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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

YENİDOĞAN YOĞUN BAKIMDA BRONKOPULMONER DİSPLAZİ TAHMİN ARACININ DEĞERLENDİRİLMESİ

EVALUATION OF THE USE OF BRONCHOPULMONARY DYSPLASIA OUTCOME ESTIMATOR IN THE NEONATAL INTENSIVE CARE UNIT

Sara EROL, Serdar BALSAK, Mustafa Şenol AKIN, Burak CERAN, Nihan Hilal HOŞAGASI, Sabriye KORKUT

[1]Ankara Bilkent Şehir Hastanesi Çocuk Sağlığı ve Hastalıkları Ana Bilim Dalı, Yenidoğan Bilim Dalı

ÖZET

AMAÇ: Bronkopulmoner displazi (BPD), günümüzde prematüre bebekleri etkileyen en önemli solunum sistemi morbiditesi olmaya devam etmektedir. Bu çalışmanın amacı, Eunice Kennedy Shriver Ulusal Çocuk Sağlığı ve İnsan Gelişimi Enstitüsü'ne (NICHD) ait BPD sonuç tahmin aracının 2022 versiyonunun doğruluğunu değerlendirmektir.

GEREÇ VE YÖNTEM: Bu retrospektif kohort çalışmada, doğum ağırlıkları 501 ile 1249 gram arasında ve gebelik haftaları 23 ile 28 hafta arasında olan prematüre bebekler değerlendirilmiştir. 1 Ocak 2021 ile 31 Aralık 2022 tarihleri arasında üçüncü basamak bir yenidoğan yoğun bakım ünitesinde doğan ve çalışma kriterlerini karşılayan prematüreler çalışmaya alınmıştır. 2022 BPD tahmin edici aracının BPD şiddeti ve mortalite tahmini konusundaki doğruluğu, hastaların klinik sonuçları temel alınarak değerlendirilmiştir.

BULGULAR: Çalışma kriterlerine uygun toplam 118 prematüre bebek dahil edilmiştir. Bebeklerin %56'sı (n=66) kızdı. Doğum ağırlıkları 530 gram ile 1240 gram arasında, gebelik haftaları ise 24 ile 28 hafta arasında değişmekteydi. 2022 BPD tahmin aracı, 1., 3., 7. ve 14. günlerde hastaların mortalite, ciddi BPD gelişimi ve BPD'siz sağkalım durumlarını; 28. günde ise ciddi BPD ve BPD'siz sağkalımı öngörmede istatistiksel olarak anlamlı düzeyde başarılı bulunmuştur (p<0,05).

SONUÇ: BPD'yi doğru bir şekilde tahmin etmek, BPD ile ilişkili morbidite ve mortaliteyi yönetme ve önleme stratejilerinin geliştirilmesi açısından kritik öneme sahiptir. BPD sonuç tahmin aracı gibi bir hesaplayıcının, ciddi BPD, mortalite ve BPD'siz sağkalımı öngörebilme yeteneği son derece değerlidir.

ANAHTAR KELİMELER: Bronkopulmoner Displazi, Prematurite, Prognoz.

ABSTRACT

OBJECTIVE: Bronchopulmonary dysplasia (BPD) remains the most important respiratory morbidity affecting premature infants to this day. The aim of this study is to evaluate the accuracy of 2022 version of the Eunice Kennedy Shriver National Institute of Child Health and Human Development BPD outcome estimator.

MATERIAL AND METHODS: This retrospective cohort study evaluated premature infants with birth weights ranging from 501 to 1249 grams and gestational ages between 23 and 28 weeks. Premature infants born between January 1, 2021, and December 31, 2022, at a tertiary-level neonatal intensive care unit who met the inclusion criteria, were included in the study. The predictive accuracy of the 2022 BPD Outcome Estimator in determining the severity of BPD and mortality was evaluated based on the patients' clinical outcomes.

RESULTS: A total of 118 premature infants who met the inclusion criteria were included in the study. Fifty-six percent (n=66) of the infants were female. The birth weights of the patients ranged from 530 g to 1240, and the gestational weeks ranged from 24 to 28 weeks. The 2022 BPD Outcome Estimator has been found to be statistically significantly robust in predicting both mortality and severe BPD as well as BPD-free survival on days 1, 3, 7, and 14, and predicting severe BPD and BPD-free survival on day 28 (p<0.05).

CONCLUSIONS: Accurate prediction of BPD is crucial for developing strategies to manage and prevent BPD-related mortality and morbidities. The ability of tools such as the BPD Outcome Estimator to predict severe BPD, mortality, and BPD-free survival is highly valuable in clinical practice.

KEYWORDS: Bronchopulmonary dysplasia, Prematurity, Prognosis.

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Yazışma Adresi / Correspondence: Doç. Dr. Sara EROL
Ankara Bilkent Şehir Hastanesi Çocuk Sağlığı ve Hastalıkları Ana Bilim Dalı, Yenidoğan Bilim Dalı
E-mail: sarasurmeli@gmail.com
Orcid No (Sırasıyla): 0000-0002-8758-7662, 0000-0003-4600-2880, 0000-0003-0055-8277, 0000-0001-5914-5325, 0000-0002-2107-4485, 0000-0003-4169-1912
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INTRODUCTION

Despite advances in obstetrics and neonatology since its first description by Northway and colleagues 50 years ago (1), bronchopulmonary dysplasia (BPD) remains the most important respiratory morbidity affecting premature infants to this day. Developments such as antenatal corticosteroids, surfactant therapy, and improvements in neonatal care have led to a decrease in BPD in more mature infants, as well as the emergence of a milder form of the disease called "New BPD" in extremely premature infants. BPD is still seen in 50% of infants weighing less than 1000 grams at birth (2). Diagnostic criteria for BPD have been subject to frequent modifications, evolving alongside changes in the understanding of its pathogenesis and definition. In 2001, the National Heart, Lung, and Blood Institute workshop established BPD classification into mild, moderate, or severe categories based on oxygen or respiratory support requirements at 36 weeks postmenstrual age and the need for oxygen supplementation for at least 28 days (3). Subsequent workshops organized by the Eunice Kennedy National Institute of Child Health and Human Development (NICHD) suggested further refinements to the 2001 definition (4). In 2019, the NICHD workshop identified respiratory support applied at 36 weeks postmenstrual age, independent of oxygen concentration, as the optimal diagnostic criterion for categorizing BPD severity (5).

Although the short and long-term results of BPD cannot be considered separately from the consequences of prematurity, studies have focused on the effects of BPD on lung functions and neurodevelopment (6). Not only the disease itself, but also the effects of postnatal steroids, which stand out as a prevention and treatment strategy, are also an important challenge (7). Only a few of the research studies and strategies developed to prevent BPD have demonstrated proven effectiveness. At this point, it is important to identify an appropriate population for new clinical trials and to develop models that predict the risk of BPD development in order to provide early intervention with proven preventive strategies (8). NICHD Neonatal Research Network (NRN) developed a tool called the "BPD outcome estimator" in 2011, which predicts the severity of BPD and the likelihood of mortality before 36 weeks postmenstrual age (9). The latest revision for the BPD outcome estimator was made in 2022 (10).

The objective of this study is to determine the accuracy of the 2022 versions of the NICHD BPD outcome estimator in predicting mortality before 36 weeks of postmenstrual age and determining the severity of BPD based on the diagnostic criteria of the NICHD Neonatal Research Network in preterm infants under the care of our tertiary-level neonatal intensive care unit (NICU).

MATERIALS AND METHODS

The study group of this retrospective cohort study included all premature infants born between January 1, 2021, and December 31, 2022, at a tertiary-level NICU, with a birth weight ranging from 501 to 1249 grams and a gestational age between 23 and 28 weeks. Infants with major congenital anomalies and those who died within the first 14 days after birth were excluded from the study.

Respiratory support and fraction of inspired oxygen (FiO_2) requirements were documented on postnatal days one, three, seven, 14, 21, and 28, along with gestational age, birth weight, and gender of patients. Furthermore, the occurrences of surgical necrotizing enterocolitis (NEC) as well as antenatal steroid administration were also recorded.

NICHD 2018 BPD grading criteria were used for the diagnosis and grading of BPD in the enrolled patients BPD severity was classified as follows: Mild BPD includes infants receiving low-level oxygen support such as hood oxygen with FiO_2 0.22–0.29, nasal cannula (NC) <1 L/min with FiO_2 0.22–0.70, or 1–<3 L/min with FiO_2 0.22–0.29, as well as ≥3 L/min flow (including nasal continuous positive airway pressure (CPAP)/ non-invasive positive pressure ventilation (NIPPV) with FiO_2 0.21. Moderate BPD includes infants on hood oxygen with FiO_2 ≥0.30, NC <1 L/min with FiO_2 ≥0.70, 1–<3 L/min with FiO_2 ≥0.30, or ≥3 L/min (CPAP/NIPPV) with FiO_2 0.22–0.29, or invasive mechanical ventilation with FiO_2 0.21. Severe BPD is defined as the need for CPAP, NIPPV, or NC ≥3

L/min with FiO_2 ≥0.30, or invasive mechanical ventilation with FiO_2 >0.21. Mortality was defined as death occurring between the 14th postnatal day and 36 weeks postmenstrual age due to persistent pulmonary parenchymal disease and respiratory failure not attributable to other neonatal morbidities (4).

The 2022 version of NICHD BPD outcome estimator integrates gestational age, birth weight, gender, ethnicity, respiratory support, and FiO_2 levels recorded on postnatal days one, three, seven, 14, and 28 to assess the probability of an infant developing mild, moderate, or severe BPD, as well as the likelihood of mortality before reaching 36 weeks of post menstrual age (PMA).

The types of respiratory support were classified as high frequency ventilation (HFV), conventional ventilation (CV), NIPPV, CPAP, NC, hood and no support. Additionally, inputs for antenatal steroid administration on day 1 and surgical NEC for days 14 and 28 have been included (10). Using 2022 version of this predictive model, individualized risk assessments for the severity of BPD or mortality were calculated at five different timepoints following birth in the study. The predictive power of the BPD estimator was tested against the actual BPD and mortality outcomes of the patients.

Ethical Committee

This study was approved by the Ankara City Hospital Clinical Research Ethics Committee No. 2 (Approval number: E2-21-620).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Visual (histograms and probability plots) and analytical methods (Shapiro-Wilk's test) were used to determine whether the data were normally distributed. Parametric data were presented as mean ± standard deviation. Nonparametric data are presented as median values (25^{th} percentile to 75^{th} percentile). Receiver Operating Characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of the 2022 BPD outcome estimator in predicting the presence of BPD, severity of BPD, and mortality. Corresponding area under the curve (AUC) values were reported with 95% confidence intervals. Results with p values less than 0.05 were accepted as statistically significant.

RESULTS

A total of 118 premature infants who met the inclusion criteria were included in the study. Fifty-six percent (n=66) of the infants were female. The birth weights of the patients ranged from 530 g to 1240 and the gestational weeks ranged from 24 to 28 weeks. 23 infants were born without receiving antenatal steroid treatment. Surgical NEC developed in 14 patients. BPD did not develop in 24.5% (n=29) of the patients. Of the cases, 16.9% (n=20) were classified as mild BPD, 19.4% (n=23) as moderate BPD, and 27.9% (n=33) as severe BPD. Thirteen patients (11%) died between the 14th day of postnatal age and the 36th postmenstrual week due to persistent parenchymal lung disease. Systemic steroid treatment was administered to 28 patients for BPD. Among patients who received systemic steroid treatment, 67.8% (n=19) developed severe BPD, 21.4% (n=6) developed moderate BPD, 7.1% (n=2) developed mild BPD, and 1 patient experienced an ex **(Table 1).**

Table 1: Demographic features of study population

Variables	Study population (n=118)
Female infants n (%)	66 (55.9)
*Birth weight (g)	965 (822.5 -1112.5)
*Gestational weeks	28 (26-28)
Antenatal steroid administration (%)	95 (80,5)
No BPD n (%)	29 (24.5)
Mild BPD n (%)	20 (16.9)
Moderate BPD n (%)	23 (19.4)
Severe BPD n (%)	33 (27.9)
Death between the 14th day of postnatal age and 36th postmenstrual week n (%)	13 (11)
Systemic steroid treatment for BPD n (%)	28 (23.7)
BPD severity in patients with systemic steroid treatment	
Mild BPD n (%)	2 (7.1)
Moderate BPD n (%)	6 (21.4)
Severe BPD n (%)	19 (67.8)
Death between the 14th day of postnatal age and 36th postmenstrual week n (%)	1 (3.59)

*Data expressed as median (25th-75th percentile)

The 2022 BPD outcome estimator has been found to be statistically significantly robust in predicting both mortality and severe BPD as well as BPD-free survival on days 1, 3, 7, and 14, and predicting severe BPD and BPD-free survival on day 28 ($p<0.05$) **(Table 2)**.

Table 2: The predictivities of the 2022 BPD estimator

		2022 BPD estimator				
	Variables	**AUC**	**p**	**Sensitivity %**	**Specificity %**	**Cutoff %**
Day 1st	Mortality	0,72	**0,01**	69	67	4
	Severe BPD	0,67	**0,004**	65,6	60	2,5
	Moderate BPD	0,58	0,2	60,9	55,2	10,4
	Mild BPD	0,41	0,18	50	44,4	26,2
	No BPD	0,78	**0,000**	74,2	75	65,9
Day	Mortality	0,68	**0,03**	61,5	77,4	4,1
3rd	Severe BPD	0,76	**0,000**	71,9	71,3	3,3
	Moderate BPD	0,56	0,36	60,9	56,2	9
	Mild BPD	0,39	0,10	45	38,2	24,2
	No BPD	0,79	**0,000**	77,4	71,6	67
Day 7th	Mortality	0,74	**0,01**	66,7	64,2	3,4
	Severe BPD	0,74	**0,000**	68,8	72,1	4,6
	Moderate BPD	0,55	0,48	56,5	52,6	13,1
	Mild BPD	0,44	0,37	45	48	34,6
	No BPD	0,83	**0,000**	74,2	71,3	55,4
Day	Mortality	0,73	**0,01**	70	75,7	3,5
14th	Severe BPD	0,74	**0,000**	70	71,4	6,3
	Moderate BPD	0,60	0,14	65,2	56,4	13,8
	Mild BPD	0,44	0,40	45	46,3	34,8
	No BPD	0,86	**0,000**	80,8	82,6	55,7
Day	Mortality	0,68	0,08	62,5	68,2	1,1
28th	Severe BPD	0,85	**0,000**	82	81,5	8,5
	Moderate BPD	0,59	0,19	60,9	54,3	18,6
	Mild BPD	0,38	0,09	40	35	22,6
	No BPD	0,87	**0,000**	87,1	84,5	75,4

AUC: Area under the curve

DISCUSSION

Worldwide, bronchopulmonary dysplasia rates have decreased in infants weighing over 1500 grams at birth with the use of antenatal steroids, surfactant replacement therapy, conservative use of mechanical ventilation and precise infection control procedures (11). However, BPD is still seen in 50% of infants weighing less than 1000 grams at birth, despite improvements in neonatology and obstetrics (1, 12). In premature babies with BPD, chronic respiratory and cardiovascular disorders, growth retardation, and negative effects on neurological development lead to inevitable high healthcare costs and prolonged hospital stays (13, 14). Despite all these known adverse outcomes, our proven methods for preventing and treating BPD are limited.

The models created to predict the development of BPD work based on antenatal and postnatal risk factors. Nowadays, artificial intelligence applications are being developed to predict the development of BPD during birth (15). The goal is to manage premature infants predicted to develop BPD with early treatment approaches and improve short and long-term outcomes. Among these developed models, NICHD BPD outcome estimator is a strong candidate for widespread use today due to its proven predictive power and user-friendly interface. Numerous studies have been conducted on the clinical utility of the BPD outcome estimator. In the retrospective cohort study conducted by Baker and Davis using the 2011 version of the BPD outcome estimator, the incidence of mortality and severe BPD before 36 weeks of age was found to be 48.1% in 187 premature infants born at or below 28 weeks. Although ROC analyses showed that these two parameters had strong predictivity, the observed rates were found to be higher than expected rates (16). In another study that used the 2011 version of the BPD outcome estimator to predict corticosteroid use for BPD treatment, a risk prediction of greater than 37% for severe BPD or mortality before 36 weeks, or less than 3% for no BPD on day 14, was found to be highly sensitive and specific for steroid treatment (17). The validity of the 2022 NICHD BPD outcome estimator in current clinical use was evaluated in a study, and it was found that the online tool had a higher rate of predicting the non-development of BPD compared to predicting the risks of death and BPD development, which was different from previous studies. Additionally, the study highlighted that the BPD outcome estimator had low sensitivity in predicting steroid use for BPD treatment (18). In our study, the 2022 BPD outcome estimator has been found to be statistically significantly robust in predicting both mortality and severe BPD as well as BPD-free survival on days 1, 3, 7, and 14, and predicting severe BPD and BPD-free survival on day 28 ($p<0.05$).

The most significant limitations of this study are its single-center and retrospective nature. With prospective and extensive population-based studies, it would be more feasible to observe the analysis of risk factors and the predictive power and clinical impacts of outcome estimators.

Accurately predicting BPD is crucial for developing strategies to manage and prevent BPD-related mortality and morbidities. It is essential to promote the widespread use of user-friendly calculators with international validity, while allowing for individualized approaches. The ability of a calculator like the BPD outcome estimator to predict severe BPD and BPD-free survival is immensely valuable. Multicenter prospective studies will provide further insights into the clinical utility of outcome prediction tools.

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