OBJECTIVES: To evaluate the accuracy of the ROPScore algorithm as a predictor of retinopathy of prematurity (ROP).

METHODS: A prospective cohort of 220 preterm infants with a birth weight ≤ 1500 g and/or gestational age ≤ 32 weeks was included. The ROPScore was determined in the sixth week of life in 181 infants who then survived until a corrected gestational age of 45 weeks. The sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) of the algorithm were analyzed.

RESULTS: ROP was found in 17.6% of the preterm infants. The sensitivity of this test for any stage of ROP was 87.5%, while that for severe ROP was 95.4% (21/22 cases). The PPV and NPV were 59.6% and 97%, respectively, for any stage of ROP and 44.7% and 99.25%, respectively, for severe ROP. The ROPScore could therefore hypothetically reduce the number of ophthalmologic examinations required to detect ROP by 71.8%.

CONCLUSION: The ROPScore is a useful screening tool for ROP and may optimize examinations and especially the identification of severe ROP.

KEYWORDS: Retinopathy of Prematurity; Preterm Infants; Algorithm.
METHODS

We performed a prospective cohort study in which we included all preterm infants born with BW ≤1500 g and GA ≤32 weeks who were admitted to the Neonatal Intensive Care Unit (NICU) of the University Hospital of Botucatu Medical School - UNESP, Brazil, from November 2012 to July 2014. The study protocol was approved by the Research Ethics Committee of the Botucatu Medical School – UNESP (no. 4051/2011), and the parents/guardians of all included infants provided written consent to participate in the study. Infants that died before completing six weeks of life or before reaching 45th weeks of corrected gestational age. No other exclusion criterion was used. ROP screening was performed between the fourth and sixth weeks after birth and repeated based on the findings of ophthalmologic examinations performed at intervals determined by the Brazilian guidelines for detecting and treating ROP, which state that exams should be performed until the retina is fully vascularized or ROP has totally regressed (13). Ophthalmologic examinations consisted of binocular indirect ophthalmoscopy after pupilary dilatation with tropicamide 0.5% and phenylephrine 2.5% and were performed using a 28-diopter lens and an eye speculum. ROP was categorized according to the International Classification of Retinopathy of Prematurity Revised (18). Clinical outcomes were defined as the onset of any stage of ROP (requiring no treatment) or severe ROP that required treatment. Each child was classified according to the most advanced ROP stage observed. The indications for treatment were based on the Early Treatment for Retinopathy of Prematurity study (ETROP) criteria (19).

ROPScore Screening was applied in the sixth week of life using a Microsoft Excel spreadsheet as proposed by Eckert et al. (14). This process required the following parameters: BW, GA, weight at the sixth week of life, the presence or absence of blood transfusion up to the sixth week of life, and oxygen in mechanical ventilation (Figure 1).

RESULTS

A total of 220 preterm infants met the inclusion criteria, thirty-eight of whom died before the sixth week of life. Thus, 181 patients (86 male and 95 female) completed the study. The prevalence of any stage of ROP was 32/181 infants (17.6%). Ten preterm infants developed low-grade ROP, and 22/181 developed severe ROP that required treatment (12.1%). The baseline demographics and clinical characteristics for this cohort are shown in Table 1.

The accuracy of the ROPScore for predicting the onset of ROP in our population was determined by ROC curves (Figure 2), and cut-off points for sensitivity and specificity were obtained for continuous score values. The ROPScore values ranged from 7.2 to 19.6 (Table 1). The best cut-off point established for any stage of ROP was 16 (87.5% sensitivity and 87.2% specificity), while that for severe ROP was 16.6 (95.4 sensitivity and 83.6% specificity). The positive and negative predictive values (PPV and NPV, respectively) for any stage of ROP and severe ROP are shown in Table 2.

DISCUSSION

In Brazil, the prevalence of ROP varies according to region, the level of neonatal care, and access to ophthalmologic

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**Figure 1** - Excel spreadsheet (Microsoft) used to calculate the ROPScore. From Eckert et al. 2012.

**Table 1** - Characteristics of the 181 premature infants included in the study.

| Characteristic                | Total Cohort | Any stage ROP | Severe ROP |
|------------------------------|--------------|---------------|------------|
| Number of patients           | 181          | 32            | 22         |
| Male                         | 86 (181)     | 10 (32)       | 6 (22)     |
| Mean BW (g)*                 | 1271.6 ± 345.6| 884.0 ± 250.0 | 763.1 ± 186.8 |
| Mean GA (weeks)*             | 29.2 ± 2.2   | 26.4 ± 1.6    | 25.9 ± 1.2 |
| Mean WG at the sixth week of life (g)* | 596.9 ± 248.0 | 407.4 ± 190.8 | 390.7 ± 162.8 |
| ROPScore range*              | 7.2 – 19.6 (13.5 ± 3.0) | 12 – 19.6 (16.0 ± 2.3) | 14.7 – 19.6 (17.9 ± 1.0) |

* Data are expressed as the mean ± SD; BW: Birth Weight; GA: Gestational Age; ROP: Retinopathy Of Prematurity; SD: Standard Deviation; WG: Weight Gain from birth to 6 weeks of life.
screening programs. The blindness caused by ROP can be prevented with timely screening (20). In the present study, the ROPScore was a useful and accurate method for predicting ROP.

Scoring systems have become widely used in neonatology, including neonatal intensive care, to help detect comorbidities. Predictive algorithms represent promising and appropriate tools that can be used to identify preterm infants at risk of developing severe ROP and reduce the excessive number of examinations performed per preterm infant (21).

The ROPScore was developed in Brazil (14) and was chosen to be tested in our population because it is simple and practical to use and requires only one weight measurement.

The incidence of severe ROP was much higher in this sample than in the population studied by Eckert et al. (14) in South Brazil (12.5% versus 5%, respectively). A comparison of the characteristics of that population versus the those of the present cohort revealed that in preterm infants who developed severe ROP, BW (908.7 g ± 232.6 versus 763.1 ± 186.8), GA (27.9 ± 2.2 versus 25.9 ± 1.2) and weight gain during the first six weeks of life (411.7 ± 277.4 versus 390.7 ± 162.8) were lower in this study than in the previous study, and this may account for the fact that more infants developed the more severe form of the disease in this study.

The cut-off point for ROPScore was higher in this cohort (16 for any stage of ROP and 16.6 for severe ROP) than in the study population in Eckert et al. (14) (11 for any stage of ROP and 14.5 for severe ROP). Piemarocchi et al. (9) evaluated ROPScore in a retrospective cohort but adjusted only the cut-off point for severe ROP, which increased from 14.5 to 15.8.

The NPV calculated in this study indicated that the probability that a preterm infant with a ROPScore below a cut-off point of 16 would not develop any stage of ROP was 97.1%, while the probability that the same infant would not develop the severe form of the disease was 99.2%. An adjusted ROPScore correctly identified 28 of 32 preterm infants who developed any stage of ROP and 21 of 22 who developed severe ROP. Despite the fact that one case of severe ROP was not identified, the adjusted ROPScore had a high NPV and was associated with high sensitivity, indicating that it was a useful tool for identifying preterm infants at greater risk and would, therefore, reduce the number of exams in clinical practice. If the ROPScore were applied, 130 of the preterm infants in this cohort would not need to be evaluated with the same frequency, resulting in a decrease of 71.8% in the total number of tests needed to detect ROP.

The introduction of such algorithms is still in the preliminary phase, and it should be stated that the goal is not to replace the current screening guidelines. However, these tools can help to reduce the number of lost diagnoses in ROP (7,9). Regardless of this positive characteristic of the function of the algorithms, there are limitations to their clinical use. First, the ROPScore calculation uses preterm weight only at the sixth week of life. Hence, this test may not detect some high-risk preterm infants in whom aggressive posterior ROP is initiated prior to weight measurement but then subsequently evolves rapidly (9). Moreover, the early hospital discharge of preterm infants that are evolving well is another factor that contributes to the loss of a weighing on the correct day and the consequent inability to apply the ROPScore.

Accordingly, other predictive models that are currently being tested in ROP in addition to the ROPScore also have limitations. For example, WINROP 2 (22) was proposed for European populations and has been validated by several studies that have shown it has good effectiveness in predicting ROP. However, some studies have shown that this score does not perform well in underdeveloped countries in...
which moderate and late preterm infants can also develop ROP (23-26). These include a study by Ko et al. (24) in which the authors concluded that WINROP was especially effective in preterm infants with BW < 1000 g or GA < 28 weeks and did not detect six neonates with severe ROP. In Brazil, Hard et al. (25), also reported that some cases with severe ROP were lost when they used WINROP, and they suggested that the algorithm needed to be reformulated with data from developing countries.

CHOP-ROP is another simple model. However, it limits GA to <30 weeks and requires daily weighing, which restricts its usefulness in clinical practice (26). A separate model, the CO-ROP, was recently proposed and is still being validated (27).

In conclusion, we demonstrate that the ROPSscore was an effective, promising, and noninvasive screening tool for predicting ROP in a Brazilian population of preterm infants. The results of Eckert et al. (14) are compatible with those obtained in this cohort with regard for a high score for sensitivity and a high VPN. With regard for ROPSscore cut-off points, although we adjusted the values for our population (16 and 16.6, for any stage and severe ROP), the cut-off values used in the original cohort (14) would have been sufficient to detect all preterm infants with severe ROP.

Although the introduction of algorithms such as the ROPSscore is still in the preliminary phase, and the goal of such algorithms is not to replace the current screening guidelines, they can help to reduce the number of lost ROP diagnoses. With regard for this function of the algorithms, one difficulty we encountered in using the ROPSscore was that it required assessing preterm weight only in the sixth week of life. Some high-risk preterm infants in whom aggressive ROP initiates prior to this weight measurement can evolve rapidly and may not be detected (9). Additionally, the early pre-term hospital discharge of infants that are evolving well is another factor that contributes to the loss of a correct weight time and therefore the loss of the ROPSscore.

Finally, the process by which a scoring system is validated is a dynamic one. In the current study, we aimed to contribute by validating the real-world usefulness of the ROPSscore in Brazil. New prospective studies are needed to determine the impact of the ROPSscore in a clinical setting in different populations.

AUTHOR CONTRIBUTIONS
El Dib R, Lucio KC and Jorge EC conceived and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Toscano TB, Augusto AC, Lucio KC and Corrente JE collected data, carried out the initial analyses, and reviewed and revised the manuscript. Jorge EC, El Dib R and Bentlin MR designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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