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Title:
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Date:
2021-06-01

Citation:
Kidman, A. M., Manley, B. J., Boland, R. A., Davis, P. G. & Bhatia, R. (2021). Predictors and outcomes of extubation failure in extremely preterm infants. Journal of Paediatrics and Child Health, 57 (6), pp.913-919. https://doi.org/10.1111/jpc.15356.

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Predictors and outcomes of extubation failure in extremely preterm infants.

Original article

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Brief points:

What is already known on this topic:

- Extremely preterm infants (<28 weeks) are at high risk for extubation failure
- Extubation Failure is associated with several neonatal morbidities

What this paper adds:

- Causes of extubation failure are multifactorial
- Higher pre-extubation mean airway pressure may be associated with extubation failure

Acknowledgements: The authors wish to thank the staff and families of the neonatal intensive care units at Monash Children's Hospital and The Royal Women's Hospital, Melbourne, Australia.

Statement of Ethics

This researched was approved by the Human Research Ethics Committee at both institutions

Disclosure Statement: The authors have no conflicts of interest to declare.

Financial Support:

AMK is supported by a PhD scholarship from the National Health and Medical Research Council (NHMRC) Centre for Research Excellence in Newborn Medicine (GNT1153176).

BJM is supported by a Medical Research Future Fund (Australia) Next Generation Clinical Researchers Career Development Fellowship (MRF1159225)

RAB is supported by a Career Development Award from the Murdoch Children's Research Institute (2015-2020).

PGD is supported by an NHMRC Practitioner Fellowship (1157782)

Author Contributions:

AMK and R.B conceptualised the audit. AMK collected the data and wrote the original draft manuscript. R.B, RAB, BJM and PGD supported and supervised the study design and statistical analysis and drafted the manuscript. Each author has reviewed the manuscript and approved submission of this version. The authors take full responsibility for the manuscript.

Predictors and outcomes of extubation failure in extremely preterm infants.

ABSTRACT

Objective: To determine predictors and outcomes of extubation failure in extremely preterm (EP) infants born <28 weeks' gestational age (GA).

Design: Retrospective clinical audit across two tertiary-level neonatal intensive care units in Melbourne, Australia.

Patients: Two-hundred and four EP infants who survived to their first extubation from mechanical ventilation.

Main outcome measures: Extubation failure (re-intubation) within 7 days after the first extubation.

Results: Lower GA (odds ratio [OR] 0.71, 95% confidence interval (CI), 0.61-0.89, *P*<0.001) and higher pre-extubation measured mean airway pressure (MAP) on the mechanical ventilator (OR 1.9 [95% CI 1.41-2.51], *P*<0.001) predicted extubation failure. The area under a receiver operating characteristic curve for GA and MAP was 0.77 (95% CI 0.70-0.82). After adjustment for GA, infants who experienced extubation failure had higher rates of bronchopulmonary dysplasia (*P*<0.001), postnatal systemic corticosteroid treatment (*P*<0.001), airway trauma (*P*<0.003), longer durations of treatment with mechanical ventilation (*P*<0.001), non-invasive respiratory support (*P*<0.001), and supplemental oxygen therapy (*P*=0.05), and longer hospitalization (*P*=0.025).

Conclusions: Lower GA and higher pre-extubation measured MAP were predictive of extubation failure within 7 days in extremely preterm infants. Extubation failure was associated with increased morbidity and extended periods of respiratory support and hospitalization.

Key Words: *Neonatology, Intensive Care, Extubation Failure, Ventilation*

INTRODUCTION

Endotracheal intubation and mechanical ventilation remain essential therapies in neonatal intensive care units (NICUs) worldwide, despite the increasing use of non-invasive respiratory support.[1] Prolonged mechanical ventilation of preterm infants is associated with ventilator-associated injury, nosocomial infection, bronchopulmonary dysplasia (BPD), neurodevelopmental impairment and mortality[1]. To reduce these risks, clinicians aim to minimize exposure to mechanical ventilation by avoiding mechanical ventilation altogether, or by extubating preterm infants who are mechanically ventilated to non-invasive respiratory support as soon as possible[1].

Some preterm infants develop respiratory failure after extubation and require re-insertion of an endotracheal tube (re-intubation). Failure rates vary widely between centres and are highest in the most immature infants.[2] Extubation failure rates rise from approximately 20% in infants born 28-31 weeks' gestational age (GA) to over 60% in extremely preterm (EP) infants born <28 weeks' GA.[1-3] Extubation failure in EP infants remains difficult to predict. The reasons for re-intubation are multifactorial, and include apnoea and increased supplemental oxygen requirement.[4,9] Previous studies have shown that extubation failure is associated with significant morbidity, including increased duration of mechanical ventilation and non-invasive respiratory support, airway trauma, feeding difficulties, delayed family unit bonding, and even death [2-4]. However, these studies have not examined specific ventilation parameters.[2-4]

Identifying predictors of extubation failure may help clinicians optimize the timing of extubation and reduce morbidities associated with extubation failure. Developing simple, bedside predictive models and optimizing post-extubation support are essential.[6,7] Retrospective studies of predictors of extubation readiness, and of extubation failure in preterm infants,[1-11] indicate that lower GA, lower birth weight, poor lung expansion on chest X-ray and higher fraction of inspired oxygen (FiO_2) prior to extubation are associated with extubation failure.[1-9] Historically, timing of extubation has been largely clinician-dependent and based on predictors such as GA, postnatal age, weight, FiO_2, or tests of spontaneous breathing.[9] Most studies aiming to find predictors of extubation failure have not included detailed consideration of pre-extubation mechanical ventilation parameters.

The aim of this study was to examine demographic characteristics and pre-extubation mechanical ventilation parameters of a contemporaneous cohort of extremely preterm infants to develop a predictive model for extubation failure within 7 days of extubation. In addition, we compared the outcomes of EP infants who were reintubated with those who did not.

METHODS

We conducted a cohort study of EP infants admitted to the NICU at Monash Children's Hospital and The Royal Women's Hospital in Melbourne, Victoria, Australia. These two tertiary perinatal centres each have >7000 births and >1400 admissions to the neonatal special and intensive care nursery per year. The Human Research and Ethics Committee at each site approved the study. Eligible infants were those born EP during a two-year period between 1 January 2016 and 31 December 2017, admitted to NICU, mechanically ventilated, and who survived to their first extubation from mechanical ventilation. Infants were excluded if they were never mechanically ventilated or died prior to their first extubation. Unplanned extubation episodes, after which the infant required immediate re-intubation without a trial of non-invasive respiratory support, were excluded. All infants received post-extubation non-invasive respiratory support. Although only the first extubation episode was evaluated, we recorded the rate of subsequent failed extubations.

Eligible infants were identified from the NICU database at each centre, and their case notes reviewed. Maternal and infant demographics and clinical variables that might predict extubation success/failure were determined *a priori* by the study investigators, based on consensus opinion and the results of previous published studies. Perinatal data included plurality, mode of birth, occurrence of preterm, pre-labour rupture of membranes, any exposure to antenatal corticosteroids and the presence of chorioamnionitis diagnosed by placental histology.

Birth information included GA, sex, birth weight, inborn/outborn birth status (i.e. born at the tertiary perinatal centre or born elsewhere), Apgar score at 5 minutes, administration of exogenous surfactant and highest level of respiratory support provided in the delivery room. Mechanical ventilator settings for the hour prior to the first extubation were extracted from nursing and medical notes. These included FiO_2, peak inspiratory pressure (set for infants receiving pressure limited ventilation and measured for those receiving volume targeted ventilation), mean airway pressure (MAP), positive end expiratory pressure, and tidal volumes (vT): set by clinicians (set Vt) and measured by the infant (measured Vt). Blood gas analysis results including pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen, base excess and lactate and most recent pre-extubation haemoglobin level were also collected. The non-invasive respiratory support settings immediately after extubation were recorded. The reasons for re-intubation were collected from the clinical notes. This included apnoea, increasing FiO_2 requirement or respiratory acidosis. Infants could have more than one reason for re-intubation.

The primary outcome was extubation failure (re-intubation) within 7 days of the first extubation. Secondary outcomes included death before NICU discharge, and serious neonatal morbidities including intra-ventricular haemorrhage, retinopathy of prematurity (ROP), airway trauma (defined as receiving either tracheostomy or cartilage grafting) and BPD (defined as the requirement for supplemental oxygen and/or respiratory support at 36 weeks' post-menstrual age), and the duration (in days) of mechanical ventilation, non-invasive respiratory support, supplemental oxygen therapy, and of the primary NICU hospital admission.

Data were analysed using IBM SPSS statistics platform (Version 25.0, Armonk, NY: IBM Corp). Variables were compared using the appropriate parametric (X^2 or *t*-test) or nonparametric (Mann-Whitney U) tests, with further analysis of variance when necessary. Birth weights were converted to z-scores using British Growth Charts published by the World Health Organization, Switzerland (2008).[19] A univariable analysis was performed comparing infants with extubation failure with infants who were successfully extubated. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. Variables that were significantly different ($P<0.05$) between groups were then included in a multivariable logistic regression. A stepwise, backwards elimination technique was then used to remove variables from the model until only statistically significant variables remained. Of the two significant variables remaining on multivariate analysis, one-way analysis of variance was performed to determine where significance occurred in the variable. To avoid co-linearity, GA but not birth weight was included in the multivariable analysis. Variables that remained statistically significant predictors of extubation failure in the multivariable analysis were included in a model used to construct a receiver operating characteristic (ROC) curve, and the area under the curve was calculated. Outcomes were compared between groups, both unadjusted and adjusted for GA.

RESULTS

During the two-year study period, 327 EP infants were admitted to the participating NICUs (Figure 1). Of these, 123 infants (38%) were never mechanically ventilated or died prior to extubation and were excluded, leaving 204 infants (64%) included in the analysis. Demographics of the included infants are shown in Table 1. Mean (SD) gestation at birth was

26.1 (1.1) weeks and mean (SD) birth weight was 766 (158) g. Fifty-three percent of the cohort were male, 87% were exposed to at least one dose of antenatal corticosteroids and 91% received exogenous surfactant. All infants received caffeine prior to extubation.

Pre-extubation variables are shown in Table 1. Infants were extubated from the following modes of mechanical ventilation: synchronized volume targeted ventilation (78%), synchronized pressure limited ventilation (19%), and high-frequency oscillatory ventilation (3%). All infants on conventional ventilation had spontaneous respiratory rates above their set prescribed ventilator inflation rate. The most commonly used initial post-extubation respiratory support was nasal continuous positive airway pressure (86%), followed by nasal intermittent positive pressure ventilation (11%), and nasal high-flow therapy (3%). Overall, 40/204 (19.6%) infants received peri-extubation corticosteroids to facilitate extubation.

Overall, 96 infants (47%) experienced extubation failure. Reasons for extubation failure (infants could have more than one) included increasing FiO_2 requirement (90%), apnoea (83%), and respiratory acidosis (40%). Re-intubation occurred at a median (IQR) of 60 (24-120) hours after extubation. Almost two-thirds (65%) of infants who experienced extubation failure on their first extubation had subsequent episodes of extubation failure.

On univariable analysis, gestational age, birth weight, multiple birth, pre-extubation MAP and pre-extubation measured tidal volume (tidal volume required to achieve PIP) were associated with extubation failure (Table 2). On multivariable analysis, only lower GA (OR 0.71 [95% CI 0.6-0.9], P<0.001) and higher pre-extubation MAP (OR 1.9 [95% CI 1.4-2.5], P<0.001) remained predictive of extubation failure. Figure 2A illustrates the proportion of infants who experienced extubation failure by each completed week of GA (Figure 2A) and according to pre-extubation MAP (Figure 2B). The rate of extubation failure increased with decreasing gestational age, from 22% at 27 weeks' gestation to 82% at 23 weeks' gestation. As both MAP and GA were highly significant on multivariable analysis, one-way analysis of variance was performed to ascertain where in the GA and MAP significance was measured. Comparing each gestation age group, infants born at 27 weeks were more likely to experience extubation success compared with less mature infants (F [4,199] = 6.3, p <0.001). Within MAP's, there was evidence of an effect of MAP on extubation failure. Extubation from MAP ≥8 cm H_2O was associated with a higher rate of extubation failure (F [5,198] = 5.8, p <0.001). GA and pre-extubation MAP were combined in a model to construct a ROC curve (Figure 3). The area under the curve was 0.77 (95% CI 0.70-0.82) i.e. the model was moderately predictive of extubation failure.

Outcomes of infants who had extubation failure were compared with infants who were successfully extubated (Table 3). After adjusting for GA, infants who experienced extubation failure had higher rates of BPD, postnatal systemic corticosteroid treatment, airway trauma, and longer durations of mechanical ventilation, non-invasive respiratory support, supplemental oxygen treatment, and NICU hospitalization compared with infants who were successfully extubated.

DISCUSSION

This retrospective, multicentre study found the combination of lower GA and higher pre-extubation MAP was moderately predictive of extubation failure in extremely preterm infants. In this cohort, the median time to extubation failure was 60 hours, highlighting the importance of optimizing early post-extubation respiratory support.

The relationship between MAP and extubation failure has been reported rarely in previous studies. Kamlin and colleagues reported a similar relationship between lower MAP and passing a spontaneous breathing test which was associated with successful extubation. [2] The predictive value of a higher pre-extubation MAP may indicate that infants with more severe lung disease, who require a higher MAP during mechanical ventilation, are more likely to experience extubation failure. Loss of lung volume following extubation may result in higher supplemental oxygen requirements, apnoea and respiratory acidosis, which are common reasons for extubation failure.[1] It may be that extubation to continuous positive airway at a set pressure similar to, or higher than, the pre-extubation MAP may be required to maintain end-expiratory lung volume after extubation.[20]

The relationship between lower GA and extubation failure is well documented.[1-11] In our study, there were no important differences in extubation failure rates between EP infants 23 to 26 weeks' GA, however infants born at 27 weeks' GA were more likely to be successfully extubated compared with more immature infants. We hypothesize this difference was due to changes in lung maturity which occur with increasing gestation. [17]

Previous studies reported that pre-extubation FiO_2 and blood gas parameters (pCO_2 and pH) were predictive of extubation failure, [1-9] but this was not confirmed in our study. This may have been because clinicians usually waited for a lower supplemental oxygen requirement and normalization of acidosis before planning extubation.[14]

We defined extubation failure as the need for re-intubation within 7 days, a commonly used definition.[1-11] This definition has advantages and disadvantages. A shorter period (prior to 72 hours) may better distinguish between re-intubation for pulmonary insufficiency and re-intubation for other reasons e.g., sepsis or surgery. Conversely, a longer period (7 days) accounts for a greater proportion of extubation failures.[15]

In this study, more infants with extubation failure developed BPD, received postnatal systemic corticosteroid treatment, and experienced airway trauma. These infants were more likely to experience subsequent episodes of extubation failure and to have a longer duration of respiratory support and supplemental oxygen. These morbidities are similar to those reported in a prior study exploring predictors and outcomes in extubation failure in 174 extremely preterm infants.[10] The mortality rate (to NICU discharge) in our study population was low (2.5%) and we did not find an increased risk of death after extubation failure.

This study is one of the first to evaluate pre-extubation ventilation parameters and included a relatively large cohort of 204 extremely preterm infants across two tertiary NICUs. Variables for analysis were chosen *a priori*. However, there are limitations to this study. The two NICUs do not have standardized extubation or re-intubation criteria, limiting the generalizability of the results. Furthermore, the authors acknowledge the multifactorial nature of neonatal morbidities in extremely preterm infants. These morbidities although are affected by extubation failure cannot be solely attributed to this pathology and other contributing factors must also be considered. The predictive model has not been validated in an independent sample from the participating centres, or externally in other retrospective cohort studies.

CONCLUSION

In our study, GA and pre-extubation MAP were predictive of extubation failure within 7 days in EP infants. Extubation failure was associated with serious morbidities and extended periods of respiratory support and hospitalization. Further research investigating predictive models of extubation readiness, extubation failure and new interventions to prevent extubation failure in this high-risk population are needed.

REFERENCES

1. Shalish W, Kanbar L, Keszler M, Chawla S, Kovacs L, Rao S *et al.* Patterns of reintubation in extremely preterm infants: a longitudinal cohort study. *Pediatric Research*. 2018;83(5):969-975.
2. Ammari A, Suri M, Milisavljevic V, *et al.* Variables associated with the early failure of nasal CPAP in very low birth weight infants. J Pediatr 2005;147:341–7.
3. Shalish W, Latremouille S, Papenburg J, Sant'Anna G. Predictors of extubation readiness in preterm infants: a systematic review and meta-analysis. 2019. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2019;104:F89-F97.
4. Manley, B.J., Yoder, B.A., Davis, P.G. Non-invasive ventilation of preterm infants An alternative to mechanical ventilation. In: Bancalari, E., Keszler, M., Davis, P.G, (Eds.) *The Newborn Lung: Neonatology Questions and Controversies.* Elsevier 2019:197-219.
5. Wright C, Sherlock L, Sahni R, Polin R. Preventing continuous positive airway pressure failure. *Clinics in Perinatology*. 2018;45(2):257-271.
6. Shalish W, Sant'Anna G. Deciphering extubation failure in extremely preterm infants: Time to embrace complexity and move forward. *The Journal of Pediatrics.* 2018;194:263.
7. Silva M, Gregório M, de Godoy M. Does heart rate variability improve prediction of failed extubation in preterm infants? *Journal of Perinatal Medicine.* 2019; 47(2):252-257.
8. Singh N, McNally M, Darnall R. Does diaphragmatic electrical activity in preterm infants predict extubation success? *Respiratory Care*. 2017;63(2):203-207.
9. Spasojevic S, Doronjski A. Risk factors associated with failure of extubation in very-low-birth-weight newborns. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2017;31(3):300-304.
10. Manley B, Doyle L, Owen L, Davis P. Extubating extremely preterm infants: predictors of success and outcomes following failure. *The Journal of Pediatrics.* 2016;173:45-49.
11. Brigham K, Gupta S, Brigham J. Predicting responses to mechanical ventilation for preterm infants with acute respiratory illness using artificial neural networks. *International Journal for Numerical Methods in Biomedical Engineering.* 2018; 34(8):e3094.

12. Davidson L, Berkelhamer S. Bronchopulmonary Dysplasia: Chronic lung disease of infancy and long-term pulmonary outcomes. *Journal of Clinical Medicine.* 2017;6(1):4.
13. SUPPORT Study Group. Early CPAP versus surfactant in extremely preterm infants. *New England Journal of Medicine*. 2010;362(21):1970-1979.
14. Al-Mandari H, Shalish W, Dempsey E, Keszler M, Davis P, Sant'Anna G. International survey on periextubation practices in extremely preterm infants. *Archives of Disease in Childhood, Fetal and Neonatal Edition*. 2015;100(5):F428-F431.
15. Giaccone A, Jensen E, Davis P, Schmidt B. Definitions of extubation success in very premature infants: a systematic review. *Archives of Disease in Childhood, Fetal and Neonatal Edition.* 2013;99(2):F124-F127.
16. Ferguson K, Roberts C, Manley B, Davis P. Interventions to improve rates of successful extubation in preterm infants. *JAMA Pediatrics* 2017;171(2):165.
17. Kamlin C, Davis P, Morley C. Predicting successful extubation of very low birthweight infants. *Archives of Disease in Childhood, Fetal and Neonatal Edition*. 2005;91(3):F180-F183.
18. Wu S, Savani R. Molecular bases for lung development, injury, and repair. In: Bancalari, E., Keszler, M., Davis, P.G. (Eds.). The Newborn Lung: Neonatology Questions and Controversies. Elsevier 2019:197-219.
19. World Health Organization. Child growth standards. 2006. www.who.int/childgrowth/software/en/.
20. Buzzella, B., Claure, N., D'Ugard, C., & Bancalari, E. (2014). A Randomized Controlled Trial of Two Nasal Continuous Positive Airway Pressure Levels after Extubation in Preterm Infants. *The Journal Of Pediatrics, 164*(1), 46-51. doi: 10.1016/j.jpeds.2013.08.040

FIGURE AND TABLE LEGENDS:

Table 1: Maternal and infant demographics

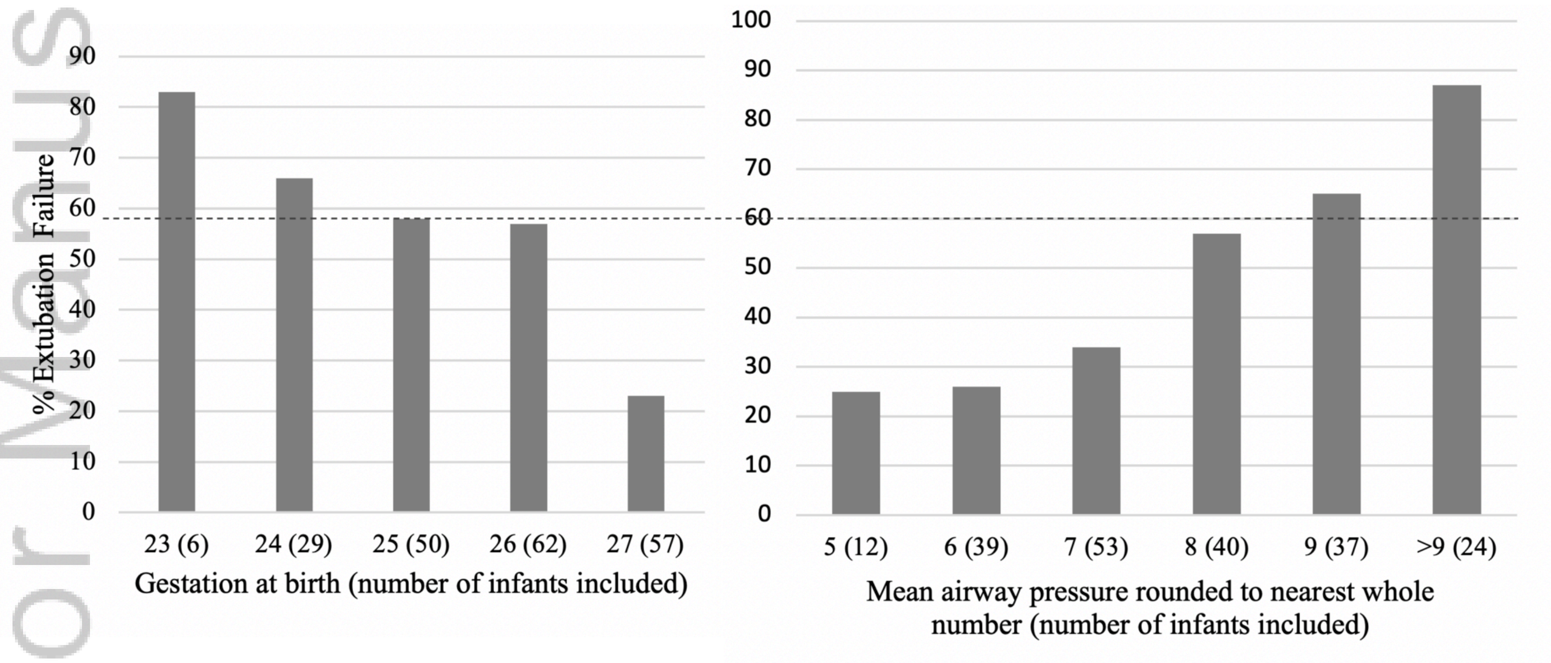
Table 2: Characteristics of infants who failed extubation, compared with those who were successfully extubated.

Table 3: Outcomes of infants who had extubation failure, compared with those who were successfully extubated.

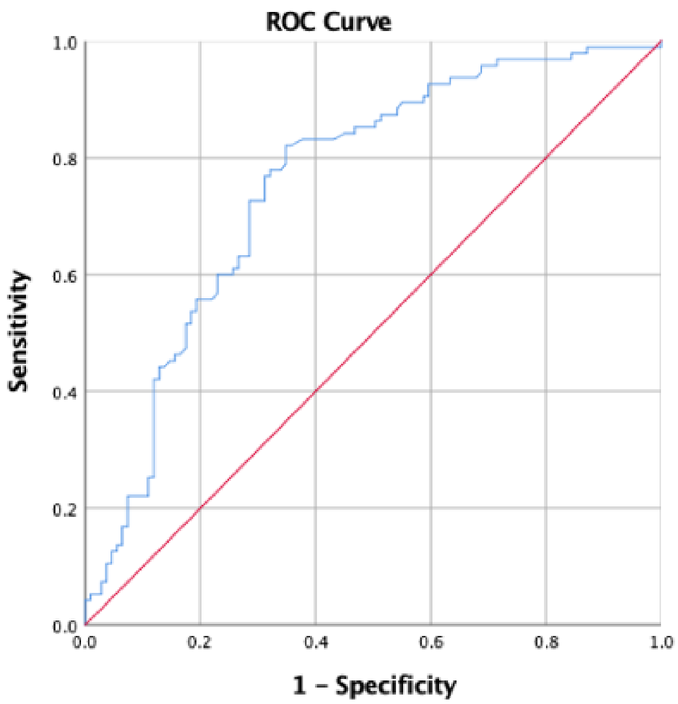
Figure 1: Flow chart of infants in the study

Figure 2A (left) and 2B (right): Rates of extubation failure (%) by gestational age (left) and mean airway pressure (right). Horizontal line represents mean rate of failure for cohort.

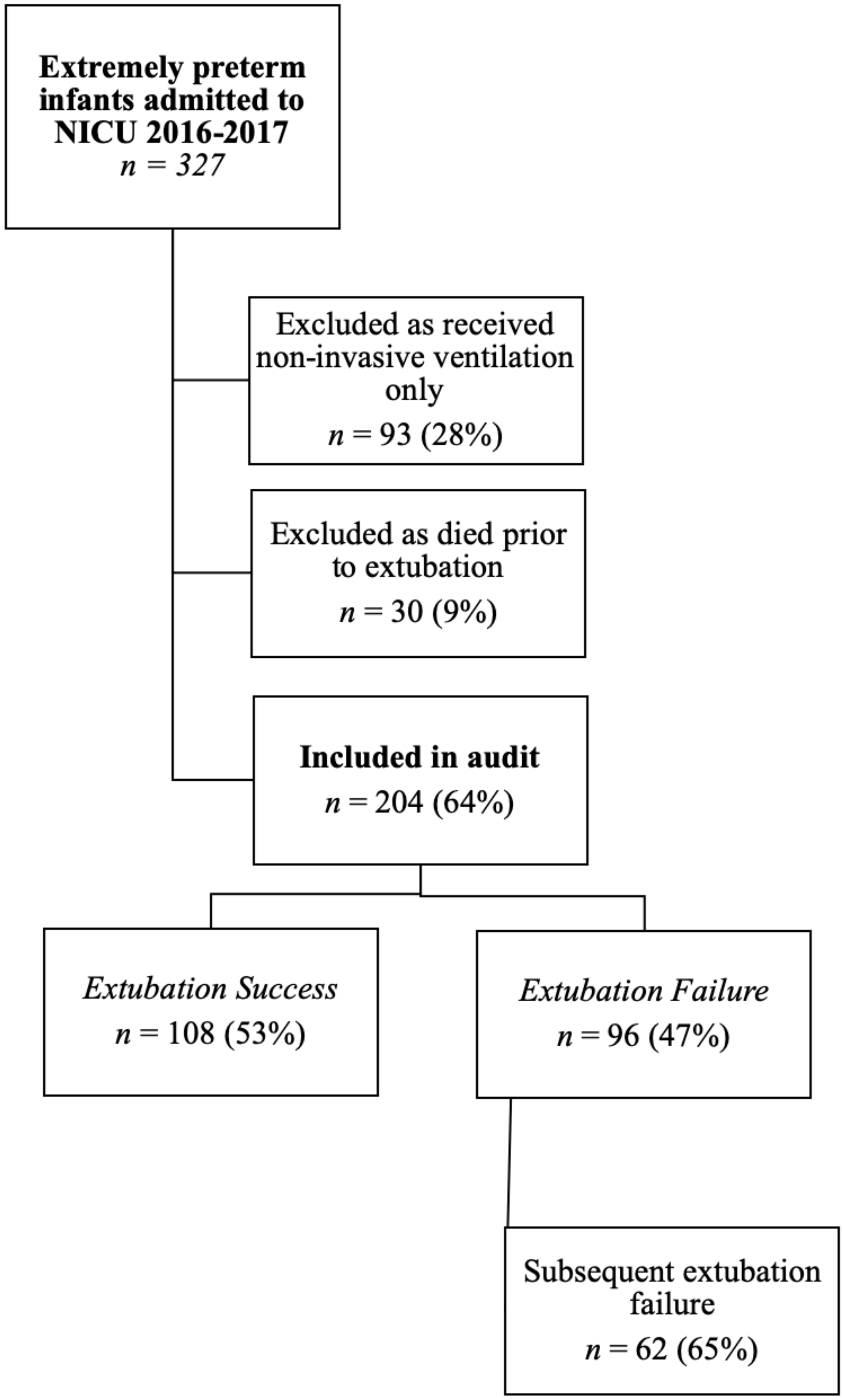
Figure 3*:* ROC curve for predicting extubation failure.



JPC_15356_Figure 2A (left) and 2B (right) REVISED.png



JPC_15356_Figure 3- ROC curve for GA and MAP in a predictive model.png



JPC_15356_Figure_1-_flow_chart_of_infants_.png

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Author Contributions:

AMK and R.B conceptualised the audit. AMK collected the data and wrote the original draft manuscript. R.B, RAB, BJM and PGD supported and supervised the study design and statistical analysis and drafted the manuscript. Each author has reviewed the manuscript and approved submission of this version. The authors take full responsibility for the manuscript.