

# Highly comparative time series analysis of oxygen saturation and heart rate to predict respiratory outcomes in extremely preterm infants

Jiaxing Qiu<sup>1</sup>, Juliann M. Di Fiore<sup>2</sup>, Narayanan Krishnamurthi<sup>3</sup>, Premananda Indic<sup>8</sup>, John L. Carroll<sup>11</sup>, Nelson Claire<sup>4</sup>, James S. Kemp<sup>10</sup>, Phyllis A. Dennery<sup>7</sup>, Namasivayam Ambalavanan<sup>5</sup>, Debra E. Weese-Mayer<sup>3</sup>, Anna Maria Hibbs<sup>2</sup>, Richard J. Martin<sup>2</sup>, Eduardo Bancalari<sup>4</sup>, Aaron Hamvas<sup>9</sup>, J. Randall Moorman<sup>1</sup>, Douglas E. Lake<sup>1</sup>

<sup>1</sup>Department of Medicine, Division of Cardiology, University of Virginia School of Medicine, Charlottesville, VA

<sup>2</sup> Department of Pediatrics, Case Western Reserve University School of Medicine, University Hospitals Rainbow Babies and Children's Hospital, Cleveland, OH

<sup>3</sup> Department of Pediatrics, Division of Autonomic Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

<sup>4</sup> Department of Pediatrics, Division of Neonatology, University of Miami Miller School of Medicine, Miami, FL

<sup>5</sup> Department of Pediatrics, Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

<sup>6</sup> Department of Pediatrics, Division of Newborn Medicine, Washington University School of Medicine, St. Louis, MO

<sup>7</sup> Department of Pediatrics, Brown University School of Medicine, Department of Pediatrics, Providence, RI

<sup>8</sup> Department of Electrical Engineering, University of Texas at Tyler, Tyler, TX.

<sup>9</sup> Ann and Robert H. Lurie Children's Hospital and Northwestern University Department of Pediatrics, Chicago, IL

<sup>10</sup> Department of Pediatrics, Division of Pediatric Pulmonology, Washington University School of Medicine, St. Louis, MO

<sup>11</sup> Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AK

E-mail: [de12k@uvahealth.org](mailto:de12k@uvahealth.org)

October 2023

# Highly comparative time series analysis of oxygen saturation and heart rate to predict respiratory outcomes in extremely preterm infants

## Abstract.

*Objective:* Highly comparative time series analysis (HCTSA) is a novel approach involving massive feature extraction using publicly available code from many disciplines. The Prematurity-Related Ventilatory Control (Pre-Vent) observational multicenter prospective study collected bedside monitor data from > 700 extremely preterm infants to identify physiologic features that predict respiratory outcomes. We calculated a subset of 33 HCTSA features on > 7M 10-minute windows of oxygen saturation (SPO<sub>2</sub>) and heart rate (HR) from the Pre-Vent cohort to quantify predictive performance. This subset included representatives previously identified using unsupervised clustering on > 3500 HCTSA algorithms. Performance of each feature was measured by individual area under the receiver operating curve (AUC) at various days of life and binary respiratory outcomes. These were compared to optimal PreVent physiologic predictor IH90\_DPE, the duration per event of intermittent hypoxemia events with threshold of 90%.

*Main Results:* The top HCTSA features were from a cluster of algorithms associated with the autocorrelation of SPO<sub>2</sub> time series and identified low frequency patterns of desaturation as high risk. These features had comparable performance to and were highly correlated with IH90\_DPE but perhaps measure the physiologic status of an infant in a more robust way that warrants further investigation. The top HR HCTSA features were symbolic transformation measures that had previously been identified as strong predictors of neonatal mortality. HR metrics were only important predictors at early days of life which was likely due to the larger proportion of infants whose outcome was death by any cause. A simple HCTSA model using 3 top features outperformed IH90\_DPE at day of life 7 (.778 versus .729) but was essentially equivalent at day of life 28 (.849 versus .850). These results validated the utility of a representative HCTSA approach but also provides additional evidence supporting IH90\_DPE as an optimal predictor of respiratory outcomes.

**Keywords:** highly comparative time series analysis, preterm infants, intermittent hypoxemia, predictive models

## 1. Introduction

### 1.1. Highly comparative time series analysis (HCTSA)

Analysis of heart rate (HR) and oxygen saturation (SPO2 or more precisely  $SpO_2$ ) vital sign time series during the stay of infants in the neonatal intensive care unit (NICU) has been shown to be useful in predicting unfavorable outcomes. This is part of larger efforts to improve care of infants using big data analytics (Vesoulis et al. 2023, Cole 2021). Notably, models for predicting sepsis have not only been developed (Griffin et al. 2003, Fairchild et al. 2017, Kausch et al. 2023) but implemented in the NICU and shown to improve outcomes in a large clinical trial (Moorman et al. 2011, Fairchild et al. 2013). Models have also been developed for other adverse outcomes during NICU stay including death (Sullivan et al. 2016, 2018, Niestroy et al. 2022), bronchopulmonary dysplasia (BPD) (Raffay et al. 2019, Gentle et al. 2023, Ramanand et al. 2023), and retinopathy of prematurity (Di Fiore et al. 2010, 2012). Vital sign data during an infant's stay has also been shown to predict long-term outcomes of cognitive impairment (Poets et al. 2015), cerebral palsy (Letzkus et al. 2022), and autism (Blackard et al. 2021).

Highly comparative time-series analysis (HCTSA) developed by Fulcher et al. (2013) is a novel method that naturally applies to HR and SPO2 data. The core concept involves using numerous time-series algorithms with a wide-ranging set of parameter values to extract a massive number of features to associate with some target outcome. They examined over 35,000 real-world and model-generated time series with more than 7,000 time-series analysis algorithms developed from a wide variety of disciplines. The MATLAB code to implement these HCTSA algorithms is publicly available at <https://github.com/benfulcher/hctsa>. The goal of using HCTSA is not necessarily to develop an optimal predictive model restricted to these algorithms. Here we use HCTSA as a tool to identify new types of algorithms for future more traditional development with sufficient understanding to be useful for clinicians.

Recently, Niestroy et al. (2022) applied  $> 3500$  HCTSA algorithms to  $> 17M$  10-minute windows of heart rate (HR) and oxygen saturation (SPO2) vital sign data collected from bedside monitors (displayed every two seconds) from 6000 infants at the University of Virginia NICU from 2009 to 2019. The data (including all HR and SPO2 time series) is publicly available at Niestroy et al. (2021). In an effort to reduce the high dimensionality of the data, a random subset of  $> 120K$  daily results was then used for unsupervised k-medoids clustering based on distance metric of mutual information. With  $k = 20$  clusters, 81% of the variance of full data was explained and identified 20 central algorithms or medoids. A medoid is defined to be a point in the cluster from which the sum of distances to other data points in the cluster is minimal.

Utilizing these clusters, they found that HCTSA algorithms can discover novel patterns associated with neonatal mortality in the next 7 days. Notably, models based solely on the cluster centers performed comparably to those considering the full feature set. This led to a hypothesis that identifying algorithms by unsupervised clustering could capture most of the predictive information in NICU vital sign data and that

motivates this work.

Based on this hypothesis, a subset of HCTSA algorithms (including at least one from each of the 20 clusters) was implemented using the publicly available code as part of the Batch Algorithm Processor (BAP) software package developed for comprehensive analysis of bedside waveform and vital sign time series data. In addition, the maximum and minimum cross-correlation of HR and SPO2 at lags up to 30 seconds were calculated which have been shown to be associated with sepsis, apnea and periodic breathing (Fairchild & Lake 2018) giving a total of 33 vital sign features calculated. The BAP software including extensive documentation is available at <https://github.com/UVA-CAMA/BatchAlgorithmProcessor>.

### *1.2. PreVent Study*

The Prematurity-Related Ventilatory Control (Pre-Vent) study was of a cohort of > 700 extremely premature infants (gestational age less than 29 weeks) across 5 NICU sites with the hypothesis that physiologic features of ventilatory control extracted from bedside monitoring data can predict unfavorable respiratory outcomes at 40 weeks post-menstrual age (PMA) (Dennery et al. 2019). The BAP was developed for Pre-Vent and used to extract a large number of physiologic (including HCTSA) features. The software was run at each of the sites remotely in a separate but uniform way while keeping raw data stored locally. A result of this processing was 33 features calculated on 7.8M 10-minute windows of HR and SPO2 data.

In the primary analysis of the Pre-Vent study, optimal logistic regression models were developed for predicting respiratory outcomes at varying days of life during the NICU stay and identified important risk factors for both physiologic and clinical models (Ambalavanan et al. 2023). Physiologic models included metrics calculated from bedside waveforms (ECG and chest impedance) and vital signs (HR and SPO2). Notably, the duration per event (DPE) of intermittent hypoxemia events with SPO2 < 90% (IH90) was most significant individual physiologic factor for predicting the primary unfavorable respiratory outcome. At day of life 28, performance of IH90\_DPE as an individual predictor performed similarly to optimal models with demographic, respiratory support and other clinical features. However, IH and physiologic models in general did not perform as well earlier in the NICU stay (day 7) where identification of higher-risk infants would have more impact.

### *1.3. Intermittent Hypoxemia*

Intermittent hypoxemia (IH) in the NICU has been widely studied (Ramirez et al. 2023, Dormishian, Schott, Aguilar, Jimenez, Bancalari, Tolosa & Claire 2023, Dormishian, Schott, Aguilar, Bancalari & Claire 2023). Definitions of IH events require fixed parameters including SPO2 threshold (e.g. 80% or 90%), min/max duration, and possibly joining rules for nearby events. These definitions can be somewhat arbitrary and susceptible to varying hospital protocols (e.g., target SPO2 ranges) or clinical practice.

IH events can also be sensitive to the averaging time of the pulse oximeter which can vary across vendor and NICU. Published physiological models relying on threshold-based events may not prove to be robust in universal and evolving applications. Using advanced time-series metrics to predict neonatal respiratory outcomes without relying on clinical definitions have not yet been fully studied.

## 2. Methods

### 2.1. Study Population

The study population consisted of the 717 extremely premature infants prospectively enrolled in Pre-Vent study and with respiratory outcome determined (Ambalavanan et al. 2023). Analysis was restricted to days where sufficient HR and SPO2 monitor data was available (at least 12 hours of each) which represented over 80 percent of the study period.

The Pre-Vent study predefined 5 mutually exclusive respiratory outcome categories which in order of decreased severity are:

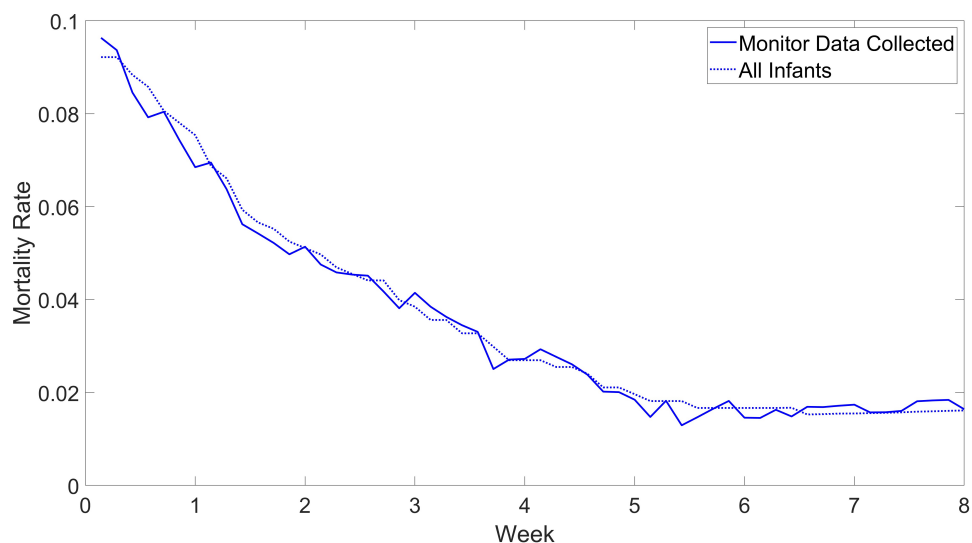
- (i) **Death:** prior to 40 weeks PMA
- (ii) **Severe:** invasive mechanical ventilation (IMV) at 40 weeks PMA
- (iii) **Moderate:** need for positive pressure at 40 weeks PMA
- (iv) **Mild:** respiratory medications, oxygen or other respiratory support either inpatient at 40 weeks PMA or at discharge prior to 40 weeks PMA
- (v) **Favorable:** none of the above

The primary outcome of the Pre-Vent study was an unfavorable outcome consisting of any of the first 4 outcomes (i.e., not favorable). Three additional binary outcomes analyzed here in order of increase severity are moderate or severe or death, severe or death and death. For each outcome, the entire cohort was used to compare having vs. not having outcome.

Predictive performance of the time series features were evaluated at day of life 7, 14, and 28 which follows the approach of the PreVent analysis (Ambalavanan et al. 2023). Table 1 shows a breakdown of the infants by binary outcomes at these time points. A particular focus was predicting an unfavorable outcome at day 7, which consisted of 584 infants and an event rate of  $265/584=45.4\%$ . An important aspect of the analysis to consider is the evolving distribution of the outcomes by day of life. Figure 1 shows how the mortality rate of surviving infants is significantly reduced by week of life. Since death outcomes include those of all causes and not necessarily related to respiratory failure, analyzing outcomes later in the NICU stay are therefore more directly associated with control of breathing. Also note in Figure 1 that there is minimal difference in mortality rate between those with monitor data and entire population suggesting there is no significant selection bias in the analysis.

**Table 1:** Sample size and distribution of binary respiratory outcome at day 7, 14, and 28 for infants with monitor data collected.

	Day 7 N=584	Day 14 N=584	Day 28 N=551
death	40 (6.8%)	30 (5.1%)	15 (2.7%)
severe\death	80 (13.7%)	71 (12.2%)	40 (10.0%)
severe\death\moderate	121 (20.7%)	110 (18.8%)	92 (16.7%)
unfavorable	265 (45.4%)	263 (45.0%)	228 (41.4%)
favorable	319 (54.6%)	321 (55.0%)	323 (58.6%)



**Figure 1:** Mortality rate by week of life. For each time point, the solid line shows the mortality rate in patients with monitoring data collected and the dotted line shows the mortality rate in all infants in study.

## 2.2. Time Series Features

The 33 new HR and SPO2 HCTSA features are described in Table 2 along with which of the 20 clusters they belonged to and a general description of the type of algorithms in the cluster. The number of the clusters are ordered in way so that nearby clusters tend to be more related. Table A1 provides more details on the exact parameters and the publicly available Matlab code used for each feature. For evaluation purposes, the features were summarized as the daily median of the every 10 minute results.

**Table 2:** Time-series features implemented in Batch Algorithm Processor (BAP).

Feature	Cluster	Cluster Name	Cluster Description
hr_mean			
hr_avgthresh	1	hr_mean	HR mean
hr_corrmean			
hr_std	2	hr_std	HR standard deviation
hr_cv			
hr_max	3	hr_max	HR maximum
hr_min	4	hr_min	HR minimum
hr_kurt	5	hr_skew	HR skewness
hr_skew			
hr_symautocorr	6	hr_autocorr	HR autocorrelation
hr_surprise	7	hr_entropy	HR entropies
hr_surprise			
hr_wavelet	8	hr_wavelet	HR wavelet decomposition
hr_probincreases	9	hr_symbolic	HR symbolic transforms
hr_entropy_diff			
sp_std	10	sp_std	SPO2 standard deviation
sp_mean			
sp_avgthres	11	sp_mean	SPO2 mean
sp_corrmean			
hr_derivative	12	hr_derivative	HR nth derivative
sp_min	13	sp_min	SPO2 minimum
sp_skew			
sp_kurt	14	sp_median	SPO2 median
sp_mean_trim			
sp_wavelet	15	sp_misc	SPO2 miscellaneous
sp_syemeigen	16	sp_symbolic	SPO2 symbolic transforms
sp_walk			
sp_autocorr	17	sp_autocorr	SPO2 autocorrelation
sp_symentropy	18	sp_entropy	SPO2 entropies
sp_symbin	19	sp_binary	SPO2 binary symbolic transforms
sp_symiqr	20	sp_more	SPO2 more symbolic transforms
xc_max			Maximum cross-correlation
xc_min			Minimum cross-correlation

The daily HCTSA results were merged with the physiological features measured on HR and SPO2 as part of PreVent study. Using the BAP, the following physiologic events were extracted from bedside sign monitor data:

- (i) IH80: Desaturation events with SPO2 < 80% for 10-300 seconds
- (ii) IH90: Desaturation events with SPO2 < 90% for 10-300 seconds
- (iii) Brady80: Bradycardia events with HR < 80 beats per minute for 5 or more seconds

These IH duration limits come from Di Fiore et al. (2012) but do vary slightly across publications. For each of these 3 events, daily features were quantified as count of events per day (count), total daily duration in events (dur) measured in minutes per day, and



average duration per event (dpe) measured in seconds per event. These 3 quantities are not independent and have relationship  $dpe=60 \times dur/count$ . These 9 clinically defined features gave a total of 42 candidate HR and SPO2 metrics for the analysis.

### *2.3. Feature Evaluation*

We evaluated the performance of each feature based on the area under the receiver operating curve (AUC) at various days of life for all 4 binary outcomes. The AUC for predicting the primary unfavorable outcome at day 7 was used to rank the features. Signature of risk curves showing estimates of the probability of the unfavorable outcome at day 7 as a function of the daily median value of each variable were made using logistic regression model including a cubic spline transformation with 3 knots to account for possible non-linearity. The top performers were then analyzed further by looking at a range of examples stratified by percentile to better understand what the algorithm was measuring and, in particular, its correlation with IH events. The trajectories of the performance of these new metrics was also analyzed for the first 8 weeks of life.

For logistic regression models, AUC was measured using cross-validation where each fold consisted of infants clustered by pregnancy so that an infant's sibling was not used to predict its outcome. Variable importance was quantified by the drop in cross-validated AUC when the variable was removed from the model.

### *2.4. Demographic and Clinical Risk Factors*

Detailed demographic information about the Pre-Vent cohort can be found in Ambalavanan et al. (2023). The sex of the infants in the study were equally represented (51% male) and the average birth weight and gestational age were 871 grams and 26.4 weeks respectively. There is also a comprehensive list of clinical risk factors for predicting respiratory outcomes at various time points. Based on this, the following were identified as the major risk factors for unfavorable respiratory outcomes and included in the presented results for comparison purposes.

- (i) BW: birthweight in grams
- (ii) GA: gestational age in weeks
- (iii) IMV: daily need for invasive mechanical ventilation
- (iv) FIO2 (or  $FiO_2$ ): value closest to noon (0.21 if on room air)

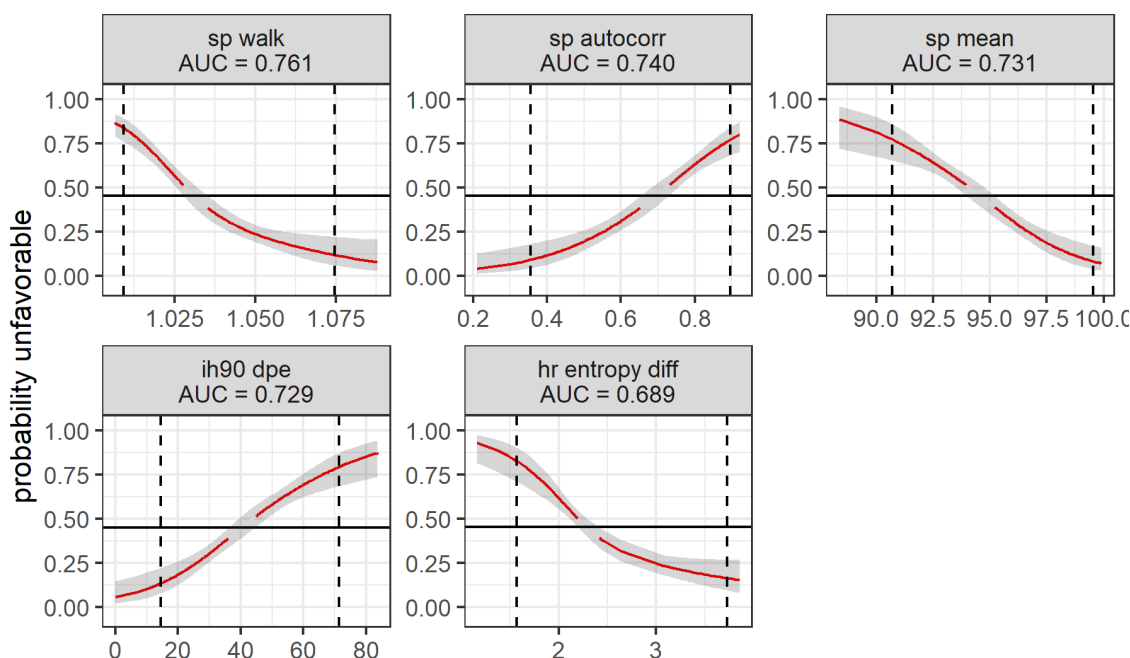
We acknowledge the importance of demographic and clinical risk factors for predicting respiratory outcomes, but the focus of this paper is on prediction using only vital signs HR and SPO2. We can justify this as still being relevant clinically for a couple of reasons. First, vital sign features are dynamic and indicate the evolving status of the infant during the NICU stay whereas demographic features are static and fixed at birth. Second, clinical features like those associated with respiratory support are often in response to changes in the vital signs of the infant and potentially not a direct informative predictor of respiratory outcomes.



It is also worth noting that we are not considering the physiologic measures of apnea and periodic breathing (calculated by BAP using chest impedance waveform) in this analysis. These features are only meaningful for infants not on mechanical ventilation and have some of the same issues with respiratory support features mentioned above. They were also not shown to be major predictors of respiratory outcomes in primary Pre-Vent analysis (Ambalavanan et al. 2023).

### 3. Results

Figure 2 shows signature of risk curves for 5 of the top predictors of an unfavorable outcome at day 7. These are discussed in more detail below.



**Figure 2:** Individual signature of risk for unfavorable outcome for top predictors at Day 7. The gray area indicates the 95% confidence intervals. The black line represents the outcome rate of .454 and the red line indicates where the confidence intervals do not include this null value. The dotted lines represent the limits of the central 95% of the daily distribution values.

Table 3 summarizes the top individual performers in order of highest AUC for predicting primary unfavorable outcome at day 7. Results and ranks (out of 42) for days 14 and 28 are also included. Comprehensive results for all features and each of the outcomes for days 7, 14 and 28 is provided in Tables A2,A3, and A4. Performance of the major clinical risk factors are also provided in Table A5 for comparison.

**Table 3:** Top performers for predicting primary unfavorable respiratory outcome and respective ranks (out of 42) at day 7, 14 and 28.

Feature	Cluster	day 7	Rank	day 14	Rank	day 28	Rank
sp_walk	17	0.761	1	0.797	1	0.851	1
sp_autocorr	17	0.740	2	0.782	3	0.841	3
sp_avgthres	11	0.735	3	0.741	7	0.784	8
sp_mean	11	0.731	4	0.732	8	0.772	10
sp_corrmean	11	0.731	5	0.731	9	0.769	11
ih90_dur		0.730	6	0.742	6	0.797	6
ih90_dpe		0.729	7	0.792	2	0.850	2
sp_mean_trim	14	0.725	8	0.720	11	0.765	12
sp_symeigen	16	0.718	9	0.749	5	0.814	5
sp_min	13	0.703	10	0.666	21	0.655	24
sp_kurt	14	0.698	11	0.750	4	0.817	4
ih90_count		0.696	12	0.663	22	0.691	16
hr_entropy_diff	9	0.689	13	0.704	13	0.688	17
hr_entropy	7	0.675	14	0.647	25	0.635	27
hr_probincreases	9	0.672	15	0.686	14	0.679	19
ih80_dpe		0.672	16	0.724	10	0.795	7
ih80_dur		0.671	17	0.706	12	0.756	13
sp_std	10	0.665	18	0.653	24	0.675	21
ih80_count		0.652	19	0.675	17	0.714	14
hr_wavelet	8	0.626	20	0.653	23	0.645	26

### 3.1. Top SPO2 HCTSA Features

The top HCTSA feature for predicting respiratory outcomes was sp\_walk which is a time series metric inspired by physics. This may not be naturally intuitive for clinicians (and others) and perhaps not that useful despite its optimal performance. The feature is based on comparing the signal's standard deviation to that of a simulated hypothetical particle (or 'walker') that moves in response to values of the time series at each point. As described in the Matlab code, the walker moves as if it had inertia (based on its mass which is an input parameter) from the previous time step so that it 'wants' to move the same amount and the original time series acts as a force changing its motion. SPO2 time series that behave very much like this simulated walk have lower ratios close to 1 which indicate higher risk of unfavorable outcomes.

This algorithm is part of a cluster of algorithms associated with the autocorrelation of the SPO2 time series and includes the central algorithm and second best performer sp\_autocorr. Autocorrelation is a standard time domain tool to evaluate, among other things, the frequency content of the signal and as such likely a more intuitive approach than that of sp\_walk. The specific parameters for sp\_autocorr was the correlation of SPO2 with a delayed copy of itself at a lag of 4 samples or 8 seconds. High values of

sp\_autocorr are associated with unfavorable outcomes and occur in signals that have some variability over a 10-minute window but do not have high frequency variations locally (over an 8 second window). Looking more closely at other lags and metrics associated with the autocorrelation of the SPO2 is a potentially promising area for future work. Both sp\_walk and sp\_autocorr were highly correlated with IH90 DPE ( $-.77$  and  $.76$  respectively) and are fundamentally measuring the same physiological status of the infant but perhaps in a more robust way.

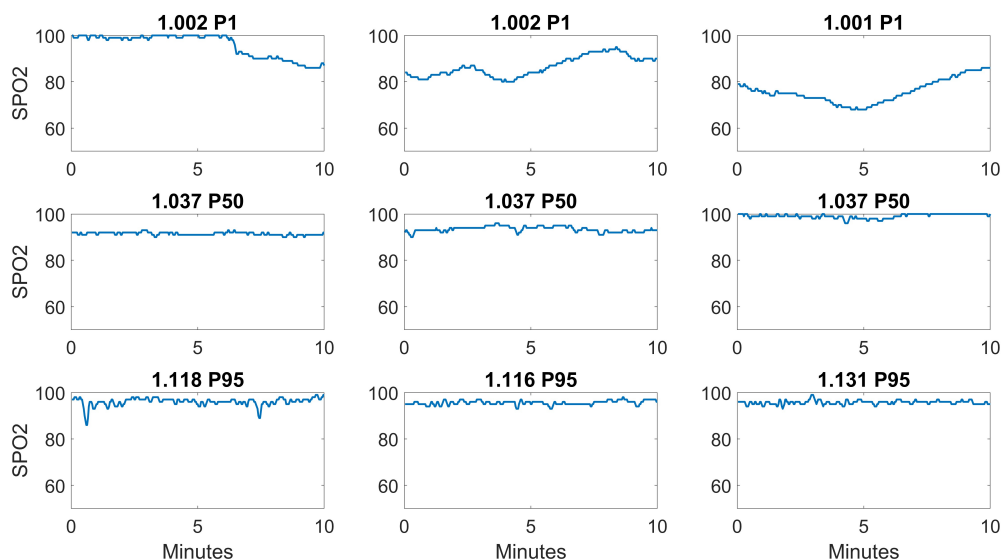
Figure 3 shows examples of 10-minute SPO2 time series from extremely premature infants on day of life 7 from publicly available dataset (Niestroy et al. 2021). Figure 3A and 3B shows the values and percentiles for sp\_walk and sp\_autocorr respectively. The top row of each figure shows higher risk examples which is low values for sp\_walk and high values for sp\_autocorr. These records are generally associated with persistent low-frequency patterns with desaturations that include long duration IH90 and IH80 events. The middle and bottom rows of these examples show median and percentiles associated with low risk. These exhibit some interesting patterns but not in a way that has consistent clinical interpretation like with high risk examples. Future work beyond the scope of this paper is needed to understand if the presence of subtle high-frequency variability in SPO2 is clinically meaningful.

Other top SPO2 features include sp\_mean and other measures from this cluster. None of these other features outperforms sp\_mean by an amount that would likely justify deviating from using a simple measure that is clinically easy to understand. Another SPO2 metric that performed well at days 14 and 28 was kurtosis. The mean and kurtosis are part of a larger group of SPO2 features that characterize a daily pulse oxygen histogram or profile. These histograms are used as a clinical tool in the NICU to evaluate target range management (Gentle et al. 2020, Goetz et al. 2022, Borenstein-Levin et al. 2020). Developing predictive models based directly on these daily SPO2 histograms is a promising area for future work. From an HCTSA perspective, this would correspond to restricting analysis to metrics that don't depend on the order of the time series values.

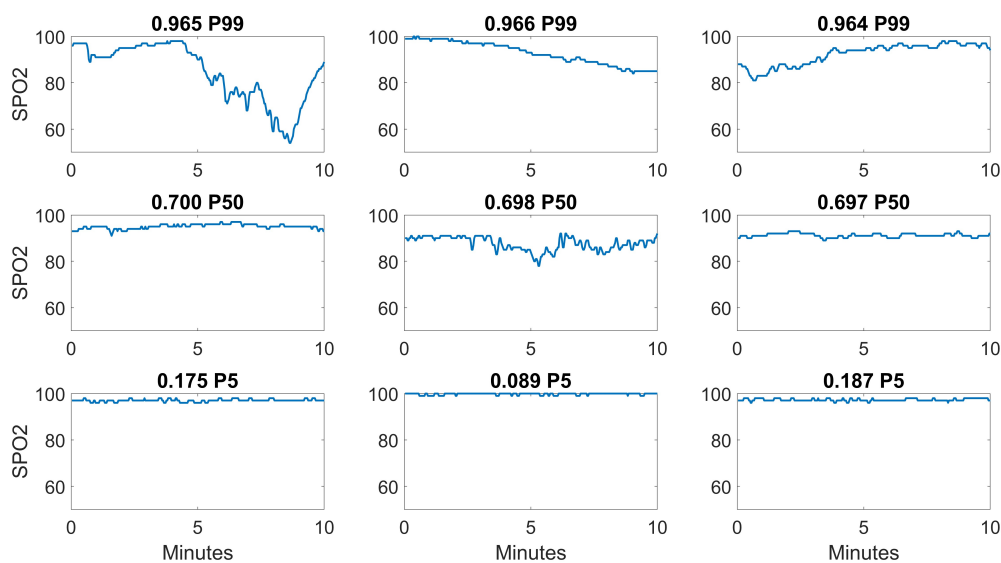
### *3.2. Top HR HCTSA Features*

The top three HR features were symbolic transformation metrics associated with discretizing the HR record into sequence of either 2 (binary) or 3 symbols that are also good measures of low HR variability associated with high risk of death. The best algorithm, hr\_entropy\_diff, specifically first quantizes the successive HR differences into 3 symbols roughly representing increasing, same and decreasing. It then looks at the distribution of all  $3^4 = 81$  possible patterns of length 4 and calculates the Shannon entropy. Low values of hr\_entropy\_diff are associated with large proportion of unchanging HR during 10-minute window. The second best algorithm, hr\_entropy, is the exact same algorithm applied to raw signal without first taking differences. The third best HR algorithm is hr\_probincreases which was previously identified as best

### A. Values and percentiles of sp\_walk



### B. Values and percentiles of sp\_autocorr



**Figure 3:** Examples of 10-minute SPO2 time series on day 7 for twp top HCTSA features sp\_walk and sp\_autocorr. The title includes feature value and its percentile, e.g. P5=5<sup>th</sup> percentile of distribution.

individual predictor of mortality in next week in the NICU (Niestroy et al. 2022). This measure transforms the HR record into binary sequence of either up (u) or down (d) based on whether HR increases or not (HR staying same is considered down). The `hr_probincreases` is the probability of the uu pattern and low values indicate high risk of mortality.

All three of these measures are related to heart rate fragmentation metrics introduced recently (Costa et al. 2017a,b) and shown to be predictive of long-term survival in large study of 3000 24 hour Holter recordings from patients of all ages (Lensen et al. 2020). A lesson learned from HCTSA is that measures that convert the HR to a simple binary time series and look for runs of ones of lengths 1,2,3,... can quantify heart-rate variability and are good candidates to predict adverse neonatal outcomes in a way clinicians can easily understand.

### 3.3. Trajectories of Predictive Performance

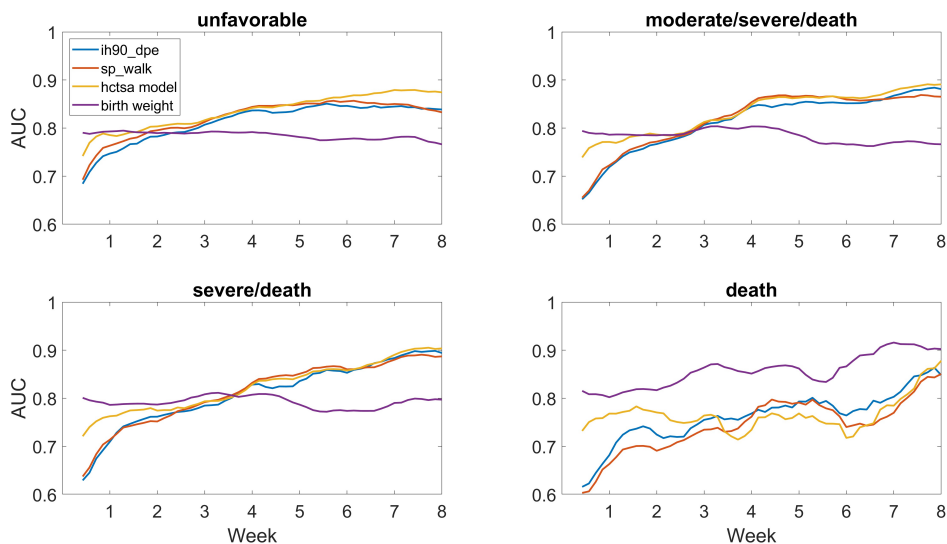
Values of the AUC for `sp_walk` and `IH90_DPE` at days 7, 14 and 28 are summarized in Table 4. Based on the individual results discussed above, a simple 3-parameter HCTSA model using features `sp_walk`, `sp_mean`, and `hr_entropy_diff` was developed at each day of life and also included. This model was considered sufficiently optimal because removing any of these features reduced AUC by more than .005 and no HCTSA feature added to the model increased AUC by more than .005 at day 7. The performance of birth weight alone is included as well for comparison.

**Table 4:** Comparison of AUC at days 7, 14 and 28 for predicting respiratory outcomes. The HCTSA model used the 3 features `sp_walk`, `sp_mean`, and `hr_entropy_diff`

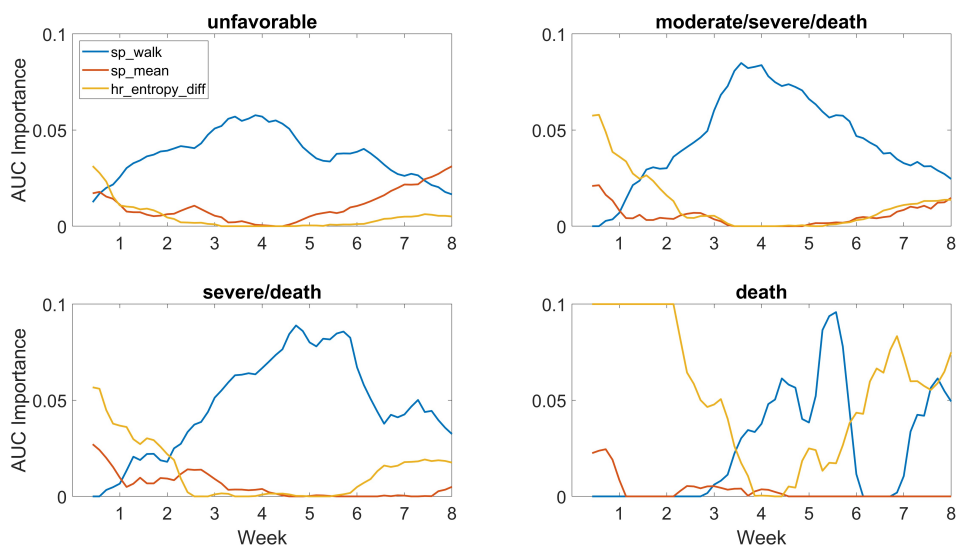
Features	Day	unfavorable	moderate/severe/death	severe/death	death
<code>ih90_dpe</code>	7	0.729	0.715	0.731	0.719
<code>sp_walk</code>	7	0.761	0.724	0.734	0.675
<code>hctsa model</code>	7	0.778	0.754	0.757	0.747
birth weight	7	0.798	0.788	0.786	0.801
<code>ih90_dpe</code>	14	0.791	0.767	0.761	0.741
<code>sp_walk</code>	14	0.797	0.763	0.738	0.689
<code>hctsa model</code>	14	0.800	0.777	0.762	0.765
birth weight	14	0.798	0.787	0.781	0.808
<code>ih90_dpe</code>	28	0.850	0.866	0.843	0.770
<code>sp_walk</code>	28	0.851	0.860	0.834	0.779
<code>hctsa model</code>	28	0.849	0.857	0.831	0.758
birth weight	28	0.792	0.801	0.802	0.849

The AUC of the models in Table 4 were calculated for each respiratory outcome from birth up to 8 weeks of life. Figure 4 shows these performance trajectory curves.

The evolving variable importance of each of the 3 features in the HCTSA model is shown in Figure 5. All these curves are smoothed by taking average over window of plus or minus two days. Detailed trajectories of the physiologic features including IH events are available for the Pre-Vent cohort (Weese-Mayer et al. 2023).



**Figure 4:** Trajectory of AUC by week of life for predicting respiratory outcomes. Results are averaged over  $\pm 2$  days.



**Figure 5:** Importance of HCTSA features by week of life measured by drop in AUC when variable is dropped from 3-parameter model. Results are averaged over  $\pm 2$  days.

For unfavorable outcome, the top HCTSA feature slightly outperformed IH90\_DPE at day 7 (.761 to .729) but was essentially equivalent at day 28 (.851 to .850). The

HCTSA model increased the AUC to .778 at day 7 but did not improve performance at day 28 (.849). Models with new HCTSA features still have a lower AUC than birth weight alone at day 7, but catch up and surpass birth weight by day 14. By week 4 or so, all the physiologic models outperform birth weight for predicting all outcomes except death.

The variable importance of the IH related HCTSA feature `sp_walk` steadily increases to day of life 28 where it is essentially the only predictor needed. The top HR metric was only an important predictor at early ages which was likely due to the larger proportion of infants whose bad outcome is death by any cause.

#### 4. Discussion

A representative subset of HCTSA algorithms predicted unfavorable respiratory outcomes in extremely preterm infants and revealed both new robust features associated with IH events and other features for improved detection early in NICU stay. This large multi-center cohort study validated the hypothesis that identifying algorithms by unsupervised clustering could capture most of the predictive information in NICU HR and SPO2 data. However, this analysis also showed that HCTSA did not outperform IH metrics later in the NICU stay and provides additional evidence supporting IH90\_DPE as an optimal predictor of respiratory outcomes.

As with all metrics based on bedside monitoring data, there are significant practical issues associated with implementation especially for wide-spread clinical use. The data used in the NICU study to perform the unsupervised clustering used in this paper was from HR and SPO2 displayed on bedside monitors every 2 seconds. The PreVent sites had a variety of bedside monitors that displayed vital signs either once every second or every 1024 milliseconds. To accommodate for this, data was sub-sampled every 2 seconds at all sites before applying algorithms. For the analysis of HR, one way to minimize variability across sites is to work directly with the interbeat RR intervals derived from ECG waveforms. However, this often involves a significant amount of additional data processing and management that may not be practical. As mentioned previously, SPO2 metrics including IH events can also be sensitive to the averaging time of the pulse oximeter which can vary across vendor and NICU.

In this study, the predictive performance of the features were analyzed at a daily level to be consistent with the PreVent study database and primary analysis. Future work would be to look at higher resolution windows of hourly or even down to individual 10-minute records. This would also involve a closer look at individual IH events and their correlation with `sp_walk` and `sp_autocorr`.

One possible limitation of this study was that the algorithms implemented in (Niestroy et al. 2022) did not include the entire HCTSA algorithm library of over 7000 features because it was not computationally feasible to implement on such a large data set. It is believed that the algorithms implemented were sufficient to be a reasonable implementation of HCTSA approach and extremely useful in developing



predictive models in NICU. Also it was not feasible to implement a much larger set of HCTSA algorithms on the Pre-Vent cohort since the data was spread out among 5 sites which led to only calculating the 33 features. Augmenting the BAP to efficiently compute a larger number of physiologic features to help address these issues will be included in future analyses of the Pre-Vent cohort.

## 5. Acknowledgements

The National Institutes of Health and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support through cooperative agreements. While NHLBI staff did have input into the study design, conduct, analysis, and manuscript drafting, the content and views expressed are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health or the U.S. Department of Health and Human Services.

Participating sites collected and stored the data while the University of Virginia, the lead data coordinating center (LDCC), analyzed the data. The co-PIs at each site had full access to his/her individual site data and take responsibility for the integrity of the raw waveforms while Drs. Randall Moorman (LDCC co-PI) and Douglas Lake (LDCC co-PI) take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

### Pre-Vent Investigators

Katy N. Krahn and Amanda M. Zimmet, University of Virginia Center for Advanced Medical Analytics, Charlottesville, VA; Bradley S Hopkins, Erin K Lonergan, Casey M. Rand: Ann and Robert H. Lurie Children's Hospital of Chicago, and Pediatric Autonomic Medicine, Stanley Manne Children's Research Institute, Chicago, IL; Arlene Zadell, Department of Pediatrics, University Hospitals Cleveland Medical Center, Rainbow Babies and Children's Hospital, Cleveland, OH; Arie Nakhmani, Department of Electrical and Computer Engineering, University of Alabama at Birmingham, Birmingham, AL; Waldemar A. Carlo, Deborah Laney, and Colm P. Travers, Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham School of Medicine, Birmingham, AL; Silvia Vanbuskirk, Carmen D'Ugard, Ana Cecilia Aguilar and Alini Schott, Division of Neonatology, Department of Pediatrics, University of Miami Miller School of Medicine, Holtz Children's Hospital – University of Miami/Jackson Memorial Medical Center, Miami, FL; and Julie Hoffmann and Laura Linneman, Washington University School of Medicine in St. Louis, St. Louis, MO.

### NIH/NHLBI

Neil Aggarwal, MD: National Institutes of Health, National Heart, Lung and Blood Institute, Division of Lung Diseases, Bethesda, MD  
Lawrence Baizer, PhD: National Institutes of Health, National Heart, Lung and Blood Institute, Division of Lung Diseases, Bethesda, MD  
Peyvand Ghofrani, MDE: National Institutes of Health, National Heart, Lung and

Blood Institute, Division of Lung Diseases, Bethesda, MD  
Aaron D. Laposky, PhD: National Institutes of Health, National Heart, Lung and Blood Institute, Division of Lung Diseases, Bethesda, MD  
Aruna Natarajan MD, PhD: National Institutes of Health, National Heart, Lung and Blood Institute, Division of Lung Diseases, Bethesda, MD  
Barry Schmetter, BS: National Institutes of Health, National Heart, Lung and Blood Institute, Division of Lung Diseases, Bethesda, MD

## **OSMB**

Estelle B. Gauda, MD (Chair): University of Toronto Hospital for Sick Children, Division of Neonatology, Toronto, Ontario  
Jonathan M. Davis, MD: Tufts Clinical and Translational Science Institute, Division of Newborn Medicine, Boston, MA  
Roberta L. Keller, MD: University of California, San Francisco School of Medicine, Department of Pediatrics, San Francisco CA  
Robinder G. Khemani, MD: Children's Hospital Los Angeles, Department of Anesthesiology and Critical Care Medicine, Los Angeles, CA  
Renee H. Moore, PhD: Drexel University Department of Epidemiology and Biostatistics, Philadelphia, PA  
Elliott M. Weiss, MD, MSME: Seattle Children's Hospital, Department of Pediatrics, Division of Bioethics, Seattle, WA

## **Funding Support**

University of Virginia (NCT03174301): U01 HL133708, K23 HD097254, HL133708-05S1  
Case Western Reserve University: U01 HL133643  
Northwestern University: U01 HL133704  
University of Alabama at Birmingham: U01 HL133536, K23 HL157618  
University of Miami: U01 HL133689  
Washington University: U01 HL133700, K23 NS111086

We give a special acknowledgement to Amanda Zimmet whose work developing the Batch Algorithm Processor was crucial to this work and success of the Pre-Vent study. We also thank Alix Zimmet for his acknowledgement skills and raising the bar for manuscript preparation.

## Appendix A. Supplemental tables

**Table A1:** HCTSA variable names and Matlab functions available to download from <https://github.com/benfulcher/hctsa>.

Feature	HCTSA Variable	Matlab code	Output Field
hr_mean	HR.mean	mean(x)	
hr_avgthresh	HR.EX.MovingThreshold.a0.25.b0.1.meanq	EX_MovingThreshold(x,0.25,0.1)	meanq
hr_corrmean	HR.CO.tc3.1..denom	CO_tc3(x,1)	denom
hr_std	HR.std	std(x)	
hr_cv	HR.DN.cv.3	DN_cv(x,3)	
hr_max	HR.Quantile.99	DN_Quantile(x,0.99)	
hr_min	HR.ST.LocalExtrema.n100.minabsmin	ST_LocalExtrema(x,'n',100)	minabsmin
hr_kurt	HR.kurt2	kurtosis(x)	
hr_skew	HR.skew2	skewness(x)	
hr_symautocorr	HR.SB.TransitionMatrix23.stdcoveig	SB_TransitionMatrix(x,'quantile',2,3)	stdeigcov
hr_surprise	HR.FC.Surprise.mean	FC_Surprise(x)	mean
hr_entropy	HR.SB.MotifThree.quantile.hhhh	SB_MotifThree(x,'quantile')	hhhh
hr_wavelet	HR.MF.arfit.sbc.7	MF_arfit(x)	sbc_7
hr_probincreases	HR.SB.MotifTwo.diff.uu	SB_MotifTwo(x,'diff')	uu
hr_entropy_diff	HR.SB.MotifThree.diffquant.hhhh	SB_MotifThree(x,'diffquant')	hhhh
sp_std	SP.std	std(x)	
sp_mean	SP.mean	mean(x)	
sp_avgthres	SP.EX.MovingThreshold.a0.25.b0.1.meanq	EX_MovingThreshold(x,0.25,0.1)	meanq
sp_corrmean	SP.CO.tc3.1..denom	CO_tc3(x,1)	denom
hr_derivative	HR.SY.StdNthDer.17	SY_StdNthDer(x,17)	
sp_min	SP.ST.LocalExtrema.n100.minabsmin	ST_LocalExtrema(x,'n',100)	minabsmin
sp_skew	SP.skew2	skewness(x)	
sp_kurt	SP.kurt2	kurtosis(x)	
sp_mean_trim	SP.DN.RemovePointsmin.0.2.mean	DN_RemovePoints(x,'min',0.2)	mean
sp_wavelet	SP.MF.arfit.sbc.7	MF_arfit(x)	sbc_7
sp_symeigen	SP.SB.TransitionMatrix22.mineig	SB_TransitionMatrix(x,'quantile',2,2)	mineig
sp_walk	SP.PH.Walkermomentum.2..sw.stdrat	PH_Walker(x,'momentum',2)	sw_stdrat
sp_autocorr	SP.AutoCorr.lag.4	CO_AutoCorr(x,4,'TimeDomainStat')	
sp_syentropy	SP.SB.MotifThree.diffquant.hhhh	SB_MotifThree(x,'diffquant')	hhhh
sp_sybin	SP.SB.TransitionMatrix21.T10	SB_TransitionMatrix(x,'quantile',2,1)	T3
sp_syimqr	SP.SB.BinaryMethod.iqr.pstretch1	SB_BinaryStats(x,'iqr')	pstretch1

**Table A2:** AUC at day 7 of all individual HR and SPO2 features on increasingly bad respiratory outcomes.

Feature	Cluster	unfavorable	moderate/severe/death	severe/death	death
hr_mean	1	0.546	0.564	0.576	0.624
hr_corrmean	1	0.547	0.566	0.578	0.626
hr_avgthresh	1	0.554	0.573	0.587	0.638
hr_std	2	0.623	0.643	0.666	0.693
hr_cv	2	0.613	0.629	0.651	0.668
hr_max	3	0.588	0.610	0.628	0.674
hr_min	4	0.490	0.500	0.493	0.517
hr_skew	5	0.550	0.540	0.526	0.492
hr_kurt	5	0.506	0.494	0.532	0.534
hr_symautocorr	6	0.610	0.578	0.555	0.630
hr_surprise	7	0.624	0.625	0.672	0.718
hr_entropy	7	0.675	0.673	0.665	0.736
hr_wavelet	8	0.626	0.635	0.649	0.689
hr_entropy_diff	9	0.689	0.706	0.709	0.765
hr_probincreases	9	0.672	0.688	0.702	0.744
sp_std	10	0.665	0.641	0.598	0.560
sp_mean	11	0.731	0.694	0.692	0.670
sp_corrmean	11	0.731	0.693	0.692	0.669
sp_avgthresh	11	0.735	0.699	0.700	0.678
hr_derivative	12	0.601	0.598	0.611	0.651
sp_min	13	0.703	0.687	0.671	0.635
sp_skew	14	0.614	0.587	0.559	0.601
sp_kurt	14	0.698	0.646	0.614	0.608
sp_mean_trim	14	0.725	0.686	0.688	0.667
sp_wavelet	15	0.540	0.503	0.549	0.570
sp_symeigen	16	0.718	0.683	0.648	0.609
sp_autocorr	17	0.740	0.702	0.692	0.645
sp_walk	17	0.761	0.724	0.734	0.675
sp_symentropy	18	0.552	0.509	0.538	0.548
sp_symbin	19	0.595	0.614	0.626	0.618
sp_symiqr	20	0.600	0.626	0.636	0.626
xc_max		0.511	0.559	0.577	0.622
xc_min		0.538	0.571	0.595	0.636
ih90_count		0.696	0.679	0.637	0.604
ih90_dur		0.730	0.715	0.691	0.658
ih90_dpe		0.729	0.715	0.731	0.719
ih80_count		0.652	0.673	0.666	0.678
ih80_dur		0.671	0.692	0.688	0.704
ih80_dpe		0.672	0.685	0.677	0.710
brady_count		0.612	0.631	0.613	0.542
brady_dur		0.595	0.615	0.595	0.517
brady_dpe		0.542	0.584	0.564	0.508

**Table A3:** AUC at day 14 of all individual HR and SPO2 features on increasingly bad respiratory outcomes.

Feature	Cluster	unfavorable	moderate/severe/death	severe/death	death
hr_mean	1	0.513	0.546	0.569	0.570
hr_corrmean	1	0.513	0.547	0.570	0.571
hr_avgthresh	1	0.522	0.558	0.581	0.587
hr_std	2	0.666	0.694	0.730	0.799
hr_cv	2	0.667	0.687	0.723	0.787
hr_max	3	0.585	0.611	0.635	0.649
hr_min	4	0.522	0.531	0.536	0.569
hr_skew	5	0.615	0.575	0.536	0.498
hr_kurt	5	0.525	0.521	0.575	0.610
hr_symautocorr	6	0.537	0.545	0.537	0.582
hr_surprise	7	0.620	0.632	0.668	0.765
hr_entropy	7	0.647	0.658	0.667	0.747
hr_wavelet	8	0.653	0.672	0.698	0.803
hr_entropy_diff	9	0.704	0.718	0.727	0.807
hr_probincreases	9	0.686	0.704	0.731	0.809
sp_std	10	0.653	0.634	0.560	0.534
sp_mean	11	0.732	0.698	0.686	0.603
sp_corrmean	11	0.731	0.696	0.687	0.603
sp_avgthresh	11	0.741	0.708	0.700	0.625
hr_derivative	12	0.629	0.637	0.668	0.745
sp_min	13	0.666	0.636	0.583	0.519
sp_skew	14	0.682	0.664	0.687	0.708
sp_kurt	14	0.750	0.725	0.711	0.668
sp_mean_trim	14	0.720	0.683	0.691	0.631
sp_wavelet	15	0.540	0.559	0.614	0.712
sp_symeigen	16	0.749	0.720	0.657	0.575
sp_autocorr	17	0.782	0.751	0.710	0.659
sp_walk	17	0.797	0.763	0.738	0.689
sp_symentropy	18	0.511	0.516	0.576	0.676
sp_symbin	19	0.672	0.685	0.663	0.694
sp_symiqr	20	0.683	0.695	0.667	0.707
xc_max		0.595	0.628	0.629	0.648
xc_min		0.623	0.661	0.674	0.714
ih90_count		0.663	0.616	0.553	0.549
ih90_dur		0.742	0.699	0.647	0.554
ih90_dpe		0.792	0.767	0.761	0.741
ih80_count		0.675	0.667	0.633	0.596
ih80_dur		0.706	0.700	0.670	0.625
ih80_dpe		0.724	0.734	0.727	0.672
brady_count		0.600	0.614	0.595	0.633
brady_dur		0.586	0.597	0.581	0.635
brady_dpe		0.536	0.549	0.538	0.641

**Table A4:** AUC at day 28 of all individual HR and SPO2 features on increasingly bad respiratory outcomes.

Feature	Cluster	unfavorable	moderate/severe/death	severe/death	death
hr_mean	1	0.524	0.588	0.608	0.581
hr_corrmean	1	0.525	0.589	0.608	0.580
hr_avgthresh	1	0.533	0.600	0.620	0.589
hr_std	2	0.657	0.679	0.696	0.678
hr_cv	2	0.651	0.655	0.669	0.656
hr_max	3	0.604	0.664	0.681	0.657
hr_min	4	0.515	0.549	0.559	0.569
hr_skew	5	0.679	0.661	0.641	0.584
hr_kurt	5	0.558	0.556	0.541	0.505
hr_symautocorr	6	0.544	0.572	0.552	0.552
hr_surprise	7	0.663	0.673	0.708	0.802
hr_entropy	7	0.635	0.642	0.626	0.673
hr_wavelet	8	0.645	0.679	0.694	0.685
hr_entropy_diff	9	0.688	0.697	0.705	0.719
hr_probincreases	9	0.679	0.702	0.715	0.751
sp_std	10	0.675	0.620	0.588	0.492
sp_mean	11	0.772	0.754	0.748	0.768
sp_corrmean	11	0.769	0.753	0.748	0.770
sp_avgthresh	11	0.784	0.771	0.766	0.790
hr_derivative	12	0.612	0.625	0.642	0.378
sp_min	13	0.655	0.595	0.577	0.543
sp_skew	14	0.783	0.779	0.767	0.752
sp_kurt	14	0.817	0.821	0.799	0.745
sp_mean_trim	14	0.765	0.750	0.759	0.790
sp_wavelet	15	0.577	0.652	0.647	0.667
sp_symeigen	16	0.814	0.794	0.750	0.691
sp_autocorr	17	0.841	0.844	0.807	0.728
sp_walk	17	0.851	0.860	0.834	0.779
sp_symentropy	18	0.532	0.543	0.554	0.621
sp_symbin	19	0.681	0.706	0.687	0.673
sp_symiqr	20	0.704	0.728	0.705	0.687
xc_max		0.606	0.652	0.648	0.590
xc_min		0.634	0.673	0.665	0.616
ih90_count		0.691	0.618	0.595	0.580
ih90_dur		0.797	0.760	0.737	0.680
ih90_dpe		0.850	0.866	0.843	0.770
ih80_count		0.714	0.669	0.655	0.604
ih80_dur		0.756	0.727	0.727	0.646
ih80_dpe		0.795	0.798	0.816	0.711
brady_count		0.542	0.541	0.468	0.430
brady_dur		0.475	0.481	0.500	0.429
brady_dpe		0.502	0.510	0.525	0.590



**Table A5:** AUC at day 7, 14 and day 28 of individual clinical features on increasingly bad respiratory outcomes.

Feature	Day	unfavorable	moderate/severe/death	severe/death	death
birth weight	7	0.798	0.788	0.786	0.801
gestational age	7	0.765	0.794	0.765	0.782
fio2	7	0.763	0.733	0.736	0.696
imv	7	0.736	0.755	0.745	0.720
birth weight	14	0.787	0.780	0.781	0.808
gestational age	14	0.770	0.779	0.748	0.780
fio2	14	0.797	0.783	0.789	0.765
imv	14	0.748	0.770	0.752	0.734
birth weight	28	0.792	0.801	0.802	0.849
gestational age	28	0.776	0.807	0.776	0.833
fio2	28	0.829	0.817	0.791	0.754
imv	28	0.737	0.789	0.777	0.722

## References

- Ambalavanan, N., Weese-Mayer, D. E., Hibbs, A. M., Claire, N., Carroll, J. L., Moorman, J. R., Bancalari, E., Hamvas, A., Martin, R. J., Di Fiore, J. M., Indic, P., Kemp, J. S., Dormishian, A., Krahn, K. N., Qiu, J., Dennery, P. A., Ratcliffe, S. J., Troendle, J. F. & Lake, D. E. (2023), 'Cardiorespiratory Monitoring Data to Predict Respiratory Outcomes in Extremely Preterm Infants.', *American journal of respiratory and critical care medicine* **208**(1), 79–97. Place: United States.
- Blackard, K. R., Krahn, K. N., Andris, R. T., Lake, D. E. & Fairchild, K. D. (2021), 'Autism risk in neonatal intensive care unit patients associated with novel heart rate patterns.', *Pediatric research* **90**(6), 1186–1192. Place: United States.
- Borenstein-Levin, L., Konikoff, L. & Solimano, A. (2020), 'Clinical quantification of SpO<sub>2</sub> instability using a new histogram classification system: a clinical study', *Pediatric Research* **87**(4), 716–720.
- Cole, F. S. (2021), 'Improving VLBW infant outcomes with big data analytics.', *Pediatric research* **90**(1), 20–21. Place: United States.
- Costa, M. D., Davis, R. B. & Goldberger, A. L. (2017a), 'Heart Rate Fragmentation: A New Approach to the Analysis of Cardiac Interbeat Interval Dynamics', *Frontiers in Physiology* **8**, 255.
- Costa, M. D., Davis, R. B. & Goldberger, A. L. (2017b), 'Heart Rate Fragmentation: A Symbolic Dynamical Approach', *Frontiers in Physiology* **8**, 827.
- Dennery, P. A., Di Fiore, J. M., Ambalavanan, N., Bancalari, E., Carroll, J. L., Claire, N., Hamvas, A., Hibbs, A. M., Indic, P., Kemp, J., Krahn, K. N., Lake, D., Laposky, A., Martin, R. J., Natarajan, A., Rand, C., Schau, M., Weese-Mayer, D. E., Zimmet, A. M. & Moorman, J. R. (2019), 'Pre-Vent: the prematurity-related ventilatory control study.', *Pediatric research* **85**(6), 769–776. Place: United States.
- Di Fiore, J. M., Bloom, J. N., Orge, F., Schutt, A., Schluchter, M., Cheruvu, V. K., Walsh, M., Finer, N. & Martin, R. J. (2010), 'A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity.', *The Journal of pediatrics* **157**(1), 69–73. Place: United States.
- Di Fiore, J. M., Kaffashi, F., Loparo, K., Sattar, A., Schluchter, M., Foglyano, R., Martin, R. J. & Wilson, C. G. (2012), 'The relationship between patterns of intermittent hypoxia and retinopathy of prematurity in preterm infants.', *Pediatric research* **72**(6), 606–612. Place: United States.
- Dormishian, A., Schott, A., Aguilar, A. C., Bancalari, E. & Claire, N. (2023), 'Pulse oximetry reliability for detection of hypoxemia under motion in extremely premature infants.', *Pediatric research* **93**(1), 118–124. Place: United States.
- Dormishian, A., Schott, A., Aguilar, A. C., Jimenez, V., Bancalari, E., Tolosa, J. & Claire, N. (2023), 'Etiology and Mechanism of Intermittent Hypoxemia Episodes in Spontaneously Breathing Extremely Premature Infants.', *The Journal of pediatrics* **262**, 113623. Place: United States.

## REFERENCES

25

- Fairchild, K. D. & Lake, D. E. (2018), 'Cross-Correlation of Heart Rate and Oxygen Saturation in Very Low Birthweight Infants: Association with Apnea and Adverse Events.', *American journal of perinatology* **35**(5), 463–469. Place: United States.
- Fairchild, K. D., Lake, D. E., Kattwinkel, J., Moorman, J. R., Bateman, D. A., Grieve, P. G., Isler, J. R. & Sahni, R. (2017), 'Vital signs and their cross-correlation in sepsis and NEC: a study of 1,065 very-low-birth-weight infants in two NICUs.', *Pediatric research* **81**(2), 315–321. Place: United States.
- Fairchild, K. D., Schelonka, R. L., Kaufman, D. A., Carlo, W. A., Kattwinkel, J., Porcelli, P. J., Navarrete, C. T., Bancalari, E., Aschner, J. L., Walker, M. W., Perez, J. A., Palmer, C., Lake, D. E., O'Shea, T. M. & Moorman, J. R. (2013), 'Septicemia mortality reduction in neonates in a heart rate characteristics monitoring trial.', *Pediatric research* **74**(5), 570–575. Place: United States.
- Fulcher, B. D., Little, M. A. & Jones, N. S. (2013), 'Highly comparative time-series analysis: the empirical structure of time series and their methods.', *Journal of the Royal Society, Interface* **10**(83), 20130048. Place: England.
- Gentle, S., El-Ferzli, G., Winter, L., Salas, A. A. & Philips Iii, J. B. (2020), 'Oxygen saturation histogram monitoring to reduce death or retinopathy of prematurity: a quality improvement initiative', *Journal of Perinatology: Official Journal of the California Perinatal Association* **40**(1), 163–169.
- Gentle, S. J., Travers, C. P., Nakhmani, A., Indic, P., Carlo, W. A. & Ambalavanan, N. (2023), 'Intermittent Hypoxemia and Bronchopulmonary Dysplasia with Pulmonary Hypertension in Preterm Infants.', *American journal of respiratory and critical care medicine* **207**(7), 899–907. Place: United States.
- Goetz, E. M., Tomlin, B. D., Rinaldo, K. E., Baumann-Blackmore, N. L., Petro, R. L., Smith, B. B., Zapata, J. Y., Lasarev, M. R., McBride, E. B. & Kaluarachchi, D. C. (2022), 'Oxygen Saturation Profiles in Healthy Term Infants in Early Postnatal Life', *American Journal of Perinatology*.
- Griffin, M. P., O'Shea, T. M., Bissonette, E. A., Harrell, F. E. J., Lake, D. E. & Moorman, J. R. (2003), 'Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness.', *Pediatric research* **53**(6), 920–926. Place: United States.
- Kausch, S. L., Brandberg, J. G., Qiu, J., Panda, A., Binai, A., Isler, J., Sahni, R., Vesoulis, Z. A., Moorman, J. R., Fairchild, K. D., Lake, D. E. & Sullivan, B. A. (2023), 'Cardiorespiratory signature of neonatal sepsis: development and validation of prediction models in 3 NICUs.', *Pediatric research* **93**(7), 1913–1921. Place: United States.
- Lensen, I. S., Monfredi, O. J., Andris, R. T., Lake, D. E. & Moorman, J. R. (2020), 'Heart rate fragmentation gives novel insights into non-autonomic mechanisms governing beat-to-beat control of the heart's rhythm', *JRSM cardiovascular disease* **9**, 2048004020948732.
- Letzkus, L., Fairchild, K., Lyons, G., Pyata, H., Ratcliffe, S. & Lake, D. (2022), 'Heart Rate and Pulse Oximetry Dynamics in the First Week after Birth in Neonatal

## REFERENCES

26

- Intensive Care Unit Patients and the Risk of Cerebral Palsy.’, *American journal of perinatology*. Place: United States.
- Moorman, J. R., Carlo, W. A., Kattwinkel, J., Schelonka, R. L., Porcelli, P. J., Navarrete, C. T., Bancalari, E., Aschner, J. L., Whit Walker, M., Perez, J. A., Palmer, C., Stukenborg, G. J., Lake, D. E. & Michael O’Shea, T. (2011), ‘Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial.’, *The Journal of pediatrics* **159**(6), 900–906.e1. Place: United States.
- Niestroy, J. C., Moorman, J. R., Levinson, M. A., Manir, S. A., Clark, T. W., Fairchild, K. D. & Lake, D. E. (2022), ‘Discovery of signatures of fatal neonatal illness in vital signs using highly comparative time-series analysis.’, *NPJ digital medicine* **5**(1), 6. Place: England.
- Niestroy, J., Levinson, M., Al Manir, S., Clark, T., Fairchild, K., Lake, D. & Moorman, R. (2021), ‘Replication Data for: Discovery of signatures of fatal neonatal illness in vital signs using highly comparative time-series analysis’. Version Number: V2.  
**URL:** <https://doi.org/10.18130/V3/VJXODP>
- Poets, C. F., Roberts, R. S., Schmidt, B., Whyte, R. K., Asztalos, E. V., Bader, D., Bairam, A., Moddemann, D., Peliowski, A., Rabi, Y., Solimano, A., Nelson, H. & Canadian Oxygen Trial Investigators (2015), ‘Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants’, *JAMA* **314**(6), 595–603.
- Raffay, T. M., Dylag, A. M., Sattar, A., Abu Jawdeh, E. G., Cao, S., Pax, B. M., Loparo, K. A., Martin, R. J. & Di Fiore, J. M. (2019), ‘Neonatal intermittent hypoxemia events are associated with diagnosis of bronchopulmonary dysplasia at 36 weeks postmenstrual age.’, *Pediatric research* **85**(3), 318–323. Place: United States.
- Ramanand, P., Indic, P., Gentle, S. J. & Ambalavanan, N. (2023), ‘Information Based Similarity Analysis of Oxygen Saturation Recordings to Detect Pulmonary Hypertension in Preterm Infants.’, *Biomedical signal processing and control* **86**(Pt C), 105358. Place: England.
- Ramirez, J.-M., Carroll, M. S., Burgraff, N., Rand, C. M. & Weese-Mayer, D. E. (2023), ‘A narrative review of the mechanisms and consequences of intermittent hypoxia and the role of advanced analytic techniques in pediatric autonomic disorders.’, *Clinical autonomic research : official journal of the Clinical Autonomic Research Society* **33**(3), 287–300. Place: Germany.
- Sullivan, B. A., McClure, C., Hicks, J., Lake, D. E., Moorman, J. R. & Fairchild, K. D. (2016), ‘Early Heart Rate Characteristics Predict Death and Morbidities in Preterm Infants.’, *The Journal of pediatrics* **174**, 57–62. Place: United States.
- Sullivan, B. A., Wallman-Stokes, A., Isler, J., Sahni, R., Moorman, J. R., Fairchild, K. D. & Lake, D. E. (2018), ‘Early Pulse Oximetry Data Improves Prediction of Death and Adverse Outcomes in a Two-Center Cohort of Very Low Birth Weight Infants.’, *American journal of perinatology* **35**(13), 1331–1338. Place: United States.

REFERENCES

27

- Vesoulis, Z. A., Husain, A. N. & Cole, F. S. (2023), 'Improving child health through Big Data and data science.', *Pediatric research* **93**(2), 342–349. Place: United States.
- Weese-Mayer, D. E., Di Fiore, J. M., Lake, D. E., Hibbs, A. M., Claire, N., Qiu, J., Ambalavanan, N., Bancalari, E., Kemp, J. S., Zimmet, A. M., Carroll, J. L., Martin, R. J., Krahn, K. N., Hamvas, A., Ratcliffe, S. J., Krishnamurthi, N., Indic, P., Dormishian, A., Dennery, P. A., Moorman, J. R. & Prematurity-Related Ventilatory Control (Pre-Vent) Investigators (2023), 'Maturation of cardioventilatory physiological trajectories in extremely preterm infants', *Pediatric Research* .