Original Research

Relationship Between the Respiratory Severity Score and Extubation Failure in Very-Low-Birth-Weight Premature Infants

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Abstract

Objective: The objective of the study is to investigate the utility of the respiratory severity score (RSS), an easy-to-use, non-invasive respiratory failure assessment tool that does not require arterial blood sampling, for predicting extubation failure in very-low-birth-weight premature infants.

Methods: Demographic characteristics, clinical course, and neonatal morbidities were retrospectively analyzed. Data were obtained from the files of infants who were admitted to our unit between February 2016 and September 2020, were born before 30 weeks' gestation, and had a birth weight <1250 g. Extubation success was defined as no need for reintubation for 72 h after extubation. RSS and RSS/kg values before each patient's first planned extubation were calculated. RSS values before extubation and risk factors for extubation failure were compared between infants in the successful and failed extubation groups.

Results: Our study enrolled 142 infants who met the inclusion criteria. The extubation failure rate was 30.2% (43/142). Early gestation, low birth weight, male sex, high RSS, grade ≥3 intraventricular hemorrhage, late-onset sepsis, low weight at the time of extubation, and postmenstrual age at the time of extubation were identified as risk factors for extubation failure. In the logistic regression analysis including these risk factors, RSS/kg remained a significant risk factor, along with late-onset sepsis (OR 25.7 [95% CI: 5.70–115.76]; *p*<0.001). In the receiver operating characteristic analysis of RSS values, at a cutoff value of 2.13 (area under the curve: 82.5%), RSS/kg had 77% sensitivity and 78% specificity (*p*<0.001). The duration of mechanical ventilation and hospital stay were prolonged in infants with extubation failure. The incidence rates of stage ≥3 retinopathy of prematurity and stage ≥2 necrotizing enterocolitis were also higher.

Conclusions: High RSS and RSS/kg values were closely associated with extubation failure and can be used as a non-invasive assessment tool to support clinical decision-making, and thus reduce the rate of extubation failure.

Keywords: Extubation failure; prematurity; respiratory severity score.

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Introduction

Although non-invasive methods have gradually gained prominence in recent years and have been used more frequently for respiratory management of premature infants with very low birth weight (VLBW), a significant number of these infants require mechanical ventilation.[1,2] Endotracheal intubation and mechanical ventilation are associated with bacterial colonization, sepsis, ventilator-associated pneumonia, and airway trauma despite their lifesaving capability. [3,4] Furthermore, as the duration of mechanical ventilation increases, so too does the risk of bronchopulmonary dysplasia (BPD) and neurodevelopmental disorder.[5,6] Therefore, performing early extubation in preterm infants, and shortening the duration of mechanical ventilation as much as possible, have become important objectives for physicians working in neonatal intensive care units.

Currently, decisions regarding extubation are usually based on subjective clinical judgments informed by blood gas values, ventilator parameters, and interpretation of the infant's clinical condition; this may lead to inappropriate extubation.[7] Previous studies conducted on extremely low-birth-weight premature infants determined that approximately one-third of extubated infants required re-intubation.[8] Extubation failure is not only associated with prolonged mechanical ventilation time but is also independently associated with increased mortality and longer hospitalization time.[9,10] Hypoxemia, bradycardia, blood pressure fluctuations, and changes in cerebral function caused by repeated endotracheal intubation and complications (such as upper airway trauma and atelectasis) are possible causes of these negative outcomes.[11,12] Although numerous studies conducted over a long period have explored ways to determine infants' readiness for extubation, and thereby increase extubation success,[13–16] no strong evidence supports the use of any particular predictor of extubation readiness over clinical judgment alone.[17]

The respiratory severity score (RSS) is a non-invasive respiratory failure assessment tool that does not require arterial blood samples. It has been used as a measure of disease severity in some large-scale multicenter studies.[18,19] In addition, its association with BPD, mortality, and short-term complications has been investigated,[20,21] and high RSS values were found to be associated with extubation failure.[22] A study in which the RSS was analyzed by weight (RSS/kg) found that RSS/kg was more useful for predicting the development of pulmonary hypertension than the RSS.[23]

Our aim in this study was to examine factors affecting extubation failure and to investigate the value of pre-extubation RSS for predicting extubation success.

Methods

This retrospective, single-center study enrolled premature infants in the neonatal intensive care unit of our hospital between February 2016 and September 2020. Approval of the study was obtained from the university's clinical research Ethics Committee (No: 2021/51-13).

Study Population

The study population consisted of infants born in our hospital, or in an external center and transferred to our unit, at a gestational age <30 weeks and birth weight <1250 g.

Inclusion Criteria

Infants who were intubated due to respiratory failure on the first postnatal day and underwent the first planned extubation were included in the study.

Exclusion Criteria

The exclusion criteria were late transfer, no previous intubation, intubation in the days following delivery, unplanned extubation, presence of a major congenital anomaly, and death or transfer to another center without extubation.

Data Collection

The demographic data of the infants included in the study (gestational age, birth weight, mode of delivery, sex, antenatal steroid therapy, 5-min Apgar score, small for gestational age [SGA] status, maternal age, preeclampsia, preterm premature membrane rupture, chorioamnionitis), findings related to clinical follow-up (duration of invasive mechanical ventilation, duration of noninvasive mechanical ventilation, duration of oxygen treatment, surfactant need, postnatal steroid therapy, pneumothorax, late-onset sepsis, grade ≥3 intraventricular hemorrhage [IVH], hemodynamically significant patent ductus arteriosus [PDA], stage ≥2 necrotizing enterocolitis [NEC], stage ≥3 retinopathy of prematurity [ROP]), length of hospital stay, BPD, and mortality data were recorded by examining patient files and online patient records.

The time of extubation, postmenstrual age (PMA), and weight of patients who underwent planned extubation were recorded. Pre-extubation RSS and RSS/kg parameters were estimated. The following formula was used to estimate RSS.

RSS: $MAP \times FiO_2$

MAP: mean airway pressure; FiO_2: inspired oxygen fraction.

RSS/kg was estimated based on the birth weight of the patient during the first 2 postnatal weeks, whereas the

current weight was used on subsequent days. In cases where MAP could not be obtained from patient records, it was estimated using the following formula.

MAP: PEEP + [(PIP − PEEP) × (Ti/(Ti + Te)]

PEEP: positive end expiratory pressure; PIP: peak inspiratory pressure; Ti: inspiratory time; Te: expiratory time.

The patients were divided into two groups: those who were successfully extubated and those who underwent failed extubation. RSS, RSS/kg, and all other variables were compared between the groups.

Respiratory Management

No standard approach for delivery room respiratory management was applied, as some of the infants had been referred from external centers. However, delivery room management for infants born in our unit was consistent with the recommendations of international guidelines.[24] Although non-invasive ventilation strategies were preferred as the primary treatment in infants with respiratory distress syndrome (RDS), to minimize barotrauma and volutrauma due to endotracheal intubation and mechanical ventilation, pressure-controlled, volume-guaranteed, synchronized conventional ventilation methods were performed in cases where invasive mechanical ventilation was required. High-frequency oscillatory ventilation (HFOV) was preferred only as a rescue method.

In our unit, the decision for intubation of hemodynamically stable infants is made by the physician based on the following parameters: PIP: 12–16 cm H_2O; PEEP: 5–6 cm H_2O; ventilation rate: <25/min; FiO_2 <30%; partial oxygen saturation (SpO_2): 90–94%, blood gas pH: ≥7.3; and partial carbon dioxide pressure (pCO_2): <55 mmHg. During the post-extubation period, neither nasal continuous positive airway pressure (NCPAP) nor nasal intermittent positive pressure ventilation (NIPPV) was uniformly applied; however, NIPPV was performed before endotracheal intubation in cases where NCPAP failed. Sedative drugs were discontinued for at least 12 h prior to planned extubation. All of the infants included in the study were given a loading dose of 20 mg/kg caffeine on the postnatal 1st day, followed by a maintenance dose of 5–10 mg/kg.

The decision to perform re-intubation despite noninvasive respiratory support required the presence of at least one of the following indices of clinical deterioration: pH <7.2 and/or pCO_2 >65 mmHg in blood gas; failure to sustain target oxygen saturation during in pulse oximetry monitoring; or recurrent (≥3) apnea attacks accompanied by bradycardia in the last 6 h or a single apnea attack that required positive pressure ventilation with a bag valve mask.

Definitions

Late transfer was considered as transfer taking place after the first postnatal day. Successful extubation was defined as no need for re-intubation during the 72 h following the extubation. Unplanned extubation was defined as spontaneous or accidental extubation without fulfillment of the extubation criteria, and application of noninvasive ventilation thereafter. Re-intubation immediately after extubation was not included in this definition. The following guidelines were used: the National Institutes of Health Consensus Classification for the diagnosis of severe BPD;[25] the modified Bell's staging criteria for stage ≥ 2 NEC;[26] the Papile classification for the diagnosis of grade ≥3 IVH;[27] and the International Classification of ROP[28] for the diagnosis of stage ≥3 ROP. The diagnosis of late-onset sepsis was based on the presence of positive blood culture after the 3rd day of life.[29]

Statistical Analysis

The data were analyzed using IBM SPSS software (ver. 23.0; IBM Corp., Armonk, NY, USA). The normality of the data was examined with the Kolmogorov–Smirnov test. Chi-square and Fisher's exact tests were conducted to compare categorical variables. The independent-sample t-test was used to compare normally distributed data for binary groups, and the Mann–Whitney U test was used to compare non-normally distributed data. Binary logistic regression analysis was used to investigate independent factors affecting extubation success. Receiver operating characteristic (ROC) analysis was performed to determine cutoff RSS and RSS/kg values for successful intubation. Quantitative data are reported as mean±standard deviation or median (Q1, Q3). Categorical data are presented as frequency (percentage). The significance level was set at $p<0.05$.

Results

A total of 243 infants who met the birth weight and gestational age criteria were admitted to our unit during the study period; of these, 142 infants met the inclusion criteria. The extubation failure rate among intubated infants was 30.2% (43/142). The flow diagram of the study is shown in Figure 1, and the demographic features of the groups are presented in Table 1. The birth weight and gestational age were significantly lower, and the proportion of males was significantly higher, in the unsuccessful extubation group. The characteristics of the groups at the time of extubation, and their ventilatory support durations, are presented in Table 2. The PMA and weight of the failed extubation group at the time of extubation were significantly lower than those of the successful extubation group, whereas
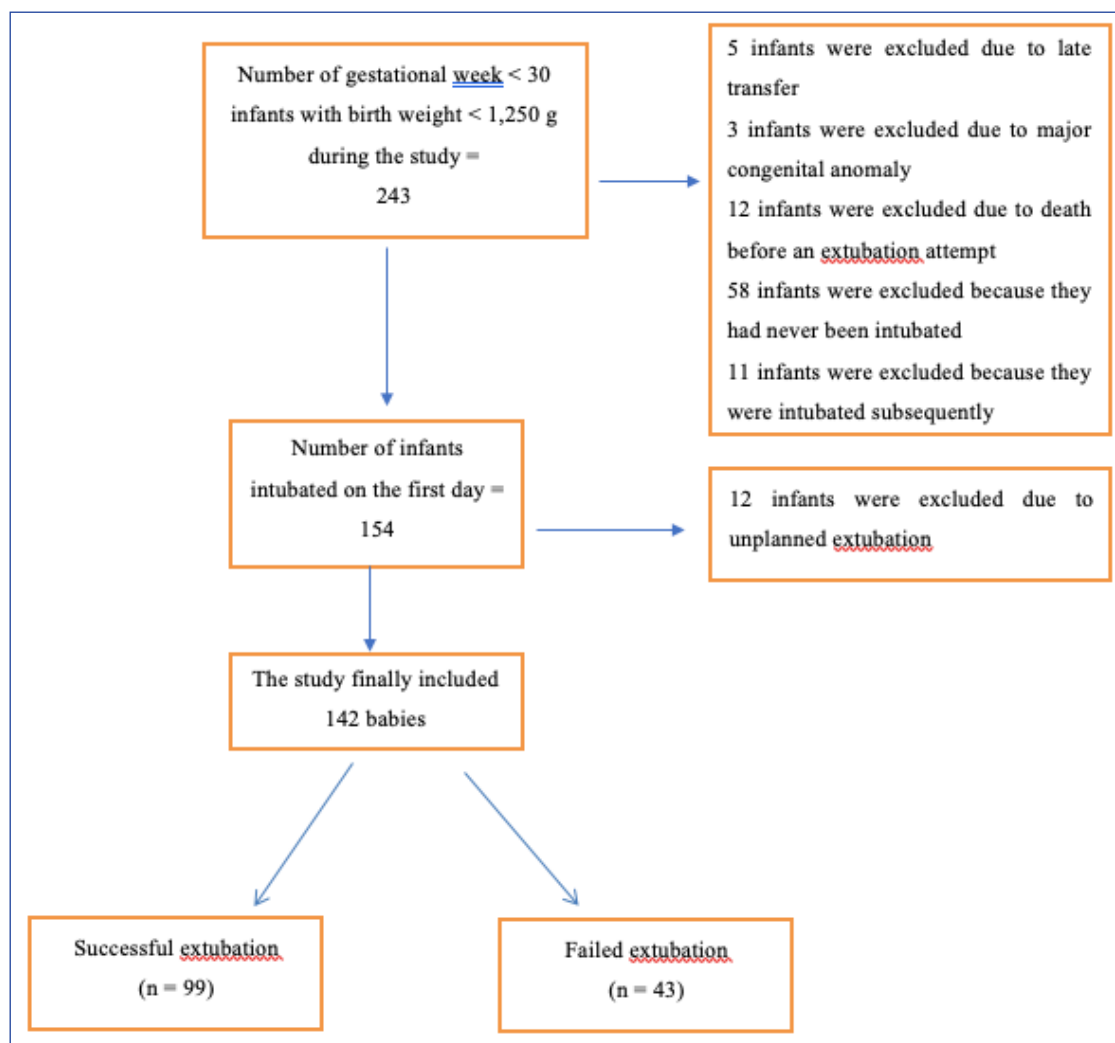
Figure 1. Flow diagram of participant enrollment.

Table 1. Demographic characteristics of the groups

	Extubation success (*n*=99)	Extubation failure (*n*=43)	*P*
Gestational age[a] (weeks)	27 (26–28)	26 (24–27)	**<0.001**
Birth weight[a] (grams)	940 (740–1080)	750 (650–930)	**<0.001**
Male, *n* (%)	39 (39.4)	27 (62.8)	**0.010**
SGA, *n* (%)	8 (8.1)	4 (9.3)	0.81
5-min Apgar score[a]	6 (6–7)	6 (5–7)	0.334
Cesarean delivery, *n* (%)	85 (85.9)	31 (72.1)	0.051
Antenatal steroid, *n* (%)	41 (31.3)	21 (48.8)	0.413
Maternal age[b], (years)	28.9±5.7	28.4±6.9	0.675
Preeclampsia, *n* (%)	19 (19.2)	9 (20.9)	0.811
Chorioamnionitis, *n* (%)	6 (6.1)	3 (7)	1.000
pPROM >18 h, *n* (%)	20 (20.2)	11 (25.6)	0.476

SGA: Small for gestational age; pPROM: Preterm premature rupture of membranes. [a]Values are presented as median (interquartile range). [b]Values are presented as mean±SD.

Table 2. Parameters at the time of extubation and respiratory support times of both groups

	Extubation success (*n*=99)	Extubation failure (*n*=43)	P
Time of extubation (days)	2 (1–6)	4 (3–5)	0.076
PMA at extubation (weeks)	28 (27–29)	26 (25–28)	**0.001**
Weight at extubation (g)	980 (800–1100)	750 (680–975)	**0.001**
RSS	1.6 (1.5–1.8)	1.9 (1.8–2.2)	**<0.001**
RSS/kg	1.7 (1.5–2.1)	2.4 (2.2–3)	**<0.001**
Duration of invasive MV (days)	3 (1–10)	14 (10–33)	**<0.001**
Duration of noninvasive MV (days)	12 (7–22)	17 (10–26)	0.098
Duration of supplemental oxygen (days)	23 (10–38.5)	21 (14.3–36.5)	0.433

PMA: Postmenstrual age; RSS: Respiratory severity score; MV: Mechanical ventilation. Values are presented as median (interquartile range).

Table 3. Clinical characteristics and neonatal morbidities of the groups

	Extubation success (*n* = 99)	Extubation failure (*n* = 43)	P
Surfactant, ≥2 doses, *n* (%)	27 (27.3)	31 (72.1)	**<0.001**
Postnatal steroid, *n* (%)	56 (56.6)	36 (83.7)	**0.002**
Pneumothorax, *n* (%)	1 (1)	3 (7)	0.083
Late-onset sepsis, *n* (%)	11 (11.1)	18 (41.9)	**<0.001**
Grade ≥3 IVH, *n* (%)	13 (13.1)	12 (27.9)	**0.034**
HsPDA, *n* (%)	35 (35.4)	22 (51.2)	0.077
Stage ≥2 NEC, *n* (%)	14 (14.1)	13 (30.2)	**0.025**
Stage ≥3 ROP, *n* (%)	18 (18.2)	16 (38.1)	**0.011**
Severe BPD, *n* (%)	18 (18.2)	9 (21.4)	0.654
Length of stay (days)[a]	75 (57–95)	91 (76.3–117.5)	**<0.001**
Severe BPD or death, *n* (%)	18 (18.2)	11 (25.6)	0.315
Death, *n* (%)	4 (4)	3 (7)	0.433

IVH: Intraventricular hemorrhage, HsPDA: Hemodynamically significant PDA, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, BPD: Bronchopulmonary dysplasia. [a]Values are presented as median (interquartile range).

Table 4. Independent predictors of extubation failure: Results of binary logistic regression analysis

	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
RSS/kg	8.72 (4.02–18.93)	**<0.001**	25.70 (5.70–115.76)	**<0.001**
Birth weight	0.64 (0.42–0.77)	**0.001**	0.52 (0.28–1.21)	0.67
Gestational age	0.67 (0.54–0.84)	**<0.001**	0.75 (0.54–1.05)	0.09
Male	0.39 (0.18–0.81)	**0.011**	0.48 (0.19–1.26)	0.14
Grade ≥3 IVH	2.56 (1.06–6.21)	**0.037**	1.72 (0.53–5.52)	0.37
Late-onset sepsis	5.76 (2.41–13.77)	**<0.001**	5.21 (1.66–16.33)	**0.005**

RSS: Respiratory severity score; IVH: Intraventricular hemorrhage.

the invasive mechanical ventilation time, RSS, and RSS/kg values were higher. The clinical characteristics and neonatal morbidities of the groups are shown in Table 3. Infants in the failed extubation group used significantly more surfactant and postnatal steroids, were more likely to be of stage ≥2 NEC, grade ≥3 IVH, and stage ≥3 ROP, were more likely to have late-onset sepsis and had a longer duration of hospitalization.

Table 5. ROC curve analysis results for the RSS and RSS/kg as predictors of extubation failure

	Cutoff	AUC (95% CI)	P	Sensitivity	Specificity	PPV	NPV
RSS	>1.78	0.80 (0.72–0.88)	<0.001	0.77 (0.64–0.89)	0.76 (0.67–0.84)	0.59	0.88
RSS/kg	>2.13	0.83 (0.75–0.9)	<0.001	0.77 (0.64–0.89)	0.78 (0.7–0.86)	0.59	0.89

RSS: Respiratory severity score, ROC: Receiver operating characteristic, AUC: Area under the receiver operating characteristic curve, PPV: Positive predictive value, NPV: Negative predictive value
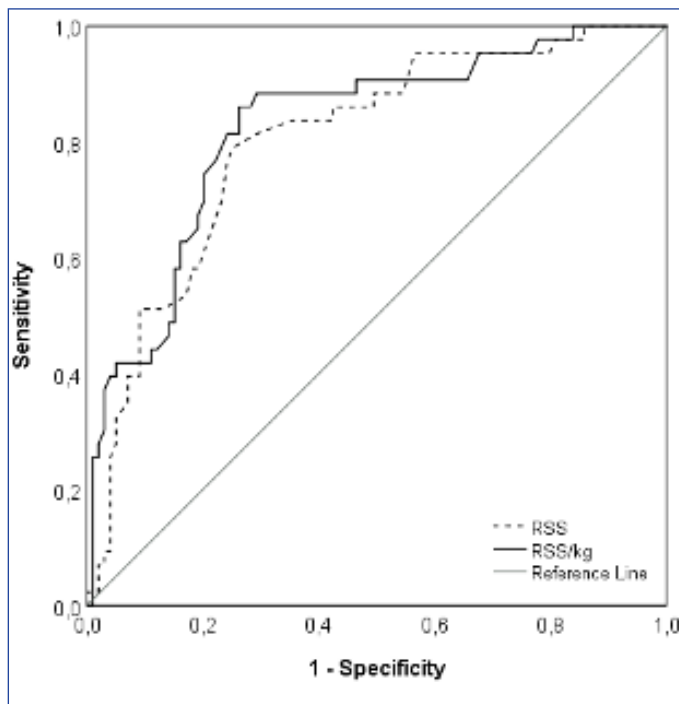
Figure 2: Receiver operating characteristic curves for the respiratory severity score (RSS) and RSS/kg.

In the multivariate logistic regression analysis, which included RSS/kg score and significant early risk factors for extubation failure, late-onset sepsis and RSS/kg remained statistically significant. The logistic regression analysis revealed that an increase in RSS/kg score increased the risk of extubation failure by a factor of 25.7 ($p<0.001$) (Table 4). The sensitivity and specificity of RSS values for predicting extubation failure are shown in Table 5, and the ROC curves are shown in Figure 2. Among the RSS values, the area under the curve (AUC) was the largest for RSS/kg, with a cut-off value of 2.13 (AUC: 83%). This value was statistically significant ($p<0.001$). The sensitivity of the RSS/kg score for determining extubation failure was 77%, and its specificity was 78%.

Discussion

Our study, which to our knowledge is the first to use RSS/kg to predict extubation failure, showed that high RSS and RSS/kg values before extubation were closely related to extubation failure. Moreover, RSS/kg had higher predictive power than the RSS. In addition, the duration of invasive mechanical ventilation and hospital stay were longer in babies with extubation failure, and some neonatal morbidities such as NEC, IVC, and ROP were observed more frequently in these infants, as expected.

Our extubation failure rate of 30.2% was consistent with the literature.[8,9,30] In previous studies, various risk factors such as lower gestational age and birth weight, male gender, low 5-min Apgar score, lack of antenatal steroid administration, and SGA were identified as factors for extubation failure.[9,13,14] In our study, the infants in the unsuccessful extubation group were born earlier and had lower birth weights, and the proportion of males was higher in this group.

Other variables emphasized by previous studies were weight at the time of extubation, PMA, vital findings, blood gas levels, ventilator parameters such as FiO_2, and MAP.[9,17,30,31] In our study, infants who experienced extubation failure had a lower weight and PMA at the time of extubation compared to infants in the successful group. The investigation of extubation duration revealed that infants were extubated predominantly in the first postnatal week, and no difference between the groups in terms of extubation time was observed.

Although the risk factors for extubation failure have been clearly defined, there is no precise assessment tool indicating when an infant is ready for extubation. Spontaneous breathing trials, heart rate variability and pulmonary mechanics have been used in previous studies.[15,16,32-34] Nevertheless, there is no strong evidence to support the use of these methods, alone or in combination, and existing predictors have low accuracy and little clinical benefit for determining extubation failure.[17]

The RSS is a simple, non-invasive, and readily available respiratory failure assessment tool. It has been used effectively in some large-scale multicenter studies as an index of lung disease severity.[18,19] Furthermore, several studies have shown its predictive value for mortality, BPD, and other short-term morbidities.[20,21,23] Mhanna et al.[22] investigated the utility of RSS for predicting extubation readiness

in very-low-birth-weight infants and found that it was the only statistically significant risk factor for extubation failure. In this study, two different RSS cut-off values were employed, and sensitivity was found to decrease as the RSS value increased, although specificity increased. Gupta *et al*.[31] used RSS as a predictor of extubation success in infants with a birth weight <1250 g. In that study, a predictor of extubation readiness was developed based on clinical and demographic data. The results showed that, in addition to higher gestational age and PMA, high pre-extubation pH, low pre-extubation FiO_2, and a low peak RSS level in the first 6 h of life were associated with extubation success. In infants with RDS, the need for MAP and FiO_2 in the 1st h of life can be dramatically reduced by surfactant use, and RSS values may vary considerably. A study in which RSS was used for various purposes demonstrated that RSS values after the 1st days of life were good predictors of severe BPD and mortality.[20] Another study showed that the mean RSS value in the first 3 days of life was a good predictor of severe IVH, BPD, ROP, and mortality.[35] In line with these results, we found that pre-extubation RSS values, rather than the values in the 1st h of life, were significantly higher for infants with extubation failure.

Although some have recommended using target oxygen saturation for infants with VLBW, the MAP value for optimal ventilation varies according to the severity of lung disease and, as shown by Seo *et al*.,[23] also by lung. In their study investigating the association between RSS and pulmonary hypertension, RSS/kg and RSS values were obtained in the first 5 days of life. They found that RSS values were higher in infants developing pulmonary hypertension only on the 2nd and 4th days, whereas RSS/kg values were higher on all 5 days. In our study, RSS/kg values were estimated along with pre-extubation RSS, and the latter values were significantly higher in infants with extubation failure.

Our groups showed significant differences in several risk factors for extubation failure, including gestational age, birth weight, male sex, grade ≥3 IVH, and late-onset sepsis. In our multivariate logistic regression analysis, only RSS/kg and late-onset sepsis were significant risk factors. Our patients were usually extubated in the 1st week of life, and their weight and PMA at the time of extubation were not significantly different from their birth weight and gestational age. Therefore, weight at the time of extubation and PMA were not included in the logistic regression analysis. Because RSS/kg was statistically significant in the logistic regression analysis, ROC analysis was performed on RSS and RSS/kg as predictors of extubation failure. Although they had similar sensitivity and specificity, RSS/kg at a cut-off value of 2.13 had slightly higher specificity

than RSS at a cut-off value of 1.78; both were statistically significant.

Extubation failure was associated with prolonged mechanical ventilation, increased mortality rates, and longer hospital stays.[9,10] In our study, no difference was detected between the groups in terms of severe BPD or mortality, but infants with extubation failure underwent longer invasive mechanical ventilation and had longer hospital stays. Additionally, the proportions of stage ≥3 ROP and stage ≥2 NEC were higher, as was the rate of postnatal steroid use among the infants in this group. We consider that the main reason for this difference in neonatal morbidities was that the infants in the extubation failure group were born earlier and had lower birth weight. However, extubation failure may have also had an impact on these results.

Our study had some limitations, i.e., it was a single-center, retrospective study. Furthermore, the number of patients was limited due to the more frequent use of noninvasive ventilation methods in the primary treatment of RDS in recent years. Consequently, the generalizability of our results is limited. Another limitation was that extubation success was defined over a period of 72 h. There is no consensus in terms of the time over which extubation success should be assessed, and durations of 2–7 days have frequently been used.[36] Approximately 25% of extubation failure cases occur after 48–72 h.[7] On the other hand, reintubation due to non-respiratory factors increases as the time elapsed after extubation increases.[8] Different results might also be obtained by investigating the causes of extubation individually. The reason why infants who experienced neonatal transport following the first postnatal day were not considered in our study was that, as late transfers occur due to severe morbidities (e.g., respiratory distress that requires HFOV, IVH, sepsis) during intensive care monitoring, including these patients would have had a direct impact on the RSS values.

Conclusions

In line with the results of previous studies, no predictor of extubation has yet proven superior to clinical judgment. Nevertheless, it is evident that RSS, which was shown to be a good indicator of lung disease severity, could be beneficial for clinicians in terms of the decision to extubate. Our study, one of the few in which RSS was associated with extubation success, indicates that pre-extubation RSS and RSS/kg values have predictive value for extubation failure. We believe that prospective studies involving more patients and centers will provide additional valuable information about the predictive value of the RSS and other respiratory parameters for extubation failure.

Disclosures

Ethics Committee Approval: This study was approved by Non-Interventional Research Ethics Committee of Biruni University (No: 2021/53-19).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.D., A.U.Z., A.B.; Design – M.D., A.U.Z., A.B.; Supervision – A.B.; Materials – M.D.; Data colection &/or processing – M.D., A.U.Z.; Analysis and/or interpretation – M.D, A.U.Z., A.B.; Literature search – M.D. A.U.Z.; Writing – M.D, A.U.Z.; Critical review – A.B.

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