



Physiology-guided Rescue Ventilation for Steroid-refractory Severe Bronchopulmonary Dysplasia: An Exploratory Case Series

Steroid Dirençli Ağır Bronkopulmoner Displazide Fizyoloji Temelli Kurtarıcı Ventilasyon: Keşifsel Olgu Serisi

Çağrı Cumhuri Gök, Emrah Can

University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Pediatrics, Division of Neonatology, İstanbul, Turkey

Abstract

Objective: To evaluate the physiological rationale and clinical impact of a protocolized rescue ventilation strategy targeting chronic lung mechanics in infants with established severe bronchopulmonary dysplasia (sBPD) who failed to respond to low-dose dexamethasone therapy (DART).

Method: This retrospective, exploratory case series included infants with sBPD who showed no improvement in oxygenation 72 hours after initiating the regimen low-dose DART. Identifying a mismatch between conventional ventilator settings and the pathophysiology of sBPD, we transitioned patients to a physiology-based strategy using volume-guarantee combined with pressure support ventilation: Low respiratory rates (20-25/min), prolonged inspiratory times (≥ 0.8 s), and higher tidal volumes (10-12 mL/kg).

Results: Seven infants [median GA 25 (24-26) weeks; median birth weight 680 (590-810) g] met the criteria for steroid refractoriness. Baseline $\text{PaO}_2/\text{FiO}_2$ was critically low [median 66 (61-70) mmHg]. Following the physiological reset, $\text{PaO}_2/\text{FiO}_2$ markedly improved to a median of 110 (90-140) mmHg by day 14. Ventilatory efficiency improved despite lower rates, as reflected by a reduction in median pCO_2 from 55 (54-63) to 45.5 (45-47) mmHg. All subjects were successfully weaned from invasive ventilation.

Conclusion: In steroid-refractory sBPD, respiratory failure may be driven by heterogeneity in mechanical time constants rather than by active inflammation alone. A ventilation strategy strictly aligned with

Öz

Amaç: Düşük doz deksametazon tedavisine (DART) yanıt vermeyen ağır bronkopulmoner displazili (sBPD) infantlarda, kronik akciğer mekaniklerini hedefleyen protokole bağlanmış kurtarıcı ventilasyon stratejisinin fizyolojik temelini ve klinik etkisini değerlendirmektir.

Yöntem: Bu retrospektif keşifsel olgu serisine, DART tedavisi başlandıktan sonraki 72 saat içinde oksijenasyonunda iyileşme görülmemeyen sBPD'li infantlar dahil edildi. Konvansiyonel ventilatör ayarları ile sBPD'nin patofizyolojisi arasındaki uyumsuzluk tespit edilerek, hastalar hacim garantili basınç destekli ventilasyon kullanan fizyoloji temelli bir stratejiye geçirildi: Düşük solunum hızları (20-25/dk), uzatılmış inspirasyon süreleri ($\geq 0,8$ sn) ve daha yüksek tidal volümler (10-12 mL/kg).

Bulgular: Medyan gestasyonel yaşı 25 (24-26) hafta ve doğum ağırlığı 680 (590-810) g olan yedi infant steroid direnci kriterlerini karşıladı. Başlangıç $\text{PaO}_2/\text{FiO}_2$ oranı kritik düzeyde düşüktü [medyan 66 (61-70) mmHg]. Fizyolojik yeniden düzenlemenin ardından, $\text{PaO}_2/\text{FiO}_2$ oranı 14. günde belirgin şekilde iyileşerek medyan 110 (90-140) mmHg'ye yükseldi. Daha düşük solunum hızları uygulanmasına rağmen ventilatuvar etkinlik arttı ve medyan pCO_2 düzeyi 55 (54-63) mmHg'den 45,5 (45-47) mmHg'ye geriledi. Tüm hastalar invaziv ventilasyondan başarıyla ayrıldı.

Sonuç: Steroid dirençli sBPD olgularında solunum yetmezliği, yalnızca aktif enflamasyondan ziyade mekanik zaman sabiti heterojenliğinden kaynaklanıyor olabilir. Bu mekaniklerle sıkı sıkıya uyumlu olarak

Address for Correspondence: Çağrı Cumhuri Gök, University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Pediatrics, Division of Neonatology, İstanbul, Turkey

E-mail: cagricumhuri1619@gmail.com **ORCID:** orcid.org/0000-0002-2498-7431

Received: 02.03.2026 **Accepted:** 22.07.2026 **Epub:** 01.10.2026

Cite this article as: Gök ÇC, Can E. Physiology-guided rescue ventilation for steroid-refractory severe bronchopulmonary dysplasia: an exploratory case series. Bagcilar Med Bull. [Epub Ahead of Print]



Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of Health Sciences University Turkey,

İstanbul Bağcılar Training and Research Hospital. This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

Abstract

these mechanics resulted in a reduction in respiratory failure and facilitated extubation, warranting prospective validation.

Keywords: Lung mechanics, rescue ventilation, severe bronchopulmonary dysplasia, steroid resistance, time-constant heterogeneity

Öz

uygulanan ventilasyon stratejisi, solunum yetmezliğinde azalma sağlamış ve ekstübasyon sürecini kolaylaştırmıştır; bu durumun prospektif çalışmalarla doğrulanması gerekmektedir.

Anahtar kelimeler: Akciğer mekanik, ağır bronkopulmoner displazi, kurtarıcı ventilasyon, steroid direnci, zaman sabiti heterojenitesi

Introduction

Bronchopulmonary dysplasia (BPD) affects nearly 20% of extremely preterm infants, and established severe BPD (sBPD) remains a primary driver of long-term morbidity (1). As the disease progresses from the acute phase to a chronic phenotype, the lung undergoes a profound physiological transition. The mechanics of established sBPD exhibit marked heterogeneity: Hyperinflated areas coexist with atelectasis, airway resistance rises significantly, and respiratory time constants become pathologically prolonged (2,3).

Despite these well-documented changes, clinicians often manage sBPD using ventilatory strategies extrapolated from acute respiratory distress syndrome (ARDS), specifically rapid rates and low tidal volumes. While this approach is protective during the acute phase, it often becomes maladaptive in the chronic phase (4). High respiratory rates in lungs with long time constants prevent complete exhalation, leading to air trapping and failure to ventilate “slow” alveolar compartments, which ultimately worsens ventilation-perfusion (V/Q) mismatch (3).

Systemic corticosteroids, particularly the low-dose dexamethasone (DART) regimen, remain a standard therapy to facilitate extubation (5-7). However, a distinct subset of infants fails to respond to this treatment. We hypothesize that in these “steroid-refractory” patients, active inflammation is no longer the primary driver of respiratory failure. Instead, the failure likely stems from a severe mismatch between conventional ventilator settings and the lung’s structural abnormalities, which include fibrosis, acquired tracheobronchomalacia, and fixed airflow obstruction (8,9).

In this study, we present a physiology-based rescue ventilation protocol tailored to overcome these specific mechanical barriers. We evaluated this strategy in a small cohort of infants with sBPD who had already failed pharmacologic rescue. Given the limited sample size, this study was designed as an exploratory case series to generate hypotheses for future prospective trials.

Materials and Methods

Study Design and Population

We conducted a retrospective, exploratory case series in a Level IV neonatal intensive care unit. The cohort included infants born at less than 32 weeks of gestation who had established sBPD and received the DART regimen but who failed to show clinical improvement.

We strictly defined “non-response” as the absence of any improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio 72 hours after initiating dexamethasone. This 72-hour window was selected because the genomic and anti-inflammatory effects of systemic dexamethasone typically manifest within 24 to 48 hours of initiation (10,11). This timeframe provides a sufficient therapeutic window to observe a clinical response while preventing unnecessary exposure to prolonged steroid therapy in infants whose respiratory failure is primarily driven by structural and mechanical constraints rather than active inflammation. Advanced imaging techniques have increasingly highlighted these fixed structural deficits as primary drivers of ongoing respiratory failure (12).

This study was approved by University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Ethics Committee (approval no: 2025/04/10/042, date: 11.04.2025). Because of the retrospective design, the requirement for parental informed consent was waived in accordance with the Declaration of Helsinki.

Ventilation Protocol

Once we confirmed steroid failure, we adjusted the ventilator settings to reflect the “two-compartment” mechanical model of sBPD. Patients were transitioned to volume-guarantee combined with pressure support ventilation (VG-PSV) mode, a strategy increasingly recognized for chronic management (13). We reduced the respiratory rate to 20-25 breaths per minute, extended the inspiratory time (T_i) to ≥ 0.8 seconds, increased the tidal volume target to 10-12 mL/kg, and titrated positive end-expiratory pressure (PEEP) to 8-10 cmH_2O to stent open airways prone to malacia (14).

Statistical Analysis

Given the exploratory nature of this case series and the heavily restricted sample size (n=7), formal statistical hypothesis testing was deliberately avoided to prevent the overestimation of treatment effects and false-positive conclusions. Instead, descriptive statistics were used to characterize the cohort. Continuous non-parametric variables are reported as medians with minimum and maximum values (minimum-maximum). In alignment with the study's primary objective, analytical focus was strictly placed on the evaluation of individual physiological trajectories and paired longitudinal mechanical ventilation trends rather than population-level comparative statistics.

Results

Seven infants met the inclusion criteria. The cohort had a median birth weight of 680 g (590-810) and a median gestational age of 25 weeks (24-26).

As detailed in Table 1, which presents individual patient trajectories, all patients exhibited severe baseline gas-exchange impairment: Median pH, 7.25 (7.20-7.32); pCO₂, 55 (54-63) mmHg; PaO₂/FiO₂, 66 (61-70) mmHg.

Transitioning these patients to the physiology-based ventilation protocol resulted in improvements in gas exchange (Table 2). The median PaO₂/FiO₂ ratio increased from 66 (61-70) mmHg at baseline to 110 (90-140) mmHg by day 14. Individual patient trends in PaO₂/FiO₂ ratios and mean airway pressures over time are illustrated in Figure 1.

Despite a reduced respiratory rate [median 22 (20-25) breaths per minute], the median arterial pCO₂ decreased from a baseline of 55 (54-63) mmHg to 45.5 (45-47) mmHg by day 14, suggesting improved alveolar clearance (Figure 2). Individual mechanical ventilation parameters (peak inspiratory pressure, PEEP, mean airway pressure) are detailed in Table 3.

Table 2. Cohort oxygenation response [median (min-max)]

Parameter	Baseline (pre-protocol)	Day 14 (post-protocol)
pH	7.25 [7.20-7.32]	7.40 [7.39-7.45]
pCO ₂ (mmHg)	55 [54-63]	45.5 [45-47]
PaO ₂ /FiO ₂ ratio	66 [61-70]	110 [90-140]

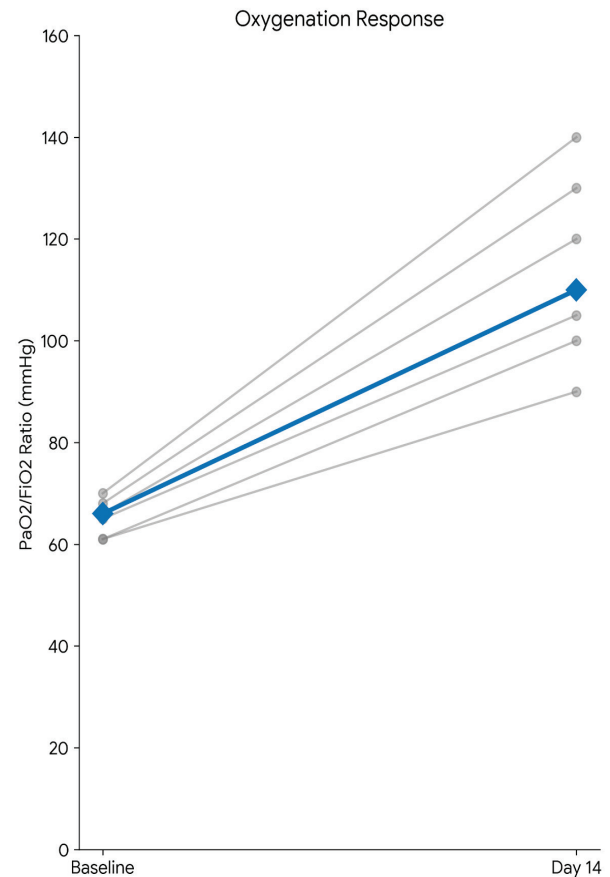


Figure 1. Paired oxygenation response. Individual PaO₂/FiO₂ ratios (grey lines) and the cohort median (blue diamond) are shown for each infant (n=7) at baseline and on day 14

Table 1. Individual baseline characteristics and steroid non-response (n=7)

Patient	GA (wks)	BW (g)	Age at protocol (days)	Pre-DART PaO ₂ /FiO ₂	72h post-DART PaO ₂ /FiO ₂
Pt 1	24	590	48	62	61
Pt 2	25	650	55	68	66
Pt 3	25	680	60	65	65
Pt 4	26	720	50	70	68
Pt 5	24	610	45	60	61
Pt 6	26	810	62	72	70
Pt 7	25	700	53	64	66
Median [min-max]	25 [24-26]	680 [590-810]	53 [45-62]	65 [60-72]	66 [61-70]

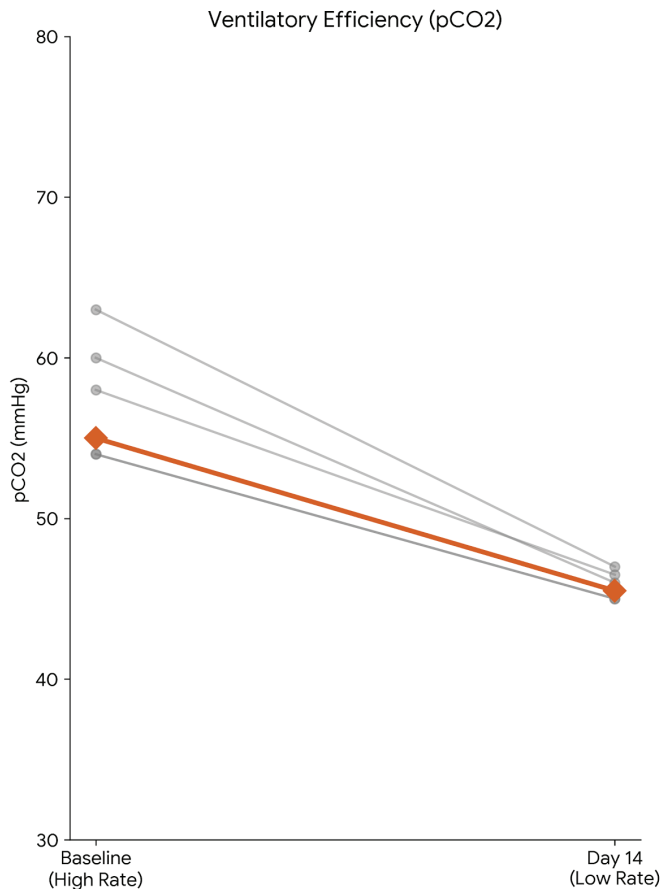


Figure 2. Paired ventilatory efficiency. Individual pCO₂ levels (grey lines) and the cohort median (orange diamond) are shown for each infant (n=7) at baseline and on day 14

Clinically, the mechanical reset was associated with successful weaning from invasive mechanical ventilation in these seven infants. None of the patients required a tracheostomy.

Discussion

In this exploratory cohort of infants with steroid-refractory sBPD, a ventilation strategy explicitly targeted at chronic lung mechanics was associated with a reduction in respiratory failure and with facilitated extubation. These preliminary observations support individualized therapy rather than relying on a “one-size-fits-all” approach. Recent advanced imaging techniques have increasingly highlighted fixed structural deficits as primary drivers of ongoing respiratory failure in these non-responders (12), necessitating adapted, long-term respiratory support strategies (13).

Our findings align closely with recent shifts in ventilatory paradigms for established sBPD. As emphasized by Sindelar et al. (3) and Gibbs et al. (4), standard ARDS-like strategies utilizing rapid rates become maladaptive in the chronic phase due to pathologically prolonged time constants. Furthermore, while Miller et al. (9) previously noted a lack of conclusive evidence for an optimal ventilator mode, our implementation of targeted volume-guarantee combined with pressure support ventilation (VG-PSV) provides a direct physiological countermeasure to the structural abnormalities of sBPD. This includes utilizing adequate PEEP to stent open airways, which is particularly critical for ventilator-dependent children with acquired tracheobronchomalacia (14), and aligns with adapting management practices to changing ventilator technologies (15).

The improvement in oxygenation may stem directly from addressing the time-constant heterogeneity. By extending Ti ≥0.8 seconds, our protocol may have facilitated the recruitment of these slow units. This targeted mechanical reassessment is crucial to mitigate the neurodevelopmental risks associated with severe BPD and its invasive

Table 3. Individual longitudinal mechanical ventilation data (baseline vs. day 14)

Patient	PIP (cmH ₂ O) pre/post	PEEP (cmH ₂ O) pre/post	MAP (cmH ₂ O) pre/post	RR (breaths/min) pre/post	Ti (seconds) pre/post	VT (mL/kg) pre/post
Pt 1	24/22	6/9	11/13	45/20	0.40/0.90	5.5/11.0
Pt 2	26/22	7/10	12/14	50/22	0.35/0.85	5.0/10.5
Pt 3	25/20	6/8	11/12	42/20	0.45/0.90	6.0/11.5
Pt 4	28/24	7/10	13/15	55/25	0.35/0.80	4.5/10.0
Pt 5	24/21	6/9	11/13	48/20	0.40/0.95	5.5/11.5
Pt 6	27/23	7/9	12/14	52/24	0.38/0.85	5.2/10.8
Pt 7	25/22	6/8	11/12	46/22	0.42/0.90	5.8/11.2

Pre: Conventional strategy targeting active inflammation, Post: Physiology-based VG-PSV strategy targeting mechanical time-constant heterogeneity, VG-PSV: Volume-guarantee combined with pressure support ventilation, MAP: Mean airway pressure, PEEP: Positive end-expiratory pressure, PIP: Peak inspiratory pressure

interventions (16). Furthermore, early mechanical optimization may reduce the reliance on recurrent anti-inflammatory therapies (17), which is particularly relevant given the variable respiratory outcomes following late postnatal DART administration (18).

In established sBPD, a “standard” tidal volume might be largely lost to anatomical dead space in such conditions. Our observations suggest that higher delivered volumes (10-12 mL/kg) may be beneficial in select cases. Furthermore, the absence of air leaks in this small cohort suggests that the sBPD lung may tolerate larger volumes under close physiological monitoring. Avoiding tracheostomy in this high-risk population remains a critical therapeutic milestone to improve long-term trajectories (19). It should be noted that while genetic or syndromic factors (such as Bardet-Biedl syndrome) can independently complicate respiratory outcomes, our cohort specifically represented acquired sBPD (20,21).

Study Limitations

This study has several important limitations. First, the lack of a control group makes it difficult to definitively attribute outcomes to the intervention; each patient effectively served as their own historical control.

Our preliminary findings suggest that for infants with established sBPD who are refractory to corticosteroids, a physiology-based ventilation strategy targeting prolonged time constants and dead space washout may improve gas exchange. Prospective studies are warranted to validate these findings and explore interpretable predictive models that can better define diagnostic criteria and optimize the timing of mechanical rescue.

Conclusion

Our results suggest that if respiratory failure is primarily mechanical, escalating anti-inflammatory therapy may be of limited benefit.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Ethics Committee (approval no: 2025/04/10/042, date: 11.04.2025).

Informed Consent: The requirement for parental informed consent was waived in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Concept: Ç.C.G., Design: Ç.C.G., E.C., Data Collection or Processing: Ç.C.G., E.C., Analysis or Interpretation: E.C., Literature Search: Ç.C.G., Writing: Ç.C.G., E.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Jensen EA, Edwards EM, Greenberg LT, Soll RF, Ehret DEY, Horbar JD. Severity of bronchopulmonary dysplasia among very preterm infants in the United States. *Pediatrics*. 2021;148(1):e2020030007.
2. McKinney RL, Napolitano N, Levin JJ, Kiehl MJ, Abman SH, Guaman MC, et al. Ventilatory strategies in infants with established severe bronchopulmonary dysplasia: a multicenter point prevalence study. *J Pediatr*. 2022;242:248-252.e1.
3. Sindelar R, Shepherd EG, Ågren J, Panitch HB, Abman SH, Nelin LD, et al. Established severe BPD: is there a way out? Change of ventilatory paradigms. *Pediatr Res*. 2021;90(6):1139-1146.
4. Gibbs K, Jensen EA, Alexiou S, Munson D, Zhang H. Ventilation strategies in severe bronchopulmonary dysplasia. *Neoreviews*. 2020;21(4):e226-e237.
5. Doyle LW, Cheong JL, Hay S, Manley BJ, Halliday HL. Late (≥ 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev*. 2021;11(11):CD001145.
6. Hysinger EB, Ahlfeld SK. Respiratory support strategies in the prevention and treatment of bronchopulmonary dysplasia. *Front Pediatr*. 2023;11:1087857.
7. Özkan H, Duman N, Tüzün F. Pathophysiologically based ventilatory management of severe bronchopulmonary dysplasia. *Türk Arch Pediatr*. 2022;57(4):385-390.
8. Akangire G, Manimtim W. Tracheostomy in infants with severe bronchopulmonary dysplasia: a review. *Front Pediatr*. 2023;10:1066367.
9. Miller AN, Kiehl MJ, El-Ferzli GT, Nelin LD, Shepherd EG. Optimizing ventilator support in severe bronchopulmonary dysplasia in the absence of conclusive evidence. *Front Pediatr*. 2022;10:1022743.
10. Gladstone IM, Ehrenkranz RA, Jacobs HC. Pulmonary function tests and fluid balance in neonates with chronic lung disease during dexamethasone treatment. *Pediatrics*. 1989;84(6):1072-1076.
11. Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. *Lancet*. 1983;1(8338):1356-1358.
12. Munidasa S, Higano NS, Willmering M, Matheson AM, Fleck RJ, Kingma PS, et al. Structural and functional lung assessment in neonates with moderate to severe bronchopulmonary dysplasia using 3D ultra-short echo time MRI. *J Magn Reson Imaging*. 2026;63(4):970-983.

13. Logan JW, Nath S, Shah SD, Nandula PS, Hudak ML. Respiratory support strategies in the management of severe, longstanding bronchopulmonary dysplasia. *Front Pediatr.* 2022;10:1016204.
14. Bansal M, Manimtim WM, Agarwal A, Alexiou S, Rice JL, Nelin L, et al. Outcomes of ventilator-dependent children with severe bronchopulmonary dysplasia and tracheobronchomalacia. *Pediatr Pulmonol.* 2025;60(4):e711100.
15. Agarwal A, McKinney RL, Baker CD, Nelin LD, Abman SH; BPD Collaborative. Adapting to changing ventilator access: Impact on management of severe bronchopulmonary dysplasia in children. *Pediatr Pulmonol.* 2024;59(6):1803-1806.
16. Taha A, Akangire G, Noel-Macdonnell J, Gladdis T, Manimtim W. The impact of early tracheostomy on neurodevelopmental outcomes of infants with severe bronchopulmonary dysplasia exposed to postnatal corticosteroids. *J Perinatol.* 2024;44(7):979-987.
17. Perrone S, Orlando S, Petrolini C, Marinelli F, Moretti S, Corradi M, et al. Current concepts of corticosteroids use for the prevention of bronchopulmonary dysplasia. *Curr Pediatr Rev.* 2023;19(3):276-284.
18. House M, Rowe J, Walters A, Liu C, Ehrlich SR, Nienaber T, et al. Respiratory outcomes following late postnatal dexamethasone administration in preterm infants with bronchopulmonary dysplasia. *Pediatr Pulmonol.* 2025;60(9):e71275.
19. Upadhyay K, Vallarino DA, Talati AJ. Outcomes of neonates with tracheostomy secondary to bronchopulmonary dysplasia. *BMC Pediatr.* 2020;20(1):414.
20. Xin-Yi Z, Yang-Li D, Ling-Hui Z. Review of the phenotypes and genotypes of Bardet-Biedl syndrome from China. *Front Genet.* 2023;14:1247557.
21. Bu Q, Wang X, Wu Y, Wang Y, Li R, Zhao Y, et al. Interpretable machine learning model for comparing and validating three diagnostic criteria for bronchopulmonary dysplasia in predicting value of respiratory prognosis of preterm infants: a retrospective cohort study. *Front Pediatr.* 2025;13:1678244.