ORIGINAL ARTICLE

Cardiorespiratory Monitoring Data to Predict Respiratory Outcomes in Extremely Preterm Infants

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Abstract

Rationale: Immature control of breathing is associated with apnea, periodic breathing, intermittent hypoxemia, and bradycardia in extremely preterm infants. However, it is not clear if such events independently predict worse respiratory outcome.

Objectives: To determine if analysis of cardiorespiratory monitoring data can predict unfavorable respiratory outcomes at 40 weeks postmenstrual age (PMA) and other outcomes, such as bronchopulmonary dysplasia at 36 weeks PMA.

Methods: The Prematurity-related Ventilatory Control (Pre-Vent) study was an observational multicenter prospective cohort study including infants born at <29 weeks of gestation with continuous cardiorespiratory monitoring. The primary outcome was either "favorable" (alive and previously discharged or inpatient and off respiratory medications/O_2/support at 40 wk PMA) or "unfavorable" (either deceased or inpatient/previously discharged on respiratory medications/O_2/support at 40 wk PMA).

Measurements and Main Results: A total of 717 infants were evaluated (median birth weight, 850 g; gestation, 26.4 wk),

53.7% of whom had a favorable outcome and 46.3% of whom had an unfavorable outcome. Physiologic data predicted unfavorable outcome, with accuracy improving with advancing age (area under the curve, 0.79 at Day 7, 0.85 at Day 28 and 32 wk PMA). The physiologic variable that contributed most to prediction was intermittent hypoxemia with oxygen saturation as measured by pulse oximetry <90%. Models with clinical data alone or combining physiologic and clinical data also had good accuracy, with areas under the curve of 0.84–0.85 at Days 7 and 14 and 0.86–0.88 at Day 28 and 32 weeks PMA. Intermittent hypoxemia with oxygen saturation as measured by pulse oximetry <80% was the major physiologic predictor of severe bronchopulmonary dysplasia and death or mechanical ventilation at 40 weeks PMA.

Conclusions: Physiologic data are independently associated with unfavorable respiratory outcome in extremely preterm infants.

Keywords: extremely premature infant; bronchopulmonary dysplasia; apnea; intermittent hypoxemia; predictive value of tests; heart rate

At a Glance Commentary

Scientific Knowledge on the Subject: Extremely preterm infants have immature control of breathing, which is often associated with apnea, periodic breathing, intermittent hypoxemia, and bradycardia. Such abnormalities in control of breathing can be detected and quantitated using mathematical analysis of high-resolution cardiorespiratory monitoring data. Extremely preterm infants also have poor respiratory outcomes, including the need for prolonged respiratory support, but the contribution of abnormal control of breathing to respiratory outcomes has not been determined.

What This Study Adds to the Field: Analysis of high-resolution cardiorespiratory data from extremely preterm infants provides important prognostic information, and physiologic data can predict unfavorable respiratory outcomes, with prediction accuracy increasing with advancing postnatal age. The physiologic variable that contributes most to prediction of unfavorable outcome is intermittent hypoxemia with oxygen saturation as measured by pulse oximetry <90%, and the physiologic variable that contributes most to prediction of highly unfavorable outcome or severe bronchopulmonary dysplasia is intermittent hypoxemia with oxygen saturation as measured by pulse oximetry <80%.

Preterm birth is a major cause of infant mortality and morbidity worldwide (1, 2) and a leading contributor to disability (3).

Abnormal control of breathing is common in preterm infants and usually manifests as apnea, intermittent hypoxemia (IH), bradycardia, and periodic breathing (PB). Apnea generally resolves by term-corrected age (4), although some infants have delayed resolution of apnea and/or bradycardia (5, 6). Extremely preterm infants may also have impaired gas exchange caused by respiratory distress syndrome and subsequent bronchopulmonary dysplasia (BPD). The combination of apnea and lung disease often leads to more prolonged episodes of IH (5). Such chronic IH is associated with worse short-term outcomes (e.g., increased respiratory support, retinopathy of prematurity) (7) and neurodevelopmental impairment (8) that are difficult to predict in the neonatal ICU (9).

Because extreme prematurity predisposes to both abnormalities of control of breathing (apnea, IH, bradycardia, and PB) and worse respiratory outcomes, the association between abnormal control of breathing and worse outcomes may be due to the common antecedent of more extreme immaturity. Respiratory outcomes such as BPD are operational definitions based on the magnitude of respiratory support and do not indicate the contribution of impaired control of breathing. Caffeine is known to decrease apnea and reduces BPD (10), suggesting that repeated apneic episodes may contribute to (and are not just associated with) pulmonary outcomes. However, although caffeine reduces apnea, hypoxemic episodes persist (11), and higher doses or extended treatment may be needed (12, 13). Importantly, preterm infants experience PB, very brief bradycardic episodes, and IH not identified by clinical cardiorespiratory monitors. The importance and relationship of these "non–clinically evident" events to outcomes is not established.

The Pre-Vent (Prematurity-related Ventilatory Control; ClinicalTrials.gov identifier NCT03174301) study was an NIH-funded (NHLBI) cooperative agreement among six academic centers (five clinical sites and one data coordinating center) with the primary goal of elucidating the role of ventilatory control as a determinant of respiratory dysfunction in preterm infants (14). The hypothesis of the Pre-Vent multicenter protocol was that features of ventilatory control instability using clinical neonatal ICU cardiorespiratory monitoring data can predict unfavorable respiratory outcomes at 40 weeks postmenstrual age (PMA), as well as other respiratory outcomes such as BPD.

Methods

Additional details regarding the methods are provided in the online supplement.

Study Population

This was a multicenter prospective cohort study including infants <29 weeks gestational age (GA) with continuously archived cardiorespiratory monitoring data (Figure 1) (14). Institutional review board approval was obtained at all sites, with waiver of consent at three clinical centers and informed consent required at two clinical centers. Oversight was provided by an observational safety monitoring board appointed by NHLBI.

Outcome

Primary outcome. Primary outcome was defined as follows:

- *Favorable*: Either *1)* an inpatient at 40 weeks PMA and not on oxygen, not on other flow/pressure respiratory support, and not on inhaled/oral/intravenous respiratory medications, or *2)* discharged home before 40 weeks PMA and not on respiratory medications, oxygen, or other respiratory support.
- *Unfavorable*: Either *1)* deceased at or before 40 weeks, *2)* inpatient on medications or O₂ or other respiratory support at 40 weeks PMA, or *3)*
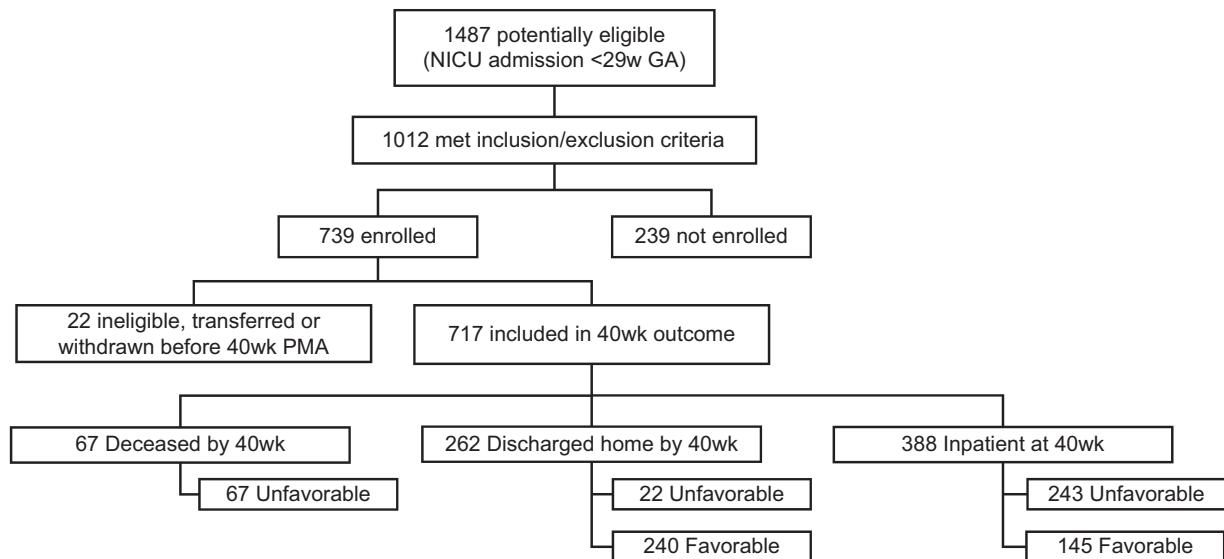
Figure 1. Flow diagram of infants studied in Pre-Vent. GA = gestational age; NICU = neonatal ICU; PMA = postmenstrual age.

discharged before 40 weeks on medications or O_2 or other respiratory support.

Unfavorable outcome was further categorized as highly unfavorable (death or invasive mechanical ventilation [IMV] at 40 wk PMA), moderately unfavorable (noninvasive mechanical ventilation/continuous positive airway pressure [CPAP] at 40 wk PMA), or mildly unfavorable (O_2 or only medications at 40 wk PMA or discharged home on medications or O_2 at <40 wk PMA).

Secondary outcomes. Prespecified secondary outcomes included the following:

1. Highly unfavorable outcome (death or IMV at 40 wk PMA)
2. Moderate or severe BPD at 36 wk PMA (Eunice Kennedy Shriver National Institute of Child Health and Human Development [NICHD] consensus definition) (15)
3. Grade 3 BPD (IMV at 36 wk PMA) (16)

Data

Clinical data consisted of baseline clinical characteristics and variables of neonatal illness severity, medications, outcomes, neonatal comorbidities, and respiratory support. Physiologic data consisted of features extracted from cardiorespiratory monitoring data (defined in the online

supplement). These features were quantified as the count of events per day, total daily duration of all events, and average duration per event (dpe) for each of the five control of breathing variables:

1. Apnea ($\geqslant$20 s [17])
2. PB (wavelet transform using a five-breath template [18])
3. IH events with oxygen saturation as measured by pulse oximetry <80% (IH80) (for 10–300 s [19])
4. IH events with oxygen saturation as measured by pulse oximetry <90% (IH90) (for 10–300 s [19])
5. Bradycardia (<80 beats/min for 5 s or longer)

Analysis

Prediction models were developed (*see* online supplement) at four time points of Day 7, Day 14, Day 28, and 32 weeks PMA using 24 hours of data as a cross-sectional snapshot. At each time point, models were developed using *1*) physiologic data variables alone, *2*) clinical variables alone, and *3*) combined physiologic + clinical variables. Additional prespecified analyses were done using the longitudinal burden of data up to the time point in each infant to determine if this improved predictive ability.

The primary outcome (favorable vs. unfavorable) was compared using multivariable logistic regression.

The cross-validated area under the curve (cvAUC) using 10-fold cross-validation was used as a primary performance measure. Penalized logistic regression (least absolute shrinkage and selection operator) selected model variables, with the final model chosen to optimize cvAUC. Goodness of fit was assessed by McFadden's pseudo R^2 (20). Additional leave-one-site-out analyses were done for validation.

Results

Patient Characteristics

Overall, 717 infants were evaluated (mean ± SD; median: birth weight [BW] 871 ± 259 g; 850 g; GA, 26.4 ± 1.7 wk; 26.4 wk) (Table 1, Figure 1). A total of 385 infants (53.7%) had a favorable outcome (BW, 989 ± 226 g; 961 g; GA, 27.2 ± 1.3 wk; 27.4 wk), whereas 332 (46.3%) had an unfavorable outcome (BW, 735 ± 226 g; 692.5 g; GA, 25.6 ± 1.7 wk; 25.4 wk).

Outcomes and neonatal comorbidities are listed in Table 2, respiratory support in Table 3, and medication use in Table E1 in the online supplement. Of the 332 infants with unfavorable outcomes, 113 (34%) had a highly unfavorable outcome (16% of total) because of either IMV at 40 weeks PMA or death before or at 40 weeks PMA (20% of unfavorable; 9% of total) (Table E2). Forty-three (13% of unfavorable; 6% of total) had a moderately unfavorable outcome (nasal IMV

Table 1. Perinatal and Demographic Information and Illness Severity by Outcome

Variable	Combined Population	Favorable Outcome	Unfavorable Outcome
Baseline information			
Birth weight, g, mean ± SD; median; 25th–75th, n	871.3 ± 259; 850; 676–1,050; n = 717	988.7 ± 226; 961; 830–1,140; n = 385	735.2 ± 226; 693; 579–848; n = 332
<10% percentile weight (Fenton), % (n/N)	11.3 (81/717)	3.1% (12/385)	20.8% (69/332)
Birth weight percentile (Fenton), mean ± SD; median; 25th–75th, n	51 ± 28; 53; 26–75; n = 715	57 ± 26; 61; 38–77, n = 385	43 ± 30; 44; 16–70; n = 330
Birth length, cm, mean ± SD; median; 25th–75th, n	33.6 ± 3.5; 33.5; 31–36; n = 697	35.1 ± 2.8; 35; 33–37, n = 376	31.8 ± 3.2; 31; 29.5–33.6: n = 321
Birth head circumference, cm, mean ± SD; median; 25th–75th, n	23.7 ± 2.5; 23.5; 22–25.5; n = 685	24.7 ± 2.1; 24.5; 23.5–26.0; n = 371	22.4 ± 2.3; 22; 21–23.5; n = 314
GA, wk, mean ± SD; median; 25th–75th, n	26.43 ± 1.71; 26.4; 25.14–28.0; n = 717	27.18 ± 1.34; 27.4; 26.1–28.3; n = 385	25.6 ± 1.7; 25.4; 24.3–26.9; n = 332
Sex (M), % (n/N)	51% (366/717)	47.5% (183/385)	55.1% (183/332)
Multiple gestation, % (n/N)	23% (165/717)	23.6% (91/385)	22.3% (74/332)
Born outside study center, % (n/N)	8.9% (64/717)	8.1% (31/385)	9.9% (33/332)
Clinical chorioamnionitis, % (n/N)	2.2% (13/591)	2.5% (8/316)	1.8% (5/275)
Histological chorioamnionitis, % (n/N)	35.9% (212/591)	35.8% (113/316)	36% (99/275)
Rupture of membranes before delivery, % (n/N)	40.7% (277/680)	43.8% (161/368)	37.2% (116/312)
Rupture of membranes for >18 h, % (n/N)	68.3% (181/265)	63% (97/154)	75.7% (84/111)
Rupture of membranes >7 d, % (n/N) Denominator N = all babies who answered yes to the above variable	32.1% (85/265)	29.9% (46/154)	35.1% (39/111)
Antenatal steroids: none, % (n/N)	8.5% (59/696)	8.0% (30/375)	9.0% (29/321)
Antenatal steroids: number of complete courses per infant, mean ± SD; median, 25th–75th; n	0.76 ± 0.58; 1; 0–1; n = 694	0.80 ± 0.59; 1.0; 0–1.0; n = 374	0.72 ± 0.55; 1.0; 0–1.0; n = 320
Maternal antibiotics, % (n/N)	77.1% (n = 516/669)	77.1% (n = 280/363)	77.1% (n = 236/306)
Presentation, vertex, % (n/N)	52.7% (n = 320/607)	54.1% (180/333)	51.1% (140/274)
Mode of birth, cesarean section, % (n/N)	67.8% (n = 486/717)	68.3% (263/385)	67.2% (223/332)
Maternal information			
Maternal race, Black, % (n/N)	51% (n = 346/678)	53.3% (195/366)	48.4% (151/312)
Maternal ethnicity, Hispanic, % (n/N)	16.1% (n = 112/696)	15.7% (59/376)	16.6% (53/320)
Maternal age, yr, mean ± SD, median, 25th–75th; n	29.36 ± 6.1; 29; 25–34; n = 717	29.47 ± 5.7; 29; 25–34; n = 385	29.22 ± 6.5; 30; 24–34; N = 332
Baby's health insurance, Medicaid/public, % (n/N)	63.2% (450/712)	63.4% (241/380)	63.0% (209/332)
Baby's health insurance, private, % (n/N)	33.4% (238/712)	34.5% (131/380)	32.2% (107/332)
Maternal hypertension, % (n/N)	40.2% (250/622)	40.2% (135/336)	40.2% (115/286)
Maternal hypertension before pregnancy, % (n/N)	59.1% (139/235)	60.6% (77/127)	57.4% (62/108)
Maternal gestational diabetes, % (n/N)	5.3% (32/603)	5.9% (19/322)	4.6% (13/281)
Maternal diabetes mellitus before pregnancy, % (n/N)	6.0% (36/599)	6.6% (21/317)	5.3% (15/282)

(Continued)

Table 1. (*Continued*)

Variable	Combined Population	Favorable Outcome	Unfavorable Outcome
Maternal asthma during pregnancy in medical record, % (n/N)	10.4% (n=62/597)	12.5% (40/321)	8.0% (22/276)
Antepartum hemorrhage, % (n/N)	16.1% (96/597)	16.3% (52/320)	15.9% (44/277)
Medications to prolong pregnancy, % (n/N)	35.9% (243/677)	34.6% (126/364)	37.4% (117/313)
Maternal tobacco smoking, % (n/N)	11.9% (73/611)	11.5% (38/331)	12.5% (35/280)
Maternal opiates (oral/intravenous) or sedatives or other illicit drugs, % (n/N)	12.6% (77/613)	13.3% (44/330)	11.7% (33/283)
Illness severity			
Apgar score at 1 min, median; 25th–75th, n	4; 2–6; n=704	5; 3–7, n=377	3; 2–5; n=327
Apgar score at 5 min, median; 25th–75th, n	7; 5.5–8; n=704	7; 6–8; n=377	6; 4–7; n=327
Resuscitation at birth: O_2, % (n/N)	89.6% (638/712)	86.3% (328/380)	93.4% (310/332)
Resuscitation at birth: CPAP, % (n/N)	58.6% (417/712)	67.1% (255/380)	48.8% (162/332)
Resuscitation at birth: bag and mask, % (n/N)	77.0% (548/712)	72.6% (276/380)	81.9% (272/332)
Resuscitation at birth: intubation, % (n/N)	53.9% (384/712)	40.0% (152/380)	69.9% (232/332)
Resuscitation at birth, chest compression, % (n/N)	2.0% (14/712)	1.1% (4/380)	3.0% (10/332)
Resuscitation at birth epinephrine, % (n/N)	0.6% (4/712)	0.5% (2/380)	0.6% (2/332)
Admission temperature to NICU, °C, mean ± SD, n	36.8 ± 0.8; n=717	36.9 ± 0.7; n=385	36.7 ± 0.8; n=332
Prophylactic indomethacin, ibuprofen, acetaminophen, % (n/N)	37.7% (n=268/710)	33.1% (n=126/381)	43.2% (n=142/329)

Definition of abbreviations: CPAP = continuous positive airway pressure; GA = gestational age; NICU = neonatal ICU.

or CPAP at 40 wk PMA), whereas 176 (53% of unfavorable; 25% of total) had a mildly unfavorable outcome.

Physiologic Data over Time
Physiologic data were graphed over chronological age (Figure 2, left panels) and PMA (Figure 2, right panels) with number of events per day (Figure 2, top panels), minutes per day (Figure 2, middle panels), and dpe (Figure 2, bottom panels) shown as trajectories over time in terms of outcome (favorable, mildly unfavorable, moderately or highly unfavorable) and as heatmaps representing individual infants. Because apnea and PB were not evaluable when infants were intubated and on mechanical ventilation, the data are shown only for times of spontaneous breathing (including noninvasive ventilation) without invasive respiratory support. These features are summarized in Table E3.

Apnea. Infants with moderately or highly unfavorable outcomes could not be analyzed for association with apnea (or PB), because there were few infants with such outcomes not intubated at the four time points. Excluding days on IMV when apnea could not be evaluated, infants with favorable outcomes initially had more apneic events and of longer daily duration in the first 4 weeks (until 33 wk PMA) than did those with mildly unfavorable outcomes but subsequently less apnea thereafter. Because infants may be intubated due to apnea, these results may not reflect the relationship between apnea and outcome. Apnea cessation (median) was generally by 8 weeks chronologic age in infants with a favorable outcome, by 12 weeks in those with a mildly unfavorable outcome, and by 35–36 weeks PMA in both groups because infants with unfavorable outcomes were more premature than those with favorable outcomes.

PB. PB, similar to apnea, was also increased in both number and duration among infants with a favorable outcome as compared with those with a mildly unfavorable outcome (as with apnea, many infants with unfavorable outcomes were intubated on IMV and were not evaluable for PB). PB persisted until 40 weeks PMA in infants with favorable and mildly unfavorable outcomes.

IH. Data are shown for IH80 and IH90. IH75 and IH85 were also investigated but did not improve prediction (data not shown). Infants with unfavorable outcomes had

Table 2. Outcomes and Other Neonatal Morbidities in Survivors Only

Variable	Combined Population	Primary Favorable Outcome	Primary Unfavorable Outcome
Favorable primary outcome			
Only on respiratory medications at discharge <40 wk PMA, % (n/N)	1.5% (11/717)	0% (0/385)	3.3% (11/332)
Only on respiratory support at discharge <40 wk PMA, % (n/N)	0.7% (5/717)	0% (0/385)	1.5% (5/332)
On respiratory medications and respiratory support at discharge <40 wk PMA, % (n/N)	0.8% (6/717)	0% (0/385)	1.8% (6/332)
Only on respiratory medications as inpatient at 40 wk PMA, % (n/N)	3.1% (22/717)	0% (0/385)	6.6% (22/332)
Only on respiratory support as inpatient at 40 wk PMA, % (n/N)	11.6% (83/717)	0% (0/385)	25.0% (83/332)
On respiratory medications and respiratory support as inpatient at 40 wk PMA, % (n/N)	19.2% (138/717)	0% (0/385)	41.6% (138/332)
Death ≤40 wk PMA, % (n/N)	9.3% (67/717)	0% (0/385)	20.2% (67/332)
Discharged alive on no respiratory medications or respiratory support <40 wk PMA, % (n/N)	33.5% (240/717)	62.3% (240/385)	0% (0/332)
Alive on no respiratory medications or respiratory support as inpatient at 40 wk PMA, % (n/N)	20.2% (145/717)	37.7% (145/385)	0% (0/332)
Secondary outcomes			
Moderate BPD (NICHD definition), % (n/N) Need for any oxygen at 36 wk PMA or discharge, whichever comes first; 36 wk survivors only	44% (288/654)	17.4% (67/385)	82.2% (221/269)
Severe BPD (NICHD definition), % (n/N) Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first; infants alive at 36 wk PMA	31.2% (204/654)	7.0% (27/385)	65.8% (177/269)
Severe BPD, % (n/N) On invasive mechanical ventilation at 36 wk PMA; infants alive at 36 wk PMA	9.9% (65/654)	0.5% (2/385)	23.4% (63/269)
Highly unfavorable outcome: death or IMV at 40 wk PMA, % (n/N)	15.8% (113/717)	0% (0/385)	34.0% (113/332)
Moderately unfavorable outcome: noninvasive positive pressure at 40 wk PMA, % (n/N)	6.0% (43/717)	0% (0/385)	13.0% (43/332)
Mildly unfavorable outcome: nasal cannula or only medications at 40 wk PMA or discharged home on medications or oxygen before 40 wk, % (n/N)	24.5% (176/717)	0% (0/385)	53.0% (176/332)
Duration of respiratory support (IMV or CPAP or O_2), d, mean ± SD; median, 25th–75th, n through discharge, up to 40 wk (infants alive at 40 wk PMA)	57.79 ± 33.21; 59, 28.25–88; n=651	38.88 ± 25.53; 36, 16–58; n=385	85.16 ± 22.12; 90; 75–101; n=266
Duration of mechanical ventilation, d, mean ± SD; median, 25th–75th, n through discharge, up to 40 wk; 40 wk survivors only	21.57 ± 28.01; 7; 1–35.75, n=651	7.94 ± 13.2; 2; 0–9.25, n=385	41.28 ± 31.83; 38; 10–65; n=266
Pulmonary hypertension diagnosis >34 wk (echocardiography proven), % (n/N) through discharge up to 40 wk; 40 wk survivors only	9.4% (61/650)	0.5% (2/385)	22.3% (59/265)
Other morbidity in 40 wk survivors			
Any intraventricular hemorrhage (grades 1–4) through exit or 36 wk PMA, % (n/N)	30.3% (197/651)	22.9% (88/385)	41% (109/266)
	10.0% (65/651)	5.7% (22/385)	16.2% (43/266)

(Continued)

Table 2. (*Continued*)

Variable	Combined Population	Primary Favorable Outcome	Primary Unfavorable Outcome
Severe intraventricular hemorrhage (grade 3 or 4) through exit or 36 wk PMA, % (n/N)	4.1% (27/651)	2.3% (9/385)	6.8% (18/266)
Periventricular leukomalacia through exit or 36 wk PMA, % (n/N)	9.4% (61/651)	4.7% (18/385)	16.2% (43/266)
Posthemorrhagic hydrocephalus through exit or 36 wk PMA, % (n/N)	2.51% (18/717)	0.52% (2/385)	4.82% (16/332)
Early-onset septicemia (blood culture positive before 72 h of age), % (n/N)	20.39% (145/711)	10.9% (42/385)	31.60% (103/326)
Late-onset septicemia (blood culture positive beyond 3 d of age) through exit up to 40 wk, % (n/N)	0.14% (1/717)	0% (0/385)	0.30% (1/332)
Antibiotic courses of ≥5 d duration without positive cultures through exit up to 40 wk, % (n/N)	57.1% (358/627)	41.4% (154/372)	80.0% (204/255)
Retinopathy of prematurity (ROP): any stage/zone through exit up to 52 wk (of infants who received an ROP exam), % (n/N)	7.9% (50/634)	1.6% (6/372)	16.8% (44/262)
Retinopathy of prematurity (ROP): severe (needing laser/bevacizumab/surgery) through exit up to 40 wk, % (n/N)	40.5% (263/650)	31.2% (120/385)	54.0% (143/265)
Patent ductus arteriosus: any (diagnosed on echocardiography) through exit up to 40 wk, % (n/N)	26.9% (175/650)	19.0 (73/385)	38.5% (102/265)
Patent ductus arteriosus: diagnosed through exit up to 40w and medically treated with indomethacin/ibuprofen/acetaminophen through exit up to 52 wk, % (n/N)	4.6% (30/650)	1.0% (4/385)	9.8% (26/265)
Patent ductus arteriosus: surgically ligated or cardiac catheter closure through exit up to 40 wk, % (n/N)	4.8% (31/650)	3.6% (14/385)	6.4% (17/265)
Necrotizing enterocolitis: medical (stage II or III) through exit up to 40 wk, % (n/N)	3.4% (22/650)	1.0% (4/385)	6.8% (18/265)
Necrotizing enterocolitis: surgical (stage II or III) through exit up to 40 wk, % (n/N)	3.1% (20/650)	1.3% (5/385)	5.7% (15/265)
Spontaneous intestinal perforation through exit up to 40 wk, % (n/N)	3,506.03 ± 1,162; 3,230; 2,611–4,125; n=649	2,946.26 ± 706; 2,855; 2,390–351; n=385	4,322.36 ± 1,213; 4,177.5; 3,347.5–5,120; n=364
Discharge weight, g, at exit up to 52 wk, mean ± SD; median; 25th–75th, n	50.5 ± 28.6; 50.4; 25.5–75.2; n=649	36.6 ± 23.5; 34.4; 16.4–55.2; n=385	70.6 ± 22.9; 76.6; 55.2–89.2; n=264
Discharge weight percentile for PMA at exit up to 52 wk, mean ± SD; median; 25th–75th, n	48.77 ± 4.67; 48; 45.5–51.50; n=649	47.07 ± 3.63; 46.5; 44.5–49.50, n=385	51.26 ± 4.9; 51; 48.0–54.5; n=264
Discharge length, cm, mean ± SD; median; range, n at exit up to 52 wk	50.6 ± 28.6; 48; 25.8– 75.2; n=649	39.9 ± 25.2; 35.8; 17.3–59.9; n=385	66.2 ± 26.0; 71.6; 48.0–88.3; n=264
Discharge length percentile for PMA, mean ± SD; median; 25th–75th, n at exit up to 52 wk	34.57 ± 2.99; 34.5; 32.94–36.13; n=649	33.35 ± 2.34; 33.5; 32–34.5; n=385	36.34 ± 2.94; 36.0; 34.5–38.0; n=264
Discharge head circumference, cm, at exit up to 52 wk, mean ± SD; median; 25th–75th, n	50.4 ± 28.6; 53.5; 28.6–73.7; n=649	38.6 ± 24.7; 37.0; 19.1–53.5; n=385	67.7 ± 24.8; 72.5; 53.5–88.0, n=264
Discharge head circumference percentile for PMA at exit up to 52 wk, mean ± SD; median; 25th–75th, n	111 ±44;199; 76–138; n = 649	86 ± 26; 83; 67–100; n=385	148 ±40; 145; 119–182; n=264
Hospital length of stay, d, mean ± SD; median; 25th–75th, n			

Table 3. Clinical Respiratory Data

Variable	Cumulative from Day 1 to 32 Wk PMA*	Day 1	Day 7	Day 14	Day 28	32 Wk PMA
Respiratory support (any) (%; n/N)	90.01% (n=714/717)	98.74% (n=707/716)	91.32% (n=642/703)	88.76% (n=608/685)	84.43% (564/668)	81.85% (n=541/661)
Any invasive IMV (%; n/N)	78.52% (n=563/717)	68.01% (n=487/716)	43.1% (n=303/703)	39.12% (n=268/685)	31.7% (n=212/668)	19.51% (n=129/661)
Mean airway pressure on IMV (mean ± SD; median, 25th–75th, n)	10.0 ± 2.8; 9.5; 8–11.1; n=563	8.0 ± 2.2; 8; 6.8–9; n=484	9.2 ± 2.2; 8.9; 7.7–10; n=303	10.2 ± 2.7; 9.9; 8.4–12; n=268	10.4 ± 2.5; 10; 8.8–12; n=209	11.0 ± 2.9; 10; 9–13; n=128
On CPAP, % (n/N)	23% (547/717)	20.3% (145/716)	26.5% (186/703)	23.2% (159/685)	21.1% (141/668)	25.6% (169/661)
On supplemental oxygen, yes/no, %	75.9% (706/717)	79.9% (572/716)	68.9% (484/703)	73.9% (506/685)	69.3% (463/668)	65.4% (432/661)
FI_{O_2} (closest to noon), mean ± SD; median, 25th–75th, n	0.33 ± 0.18; 0.26; 0.21–0.37; n=717	0.28 ± 0.12; 0.24; 0.21–0.30; n=716	0.30 ± 0.15; 0.24; 0.21–0.32; n=703	0.34 ± 0.19; 0.26; 0.21–0.36; n=685	0.32 ± 0.17; 0.25; 0.21–0.36; n=668	0.30 ± 0.16; 0.23; 0.21–0.32; n=661
FI_{O_2} closest to noon is >30%=yes, % (n/N)	34.6% (571/717)	23.5% (168/716)	26.0% (183/703)	34.7% (238/685)	32.6% (218/668)	25.9% (171/661)
Maximum Pa_{CO_2}, %, mean ± SD; median, 25th–75th, n	52.2 ± 13; 40; 44–59; n=575	47.9 ± 11.5; 46; 40–54; n=418	55.3 ± 11.3; 54; 48–64, n=93	59.4 ± 32; 50; 43–58.5; n=15	58.6 ± 17.9; 53.5; 43.5–73; n=8	51.0 ± 4.6; 51.5; 48–54.1; n=4
Max capillary or venous P_{CO_2}, %, mean ± SD; median, 25th–75th, n	53.0 ± 10.5; 52; 46–59; n=693	46.6 ± 11; 45; 40–51; n=250	50.8 ± 10.7; 49; 44–57; n=425	54.1 ± 10.4; 53; 47–60; n=685	53.2 ± 10.4; 52; 46–59; n=322	53.7 ± 10.2; 52; 47–60; n=221
Longitudinal burden of respiratory support: number of days alive and off ventilation, mean ± SD; median, 25th–75th, n	N/A	N/A	3.8 ± 3.4; 4; 0–7; n=703	8.1 ± 6.4; 11; 0–14; n=685	17.2 ± 12; 23; 2–28; n=668	22.8 ± 12.9; 24; 14–31; n=661
Number of days alive and off ventilation in past 2 wk, mean ± SD; median, 25th–75th, n	N/A	N/A	N/A	N/A	9 ± 6.2; 14; 0–14; n=668	10.8 ± 5.4; 14; 9–14; n=661

Definition of abbreviations: IMV = invasive mechanical ventilation; PMA = postmenstrual age.
*For the cumulative data column, % is the percentage of days until 32 weeks PMA; *n/N* represents infants on any day until 32 weeks PMA.

Postnatal (Chronological) Age
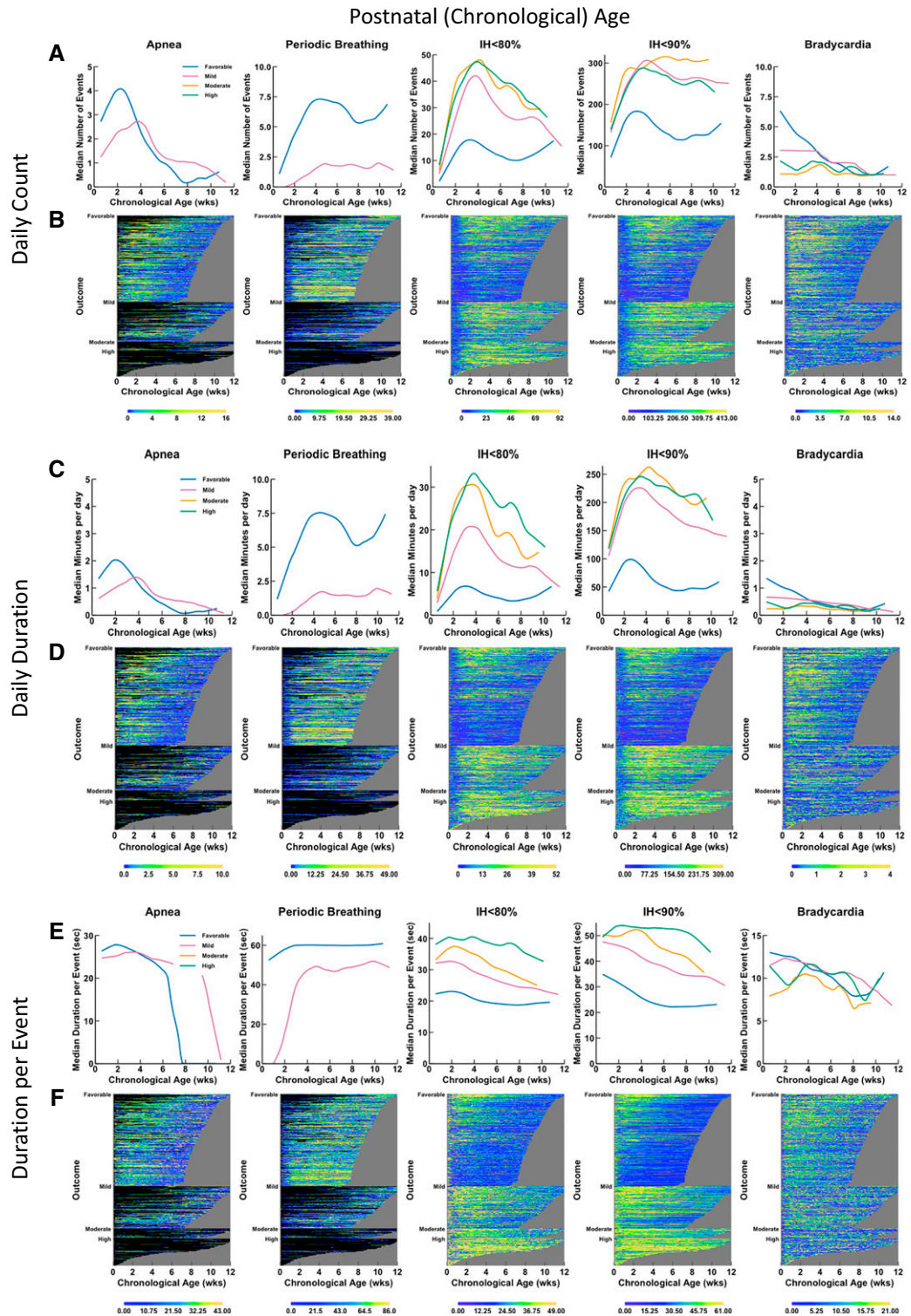
Figure 2. Trajectories and heat maps for daily counts, daily duration, and median duration per event of apnea, periodic breathing, intermittent hypoxemia (IH) ≤80%, IH ≤90%, and bradycardia for infants enrolled in Pre-Vent. Chronologic (postnatal) age is shown on the *x*-axis in the left panels (*A–F*) and postmenstrual age is shown on the *x*-axis in the right panels (*G–L*). Data are shown from 3 days of age, and a minimum number of 30 infants was required to calculate a trajectory curve. Only infant days that have at least 12 hours of signal available are included. Top row of graphs (*A, G*) and heatmaps (*B, H*) show data for daily counts, whereas the middle row of graphs (*C, I*) and heatmaps (*D, J*) show data for daily duration of events, and bottom row of graphs (*E, K*) and heatmaps (*F, L*) show data for median duration per event. The top row of graphs (*A, G*) shows trajectories of daily count of event by outcome (color-coded lines), with the number of events on the *y*-axis and age on the *x*-axis. The second row of panels shows heatmaps (*B, H*) for daily counts of events. The heat map shows data for all infants, with each infant per horizontal line, grouped by outcome as favorable (at top),
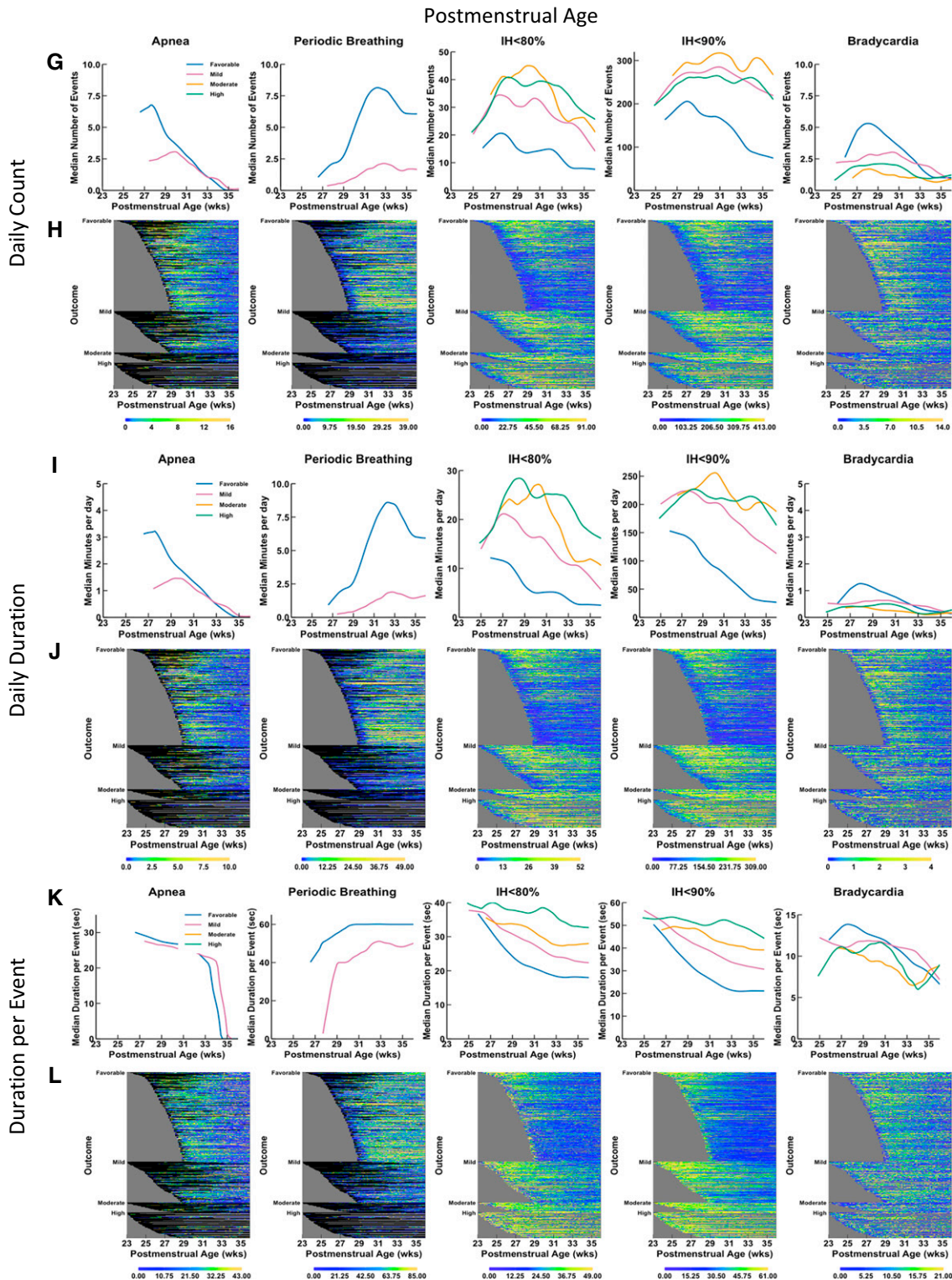
Figure 2. (*Continued*). mildly unfavorable (in middle), and moderately or highly unfavorable (at bottom). Within each category of outcome, infants are grouped by gestational age with oldest infants at the bottom and youngest infants at the top, with the data plotted horizontally by chronological age on the *x*-axis. Color coding for number of events per day is shown with yellow indicating more events and deepening shades of blue indicating fewer events. Black indicates no data, such as for apnea or periodic breathing when the infant is on a ventilator. The gray area represents data truncation when the infant has reached 36 weeks, 6 days postmenstrual age, the predetermined endpoint for the Pre-Vent physiologic outcomes analysis. The middle row of graphs (*C, I*) shows trajectories of daily duration of event by outcome (color-coded lines), with the number of events on the *y*-axis and the age on the *x*-axis. The second row of panels shows heatmaps (*D, J*) for daily duration of the events. The lower row of graphs (*E, F*) shows trajectories of median duration per event by outcome (color-coded lines), with the number of events on the *y*-axis and the chronologic age on the *x*-axis. The bottom row of panels shows heatmaps (*F, L*) for median duration per event.

Table 4. Model at 7 Days of Age, Including Survivors to Day 7 (Limited to Importance 0.0005 or More)

Variable (Selected by LASSO)	AUC C-Statistic	Importance of Variable	OR (95% CI) or Similar	P Value
Clinical variables alone model	0.841			
Gestational age		0.0117	0.51 (0.39–0.68)	<0.00001
SGA		0.0070	4.73 (2.04–10.97)	0.0003
$F_{I_{O_2}}$ >0.3*		0.0050	2.28 (1.35–3.83)	0.002
IMV		0.0036	2.53 (1.27–5.05)	0.008
Positive pressure		0.0035	1.95 (1.1–3.47)	0.022
Black race		0.0028	0.57 (0.37–0.89)	0.014
Supplemental oxygen >12 h/24 h		0.0026	1.76 (1.11–2.78)	0.016
Growth percentile		0.0024	0.74 (0.58–0.93)	0.010
Apgar 1-min score		0.0023	0.79 (0.65–0.96)	0.016
Sedatives		0.0014	2.42 (1.12–5.21)	0.024
Male		0.0012	1.40 (0.96–2.04)	0.084
Physiologic variables alone model	0.792			
PB dpe		0.0179	0.56 (0.42–0.73)	0.00004
IH90 daily duration		0.0099	1.66 (1.2–2.32)	0.003
IH90 dpe		0.0006	1.15 (0.87–1.53)	0.321
Combined model (physiologic model + clinical model)	0.846			
SGA		0.0233	9.57 (4.18–21.91)	<0.00001
Gestational age		0.0095	0.53 (0.39–0.71)	0.00002
PB dpe		0.0064	0.60 (0.45–0.81)	0.0009
$F_{I_{O_2}}$ >0.3*		0.0046	2.04 (1.16–3.58)	0.013
Black race		0.0038	0.61 (0.39–0.97)	0.035
IH90 daily duration		0.0038	1.45 (1.01–2.09)	0.045
Positive pressure		0.0027	2.04 (1.04–4.01)	0.037
Apgar 1-min score		0.0025	0.77 (0.63–0.95)	0.017
Caffeine		0.0006	0.63 (0.27–1.49)	0.295
IMV		0.0006	1.72 (0.74–4.0)	0.208

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; dpe = duration per event; IH90 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <90%; IMV = invasive mechanical ventilation; LASSO = least absolute shrinkage and selection operator; OR = odds ratio; PB = periodic breathing; SGA = small for gestational age.
*When $F_{I_{O_2}}$ is listed as a variable, it is the continuous variable of $F_{I_{O_2}}$ value closest to noon. If $F_{I_{O_2}}$ >0.3 is listed, it is the binary variable $F_{I_{O_2}}$ >0.3.

increased IH80 and IH90 counts and daily duration. IH90 dpe and IH80 dpe discriminated best among the different categories of outcome, with different trajectories over time between infants with favorable, mildly unfavorable, moderately unfavorable, and highly unfavorable outcomes (Figures 2E and 2F). The median daily counts, daily duration, and dpe for the infants with favorable and unfavorable outcomes diverged from the earliest time point (25 wk PMA), with dpe again illustrating maximal separation among different outcomes (Figures 2K and 2L).

Bradycardia. Bradycardia trajectories of infants with favorable outcomes and different categories of unfavorable outcomes had overlap, with convergence by ~14 weeks chronologic age or 33 weeks PMA for counts and daily duration.

Primary outcome. The primary outcome was measured using unfavorable versus favorable outcome models with 24-hour (snapshot) data.

Physiologic Models

Physiologic data predicted unfavorable outcomes, with the accuracy of prediction increasing with advancing postnatal age (Tables 4–7, Figures 3 and 4). The AUC of the receiver operating characteristic curve (ROC) of models improved from 0.792 at Postnatal Day 7 to 0.825 at Day 14, 0.855 at Day 28, and 0.845 at 32 weeks PMA. The primary variables contributing the most overall to predictive accuracy were IH <90% (IH90) duration per event (IH90dpe), followed by IH90 total duration per day and IH90 count per day. In contrast, longer PB and apnea events (dpe) were associated with favorable outcomes, but these variables could be evaluated only in infants not on a ventilator, and many infants with unfavorable outcome were mechanically ventilated at earlier time points.

Clinical Models

Clinical data models predicted unfavorable outcomes with good accuracy at Day 7 (AUC

of ROC, 0.841), which remained relatively stable over time (0.849 on Day 14, 0.864 on Day 28, and 0.871 at 32 wk PMA) (Tables 4–7, Figure 3). At Day 7, lower GA, being small for gestational age (SGA), on high (>0.3) $F_{I_{O_2}}$, and on IMV or positive pressure (including CPAP or nasal IMV) were the major contributors to unfavorable outcomes. These variables were also important at Days 14 and 28, although the relative importance was different because GA (most important on Day 7) was replaced by IMV on Day 14 and Day 28 as the most contributory variable. Black infants had lower odds of unfavorable outcome at Days 7 and 14, although this was no longer statistically significant at Day 28 or 32 weeks PMA. At 32 weeks PMA, being SGA, on IMV, and of lower GA were the major contributors.

Physiologic and Clinical Models

Models combining physiologic and clinical data had good accuracy, with AUC of ROC of 0.846 at Day 7, 0.854 on Day 14, 0.872 on

Table 5. Model at 14 Days of Age, Including Survivors to Day 14 (Limited to Importance 0.0005 or More)

Variable (Selected by LASSO)	AUC C-Statistic	Importance of Variable	OR (95% CI) or Similar	P Value
Clinical variables alone model	0.849			
IMV		0.0170	6.70 (3.2–14)	<0.00001
SGA		0.0153	7.69 (3.57–16.56)	<0.00001
Positive pressure		0.0117	3.47 (1.9–6.32)	0.0001
F_{IO_2}*		0.0069	1.66 (1.15–2.38)	0.006
Black race		0.0022	0.61 (0.39–0.94)	0.027
Gestational age		0.0021	0.64 (0.49–0.83)	0.0007
Apgar 1-min score		0.0014	0.81 (0.67–0.99)	0.035
Temperature at admission		0.0013	0.84 (0.68–1.05)	0.121
Hispanic ethnicity		0.0006	0.60 (0.33–1.07)	0.085
Sedatives		0.0005	2.30 (0.96–5.50)	0.062
Physiologic variables alone model	0.825			
IH90 dpe		0.0156	1.71 (1.29–2.27)	0.0002
PB dpe		0.0094	0.57 (0.42–0.77)	0.0002
IH90 count		0.0038	1.30 (1.05–1.61)	0.014
Apnea dpe		0.0005	0.83 (0.62–1.10)	0.184
Combined model (physiologic model + clinical model)	0.854			
SGA		0.0083	6.00 (2.65–13.59)	0.00002
Positive pressure		0.0047	2.84 (1.46–5.56)	0.002
PB dpe		0.0046	0.58 (0.42–0.81)	0.001
Gestational age		0.0041	0.62 (0.47–0.82)	0.0009
F_{IO_2}*		0.0016	1.38 (0.96–1.97)	0.082
IH90 dpe		0.0016	1.25 (0.91–1.72)	0.162
Male		0.0014	1.36 (0.89–2.09)	0.153
Apnea dpe		0.0010	0.83 (0.60–1.15)	0.267
Apgar 1-min score		0.0010	0.82 (0.67–1.01)	0.062
Sedatives		0.0008	2.09 (0.87–4.99)	0.097

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; dpe = duration per event; IH90 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <90%; IMV = invasive mechanical ventilation; LASSO = least absolute shrinkage and selection operator; OR = odds ratio; PB = periodic breathing; SGA = small for gestational age.
*When F_{IO_2} is listed as a variable, it is the continuous variable of F_{IO_2} value closest to noon. If F_{IO_2} >0.3 is listed, it is the binary variable F_{IO_2} >0.3.

Day 28, and 0.879 at 32 weeks PMA (Tables 4–7, Figure 3). This accuracy was comparable to that with clinical data alone (less than 0.01 increase in AUC). The major clinical variables included in this model were SGA and GA on Day 7, SGA and positive pressure on Day 14, F_{IO_2} and SGA on Day 28, and SGA and GA at 32 weeks PMA. The major physiologic variables were those related to IH90 and PB (absence of PB in nonventilated infants and duration of PB if present).

Secondary outcomes evaluated using 24-hour data at 28 days of age were as outlined below.

1. Highly unfavorable outcome (Death or IMV at 40w PMA) (Table 8; Figure 4). The physiologic model had overall model accuracy of 0.842 (cvAUC), with the important variables in order of contribution to AUC being higher IH80 dpe, followed by lower PB count, and increased bradycardia daily duration. The clinical model had accuracy of 0.862 with the important variables being use of mechanical ventilation, lower GA, SGA, higher F_{IO_2}, being male, lower 1 minute Apgar, and non-Hispanic ethnicity. The combined model had accuracy of 0.872, with major variables being SGA, lower GA, use of sedatives, higher IH80 dpe, non-Hispanic ethnicity, and IH90 count and IH90 dpe.

2. BPD at 36 weeks PMA (NICHD definition) (Table 9; Figure 4). The physiologic model had an accuracy of 0.875, with major variables being higher IH90 dpe and IH90 daily duration, and lower Apnea dpe. The clinical model had an accuracy was 0.883, with important contributors being use of IMV, higher F_{IO_2}, use of positive pressure (CPAP, non-invasive or invasive ventilation), prolonged supplemental oxygen (>12 h/24 h), SGA, lower 5 minute Apgar, and lack of caffeine use. The combined model had an accuracy of 0.894, with major contributors being higher F_{IO_2}, use of positive pressure, non-Black race, higher IH90 daily duration, SGA, lower Apnea dpe, use of IMV, use of supplemental oxygen, non-Hispanic ethnicity, and lower 5 minute Apgar.

3. Grade 3 BPD (Jensen and colleagues [16]. definition) (Table 10; Figure 4). The physiologic model had an accuracy of 0.871, with major contributors being higher IH80 dpe, and lower PB daily duration and Apnea daily duration. The clinical model had an accuracy of 0.887, with major contributors being use of IMV, sedation, SGA, lower 1 minute Apgar, lower GA, black race, and high F_{IO_2} (>0.3). The combined model had an accuracy of 0.900, with major contributors being use of sedatives, SGA, IH80 dpe, lower GA, less PB daily duration, less apnea daily duration, and lower 1 minute Apgar.

Table 6. Model at 28 Days of Age, Including Survivors to Day 28 (Limited to Importance 0.0005 or More)

Variable (Selected by LASSO)	AUC C-Statistic	Importance of Variable	OR (95% CI)	P Value
Clinical variables alone model	0.864			
IMV		0.0169	6.86 (3.64–12.92)	<0.00001
F_{IO_2}*		0.0085	1.82 (1.24–2.69)	0.002
Positive pressure		0.0053	2.51 (1.48–4.27)	0.001
SGA		0.0039	3.55 (1.53–8.21)	0.003
Apgar 1-min score		0.0026	0.76 (0.62–0.93)	0.007
Supplemental oxygen >12 h/24 h		0.0026	1.97 (1.15–3.39)	0.014
Birth weight		0.0020	0.73 (0.53–1.00)	0.050
Diuretics		0.0008	2.37 (0.80–7.0)	0.118
Male		0.0008	1.34 (0.89–2.01)	0.156
Physiologic variables alone model	0.855			
IH90 dpe		0.0246	2.92 (2.04–4.18)	<0.00001
IH90 count		0.0042	1.48 (1.21–1.81)	0.0002
PB duration		0.0010	0.69 (0.44–1.08)	0.103
Apnea dpe		0.0009	0.83 (0.64–1.06)	0.142
Combined model (physiologic model + clinical model)	0.872			
F_{IO_2}*		0.0092	1.89 (1.28–2.79)	0.0014
IH90 count		0.0067	1.49 (1.20–1.84)	0.0003
SGA		0.0054	4.11 (1.69–9.97)	0.002
Positive pressure		0.0041	3.00 (1.59–5.65)	0.0007
IMV		0.0024	3.70 (1.56–8.74)	0.003
Apnea dpe		0.0019	0.77 (0.58–1.02)	0.068
Hydrocortisone		0.0019	2.91 (0.92–9.19)	0.069
Multiple gestation		0.0011	0.75 (0.45–1.26)	0.277
IH90 dpe		0.0008	1.62 (1.11–2.38)	0.013

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; dpe = duration per event; IH90 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <90%; IMV = invasive mechanical ventilation; LASSO = least absolute shrinkage and selection operator; OR = odds ratio; PB = periodic breathing; SGA = small for gestational age.
*When F_{IO_2} is listed as a variable, it is the continuous variable of F_{IO_2} value closest to noon. If F_{IO_2} >0.3 is listed, it is the binary variable F_{IO_2} >0.3.

Snapshot (24 h) versus longitudinal models for outcome. Compared with the snapshot (24 h) model at Day 28, the aggregate model (summary data up to 28 d) and mixed effects model (longitudinal model using all daily data to 28 d) for unfavorable, highly unfavorable, moderate/severe BPD (NICHD [15]), and grade 3 BPD (Jensen and colleagues [16]) had an accuracy about 0.01 AUC higher (Table E4).

Validation of models. In addition to 10-fold cross-validation, leave-one-site-out analysis was done for internal validation. Although there was some variation in performance across sites as expected, out-of-sample AUCs remained high for all models (Table E5). Understanding the subtlety of site differences remains a topic for further research.

Discussion

The major findings of our study were that mathematical models based on cardiorespiratory bedside monitoring can

identify alterations in physiologic measures that are independently associated with unfavorable respiratory outcomes in extremely preterm infants. We defined the association of specific parameters of abnormal physiologic data (apnea, PB, IH, and bradycardia) with respiratory outcome at 40 weeks PMA. Both physiologic and clinical variables contributed to good prediction models, with the contribution by physiologic variables increasing with postnatal age. The major physiologic variable associated with unfavorable respiratory outcome was IH90, with the best predictor being the IH90dpe.

Although apnea and bradycardia are traditional measures of abnormal control of breathing, our study suggests that IH90 and IH80 may be valuable biomarkers for poor respiratory outcomes. Our observation of IH90 and IH80 as predictors is consistent with recent publications on the association between IH80 daily duration and prolonged IH80 events with BPD (21, 22) and prolonged IH80 with pulmonary hypertension and death in infants with

BPD (23). Because IH90 events were much more frequent than IH80 in our study, and because they were closer to the usual oxygen saturation targets (91–95%) (24–26), this suggests that inclusion of periods of "milder" hypoxemia creates a more sensitive biomarker of worse outcome than IH80. An explanation for how IH may be mechanistically associated with worse outcome requires further study. It is possible that it is not just brief hypoxemia but the associated reoxygenation and oxidative stress that contribute to morbidity (8). It is not clear if avoidance of or shortening the duration of IH events, such as with automated control of inspired oxygen concentration ("closed-loop automated oxygen control") (27, 28), would reduce unfavorable outcomes or whether IH90 is simply a marker of illness severity. It is possible that the risk factors identified in the prediction models lie on causal pathways, but our intent was not causal analysis. For example, IH90 and IH80 were associated with worse outcome, and it needs to be determined if IH is in the causal pathway. If IH

Table 7. Model at 32 Weeks Postmenstrual Age, Including Survivors to 32 Weeks Postmenstrual Age (Limited to Importance 0.0005 or More)

Variable (Selected by LASSO)	AUC C-Statistic	Importance of Variable	OR (95% CI)	P Value
Clinical variables alone model	0.871			
SGA		0.0142	6.76 (2.92–15.64)	0.00001
IMV		0.0136	6.86 (3.43–13.71)	0.00000
Gestational age		0.0105	0.56 (0.43–0.72)	0.00001
Positive pressure		0.0079	2.51 (1.57–4.01)	0.0001
F_{IO_2}*		0.0050	2.17 (1.36–3.46)	0.001
Apgar 1-min score		0.0034	0.77 (0.62–0.95)	0.015
Diuretic		0.0033	2.96 (1.42–6.15)	0.004
Supplemental oxygen >12 h/24 h		0.0022	2.09 (1.27–3.44)	0.004
Black race		0.0011	0.66 (0.41–1.08)	0.098
Physiologic variables alone model	0.845			
IH90 dpe		0.0146	2.57 (1.74–3.81)	<0.00001
PB count		0.0084	0.53 (0.33–0.87)	0.012
IH90 count		0.0067	1.54 (1.23–1.93)	0.0002
Apnea dpe		0.0028	0.80 (0.62–1.02)	0.07
Combined model (physiologic model + clinical model)	0.879			
SGA		0.0101	5.33 (2.13–13.32)	0.0003
Gestational age		0.0052	0.58 (0.43–0.79)	0.0005
PB count		0.0037	0.63 (0.39–1.01)	0.054
Positive pressure		0.0025	1.94 (1.12–3.33)	0.017
IH90 count		0.0020	1.33 (1.03–1.70)	0.027
IMV		0.0018	2.63 (0.99–6.99)	0.053
Diuretic		0.0018	2.75 (1.24–6.08)	0.013
IH90 dpe		0.0016	1.62 (1.14–2.29)	0.007
Apgar 1-min score		0.0014	0.81 (0.64–1.03)	0.080
F_{IO_2} >0.3*		0.0014	2.32 (1.25–4.31)	0.008
Apnea dpe		0.0012	0.82 (0.63–1.07)	0.144
Black race		0.0011	0.65 (0.41–1.05)	0.075

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; dpe = duration per event; IH90 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <90%; IMV = invasive mechanical ventilation; LASSO = least absolute shrinkage and selection operator; OR = odds ratio; PB = periodic breathing; SGA = small for gestational age.
*When F_{IO_2} is listed as a variable, it is the continuous variable of F_{IO_2} value closest to noon. If F_{IO_2} >0.3 is listed, it is the binary variable F_{IO_2} >0.3.

contributes to lung damage, reducing IH would increase favorable outcome, but if reoxygenation or clinical therapy of IH causes unfavorable outcome, perhaps increasing ventilator settings/F_{IO_2} to reduce IH would increase lung injury and make outcomes worse.

We also found that baseline clinical variables such as GA and SGA were strongly

Figure 3. Graph of predictive accuracy of models using clinical, physiologic, and combined (clinical and physiological) variables at different postnatal time points (Postnatal Days 7, 14, and 28 and 32 wk PMA). PMA = postmenstrual age.

associated with unfavorable outcome. Respiratory outcomes such as BPD are strongly dependent on the magnitude of immaturity (29, 30). Models using BW and GA in combination with respiratory support variables such as F_{IO_2} have good predictive accuracy (30). Our models confirm that GA or BW is an important variable soon after birth, whereas the magnitude of respiratory support becomes increasingly important with advancing postnatal age (31). SGA preterm infants are known to be at higher risk of BPD (32–34), probably because of impairment of lung development at critical developmental stages.

Models combining physiologic and clinical data did not substantially improve overall predictive performance compared with models with only clinical variables or models with only physiologic variables at later time points, even though the contributing variables were different. It is possible that predictive accuracies higher
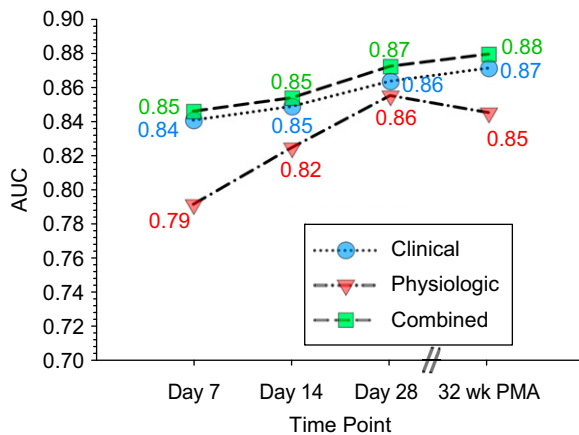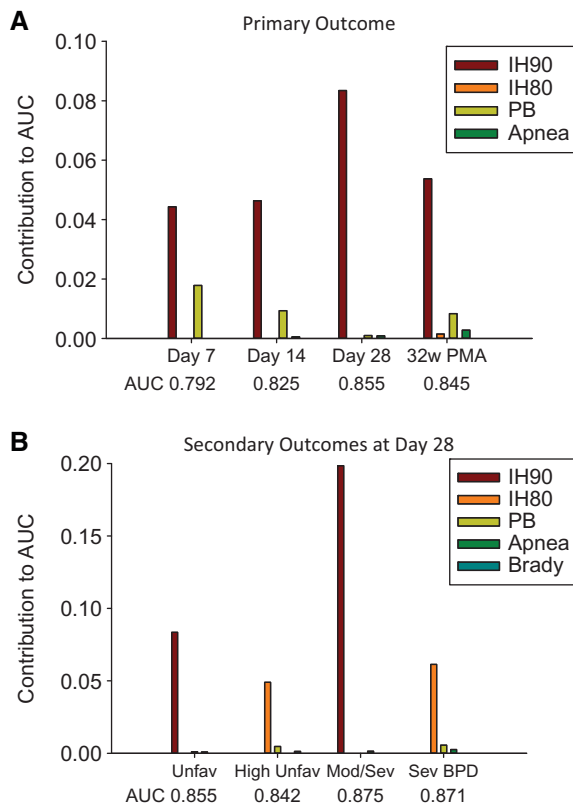
Figure 4. Graph showing contributions of different physiologic variables (each variable incorporating different features: duration per event, daily duration, and count) to outcome. (*A*) Unfavorable versus favorable outcome at different time points. (*B*) Primary and secondary outcomes at Postnatal Day 28. AUC = area under the curve; BPD = bronchopulmonary dysplasia; IH80 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <80%; IH90 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <90%; PB = periodic breathing; PMA = postmenstrual age.

Major strengths of this study are the analysis of a large multicenter prospective cohort with high-resolution cardiorespiratory data. Events such as apnea, PB, IH, and bradycardia were measured using sophisticated algorithms. However, some limitations need to be acknowledged. One limitation is that the outcomes are short term by 40 weeks PMA/discharge, and longer-term respiratory outcomes are pending follow-up evaluation. Short-term outcomes also introduce time-related bias because prediction at later time points is closer to the outcome. Also, apnea or PB could not be detected during IMV because of the intervention of mechanical breaths. Thus, apnea and PB could not be adequately characterized in infants with the anticipated highest likelihood of worse outcomes.

It is essential to consider the relevance of our results for the field of neonatology. Despite advances in neonatal care and reductions in neonatal mortality and many neonatal morbidities, the rate of BPD in extremely preterm infants has increased in recent years (36), indicating that additional research on the causes of respiratory morbidity is essential. Our data demonstrate that although clinical variables such as BW, GA, and magnitude of respiratory support are strong predictors of respiratory outcome, physiologic data that reflect abnormalities of control of breathing are also associated with poor outcome. Although there is only incremental improvement in prediction accuracy in combining physiologic and clinical variables, physiologic data alone are independent predictors of unfavorable respiratory outcome. Indeed, many clinical parameters such as respiratory support may be responses to physiologic instability. It is probable that better and clinically accessible quantitative measurements of IH90 and IH80 would advance clinical care. It is possible that IH90 is a more sensitive marker of worse outcome than apnea or bradycardia, which are less frequent and associated with more severe or prolonged IH. IH may also be secondary to agitation and other behavioral changes in addition to abnormal control of breathing and hence may have additional predictive value. Early prediction of outcomes by IH estimation, perhaps in combination with clinical models (30) and other measures such as lung ultrasound (37, 38), may enable selective use of potential therapies, reducing adverse effects of such therapies in infants at lower risk and targeting therapies to those at higher risk

than 0.90 may not be achievable, because accuracies above 0.85 are already excellent, and some infants develop severe illness later (e.g., necrotizing enterocolitis, sepsis) with respiratory deterioration. Future studies may address discordance in prediction to identify unidentified or unmeasured risk factors. Some changes in clinical data (e.g., respiratory support) may be in response to changes in physiologic measures (e.g., increases in F_{IO_2} secondary to frequent IH or provision of CPAP in response to frequent apnea), and some changes in physiologic data may be secondary to clinical therapies (e.g., CPAP or caffeine). Hence, it is necessary to consider the interdependence of the physiologic and clinical data variables in their contribution to outcomes.

It is important to compare and contrast the physiologic variables associated with the secondary outcomes versus the primary outcome. IH80 dpe was a major physiologic predictor of the "highly unfavorable" outcome and grade 3 BPD (16) outcome, whereas IH90 dpe and IH90 daily duration were predictors of the moderate/severe BPD (15) outcome. The deeper desaturations (IH80) are associated with increased severity of unfavorable outcome or BPD, whereas desaturations closer to target range (IH90) are associated with less unfavorable outcomes. SGA and use of sedatives were also stronger contributors to the highly unfavorable and severe BPD outcomes, whereas variables such as F_{IO_2} and use of positive pressure were associated with moderate-severe BPD. The use of sedatives is common in the neonatal ICU, especially in younger gestation and SGA infants who remain intubated at older postnatal ages (35) and hence may be a marker for severe lung disease, with the need for sedation reflecting infant agitation in the setting of prolonged mechanical ventilation.

Table 8. Secondary Outcomes: Highly Unfavorable Outcome at 40 Weeks Postmenstrual Age (Limited to Importance 0.0005 or More)

Variable (selected by LASSO)	AUC C-Statistic	Importance of Variable	OR (95% CI)	P Value
Clinical variables alone model	0.862			
IMV		0.0156	3.92 (1.65–9.32)	0.002
Gestational age		0.0135	0.52 (0.33–0.80)	0.003
SGA		0.0133	4.77 (2.11–10.76)	0.0002
F_{IO_2}*		0.0024	1.28 (0.95–1.72)	0.101
Male		0.0018	1.80 (0.96–3.39)	0.068
Apgar 1-min score		0.0016	0.79 (0.55–1.12)	0.183
Hispanic ethnicity		0.0005	0.49 (0.20–1.20)	0.120
Physiologic variables alone model	0.842			
IH80 dpe		0.0490	1.86 (1.27–2.71)	0.001
PB count		0.0047	0.13 (0.01–2.37)	0.170
Bradycardia daily duration		0.0013	1.32 (1.02–1.71)	0.038
Combined model (physiologic model + clinical model)	0.872			
SGA		0.0134	4.73 (1.98–11.31)	0.0005
Gestational age		0.0112	0.50 (0.33–0.76)	0.001
Sedatives		0.0065	3.10 (1.26–7.65)	0.014
IH80 dpe		0.0056	1.69 (1.03–2.78)	0.038
Hispanic ethnicity		0.0025	0.45 (0.19–1.09)	0.078
IH90 count		0.0013	1.24 (0.90–1.71)	0.192
IH90 dpe		0.0013	1.50 (0.93–2.41)	0.097

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; dpe = duration per event; IH80 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <80%; IH90 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <90%; IMV = invasive mechanical ventilation; LASSO = least absolute shrinkage and selection operator; OR = odds ratio; PB = periodic breathing; SGA = small for gestational age.
*When F_{IO_2} is listed as a variable, it is the continuous variable of F_{IO_2} value closest to noon. If F_{IO_2} >0.3 is listed, it is the binary variable F_{IO_2} >0.3.

Table 9. Secondary Outcomes: Moderate-Severe Bronchopulmonary Dysplasia (Eunice Kennedy Shriver National Institute of Child Health and Human Development) Outcome at 36 Weeks Postmenstrual Age (Limited to Importance 0.0005 or More)

Variable (Selected by LASSO)	AUC C-Statistic	Importance of Variable	OR (95% CI)	P Value
Clinical variables alone model	0.883			
IMV		0.0182	9.47 (4.87–18.43)	<0.00001
F_{IO_2}*		0.0104	1.87 (1.23–2.84)	0.0035
Positive pressure		0.0094	4.10 (2.37–7.08)	<0.00001
Supplemental oxygen >12 h/24 h		0.0072	3.94 (2.26–6.86)	<0.00001
SGA		0.0051	4.22 (2.06–8.67)	<0.0001
Apgar 5-min score		0.0014	0.77 (0.62–0.96)	0.0213
Caffeine		0.0007	0.66 (0.26–1.71)	0.397
Physiologic variables alone model	0.875			
IH90 dpe		0.0122	2.78 (1.83–4.20)	<0.00001
IH90 daily duration		0.0084	1.95 (1.46–2.61)	0.00001
Apnea dpe		0.0014	0.82 (0.64–1.06)	0.128
Combined model (physiologic model + clinical model)	0.894			
F_{IO_2}*		0.0102	1.84 (1.22–2.79)	0.0038
Positive pressure		0.0059	3.53 (1.82–6.84)	0.0002
Black race		0.0059	0.50 (0.29–0.86)	0.012
IH90 daily duration		0.0057	1.62 (1.20–2.19)	0.002
SGA		0.0035	4.12 (1.80–9.43)	0.001
Apnea dpe		0.0032	0.73 (0.54–1.0)	0.047
IMV		0.0026	3.85 (1.62–9.15)	0.002
Supplemental oxygen		0.0023	2.78 (1.19–6.51)	0.019
Hispanic ethnicity		0.0021	0.58 (0.27–1.25)	0.165
Apgar 5 min		0.0020	0.71 (0.55–0.92)	0.009

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; dpe = duration per event; IH90 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <90%; IMV = invasive mechanical ventilation; LASSO = least absolute shrinkage and selection operator; OR = odds ratio; PB = periodic breathing; SGA = small for gestational age.
*When F_{IO_2} is listed as a variable, it is the continuous variable of F_{IO_2} value closest to noon. If F_{IO_2} >0.3 is listed, it is the binary variable F_{IO_2} >0.3.

Table 10. Secondary Outcomes: Grade 3 Bronchopulmonary Dysplasia (Invasive Mechanical Ventilation; Jensen and Colleagues) Outcome at 36 Weeks Postmenstrual Age (Limited to Importance 0.0005 or More)

Variable (Selected by LASSO)	AUC C-Statistic	Importance of Variable	OR (95% CI)	P Value
Clinical variables alone model	0.887			
IMV		0.0207	6.96 (3.11–15.56)	<0.00001
Sedatives		0.0125	4.44 (1.97–10)	0.0003
SGA		0.0067	3.75 (1.70–8.25)	0.001
Apgar 1-min score		0.0063	0.72 (0.53–1.0)	0.0465
Gestational age		0.0027	0.68 (0.47–1.0)	0.050
Black race		0.0020	1.79 (1.03–3.13)	0.0396
F_{IO_2} high		0.0006	2.25 (1.15–4.43)	0.0185
Physiologic variables alone model	0.871			
IH80 dpe		0.0614	1.70 (1.18–2.45)	0.0047
PB daily duration		0.0056	0.02 (0.01–0.50)	0.0183
Apnea daily duration		0.0025	0.60 (0.31–1.18)	0.138
Combined model (physiologic model + clinical model)	0.900			
Sedatives		0.0164	4.78 (1.65–13.86)	0.004
SGA		0.0092	4.01 (1.66–9.71)	0.002
IH80 dpe		0.0087	1.60 (1.02–2.53)	0.042
Gestational age		0.0087	0.57 (0.38–0.87)	0.009
PB daily duration		0.0042	0.05 (0.01–0.72)	0.027
Apnea daily duration		0.0025	0.50 (0.23–1.08)	0.079
Apgar 1-min score		0.0009	0.83 (0.51–1.34)	0.442
Steroids		0.0008	0.51 (0.22–1.18)	0.118
Apgar 5-min score		0.0008	0.82 (0.54–1.25)	0.361
Hispanic ethnicity		0.0006	0.70 (0.32–1.53)	0.369
IMV		0.0005	2.80 (1.04–7.51)	0.041

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; dpe = duration per event; IH80 = intermittent hypoxemia events with oxygen saturation as measured by pulse oximetry <80%; IMV = invasive mechanical ventilation; LASSO = least absolute shrinkage and selection operator; OR = odds ratio; PB = periodic breathing; SGA = small for gestational age.

(39). Future clinical studies may identify mechanisms regulating IH (e.g., by alterations in peripheral chemosensitivity [40]), determine optimal interventions to reduce IH (e.g., by servo-controlled oxygen supplementation, increasing caffeine dose or duration, prolonged CPAP), and then test in randomized trials if such interventions improve outcomes in preterm infants. ∎

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