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Corticosteroid response predicts bronchopulmonary dysplasia status at 36 weeks in preterm infants treated with dexamethasone: A pilot study

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Abstract

Importance: A major barrier to therapeutic development in neonates is a lack of standardized drug response measures that can be used as clinical trial endpoints. The ability to quantify treatment response in a way that aligns with relevant downstream outcomes may be useful as a surrogate marker for new therapies, such as those for bronchopulmonary dysplasia (BPD).

Objective: To construct a measure of clinical response to dexamethasone that was well aligned with the incidence of severe BPD or death at 36 weeks' postmenstrual age.

Design: Retrospective cohort study.

Setting: Level IV Neonatal Intensive Care Unit.

Participants: Infants treated with dexamethasone for developing BPD between 2010 and 2020.

Main Outcome(s) and Measure(s): Two models were built based on demographics, changes in ventilatory support, and partial pressure of carbon dioxide (pCO_2) after dexamethasone administration. An ordinal logistic regression and regularized binary logistic model for the composite outcome were used to associate response level to BPD outcomes defined by both the 2017 BPD Collaborative and 2018 Neonatal Research Network definitions.

Results: Ninety-five infants were treated with dexamethasone before 36 weeks. Compared to the baseline support and demographic data at the time of treatment, changes in ventilatory support improved ordinal model sensitivity and specificity. For the binary classification, BPD incidence was well aligned with risk levels, increasing from 16% to 59%.

Conclusions and Relevance: Incorporation of response variables as measured by changes in ventilatory parameters and pCO_2 following dexamethasone administration were associated with downstream outcomes. Incorporating drug response phenotype into a BPD model may enable more rapid development of future therapeutics.

Keith Feldman and Christopher R. Nitkin contributed equally as co-first authors.

KEYWORDS

bronchopulmonary dysplasia (BPD), evidence-based medicine and outcomes, neonatal pulmonary medicine, pharmacology

1 | INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common pulmonary disorder associated with preterm birth.[1] Affected infants suffer from prolonged hospitalization[2] and often require respiratory support after discharge, up to and including tracheostomy and home ventilation.[3] They can also experience long-term changes in pulmonary function[4] with associated increased rates of respiratory illness requiring inpatient hospitalizations.[5] Despite the frequent incidence and severity of this disease, there are currently no Food and Drug Administration (FDA)-approved therapies for treatment or prevention.

A major barrier to such therapeutic development and labeling is a lack of standardized drug response measures that can be used as clinical trial endpoints. However, as BPD can only be assessed at or after 36 weeks, identifying surrogate endpoints is essential for accelerating therapeutic research. Critically, these endpoints, known as pharmacodynamic biomarkers, must correlate with a clinically meaningful downstream outcome to be used for drug approval.[6]

Accordingly, this study aimed to construct a quantitative measure of drug response that could serve as a surrogate endpoint in the development of BPD therapies based on clinical factors available at the time of steroid administration and short-term clinical response to steroid therapy.

With respect to current treatments, we focus on dexamethasone, a systemic corticosteroid utilized in the preterm neonatal population to facilitate improved lung function and extubation from mechanical ventilation.[7] The clinical use of dexamethasone for improved lung function spans multiple age groups, but is most typically used in the first 1–2 months of life. The use of dexamethasone in the patient population at risk for BPD is therefore understudied, and responses to dexamethasone vary greatly, with some infants experiencing significant improvements, others deriving no benefit, and an important minority experiencing worsening clinical status.[8] As such, it represents an excellent candidate for the development of a drug response biomarker.

By integrating clinical factors with drug response measures to predict 36-week BPD status, we anticipate that this type of prediction could serve as a surrogate endpoint in clinical trials investigating novel therapies for BPD.

2 | METHODS

2.1 | Study design and cohort selection

This study represents a retrospective observational cohort analysis of infants admitted to Children's Mercy Kansas City (CMKC) Intensive Care Nursery (ICN) who received dexamethasone per the protocol from Dexamethasone: A Randomized Trial (DART) study[7] from January 1, 2010 to May 31, 2020. The study was approved by the Children's Mercy Kansas City Institutional Review Board (protocol #11120563).

As treatment with the DART protocol is not discretely labeled in a consistent manner in the electronic medical record (EMR), all infants who received dexamethasone were extracted from the EMR as a screening step. Several exclusion criteria were applied to obtain the final study cohort. First, only infants receiving doses of dexamethasone scheduled every 12 h were included; 8-h dosing is only used for periextubation and outside the scope of this study. Next, those who received dexamethasone for airway edema in the periextubation period were excluded, as were those who did not receive a standard 7- or 10-day course. Infants who did not have a blood gas monitored on prespecified, key drug treatment days were excluded during model development. If an infant received more than one course of dexamethasone while admitted to the CMKC ICN, only the first course was studied. Preadmission courses were also excluded. Finally, all infants who had not fully completed their DART course before 36-week BPD assessment were excluded.

2.2 | Study variables

The data collected and analyzed as part of this manuscript can be broken into two high-level categories: *study variables* (comprised of demographic and physiologic data around the time of steroid administration) and *downstream BPD outcomes* (comprised of two validated BPD classification tools). Details regarding the collection and definition of data in each category may be found in the respective sections to follow. The primary study data were comprised of detailed demographic, steroid administration, ventilatory support, and blood gas elements collected directly from an infant's EMR. As the majority of these data were automatically extracted from the record, manual validation was performed for approximately 10% of charts.

Demographic data included gestational age (GA) at birth, birthweight (BW), sex, and race. In line with emergent best practices, maternal race data were collected and observationally reported for the study cohort. However, it was not used in analysis or modeling since the biological plausibility is not justified.[9,10] Drug dosing details about the steroid administration were collected. These included the course length (7 or 10 days) and day-of-life (DOL) steroids were initiated. Our local practice is to prefer 7-day courses, but allow for 10-day courses, as we had previously shown no significant difference in outcome.[11] The difference in dose is 0.72 versus 0.89 mg/kg/course for the 7- and 10-day courses, respectively. Although similar, we aimed to account for any potential variance in response scores that may result from this difference.

Short-term drug response phenotype was quantified using the respiratory severity score (RSS). We collected respiratory support data at selected points around the time of dexamethasone administration: Day 0 (day of administration) and Day 6 after administration. Where each day was defined as the 24-h period from midnight to midnight. In addition, granular timestamped data were extracted over the course of steroid administration and at standardized developmental timepoints. These timepoints included 36 weeks postmenstrual age (PMA) and 40 weeks PMA, and date of discharge from the ICN.

For each timepoint, a list of all utilized ventilator modes was obtained in addition to the average (mean) effective fraction of inspired oxygen (FiO_2), and mean airway pressure (MAP). These data were used to compute an RSS, defined as ($MAP*FiO_2$).[12] In nasal canula support where no MAP is available, a baseline value of 1 was used to allow for differentiation within FiO_2 levels.[13] This allowed us to preserve the nuance in RSS for different effective FiO_2 levels. For those days in which multiple modes of ventilation were used, the highest support level was selected based on the ordering (lowest to highest): nasal canula, noninvasive ventilation, invasive mechanical ventilation, and high-frequency oscillatory ventilation. For convenience, the numerous specific ventilator modes and interfaces at each level were grouped into three broad categories: extubated (e.g., nasal cannula, continuous positive airway pressure), intubated conventional ventilation (e.g., synchronized intermittent mandatory ventilation-Pressure control), and intubated high-frequency oscillatory ventilation (HFOV). Similarly, all blood gas and serum chemistry values were also collected on each respective day, and the mean value per day was used for analysis, without differentiating between types of sampling (e.g., capillary, venous, or arterial).

Based on the overarching hypothesis that change in physiologic parameters over the period of dexamethasone administration is associated with downstream 36-week BPD outcomes, we also computed two derived variables representing the ratio of Day-0 and Day-6 RSS and ratio of Day-0 and Day-6 partial pressure of carbon dioxide (pCO_2) values for each infant.

2.3 | Outcomes

Steroid response was quantified by the presence and severity of BPD at 36-week PMA. Given the known variance in BPD definition, outcomes for each infant were determined using two well-established scales introduced by the 2017 BPD Collaborative (BPDC)[14] and the 2018 Neonatal Research Network (NRN).[15] These scales were selected as they allow for a wider classifier of BPD even for infants who did not utilize a full 28 days of supplemental oxygen.

2.4 | Model specification and validation

Associations of steroid response data to downstream BPD outcomes were analyzed using ordinal logistic regression across three-level groupings derived from the NRN and BPDC classifications. For reference, the NRN model was grouped in terms of increasing severity: (A) Grade 1, (B) Grade 2, and (C) Grade 3, while the BPDC was aggregated as (A) None/Mild/Moderate, (B) Severe Type-1, and (C) Severe Type-2. In both cases, infants who died before assessment were classified at the highest severity level. The complete model specification included GA, DOL steroids were initiated, BW, sex (reference female), dexamethasone course length (reference 7 days), Day-0 ventilator mode (reference intubated conventional ventilation), Day-6 ventilator mode (reference intubated conventional ventilation), Day-0 RSS, RSS ratio (Day 0/Day 6), Day-0 pCO_2, and pCO_2 ratio (Day 0/Day 6). BW, DOL of steroid administration, and RSS were log-transformed to account for heavy right tails. Reference days used to compute baseline and change (Day 0 and Day 6, respectively) were selected based on the following criteria: Day 0 (day steroids were initiated) was used to guard against bias in an infant's state before beginning the DART course (i.e., infants with increasing RSS influencing the decision to start steroids), while Day 6 was selected, as a subset of infants in our neonatal intensive care unit receive a 7-day course of DART, and we sought to capture change during steroid course of all infants.

For both classification paradigms, model performance was estimated using a 10,000-iteration bootstrap. At each iteration, data were drawn with replacement until the original size of the data set was reached and stratified to reflect the proportion of the three BPD severity levels in the respective classification from the original cohort. By drawing with replacement, approximately 36.8% of the original data is expected, on average, to be left out, known as the *out-of-bag* (OOB) sample. Finally given the imbalance between classification levels, training data were oversampled with synthetic instances using an extension of the SMOTE algorithm that accounts for nominal features.[16]

Predictive performance was quantified in two ways. First, models were retrained on each bootstrapped replicate and a class-weighted sensitivity, specificity, positive predicted value (PPV), negative predictive value NPV), and macro F1 (harmonic mean of precision and recall) were computed on the corresponding OOB samples. As the ordinal model provides a class probability for each outcome level, discrete classes were assigned to the highest predicted probability. Second, the proportion of infants at each of the assigned BPD classification levels could be computed at each of the three risk levels for the OOB samples at each iteration. In this way, we can explore misclassification to evaluate how risk levels may be over/underestimated.

To verify these results reflected information derived from measures of steroid response and were not simply a product of the known risk factors (e.g., BW, DOL steroids were started), all analyses were replicated using a baseline model specified with only demographic factors (GA, BW, sex), baseline steroid data (steroid course length, DOL dexamethasone was initiated), and Day-0 respiratory status (mode of ventilation, RSS, and pCO_2). Paired *t* tests were performed to compare the performance of each metric between the baseline and complete models at each iteration.

2.5 | Case study

Given the variability among low and mid-levels of BPD classification, the final component of this manuscript undertakes a case study focusing on the clinical utility of predicting infants at the highest severity levels, which for both NRN and BPDC indicate those still receiving invasive mechanical ventilation at 36-weeks. In this way, rather than a probability for each BPD level, we intend to use steroid response characteristics to provide a bedside clinician with a single well-calibrated risk prediction for later invasive ventilator use.

To assess the ability to differentiate severe BPD (NRN: Grade 3; BPDC: Severe Type 2) versus all lower classifications, a regularized logistic model, and the corresponding baseline was specified as previously described. A 10,000-iteration bootstrap was again used to estimate model performance and the proportion of infants with severe BPD that fell into each of the discretized intervals was reported. For additional measures of confidence, an overall *C*-statistic was computed.

Finally, we studied the clinical outcomes of sample infants at each risk level. Using a leave-one-out paradigm, the model was trained on all but one infant's data and then used to predict the risk level for the held-out infant. From the set of predicted risk levels, three infants were selected: one low (Level 1), one medium (Level 2), and one high risk (Level 3). Chart review was then performed on each infant to better understand the presentation and morbidities associated with varying risk predictions.

3 | RESULTS

In total, 486 courses of dexamethasone were administered during the study period to 196 infants (Figure 1). Of these, 93 and 103 were determined to have been on a 7- or 10-day DART course, respectively. Infants who had not completed their DART course before 36-week BPD assessment ($n = 58$), those who were not classifiable by both of the BPD outcome metrics ($n = 2$), and those missing blood gases on Day 0 or Day 6 were excluded ($n = 20$). In total, this yielded a final cohort of 95 infants with complete data utilized for all analyses. The demographic data and respiratory data for the cohort are displayed in Table 1.

Looking first at the overall predictive performance of the steroid response metric with 36-week BPD status. Table 2 describes the performance metrics across the 10,000 bootstrap iterations. Results are provided for both the Baseline Model and the Full Model and for

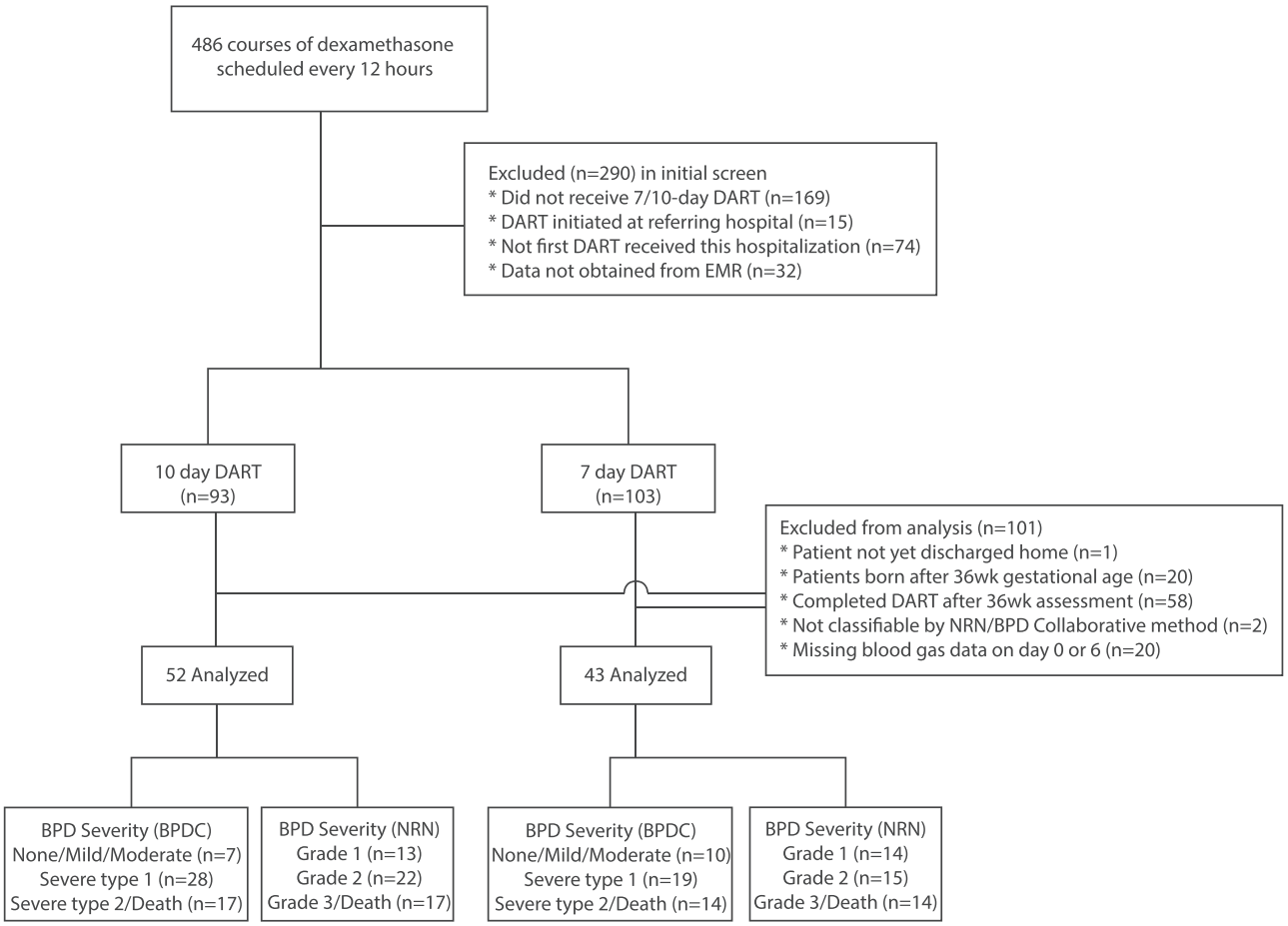

FIGURE 1 Cohort selection diagram. BPDDC, Bronchopulmonary Dysplasia Collaborative; DART, Dexamethasone: A Randomized Trial; NRN, Neonatal Research Network.

TABLE 1 Demographic and respiratory variables of Dexamethasone-Treated Cohort

Characteristic	Entire Cohort (*n* = 95)
Gestational age at birth, median [IQR](wks)	25wk 1d [22wk 1d–30wk 0d]
Birthweight, median [IQR] (g)	742 [420–1510]
Sex (*n*)	
Male	65
Female	30
Race (*n*)	
White	41
Black	38
Other	16
DART course length (*n*)	
7 days	43
10 days	52
Day of life of dexamethasone initiation (mean (SD))	32 (11.0)
Discharge age (DOL) (mean (SD))	150 (68)
Death (*n*, %)	10, 10.5%
Age at death (days) (mean (SD))[a]	95 (66)
RSS (mean (SD))	
Day 0	914.0 (346.9)
Percent change (Days 6–0)	55 (24)
pCO_2 (mean (SD))	
Day 0	54.4 (6.7)
Percent change (Days 6–0)	95 (16)
Vent mode baseline (*n*)	
Intubated HFOV	65
Intubated conventional	26
Extubated	4
Vent mode Day 6 (*n*)	
Intubated HFOV	21
Intubated conventional	41
Extubated	33

Abbreviations: d, days; DART, Dexamethasone: A Randomized Trial; DOL, day-of-life; HOFV, high-frequency oscillatory ventilation; IQR, interquartile range; LOS, length of stay; pCO_2, partial pressure of carbon dioxide; RSS, respiratory severity score; wk, weeks.

[a]LOS or age at death depends on survival.

both BPDC and NRN classifications. In all cases, the full model including measures of drug response significantly outperformed the baseline approach in predicting the true 36-week BPD status of the infant ($p < 0.05$).

TABLE 2 Predictive performance [mean (SD)] of ordinal models across both BPD classification definitions

	BPD Collaborative	Neonatal Research Network
Baseline Model		
Sensitivity	0.40 (0.07)	0.39 (0.07)
Specificity	0.68 (0.06)	0.69 (0.04)
F1	0.40 (0.08)	0.38 (0.07)
PPV	0.44 (0.098)	0.40 (0.08)
NPV	0.63 (0.05)	0.68 (0.04)
Full Model		
Sensitivity	0.54 (0.08)	0.51 (0.08)
Specificity	0.73 (0.06)	0.75 (0.05)
F1	0.54 (0.08)	0.51 (0.08)
PPV	0.57 (0.08)	0.52 (0.09)
NPV	0.70 (0.05)	0.74 (0.056)

Note: For both the BPD Collaborative classification system and NRN classification system, the addition of drug response data improve sensitivity and specificity. Baseline model contains only demographic factors (GA, BW, sex), steroid data (steroid course length, DOL dexamethasone was initiated), and Day-0 respiratory status (RSS and pCO_2). Full Model also includes drug response information in the change ratios of RSS, pCO_2, and ventilator mode on Day 6. The F1 represents a harmonic mean between precision and recall, used to quantify predictive performance across imbalanced outcomes.

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birthweight; DOL, day-of-life; GA, gestational day; NPV, negative predictive value; NRN, Neonatal Research Network; pCO_2, partial pressure of carbon dioxide; PPV, positive predictive value; RSS, respiratory severity score.

Looking further into how these performance metrics manifest in results that would be provided to practitioners, we find the full model risk level to be well aligned to overall BPD severity. Figure 2A,B illustrates the proportion of infants across the three predicted risk levels broken down by true BPDC and NRN levels respectively; distributions are shown over the 10,000 bootstrap iterations. In both cases, the full model showed the highest proportion of infants in the correctly assigned categories (e.g., highest portion of Level-2 infants were seen at the second risk level for the NRN classification), while the baseline model shows a significant trend in the mean often classifying most infants at the middle-risk level (Level-2/Severe Type-1) across all risk levels.

3.1 | Case study

With respect to identifying infants at the highest 36-week BPD severity, Figure 3 presents the results of predicting severe BPD/death across five risk levels. It should be noted that between the two BPD classification schemes, stratification of severe BPD (NRN: Grade 3 and BPDC: Severe Type-2) versus all lower classifications resulted in the same cohort groupings. Thus, only a single set of results are presented.

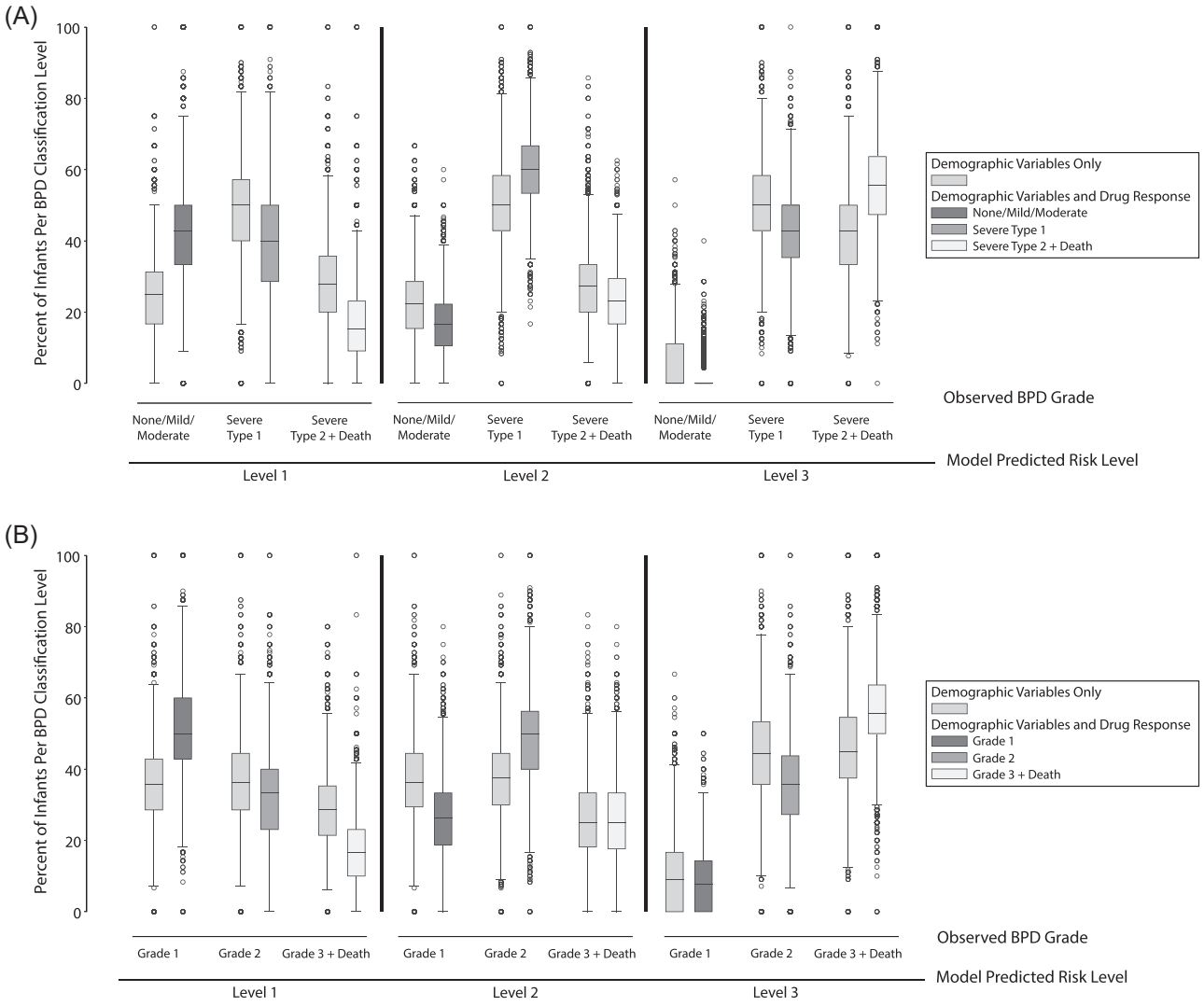

FIGURE 2 Ordinal Risk Model for Bronchopulmonary Dysplasia (BPD) classification using (A) the BPD Collaborative (BPDC) Definition or (b) the Neonatal Research Network (NRN) definition. Level 1 corresponds with BPDC None/Mild/Moderate and NRN Grade-1, Level 2 corresponds to BPDC Severe Type-1 and NRN Grade-2, and Level 3 corresponds to BPDC Severe Type-2 + Death and NRN Grade-3 + Death. For each definition, the *x*-axis presents two nested levels. First, data are broken down by the predicted BPD classification level, 1–3. Within the infants who received a given model-prediction Level. Second, we computed the proportion of infants based on the observed 36-week BPD classification per level. For example, NRN Definition – Predicted Level 1 represents all infants who were predicted by the model to have an outcome of Grade-1 BPD at 36 weeks (left side of panel B). For that cohort, >50% of these infants were correctly classified as Grade 1 by the Full Model (dark gray), ~30% were incorrectly predicted at Grade 2 (medium gray). A smaller percentage of infants predicted to be Level-1 infants ended up with Level-3 BPD classification at 36 weeks (light gray). For each of the three levels, we present a paired boxplot for the estimated performance of the demographics + baseline-only model. In this same example, for infants with baseline model prediction of Level 1, the proportion of infants with Level 1 (correct), Level 2 (incorrect), and Level 3 (incorrect) are nearly equal, strongly indicating the model utilizing steroid response can better capture downstream outcome.

Again, the Baseline Model predicted similar risk across the first four levels (30%–40% severe BPD incidence) with an increase at Level 5. However, the Full Model appropriately aligned increased risk of severe BPD with increasing level, moving from ~16% incidence at Level 1 to 36% at Level 3 and 59% at Level 5, with an increased percent of infants experiencing severe BPD or death with increasing risk level. In line with visual observations, calibration measures of *C*-statistic also significantly improved between the Baseline and Full models with a mean (SD) of 0.57 (0.09) and 0.71 (0.08), respectively.

To better illustrate the clinical utility of the full predictive model, we present case studies of four infants in the data set (Table 3). In three of the four randomly chosen infants, the 36-week BPD Risk Projection was correct, and in one of the four infants, the Risk Projection was incorrect. Overall, the Risk Projection was correct in 63/95 infants. As shown in Table 3, none of the infants was extubated by Day 6, but three were weaned from HFOV to conventional ventilation. All subjects had reductions in FiO_2 and reductions in RSS, but changes in MAP were less consistent.

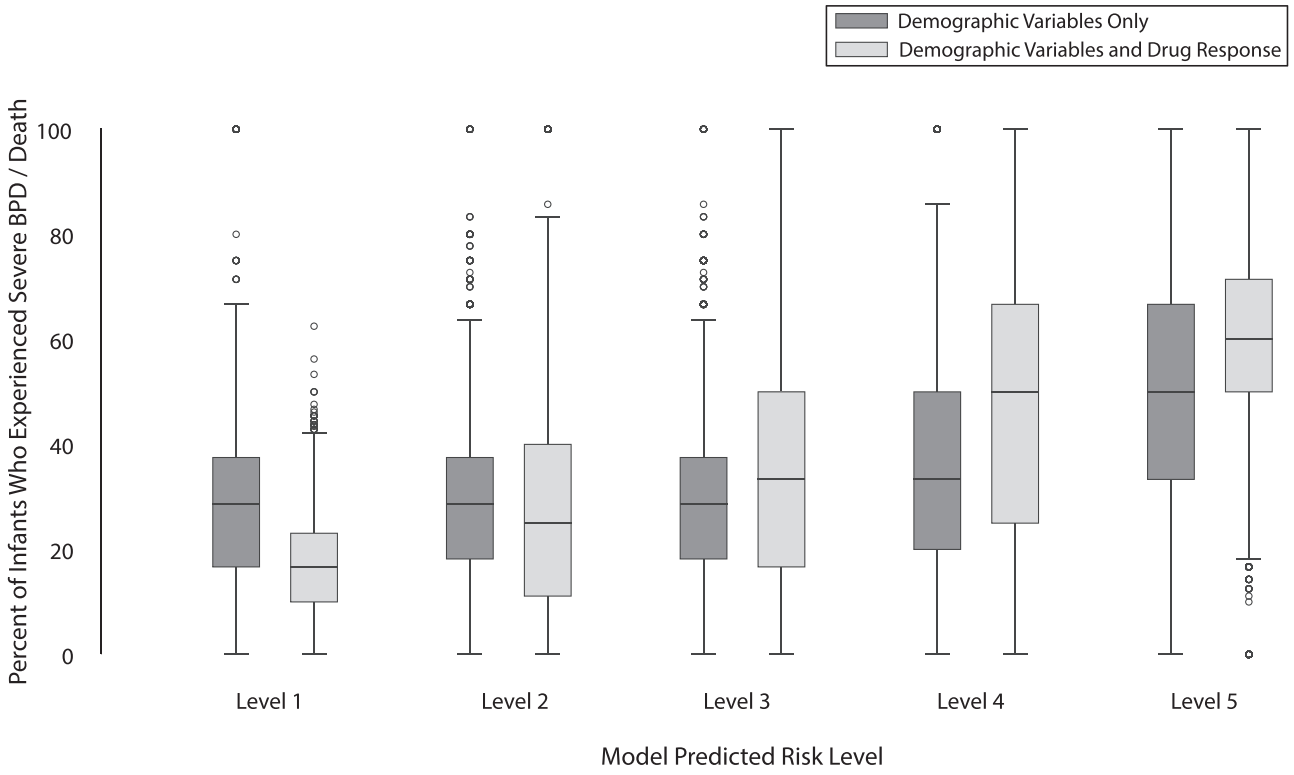

FIGURE 3 Binary Risk Model. For each infant, estimated risk for 36-week severe BPD/death was estimated across five-risk levels from lowest (Level 1) to highest (Level 5). Boxplots represent the proportion of infants with the outcome who were predicted with respective levels both the demographics + baseline risk (blue) and demographics + baseline risk + drug response models (red). Results demonstrate the model containing drug response is better aligned to true outcomes—lowest proportions at Level 1 and highest proportions at predicted Level 5.

TABLE 3 Case study assessing whether risk prediction (Full Model) correlates with clinical outcomes in four random infants

		Day 0			Day 6						
Subject	GA	pCO_2	Vent	FiO_2	pCO_2	Vent	FiO_2	Baseline RSS	Delta RSS	Model prediction	Clinical outcome
49	26 4/7	53.60	HFOV	64.52	38.35	CV	26.00	9.03	7.34	1	Correct
107	23	62.00	HFOV	82.46	54.95	CV	45.67	8.06	4.35	3	Correct
173	23 1/7	54.70	HFOV	44.3	58.10	CV	57.56	5.32	5.76	5	Correct
86	24	53.13	HFOV	90.42	48.95	HFOV	62.50	11.76	7.19	3	Incorrect

Abbreviations: FiO_2, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; pCO_2, partial pressure of carbon dioxide; RSS, respiratory severity score.

4 | DISCUSSION

Our study demonstrates that the addition of drug response enhances predictive power for BPD over baseline prediction utilizing demographics and respiratory support alone. To our knowledge, this is the first study to develop a steroid response model which can reliably predict BPD status at 36 weeks' PMA. Our results suggest that response to therapy may be a potential surrogate endpoint for future clinical trials of BPD.

Despite thousands of infants beingexposed to various therapies for BPD prevention and treatment, to date there remains no FDA-approved drugs for this indication.[17] While many challenges exist, a major barrier to drug development and regulatory approval in neonates is the lack of reproducible, quantitative drug response phenotypic biomarkers. Changes in the RSS[12] and Pulmonary Severity Score[18] have been suggested as a way to track drug response, but these measures are limited by the use of treatment parameters (e.g., level of ventilatory support, amount of supplemental oxygen, etc.) as a surrogate to monitor changes in respiratory function. Here, we present a drug response model that accounts for baseline clinical characteristics and quantifies drug response by measuring changes in respiratory support (by RSS) and function (by pCO_2).

In addition to the role in modeling response to dexamethasone, our findings suggest that response scoring holds potential as

surrogate endpoints in other drug studies. Doing so may encompass two routes. First, utilizing the relationships between changes in physiologic (pCO_2) and ventilatory parameters (RSS, mode) established to measure similar values during the course of a new drug, assessing the degree of change and alignment with change ratios identified in this study and their association to downstream BPD outcomes. However, we acknowledge that our findings may not directly translate to other drugs and as a secondary route, given sufficient training data (i.e., observational use of candidate drugs being retargeted), it may be possible to generate drug-specific change measures incorporating parameters such as changes in blood gas values, FiO_2, MAP, and mode of ventilation over a course of therapy may indicate utility versus futility to a novel outcome measure.

As an example, for a novel BPD preventive measure like mesenchymal stem cell therapy,[19] there may be a similar "drug response score" that would provide meaningful short- to medium-term therapeutic efficacy information before 36 weeks' PMA. Other therapies provided at the beginning of life, particularly for extremely low GA neonates with months until 36 weeks' PMA assessment of BPD, such as intratracheal corticosteroid steroid and surfactant combined therapy,[20] would also benefit from an efficacy signal in a surrogate endpoint early on, to determine if continued treatment was merited.

One advantage of our model is that it requires limited clinical data, focusing on measurements readily available at the bedside (e.g., blood gas values, FiO_2, and MAP). Other models based on demographic variables, comorbidities of prematurity, and days requiring mechanical ventilation have been proposed and validated,[21,22] but they do not incorporate measures of drug response. More advanced predictive models based on imaging have been explored, utilizing lung ultrasound,[23–26] computed tomography,[27] and magnetic resonance imaging.[28,29] However, these require specialized operator training or equipment not readily available at every institution. Of note, predictive models based on serum levels of specific biomarkers such as soluble B7-H3 or IL-18[30] rely on laboratory capabilities unavailable outside the research setting. Similarly, models based on ventilator flow loops[31] or oxygen desaturations[32] require custom software. Scores that incorporate readily available clinical data, such as N-terminal-prohormone B-type natriuretic peptide levels[33] and Score for Neonatal Acute Physiology scores[34] are attractive, but do not include drug response. Furthermore, while there exist clinical scores quantifying response to conditions such as hydrocortisone for hypotension[35,36] and a composite ventilation score to quantify response to dexamethasone,[37] these approaches are not closely tied to downstream outcomes precluding their use in the comparisons needed for drug development.

Important limitations for the analysis presented here include the retrospective nature and risk of confounding by indication. In addition, not all infants who received dexamethasone were intubated on mechanical ventilation. Some were on noninvasive positive pressure while others were on high flow nasal cannula with high oxygen requirement, though these subjects were a minority of the cohort. We focused specifically on infants who received dexamethasone per the DART study,[7] representing a targeted population in whom measuring response to steroid administration offers a direct relationship to downstream BPD outcomes. Furthermore, some subjects were missing data, particularly related to laboratory values, and had to be excluded from the analysis. With regard to the sampling technique of the pCO_2, clinical decision making in our unit does not typically vary between arterial, venous, or capillary sampling. Our decision to model change *within* the values of a single infant may result in values that are less sensitive to differing collection methods (as we can expect values to be internally consistent). However, we acknowledge this may introduce bias into our approach, and the use of the model may benefit from additional standardization of sample collection techniques in future works.

Finally, heterogeneity around the clinical decisions about management, such as how and when to wean ventilatory support, likely influenced our findings and may limit generalizability to other centers. For example, clinicians at our center typically calculate predicted outcomes using the NICHD Neonatal BPD Outcome Estimator,[38] and if the combined outcome of severe BPD or death is ≥35%, usually elect to prescribe dexamethasone.[39] In addition, if patients are full-term corrected GA and continue to require invasive mechanical ventilation (and occasionally noninvasive positive pressure), a dexamethasone course is often prescribed in an effort to wean and potentially avoid the need for tracheostomy. Hydrocortisone is not typically used in our unit for respiratory support, although it is commonly used for circulatory support. Prednisolone is also often employed to varying degrees.[40] Prospective studies should make efforts to harmonize approaches to ventilatory management to reduce heterogeneity and increase generalizability. Future goals for this study include prospective validation and the assessment of additional collection time points, as well as increased granularity around respiratory response beyond the RSS that could be computed automatically from EMR data.

With similar performance across two nationally recognized BPD classification definitions (NRN/BPDC), we anticipate the risk stratification and predictive model presented here may be a significant forward step for future drug development in the capacity to serve as a surrogate endpoint in novel BPD therapeutics research.

AUTHOR CONTRIBUTIONS

Keith Feldman: Conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), writing—original draft (lead), writing—review and editing (lead). **Christopher Nitkin**: Conceptualization (lead), data curation (lead), methodology (supporting), writing—original draft (lead), writing—review and editing (lead). **Alain Cuna**: Conceptualization (equal), data curation (equal), writing—review and editing (equal). **Alexandra Oschman**: conceptualization (equal), data curation (equal), writing—review and editing (equal). **William Truog**: Conceptualization (equal), data curation (equal), writing—review and editing (equal). **Mike Norberg**:

Conceptualization (equal), data curation (equal), writing—review and editing (equal). **Michael Nyp**: Conceptualization (equal), data curation (equal), writing—review and editing (equal). **Jane Taylor**: Conceptualization (equal), data curation (equal), writing—review and editing (equal). **Tamorah Lewis**: Conceptualization (lead), methodology (lead), writing—review and editing (lead).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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