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ABSTRACT

A strategy of early extubation to noninvasive respiratory support in preterm infants could be boosted by the availability of a decision support tool for clinicians. Using the Heart Rate Characteristics index (HRCi) with clinical parameters, we derived and validated predictive models for extubation readiness and success.

Peri-extubation demographic, clinical and HRCi data for up to 96 h were collected from mechanically ventilated infants in the control arm of a randomised trial involving eight neonatal centres, where clinicians were blinded to the HRCi scores. The data was used to produce a multivariable regression model for the probability of subsequent re-intubation. Additionally, a survival model was produced to estimate the probability of re-intubation in the period after extubation.

Of the 577 eligible infants, data from 397 infants (69%) were used to derive the pre-extubation model and 180 infants (31%) for validation. The model was also fitted and validated using all combinations of training (five centres) and test (three centres) centres. The estimated probability for the validation episodes showed discrimination with high statistical significance, with an area under the curve of 0.72 (95% CI 0.71–0.74; p<0.001). Data from all infants were used to derive models of the predictive instantaneous hazard of re-intubation adjusted for clinical parameters.

Predictive models of extubation readiness and success in real-time can be derived using physiological and clinical variables. The models from our analyses can be accessed using an online tool at www.heroscore.com/extubation, and have the potential to inform and supplement the confidence of the clinician considering extubation in preterm infants.

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Using the Heart Rate ~~Variability~~Characteristics index [Q3], we have derived models predicting extubation outcomes for preterm infants, both for extubation readiness and success. These models are intended as a decision support tool for clinicians. https://bit.ly/2LKNEKk

Introduction

Although the benefits of noninvasive respiratory support have been demonstrated in large randomised trials [1], mechanical ventilation remains a necessity in many preterm infants. In ventilated infants, early extubation to noninvasive respiratory support improves clinical outcomes [2], while long-term mechanical ventilation is associated with serious adverse outcomes [3, 4]. Approximately 40% of intubations are associated with adverse events, including cardiorespiratory instability, upper airway trauma, lung atelectasis and infection [5, 6], while serious sequelae such as hypotension, chest compressions, pneumothorax and death have been reported in 9% [7]. Consequently, clinician anxiety about extubation failure, particularly at lower gestational ages, influences extubation thresholds and peri-extubation practices [8].

Clinicians have used a range of parameters to predict extubation readiness, including ventilation and lung function indices [9–11] and demographic variables [12–14]. Only one of these studies was a small randomised trial of 42 preterm infants, showing that a minute volume ratio of ≥0.5 (continuous positive airway pressure (CPAP) *versus* ventilator breaths) was as good as clinical judgement in predicting extubation success [9]. However, a large number of different parameters explored and published to predict extubation readiness suggest that, in isolation, no single parameter is accurate or clinically useful [15].

Changes in autonomic activity, including loss of heart rate variability, were reported as a key factor in adults failing to wean from mechanical ventilation [16]. The Heart Rate Characteristics index (HRCi) is an hourly numerical score derived from a mathematical model that analyses continuous ECG data from routine real-time monitoring for heart rate variability, asymmetry and entropy

(www.heroscore.com). An acute rise in the HRCi (spike) has been validated in newborn studies to increase the risk of clinical adverse events in the subsequent 6–24 h [17, 18]. A respiratory deterioration is commonly preceded by a spike in the HRCi [19]. We have recently published an exploratory model in neonates using a relatively small sample size showing that a combination of the HRCi and other clinical parameters can predict extubation readiness and impending failure of extubation (re-intubation) [20]. In the present study, we have attempted to improve and validate predictive models of extubation readiness and success in preterm infants using clinical parameters and the HRCi, by re-analysing a large data set from the control arm of a randomised controlled trial (RCT) [21].

Methods

Detailed methods of the original RCT have been published previously [21]. Eligible infants (<32 completed gestational weeks at birth) were randomised in eight neonatal intensive care units in the USA, either to the experimental group where the HRCi (HeRO; Medical Predictive Science, Charlottesville, VA, USA) was displayed to the clinicians or to the control group where the HRCi was masked. Data for this study were obtained from the subset of infants who were mechanically ventilated and randomised to the arm where the HRCi was masked. The following de-identified data for the first extubation episode from each infant were extracted: sex, gestational age, birthweight, date/time of birth, date/time of intubation, date/time of extubation, date/time of re-intubation (if applicable) and the hourly HRCi during the episode. Each extubation episode started 24 h before extubation or at intubation if mechanical ventilation was initiated only during this period. The extubation episode ended either 72 h after extubation or at re-intubation if this happened within the 72-h post-extubation window. Thus, a maximum of 96 h was included in each episode from start to finish (supplementary figure S1). Infants were considered "cases" if they were re-intubated within 72 h after extubation or "controls" if they were not. Patients who died during the episode were primarily planned extubations and were excluded from the analysis [22]. The hourly HRCi scores from each episode were grouped into 6-h epochs (seven scores) (supplementary figure S2) and the mean HRCi scores were used for all subsequent analyses. If some of the scores were missing, then the mean of the available scores were used instead. The extubation episodes were marked with "ABX" if the infant was commenced on antibiotics for clinically suspected infection lasting at least 5 days within 72 h before or after extubation. Similarly, episodes were marked with "PosBC" if the infant had a positive blood culture (contaminants excluded) from a sample taken within 72 h both before and after extubation. Infants born small for gestational age were defined as body weight below the 10th percentile and identified using data from a current US cohort [23].

Statistical analysis was conducted using R for Windows version 3.3.2 (R Core Team, Vienna, Austria). Descriptive data are presented as mean and 95% confidence interval or median and interquartile range (IQR) for continuous variables, and as number (percentage) for categorical variables. Continuous variables were compared between cases and controls using the Mann–Whitney U-test; categorical variables were compared using Fisher's exact test (two-sided). Correlation between variables was calculated using Spearman's coefficient. Continuous variables were transformed into their natural logarithms if they had a skewed distribution before analysis. Each explanatory variable was initially assessed through a univariable logistic model, with re-intubation as the binary outcome. Statistically significant variables ($p<0.05$) were then included in further multivariable models. Pre-extubation model performance was assessed using receiver operator characteristic curves and by analysing the area under the curve (AUC) values, which were compared using the DeLong method.

Pre-extubation model

The pre-extubation model was created using only the first extubation episode from each infant. A multivariable logistic regression model was fitted utilising clinical and physiological variables including the HRCi to produce the probability of re-intubation for each individual. The model was tested using two different methods. In the first method, all eight centres in the original trial were randomly split into a training group (five centres) and test group (three centres), to give a total of 56 combinations. Data from infants in the training group were used to fit the model using multivariable logistic regression analysis and the test group was used to calculate an AUC for the test data. In the second method, the database of all eligible infants was randomly split into two parts: two-thirds were used to create the predictive model (model cohort) and the remaining one-third was used to validate the model (test cohort).

Post-extubation model

Following extubation (supplementary figure S1), an estimation of the likelihood of re-intubation was given by a hazard function (the hazard being the instantaneous risk of re-intubation). B-splines were used to model the shape of the hazard within a generalised linear mixed models framework and the smoothness of the curve was controlled by implementing an autoregressive structure on the baseline hazard coefficients [24]. Further details of the model are presented in the supplementary material.

Prototype application

An R package called Shiny (shiny.rstudio.com) was used to build an interactive web application to run the models and offer the

option of the predictive tool to clinicians with or without access to the HRCi. The web application can be accessed at www.heroscore.com/extubation.

Results

Description of the cohort

The first extubation episodes from the cohort of 577 infants (supplementary table S1) were included for analysis. Data from 397 infants were used to train the pre-extubation model and 180 infants were used to test the model. Comparative demographics, clinical variables and HRCi scores of the model and test cohorts are presented in table 1; no statistically significant differences were observed between the two groups. The model and test groups were further subdivided into cases and controls; comparative data for all four groups are presented in supplementary table S2.

TABLE 1 Comparison of the model and test cohorts **[Q9]**

	Model	Test	p-value
Total infants	397	180	
Positive blood culture	38 (9.6)	14 (7.8)	0.470
Antibiotic use	90 (22.8)	37 (20.6)	0.540
Gestational age weeks	26.6 (26.4–26.8)	26.7 (26.4–27.1)	0.279
Birthweight g	857 (833–881)	864 (829–900)	0.748
Small for gestational age	49 (12.3)	25 (13.9)	1.00
Age at extubation weeks	29.1 (28.8–29.4)	29.2 (28.7–29.6)	0.901
Ventilation h	311 (266–357)	298 (226–370)	0.748
Mean pre-extubation ~~hero~~HRCi score **[Q10]**#	1.59 (1.43–1.74)	1.45 (1.24–1.66)	0.325

Data are presented as n, n (%) or mean (95% CI), unless otherwise stated. #: mean score of pre-extubation epoch (seven scores), starting from −6 h (or less if intubated closer to extubation or scores missing) to 0 h (extubation event). Continuous variables were compared between cases and controls using the Mann–Whitney U-test; categorical variables were compared using Fisher's exact test.

Before ~~running~~deriving the models, a correlation matrix was created to include all the factors from the whole cohort to identify any significant associations between factors and avoid overfitting of the model (supplementary table S3). Body weight and gestational age were highly correlated with each other, and therefore only body weight was used in all subsequent models.

Univariable model

A univariable regression model compared 91 cases and 306 controls in the training cohort (397 infants), to identify statistically significant variables for the final models, and the results are presented in table 2. As evident from table 2, body weight, post-menstrual age **[Q4]** at extubation, use of antibiotics (as defined earlier) and log of the pre-extubation HRCi scores were statistically significantly different between cases and controls and were included in further models.

TABLE 2 Univariable analysis of relevant demographic variables, clinical variables and Heart Rate Characteristics index (HRCi) scores (cases *versus* controls) for all infants **[Q11]**

	Estimate	SE	*z*-value	p-value	r^2
Birthweight kg	−2.0421	0.5601	−3.6460	0.0003	0.0323
Log ventilation duration h	0.0465	0.0735	0.6332	0.5266	0.0010
Post-menstrual age at extubation weeks	−0.1949	0.0497	−3.9188	0.0001	0.0498
Antibiotics	1.0481	0.2619	4.0019	0.0001	0.0428

Positive blood culture	0.3512	0.3795	0.9255	0.3547	0.0022
Log pre-extubation HRCi score	0.6521	0.1506	4.3312	0.0000	0.0503

Pre-extubation model (www.heroscore.com/preext)

The significant variables from the univariable analysis on infants in the training cohort were used in a multivariable model to calculate adjusted estimates of the probability of re-intubation (table 3). A model was constructed to predict outcomes before extubation. All significant factors from the univariable model were independent predictors contributing to the probability of re-intubation, except post-menstrual age at extubation which failed to reach statistical significance. The estimate (logistic regression coefficient), which gives the change in the log odds of the probability of re-intubation by 72 h, was directly related to an increase in the pre-extubation HRCi scores and use of antibiotics, but inversely related to body weight and post-menstrual age at extubation. Thus, for every unit increase in pre-extubation HRCi score, the log odds of re-intubation increased by 0.56, for use of antibiotics it increased by 0.93 and for every unit increase in birthweight it decreased by 1.63. The r^2-value indicates an overall fit of the model, showing what proportion of re-intubation can be explained by the explanatory variables. As post-menstrual age at extubation is a clinically significant parameter to most clinicians considering extubation readiness, this variable was left in the model. Thus, our model predicts the probability of re-intubation of patients in our cohort within 72 h of extubation under current clinical practice.

TABLE 3 Adjusted estimates for significant independent variables to predict the probability of re-intubation after extubation, from the first episode for each infant **[Q12]**

	Estimate	SE	*z*-value	p-value	r^2
Log pre-extubation HRCi score	0.5631	0.1651	3.4109	0.0006	0.1287
Birthweight kg	−1.6261	0.6077	−2.6758	0.0075	
Post-menstrual age at extubation weeks	−0.0912	0.0491	−1.8575	0.0632	
Antibiotics	0.9326	0.2867	3.2535	0.0011	

HRCi: Heart Rate Characteristics index.

As HRCi monitoring is not yet routine in many neonatal units, we constructed a second model excluding the HRCi, to make the app relevant to a wider range of clinicians. Results are presented in supplementary table S4 and this model is included in the Shiny app.

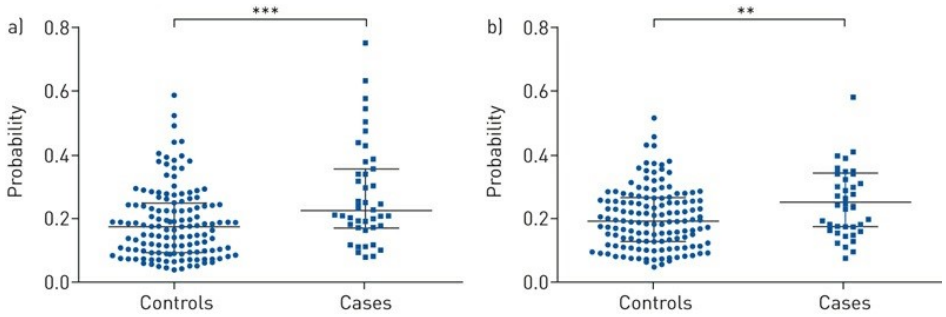
Pre-extubation model validation: method 1

Using groups of centres as training sets (five centres) and test sets (three centres) the models were fitted and validated. In total, all 56 possible combinations of training and test sets were fitted and tested to produce AUC values of probability of re-intubation with or without HRCi scores (supplementary table S5), which were all compared using the DeLong method. As is evident from the results, using the model with the HRCi score produced consistently higher AUCs (mean 0.72, 95% CI 0.71–0.74) compared with those from the model without HRCi scores (mean 0.68, 95% 0.66–0.69) and 25 of the 56 combinations (44.6%) were significantly different.

Pre-extubation model validation: method 2

Using the results from the multivariable model, the probability of re-intubation was calculated for all episodes in the test cohort. Median (IQR) probability of re-intubation was significantly higher in the cases than controls: model with the HRCi included (median probability controls 0.18 (0.10–0.25) *versus* cases 0.23 (0.17–0.35); p<0.001) (figure 1a) and model without the HRCi (0.19 (0.13–0.26) *versus* 0.25 (0.18–0.34); p<0.01) (figure 1b). Using receiver operator characteristic curves to assess model performance, AUC for the model with the HRCi included was 0.68 (95% CI 0.59–0.77; p<0.001) and the model without the HRCi was 0.65 (95% CI 0.56–0.75; p<0.01) (supplementary figure S3). No significant difference was found between the AUCs of the two curves using the DeLong method (p=0.44).

FIGURE 1 Scatter plots of probability of re-intubation: a) pre-extubation model including Heart Rate Characteristics index (HRCi) scores and b) pre-extubation model excluding HRCi scores. Each data point is an episode. Bars represent median and interquartile range. ***: p<0.001; **: p<0.01. **[Q6]**



Arranging the probability scores from the test cohort in deciles from the model incorporating the HRCi, a strategy for risk stratification is proposed to aid interpretation of the probability scores (supplementary table S6). Probability scores <0.16 in the test cohort had an overall low risk of re-intubation (<15% re-intubated). If scores were between 0.16 and 0.21, there was a moderate risk of re-intubation (15–30% re-intubated), and higher scores (>0.21) were stratified as a high risk for re-intubation (overall, >30% of infants were re-intubated with such a score). Clinicians can use this stratification system to interpret probability scores from the model for the real risk of re-intubation.

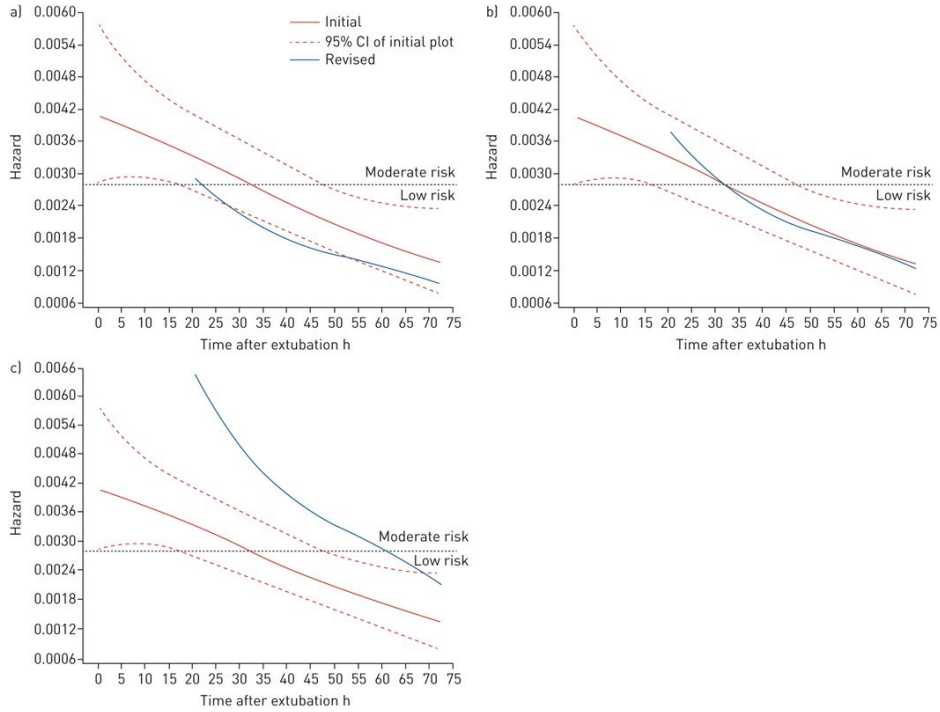
For the online application, data from the first extubation episode from all eligible infants (n=577) were used to recreate the model. AUCs were calculated for each step in the model using the same data (supplementary table S7), which suggest that HRCi scores were the main contributor (68%) to the model; the other variables together contributed another 4% to reach a final AUC of 0.72 (95% CI 0.68–0.77).

Post-extubation model (www.heroscore.com/postext)

The instantaneous hazard of the test cohort in the first hour after extubation was calculated from the HRCi to create a distribution table (supplementary table S8). An instantaneous hazard score in the first hour after extubation <0.0029 was found to have a low risk of re-intubation (<15% re-intubated), scores between 0.0029 and 0.0077 had a moderate risk of re-intubation (15–30% re-intubated), and scores >0.0077 had a high risk of re-intubation (>30% re-intubated).

Adjusting for body weight, post-menstrual age at extubation and use of antibiotics, hazard models (with 95% confidence intervals) were created for combinations of the above factors at various time-points and HRCi after extubation. These plots are dynamic, fully adaptable to the clinical parameters in the model, and offer a visual representation in the Shiny app of the change in hazard over time and with changing clinical condition. The risk stratification ranges from supplementary table ~~4~~8 are **[Q5]** also represented on the plots to help interpret the hazard scores. Representative plots are presented in figure 2a–c, with an illustration of revised hazard plots at a different time-point when the HRCi changes. Clinicians will be able to examine and compare the projected pattern of the hazard at different time-points using all combinations of clinical variables and the HRCi derived from their patients to aid their clinical decisions.

FIGURE 2 Representative hazard plots of an infant with birthweight 1.2 kg, extubated at 30 weeks of post-menstrual age on antibiotics. Plots show baseline hazard for the infant just after extubation with a Heart Rate Characteristics index (HRCi) of 1 and revised hazard, which was recalculated at 20 h of age, with a) a decrease in the HRCi score to 0.5, b) a minor increase in the HRCi score to 2 and c) a significant increase in the HRCi score to 5. While birthweight and post-menstrual age at extubation remain unchanged, the model can be adjusted for use of antibiotics and HRCi scores at any time-point. **[Q7] [Q8]**



Discussion

To the best of our knowledge, this is the first large-scale analysis of multiple clinical variables and the HRCi to create clinically useful models for the prediction of extubation readiness and success in preterm infants. Applying rigorous methods, we have validated the predictive models and believe that these will serve as an additional tool for clinicians faced with such critical decisions daily.

The association of mechanical ventilation with bronchopulmonary dysplasia is well established [4, 25], prompting clinicians to attempt early extubation to noninvasive respiratory support. However, extubation failure rates are high in preterm infants [26]. A recent longitudinal study suggested that the majority of extubation failures in preterm infants (68%) were due to respiratory causes [27], possibly contributed by de-recruitment of the lungs and respiratory failure after extubation. An observational study has suggested that the cumulative duration of mechanical ventilation is associated with chronic respiratory morbidity [28]. Thus, accurately predicting extubation readiness and success is critical to improve outcomes, and we believe our study is a significant step in that direction.

Our post-extubation model allows the clinician to review the probability of re-intubation in real-time. This offers an opportunity for the clinician to escalate in the early post-extubation phase the range and level of noninvasive respiratory support (high flow oxygen therapy, CPAP and noninvasive positive pressure ventilation) to maximise the chances of extubation success, balancing this with patient comfort and operator choice. A real-time trend in the probability of success following extubation may help in optimising this choice.

Our definition of clinical variables is worth discussing. As a change in HRCi score precedes clinical status change by at least 6 h [21], we chose a 6-h epoch for analysis before the extubation episodes. Clinical experience and available evidence suggest that re-intubation within 48 h of extubation is associated with poorer outcomes [29]; we chose a 72-h pragmatic period to define the success of extubation. Sepsis is a known cause for extubation failure and can also increase HRCi scores [21]. Considering the sensitivity of traditional blood cultures is modest and depends on the technology used and volume of blood inoculated [30], we chose to include clinician-suspected sepsis in our model. We pragmatically accepted antibiotic use for at least 5 days by experienced clinicians in an intensive care setting as a surrogate for that diagnosis. Indeed, in our cohort, "clinical sepsis" was found to be significantly different between cases and controls, while positive blood culture was not. We acknowledge the subjectivity involved in the diagnosis of clinical sepsis, and while using our app we encourage clinicians to choose "yes" for antibiotics only if they have real clinical concerns and are intending to use antibiotics for at least 5 days.

An AUC of 0.7–0.8 has been categorised as "acceptable" (*versus* "excellent" and "outstanding" for higher AUCs) [31]. Whether an AUC of 0.72 can produce sufficient discrimination for a potential clinical decision support tool depends upon the state of clinical practice. For a clinical situation like extubation readiness, where the clinical assessment has to be not only accurate but also timely (both aspects being vulnerable to variation in subjective assessment and personal practice bias of clinicians), a relatively low AUC of a dynamic model may still be an improvement. As an example, we offer the HRCi for its originally intended purpose: prediction of risk of infection in neonates. The HRCi was previously reported to have an AUC of 0.70–0.75 for various definitions

of sepsis or infection [32, 33], yet reporting the HRCi to clinicians in real-time led to a 40% reduction in mortality after infection in a very large RCT [34]. Considering the paucity of dynamic data informing clinicians of extubation readiness in neonates, we feel that clinicians are likely to find our proposed predictive model for extubation useful as a decision support tool. It is important to note that both the pre- and post-extubation models report the probability that the patient will be re-intubated, not whether the patient should be re-intubated.

Adult studies of peri-extubation practices have identified that mortality after extubation failure (or re-intubation) is very high, reported to be ~42%. However, mortality after extubation failure in neonates is less common (one out of 162 infants) in published studies [5], even more so with unplanned extubations. The majority of deaths in neonates following extubation are a planned outcome as part of the withdrawal of intensive care for progression to palliative care [35, 36]. Planned extubation as part of the palliative care process in neonatal medicine is now well established with peer-reviewed guidelines directing the standard of care [35, 37–39]. In our study cohort, mortality within the 72 h after extubation was primarily due to the withdrawal of life-prolonging respiratory support in infants who were not expected to survive. Thus, they did not reflect the success or failure of the extubation decision and were excluded from the cohort *a priori*.

In sick preterm infants, a large volume of real-time data is generated from physiological monitoring and life support devices (*e.g.* ventilators and infusion pumps) [40]. Computerised processing and analysis of this "big data" can potentially aid decision tools by unearthing hidden trends and overlooked patterns [41–44]. While this is a work in progress with immense potential [45], the HRCi is a validated computerised tool using a single physiological parameter, *i.e.* heart rate, and currently available as a decision-making tool [21].

Our study has several strengths. The masking of the HRCi scores to the clinicians in our cohort means that clinical management and the decision to extubate (and re-intubate) were unbiased and representative of the actual clinical practice. We excluded repeat episodes of intubation and extubation in the same infant, reducing unmeasured confounders. Our model was also validated in both combinations of all centres as training and test groups as well as in a randomly allocated group of infants from the same cohort, which are statistical approaches commonly used in previous studies [46, 47]. We have treated extubation readiness (before the actual act of extubation) and extubation success (remaining extubated for a specified period) separately, and have presented prediction models for both. While the more common and crucial decision is often making a judgement on extubation readiness, the real-time probability of extubation failure in the post-extubation period depicted by the visual output may lead to an escalation of type and level of noninvasive respiratory support at the right time, thus avoiding re-intubation

Our study has limitations. While our model and validation have achieved high statistical significance, the significance of the potential clinical benefit will only become apparent when this is used in practice. Despite the large and disparate cohort representing practices in eight different neonatal centres, it would have been ideal to externally validate the model in a separate cohort of infants. As the HRCi is now in routine clinical use in many neonatal units for predictive monitoring of wellbeing, it is both clinically and ethically unacceptable for clinicians to be blinded to the HRCi data in such units to build up a cohort. We would be keen to collaborate with other groups who are using HRCi monitoring to evaluate the performance of our model. We did not have data on mode of noninvasive respiratory support and blood gases to determine the appropriateness of re-intubation and these parameters could potentially improve the model further. However, it is also important to keep the model simple and usable in routine clinical practice by using the minimum number of the most discerning variables.

In summary, we have constructed and validated a predictive model of extubation readiness and success, and offer our model as a decision support tool for clinicians in the complex decision-making process to extubate and manage infants in the peri-extubation period.

Footnotes

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Author contributions: M. Chakraborty conceptualised the study, analysed and interpreted data, wrote and revised drafts of the manuscript, and approved the final draft. W.J. Watkins analysed and interpreted data, wrote code for online applications, revised drafts of the manuscript, and approved the final draft. K. Tansey analysed data, wrote code for online applications and approved the final draft. W.E. King collected original data, revised drafts of the manuscript and approved the final draft. S. Banerjee conceptualised the study, interpreted data, revised drafts of the manuscript and approved the final draft; this author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Conflict of interest: S. Banerjee has nothing to disclose.

Conflict of interest: M. Chakraborty has nothing to disclose.

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