: ciężka ROP rozwinęła się u 15,1% dzieci wymagających intubacji w ciągu 3 minut życia i tylko u 3,7% noworodków niewymagających intubacji ($p = 0{,}001$). Nie stwierdzono statystycznych różnic w występowaniu ROP w zależności od masażu serca i podawania adrenaliny. **Wnioski:** Konieczność intubacji i stężenie tlenu podawanego podczas resuscytacji istotniej korelują z rokowaniem wystąpienia retinopatii wcześniaków w porównaniu z jedynie oceną w klasycznej skali Apgar.

Słowa kluczowe: algorytm, skala Apgar, rozszerzona skala Apgar, automatyczny detektor interakcji za pomocą chi-kwadrat, retinopatia wcześniaków

INTRODUCTION

Retinopathy of prematurity (ROP) is the leading cause of preventable but untreatable blindness in children worldwide[1–4]. The disease was first described in the 1940s by Boston ophthalmologists Theodore and Terry. Immaturity is an apparent cause of the disease's development[5].

Preterm retinopathy is a developmental disorder characterised by abnormal vascular proliferation in the retinas of premature infants with incomplete retinal vascularisation[6]. The retina and retinal vasculature develop during pregnancy, which links the degree of retinal immaturity to the newborn's prematurity[7]. Therefore, premature birth remains the most significant risk factor for ROP. The International Classification of Retinopathy of Prematurity distinguishes five stages of ROP. The early stages (1 and 2) usually do not require treatment, as the disease regresses spontaneously in 80% of neonates[4]. Thus, our study focused on the severe ROP (sROP) stages that required treatment. In Poland, ROP screening is performed for all newborns born before 32 weeks gestational age (GA) or with a body weight of less than 1,500 g. Relatively mature newborns are screened for additional risk factors, such as intrauterine growth restriction (IUGR), intensive oxygen therapy, or post-therapeutic hypothermia[8,9].

In recent years, the survival rate of extremely premature infants who are prone to later complications such as ROP has increased due to improved maternal and neonatal care[6]. The survival of increasingly immature newborns necessitates changes in the ROP classification. The concept of the most aggressive form of retinopathy in extremely immature preterm infants, known as posterior aggressive ROP – APROP (aggressive posterior retinopathy of prematurity), was introduced. Intravitreal injection of anti-VEGF preparations has been shown to result in rapid regression of retinal lesions, particularly during extreme prematurity. The advantage of this method is that it does not cause retinal damage, which is unavoidable with laser photocoagulation, thereby enabling normal retinal development. Indications for this treatment include APROP, rapid lesion progression, and progression despite laser therapy[10,11].

Several studies have reported the influence of postnatal management on the incidence of multiple complications, such as ROP, in preterm infants during the neonatal period[12–15]. Conventionally, the general condition of a newborn is assessed in the first few minutes of life using the Apgar score (AS). This scale reflects the impact of intrauterine and parturition factors on the newborn's condition and indicates the need for postnatal intubation[16–18]. Interestingly, it has not been used as a prognostic tool to date.

However, medical practitioners are actively searching for correlations between the general condition of newborns at birth and their subsequent development[16]. According to Marinov et al., Bulgarian neonatologists routinely use the 5-minute AS (Apgar 5) to assess a newborn's environmental adaptation. A low score at the 5th minute is a known risk factor for the development and progression of ROP, either individually[17] or in combination with other perinatal indicators[18,19]. The American Academy of Pediatrics (AAP), the Fetal and Newborn Committee, American College of Obstetricians and Gynecologists (ACOG), and the Committee on Obstetric Practice have proposed an expanded version of the AS which objectively and accurately describes the postpartum condition of newborns[16,20]. The expanded AS, developed in 2006, includes a description of various elements of resuscitation in addition to the classic AS, such as postpartum resuscitation procedures and their outcomes[16,21]. Multivariate analyses demonstrated the presence of other independent risk factors for ROP, including low birth weight (BW), low gestational age, assisted ventilation for more than 1 week, surfactant therapy, multiple blood transfusions, low caloric intake, hyperglycaemia, and insulin therapy[22]. However, studies on predictors of ROP during the early hours after birth are scarce[6].

The present study investigated whether interventions performed in the labour ward could reliably predict the occurrence of ROP as a severe complication of prematurity. Additionally, it aimed to show that precise information on delivery room management or the expanded AS can have prognostic value for early complications in the neonatal period. There are few scientific reports on the prognostic value of the expanded AS.

MATERIALS AND METHODS

Selection of study participants

This single-centre study was based on a retrospective analysis of the medical records of neonates born between 2009 and 2011 at the 2nd Department of Gynaecology and Obstetrics and treated in the Department of Neonatology and Neonatal Intensive Care at Warsaw Medical University (WUM). The data were sufficient for statistical analyses.

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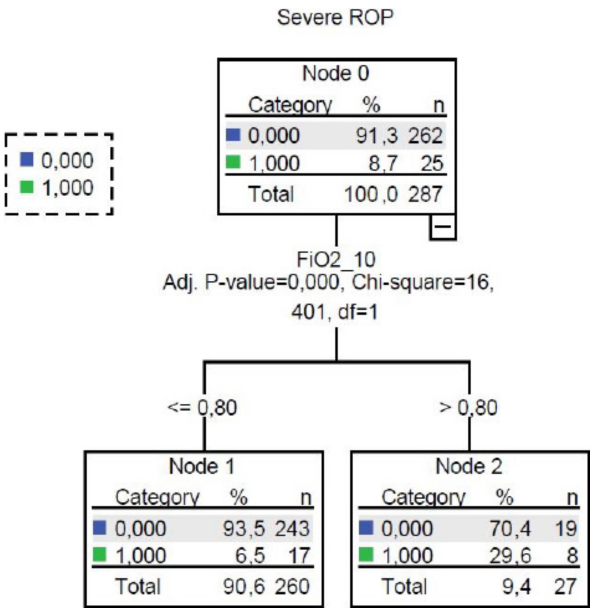

Fig. 1. Decision tree for sROP and fraction of inspired oxygen at 10 minutes of life

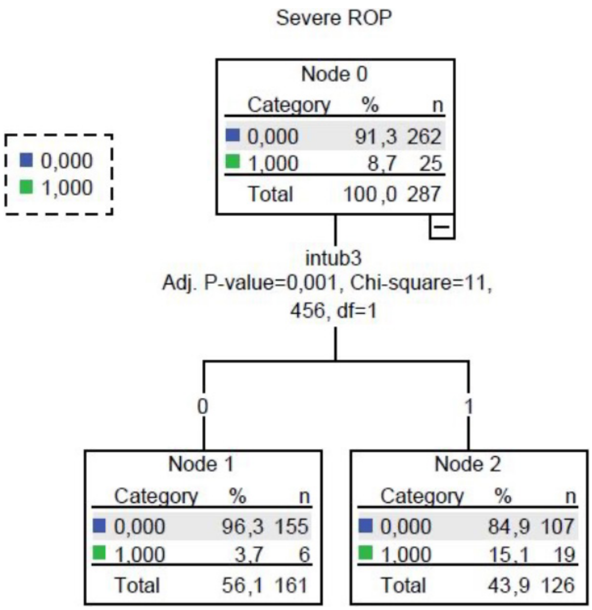

Fig. 2. Decision tree for sROP and the parameter – intubation at 3 minutes of life

The study group consisted of 287 infants (154 boys and 133 girls) born between 22 and 32 weeks of gestational age. The study included neonates who required resuscitation in the first minutes after birth (ventilation using a mask ventilator, intubation, oxygen concentration used, chest compressions, and epinephrine use) and with an AS ≤7 in the first minute after birth. The exclusion criteria were AS >7, significant congenital disorders, and lack of resuscitation interventions. Children who died before the ROP test were excluded from the analysis (n = 21). Several parameters were used as inputs for the chi-square-based automatic dependency detection algorithm, chi-square automatic

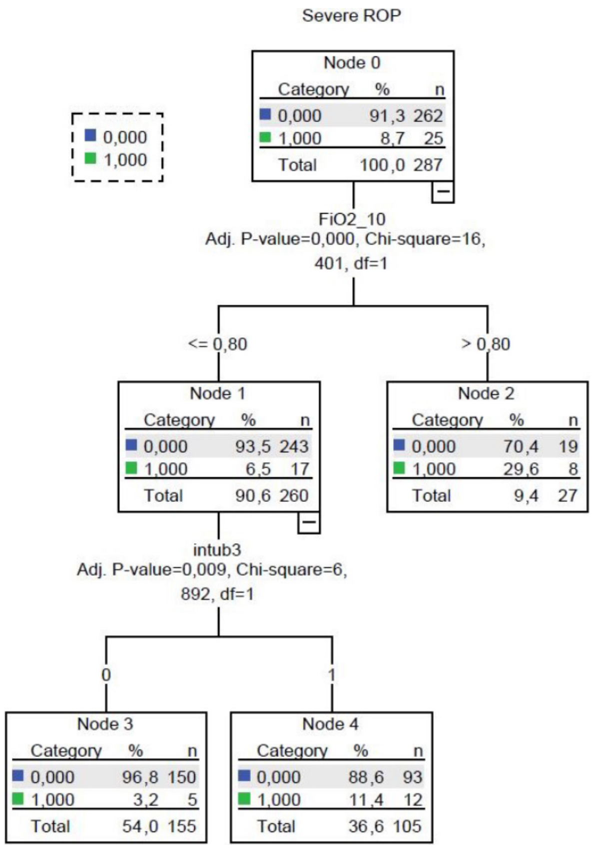

Fig. 3. Decision tree for sROP and oxygen concentration at 10 minutes of life

interaction detection (CHAID; decision tree), including AS at 1, 3, 5, 10, and 15 minutes after birth, the maximum measured AS value at 1, 3, 5, and 10 minutes after birth (AS max), and the course of resuscitation documented according to the expanded AS (ventilation with mask ventilator, intubation, oxygen concentration, chest compressions, and epinephrine use).

Statistical analysis

This study examined the relationship between numerical (continuous) and categorical (nominal) variables. An independent Student's t-test was used to analyse the variation in means for two variables: (1) GA and (2) the fraction of inspired oxygen (FiO_2) received by the newborn at 10 minutes of life (FiO_2_10), both grouped according to the distribution of sROP (the nominal variable). The Shapiro–Wilk test was used to examine whether GA and FiO_2_10 levels followed a normal distribution. Levene's test was also used to verify the equality of variances, with a correction made to the t-test because of the possibility of unequal variances.

The distribution of categorical variables was analysed using the chi-square test, for example, sex and severity of ROP. CHAID decision trees (Figs. 1–3) were used for the multivariate analysis of variables, including the selection

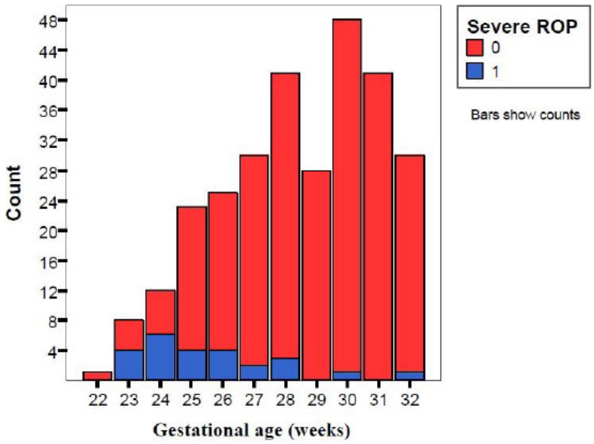

Fig. 4. Frequency distribution of severe retinopathy of prematurity (sROP) by pregnancy week

	Week	sROP		Total	Percentage
		0	1		
Gestational age	22	1	0	1	0.0%
	23	4	4	8	50.0%
	24	6	6	12	50.0%
	25	19	4	23	17.4%
	26	21	4	25	16.0%
	27	28	2	30	6.7%
	28	38	3	41	7.3%
	29	28	0	28	0.0%
	30	47	1	48	2.1%
	31	41	0	41	0.0%
	32	29	1	30	3.3%
Total		262	25	287	8.7%
sROP – severe retinopathy of prematurity.					

Tab. 1. Prevalence of sROP in relation to gestational age (in weeks)

Gestational age	ROP	sROP	Percentage
22–25	44	14	31.82%
26–27	55	6	10.91%
28–29	69	3	4.35%
30–31	89	1	1.12%
ROP – retinopathy of prematurity; **sROP** – severe retinopathy of prematurity.			

Tab. 2. Prevalence of sROP according to gestational age range (in weeks)

of the best predictors and division of numeric variables (discretisation), in the context of the homogeneity of decision nodes. Kendall's tau and Spearman's rho correlations were used to analyse correlations between numeric variables (which deviated from the normal distribution), such as FiO_2 received by the newborn at 10 minutes of life (FiO_2_10) and GA. Chi-square tests with Bonferroni correction ($p < 0.05$) were used for variable selection and decision-tree node partitioning. In addition to the decision trees, a p-value of 0.05 was considered statistically significant. All analyses were performed using the statistical package SPSS 15.0.

Sex	Severe ROP		Total	Percentage
	0	1		
Men	144	10	154	6.5%
Women	118	15	133	11.3%
Total	262	25	287	8.7%
ROP – retinopathy of prematurity.				

Tab. 3. Incidence of ROP by sex

RESULTS

The distribution of the analysed group (≤32 weeks GA) is shown in Fig. 4 and Tab. 1.

The frequency of sROP is presented according to gestational age (in weeks). For each gestational week, the number of infants with (1, blue) or without (0, red) sROP is shown ($n = 287$).

The frequency of sROP by GA is depicted in Fig. 1 and Tab. 1, and the additional frequency of sROP across different GA ranges is presented in Tab. 2. The percentage of sROP occurrence ranged from 1.12% to 31.82% (Tab. 2).

Student's t-test revealed a statistically significant 3-week difference between the mean GA of newborns with and without sROP (25.6 vs. 28.7 weeks, respectively; $p < 0.001$).

Tab. 3 shows that sROP occurred in 10 out of 154 boys (6.5%) and 15 out of 133 girls (11.3%). The study group showed no significant gender differences in the occurrence of sROP (chi-square: $p = 0.221$ and Fisher's exact test: $p = 0.207$).

An analysis of the parameters of the expanded AS yielded the following results.

Parameter analysis: FiO_2

A significantly different mean concentration of oxygen administered at the 10th minute was observed between neonates who developed sROP ($FiO_2 = 0.64$) and those who did not ($FiO_2 = 0.48$; $p < 0.044$, t-test).

Using a decision tree algorithm with a set of factors from the expanded AS, 29.6% sROP penetration (i.e. 8 of 27 children) was identified for oxygen concentrations at 10 minutes, with a level >0.8. Conversely, for oxygen concentrations ≤0.8, the sROP penetration was 6.5% (i.e. 17 out of 260 children); chi-square test p-value <0.001 (Fig. 1).

A decision tree was generated to examine the relationship between the occurrence of sROP and the variable (FiO_2_10) at 10 minutes after birth in preterm infants born ≤32 GA ($n = 287$). The decision classes relating to the presence or absence of sROP are marked as follows: 1– green colour – neonates with sROP; 0 – blue colour – neonates without sROP. Node 1 represents preterm infants who received FiO_2 ≤0.8 ($n = 260$), while Node 2 represents preterm infants who received FiO_2 >0.8 ($n = 27$). Pearson's chi-square test (with Bonferroni correction for multiple comparisons) was used to assess statistical significance: p <0.001.

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The Kendall and Spearman correlation analyses show that excess oxygen must be administered to neonates with a lower GA. Oxygen concentration measured at 10 minutes and GA were the most strongly negatively correlated variables, comparing other variable variants, with Kendall's tau_b at −0.374 and Spearman's rho at −0.473.

Parameter analysis: intubation

Using a decision tree based on the factors of the expanded AS, 19 children with sROP were identified (penetration rate: 15.1%) among 126 children while evaluating the parameter "intubation in the delivery room at 3 minutes". Additionally, 6 children with sROP were identified among 161 non-intubated children (penetration rate: 3.7%, $p = 0.001$; Fig. 2).
A decision tree was generated to examine the relationship between sROP and the expanded AS parameter (intubation in the delivery room at 3 minutes of life) for newborns with a GA of ≤32 weeks. Decision classes related to the presence or absence of sROP are marked as follows: 1 – green colour for neonates with sROP; 0 – blue colour for neonates without sROP ($n = 287$). Pearson's chi-square test, with Bonferroni correction for multiple comparisons, was used to assess statistical significance: $p < 0.002$.

Parameter analysis: chest compressions and epinephrine

We also analysed other components of the expanded AS, such as the need for chest compressions and epinephrine administration. A total of 11 infants required chest compressions, and two were diagnosed with sROP ($p = 0.25$). Of the 10 neonates who required epinephrine administration during delivery room resuscitation, four survived, with one diagnosed with sROP ($p \approx 1.00$). However, the chi-square test showed no statistical significance, with p-values of 0.25 for chest compressions and ≈1.00 for epinephrine.

Parameter analysis: FiO_2 and intubation

A decision tree was generated to analyse the dependence of sROP incidence on the parameter oxygen concentration received (FiO_2_10) at the 10th minute after birth in preterm infants born ≤32 weeks GA ($n = 287$). Furthermore, a decision tree was generated to examine the relationship between sROP incidence and intubation at 3 minutes of life in preterm infants who received FiO_2 ≤0.8 at the 10th minute after birth ($n = 260$). Decision classes related to the presence or absence of sROP were marked as follows: 1 – green colour for neonates with sROP; 0 – blue colour for neonates without sROP. Node 1 represents preterm infants who received FiO_2 ≤0.8 at the 10th minute after birth. Node 2 represents preterm infants who received FiO_2 >0.8 at the 10th minute after birth. Node 3 represents preterm infants who did not require intubation at 3 minutes of life. Node 4 represents preterm infants who required intubation at 3 minutes of life. Pearson's chi-square test (with Bonferroni correction for multiple comparisons) assessed statistical significance: $p < 0.01$ for both splits.
Using a decision tree to indicate sROP dependencies based on the factors of expanded AS, a multivariate analysis was performed for oxygen concentration at 10 minutes and intubation at 3 minutes (Fig. 3).
Compared to the previous decision tree (Fig. 2), new results were obtained for oxygen concentration at 10 minutes ≤0.8. With additional intubation at 3 minutes, 11.4 concentration of sROP was reached (12 out of 105 children). When intubation was not performed (oxygen concentration at 10 minutes ≤0.8.), sROP penetration was reduced to 3.2% (5 out of 155 children).
A 2-depth decision tree constructed from several expanded AS variables identified three subsets with different risks of sROP. The lowest risk of sROP occurred when the infant's FiO_2_10 was ≤0.8, and the infant was not intubated at 3 minutes of life, resulting in a 3.2% incidence of sROP. A moderate risk (11.4%) was observed when FiO_2_10 was ≤0.8, and the baby was intubated at 3 minutes of life. The highest risk of sROP (29.6%) was associated only with FiO_2_10 higher than 0.8.

DISCUSSION

Early GA and low BW have traditionally been considered significant risk factors for ROP and are used as screening criteria worldwide[2,14]. Several studies have identified other risk factors associated with the severity of ROP. These include supplemental oxygen, prolonged mechanical ventilation, AS, pulmonary complications, anaemia, intraventricular haemorrhage, necrotising enterocolitis, and sepsis[19,23–27]. All these complications are associated with multifactorial pathogenesis and often depend on the perfusion of cells and tissues, and oxygenation status[16]. Analysis aimed to determine measurable values and cut-off points to identify children at the highest risk of sROP. As the pathogenesis of ROP is multifactorial, understanding perinatal ROP risk factors may facilitate the early identification of high-risk infants[1,28]. In the most extensive analysis of perinatal ROP risk factors (both prenatal and postnatal), Ying et al. found that ROP risk depends mainly on BW and GA, with minimal influence from other factors[1]. These findings align with previous studies in different populations, which confirm that increasing prematurity is a vital risk factor for ROP. Low BW and early GA are indicators of neuronal and vascular immaturity at birth, and are key factors in ROP development[1]. This finding is consistent with the data from the present study, which show that immaturity and GA are the most common risk factors for ROP. The average GA of the children with and without ROP was 25 and 28 weeks, respectively.
A comparison of our study with a relatively large cohort study conducted in Denmark by Slidsborg et al., which used screening criteria for newborns similar to those in Poland,

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demonstrated that the correlations between GA and ROP rates (Tab. 2) in specific GA groups were identical[3]. Several previous studies have reported that male sex may be associated with a higher risk of severe ROP[1]. However, no difference in the incidence of ROP based on the newborn's sex was observed in the present study.

As mentioned in the Introduction, immaturity was seen as an apparent cause of disease development during its first description. Excessive oxygen supplementation was later found to cause ROP[3,29]. Kendall's and Spearman's tests revealed a negative correlation between the oxygen concentration required by newborns and GA. This, in turn, linked preterm birth, and therefore retinal immaturity, to ROP, as more supplemental oxygen is needed in immature babies due to their relatively poor condition. These findings are consistent with both clinical practice and scientific literature.

The AS score may be the first measurable risk factor for predicting the likelihood of oxygen therapy[2]. In a study involving 957 infants, Ke et al. noted that a low AS score at 5 minutes was a significant risk factor for ROP progression to a stage that required treatment[see 2]. However, the authors did not demonstrate that independence was a factor. In a study of 122 cases, Abrishami et al. assumed that AS scores in infants with ROP were lower than those without ROP. However, their multivariate study failed to identify AS scores as an independent factor[30]. A study by Marinov et al. in Bulgaria found that an AS of 6 or less at 5 minutes was not a statistically significant risk factor for an increased incidence of ROP but was an important risk factor for low-grade ROP at a stage requiring treatment[18].

Eftekhari Milani et al. showed that the 5-minute AS was a statistically independent risk factor for ROP. However, despite similar findings, a robust screening criterion for ROP may not have been applied, although it could be a good predictor of progression to ROP[2]. In another study, logistic regression analysis showed that an AS of 5–6 was a significant independent risk factor for ROP progression to a stage requiring treatment[18]. Fortes Filho et al. analysed the Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II) to predict mortality and morbidity in the NICU. SNAPPE-II includes AS. The authors demonstrated that the SNAPPE-II score was a significant risk factor for developing severe ROP in 304 premature infants. The authors compared infants without ROP symptoms to those with sROP (requiring treatment). The AS at 5 minutes, when 6 or less, is a non-invasive marker routinely used in neonatology. In this study, it proved to be a significant and independent risk factor for the progression of overt ROP to a stage requiring treatment[18]. Similar conclusions were drawn by Yang et al., who reported that a low AS at 5 minutes of life is a significant factor in the development of ROP requiring treatment[see 2].

Delivery room management was analysed in greater depth, in addition to the assessment of AS. In addition to BW and GA, several perinatal risk factors were significantly associated with sROP. Delivery room intubation was significantly associated with a higher risk of sROP. Our study mainly focused on analysing the expanded AS as a predictor of ROP. It was found that the FiO_2 received by the newborn at 10 minutes was a statistically significant parameter. 29.6% of newborns with severe ROP had oxygen concentrations >0.8, while fewer than 6.5% of cases occurred at oxygen concentrations ≤0.8. Analysis of the present study also showed a significant effect of the delivery room intubation parameter, a component of the expanded AS. Approximately 15% of infants requiring intubation within 3 minutes of life developed severe ROP. However, only 3.7% of non-intubated newborns had sROP.

There are plans to identify specific elements of the expanded AS that can help predict early complications in preterm infants. Previous studies have examined intraventricular and intraparenchymal haemorrhage[31] and the risk of death[16]. This study determined the extent to which the first few minutes of a preterm infant's life could influence the development of complications. Therefore, all necessary resuscitation or delivery room transition procedures should be performed to ensure the most effective and beneficial treatment for the newborn.

The present study evaluated the risk of severe ROP in preterm infants based on their postnatal status. As mentioned above, oxygen concentration is an important criterion often associated with the need for intubation. Intubation at 3 minutes was the most significant criterion (although assessments at 1, 5, and 10 minutes were also statistically significant). This study focused on assessing perinatal risk factors that can help predict the risk of ROP after birth. However, we did not evaluate the emerging risk factors that could have a significant predictive value for ROP risk stratification.

Early detection and timely treatment of ROP can reduce the risk of retinal detachment and blindness[2]. As mentioned earlier, ROP treatment includes laser photocoagulation or intravitreal administration of anti-VEGF preparations. Diode or argon laser therapy remains the treatment of choice for patients with ROP. A detached retina or vitreoretinal surgery is performed in the advanced stages of the disease. Treatment should be initiated no later than 72 hours after diagnosis; however, in cases of aggressive posterior retinopathy of prematurity (AP-ROP), efforts should be made to keep the time to treatment as short as possible[10,11].

As the pathogenesis of ROP is multifactorial, understanding the risk factors for ROP, particularly perinatal risk factors, can assist in the early detection of high-risk infants at birth, enabling timely treatment of ROP and ultimately reducing the incidence of blindness due to ROP[1].

CONCLUSIONS

Expanded AS variables show clinical utility in predicting the occurrence of prematurity-related pathologies, such as severe retinopathy of prematurity. The parameter of the

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expanded AS with the greatest discriminatory power was the oxygen concentration at 10 minutes of life. Intubation at 3 minutes of life also plays a vital role in improving the assessment of a newborn's health status, enabling doctors in labour wards to choose the most appropriate and effective interventions.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study: AG, JEPG. Collection, recording and/or compilation of data: AG, JEPG. Analysis and interpretation of data: AG, JEPG, PB. Writing of manuscript: AG, JEPG. Critical review of manuscript: JEPG, RB. Final approval of manuscript: AG, RB.

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