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Duration of mechanical ventilation and prediction of bronchopulmonary dysplasia and home oxygen in extremely preterm infants

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Short title: Duration of ventilation, BPD and home oxygen

Abstract

Aim

To determine if the duration of invasive ventilation predicted the development of bronchopulmonary dysplasia (BPD) and need for discharge home on supplementary oxygen in extremely preterm infants.

Methods

Retrospective whole population study of all infants <28 weeks of gestation admitted to a neonatal unit in England between 2014-2018. BPD development was defined as any respiratory support at 36 weeks postmenstrual age. The performance of the duration of mechanical ventilation to predict BPD or discharge home on oxygen was assessed by receiver operator characteristic curve analysis.

Results

The 11,806 infants had a median (IQR) gestational age of 26.0(24.9-27.1) weeks and birth weight of 0.81(0.67-0.96) kg. At discharge from neonatal care 9,415 infants (79.7%) were alive. The incidence of BPD was 57.5% and of home oxygen 29.4%. Mechanical ventilation duration had areas under the curve of 0.793 and 0.703 in predicting BPD and home oxygen respectively. Mechanical ventilation for >8 days predicted BPD development with 71% sensitivity and 71% specificity and mechanical ventilation for >10 days predicted discharge on home oxygen with 66% sensitivity and 65% specificity.

Conclusion

In extremely preterm infants, the duration of invasive support predicted BPD and need for home oxygen with moderate sensitivity and specificity.

Key words: extremely preterm infants, mechanical ventilation, bronchopulmonary dysplasia, home oxygen, England, neonatal outcomes

Funding: none

Conflict of interest: none

Key notes

- A longer duration of invasive mechanical ventilation in extremely preterm infants is associated with the development of bronchopulmonary dysplasia (BPD) and need for discharge home on supplementary oxygen.

- In this whole population study of extremely preterm infants in England, the incidence of BPD was 57.5% and of home oxygen 29.4%.
- A longer duration of ventilation predicted the development of BPD and the need for discharge on home oxygen.

Introduction

Extremely prematurely born infants often develop bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity with multi-system and long-lasting morbidity (1). Despite improvements in neonatal care, the incidence of the disease has risen over the past years due to the improved survival of extremely preterm infants (2, 3). The sequelae of BPD persist in childhood, adolescence and early adulthood with frequent rehospitalisation, persistent respiratory function abnormalities and neurodevelopmental impairment (4, 5).

In the United Kingdom, 36-62% of infants born prior to 27 weeks of gestation with moderate or severe BPD go home on supplementary oxygen (6) with significant utilisation of health resources and a burden for the infants and families (7). Accurate prediction of BPD and need for home oxygen (8) is evasive due to the multifactorial pathophysiology of the disease and the impact of significant postnatal events that are associated with an increased incidence of BPD such as necrotising enterocolitis (NEC) and patent ductus arteriosus (PDA) (9). Early prediction of BPD development can assist in identifying high risk infants that would benefit from early interventions and early prediction of home oxygen can ensure timely initiation of the process for appropriate home set-up for supplementary oxygen and facilitate early discharge.

Invasive mechanical ventilation is a lifesaving intervention for the majority of extremely preterm infants but is associated with significant side effects. Positive pressure ventilation can lead to lung overdistension which can stimulate the release of products that promote an inflammatory cascade (10). Mechanical ventilation in preterm infants can thus be a stimulus for systemic inflammation, and a duration of invasive mechanical ventilation greater than seven days in newborns has been positively associated with a larger postnatal systemic inflammatory response (11). In a recent cohort study of extremely low birth weight infants, a greater number of mechanical ventilation courses largely accounted for the increased risk of BPD and use of supplemental oxygen at discharge among survivors (12).

Infants of younger gestation, lighter weight and male gender are ventilated for longer periods and postnatal events such as NEC or PDA are frequently associated with prolonged mechanical ventilation (9). We thus hypothesised that the duration of invasive mechanical ventilation could be used to accurately predict BPD and home oxygen in extremely preterm infants. Our aim was to test this hypothesis.

Methods

Study design and participants

A retrospective, whole-population study was conducted. A predefined dataset was acquired from the National Neonatal Research Database (NNRD), Imperial College London, UK. The NNRD is approved by the National Research Ethics Service (10/H0803/151), Confidentiality Advisory Group of the Health Research Authority (8-05[f]/2010) and the Caldicott Guardians and Lead Clinicians of contributing hospitals.

As the study used data held in an existing database, participation did not require approval from individual Trusts, but only from the NHS Trust holding the database (Chelsea and Westminster NHS Foundation Trust) which was obtained. This study was approved by the West Midlands - Edgbaston Research Ethics Committee (REC reference: 19/WM/0172) and the UK Health Research Authority (HRA) (IRAS project ID: 259225).

All live-born infants before 28 completed weeks of gestation and admitted to a neonatal unit in England between 1/1/2014 and 31/12/2018 were included. The following variables were collected: maternal age (years), administration of antenatal steroids (yes/no), gestational age (GA) at birth (weeks), birth weight (kg), Apgar score at five minutes of age, sex (male/female), surfactant administration (yes/no), duration of invasive ventilation (days), BPD development defined as any need for respiratory support at 36 weeks postmenstrual age (PMA) (13), administration of postnatal corticosteroids (defined as parenteral administration of dexamethasone or hydrocortisone for more than five consecutive days - yes/no), surgical intervention for necrotising enterocolitis (yes/no), surgical ligation of PDA (yes/no), intraventricular haemorrhage grade 3-4 (yes/no), periventricular leucomalacia (yes/no), death before discharge from neonatal care (yes/no), PMA at discharge (weeks), weight at discharge (kg), discharged on home oxygen (yes/no). Full invasive intensive care, support from birth and admission to a neonatal intensive care unit was provided as normal practice to infants at 24 weeks of gestation and above, and in some infants below 24 weeks of gestation depending on the clinical condition and parental wishes (14).We calculated the birth weight z-score (ΔWz) using the UK-World Health Organization (WHO) preterm reference chart (15) and the Microsoft Excel add-in LMS Growth (version 2.77; www.healthforchildren.co.uk). The birth weight z-score was not calculated for infants born <23 completed weeks of gestation, as there were no reference data. As the majority of the deceased infants died before the diagnosis of BPD at 36 weeks PMA they were excluded from the analysis relating to the subsequent development of BPD or discharge on home oxygen.

Statistical analysis

The data were tested for normality with the Kolmogorov-Smirnov test, were found to be non-normally distributed and thus presented as median (interquartile range). Differences in gestational age, birth weight z-score, duration of mechanical ventilation, incidence of NEC and PDA between infants that developed BPD and the infants that did not and the infants who went home on oxygen and the infants that did not were assessed for statistical significance using the Mann Whitney U test or χ^2 test as appropriate. Two separate multivariable, binary logistic regression models with development of BPD and discharge on home oxygen were constructed to examine the independent associations of the duration of mechanical ventilation with the development of BPD and discharge home on supplementary oxygen after correcting for potential confounders that were different ($p<0.05$) between infants with and without BPD and infants that were or not discharged on home oxygen. Multi-collinearity among the independent variables in the regression analysis was assessed by examining a correlation matrix for the independent variables. The performance of the

duration of mechanical ventilation to predict BPD or discharge home on oxygen was assessed by receiver operator characteristic curve analysis and estimation of the corresponding area under the curve (AUC).

Statistical analysis was performed using SPSS software, version 26.0 (IBM, Armonk, NY, USA).

Results

During the period of the study 11,806 infants were born alive below 28 completed weeks of gestation and were admitted to a neonatal unit in England (figure 1). They had a median (IQR) GA of 26.0 (24.9 - 27.1) weeks, a birth weight of 0.81 (0.67 - 0.96) kg and a birth weight z-score of -0.38 (-0.88 to 0.01) (table 1). The incidence of BPD was 57.5 % and 20.3 % of the infants died before discharge from neonatal care (table 1). Of the infants that were alive at discharge from neonatal care with available data (*N*=8,494), 435 (5.1 %) infants were not invasively ventilated at all and 2,011 (23.7%) infants were ventilated for 1 - 3 days (figure 2).

BPD

The median (IQR) duration of mechanical ventilation in the BPD infants (*N*=6,105) was higher [18 (7-35) days] compared to no BPD [*N*= 2389, 4 (2-10) days, p<0.001]. The median (IQR) GA of the BPD infants that was lower [26.0 (24.9 – 27.0) weeks] compared to no BPD [26.9 (26.0 – 27.4) weeks, p<0.001]. The median (IQR) birth weight z-score of the BPD infants [-0.44 (-0.95 – 0.01)] was lower compared to no BPD [-0.23 (-0.68 – 0.19), p<0.001]. A higher proportion of infants with BPD were male (55.5%) and had surgery for NEC (6.3%) and PDA ligation (6.6%) compared to the no BPD infants (47.7%, 3.6%, 0.7% respectively, p<0.001 for all). Following multivariable, binary logistic regression the duration of mechanical ventilation was independently associated with a development of BPD after correcting for GA, birth weight z-score, gender, NEC and PDA (adjusted p<0.001 odds ratio=1.079, 95% CI=1.071 – 1.088). The receiver operator characteristic curve analysis demonstrated that in predicting BPD the duration of mechanical ventilation had an AUC of 0.793 and the GA an AUC of 0.746 (Fig. 3a). A duration of mechanical ventilation of more than 8 days predicted the development of BPD with 71% sensitivity and 71% specificity.

Home oxygen

Of the 3,464 infants that went discharged on home oxygen, 3,140 (91%) were diagnosed with BPD at 36 weeks PMA. The median (IQR) duration of mechanical ventilation of the infants that were discharged on home oxygen was higher [19 (7 - 35) days] compared to no home oxygen [*N*=4,944, 6 (2 – 16) days, p<0.001]. The median (IQR) GA of the infants on home oxygen was lower [25.9 (24.7 – 26.9) weeks] compared to infants not on home oxygen [26.7 (25.7 – 27.4) weeks, p<0.001]. The median (IQR) birth weight z-score of the infants on home oxygen [-0.45 (-0.96 - 0.02)] was lower compared to the infants not on home oxygen [-0.28 (-0.73 – 0.15), p<0.001]. A higher proportion of infants on home oxygen were male (55.3%) and had PDA ligation (7.3%) compared to infants not on home oxygen (50.1% and 4.1% respectively, p<0.001 for both). A lower proportion of infants on home oxygen had surgery for NEC (3.2%) compared to infants not on home oxygen (5.7%, p<0.001). Following multivariable binary logistic regression

the duration of mechanical ventilation was independently associated with discharge on home oxygen after correcting for GA, birth weight z-score, gender, NEC and PDA (adjusted p<0.001 odds ratio=1.034, 95% CI=1.029 – 1.039). The receiver operator characteristic curve analysis demonstrated that in predicting discharge on home oxygen the duration of mechanical ventilation had an AUC of 0.703 and the GA an AUC of 0.641 (Fig. 3b). A duration of mechanical ventilation of more than 10 days predicted discharge on home oxygen with 66% sensitivity and 65% specificity.

Discussion

We have reported that extremely preterm infants that develop bronchopulmonary dysplasia or are discharged home on supplementary oxygen are ventilated for longer periods compared to their counterparts that do not develop the disease or are not discharged home on oxygen. We have also demonstrated that the duration of invasive ventilation can be used in extremely preterm infants to predict the development of bronchopulmonary dysplasia and the need for home oxygen with moderate sensitivity and sensitivity but with higher accuracy than the gestational age.

Previous studies have reported a higher ability of the duration of invasive ventilation to predict later respiratory outcomes. We have previously reported that in 454 infants less than 32 weeks of gestation, requirement for mechanical ventilation at one week of age was 99% sensitive and 67% specific in predicting development of BPD and predicted severe BPD with 63% sensitivity and 92% specificity. Mechanical ventilation at one week gave areas under the receiver operator characteristic curves for the development of BPD and severe BPD of 0.77 and 0.83, respectively (16). The differences of that study with the current whole population study might be explained by a larger variation of clinical practice and the smaller gestational age of the included infants in the current whole population study. Escobar et al recently studied 53 extremely premature infants and reported that a duration of ventilation exceeding 36 days was related to a greater chance of developing moderate to severe BPD, a finding which was consequently confirmed in a small validation sample of 16 extremely preterm infants (17). In that smaller study, however, the prediction time point was relatively late in postnatal life compared to our study (36 compared to 8 days). Our results are also in agreement with Jensen et al who studied 3,343 extremely low birth weight infants and reported that among the survivors, exposure to a greater number of mechanical ventilation courses was associated with a progressive increase in the risk of BPD and use of supplemental oxygen at discharge (12).

We report a relatively high incidence of BPD at 57.5% compared to other population studies. Schmolzer et al in a meta-analysis of randomised trials comparing CPAP with intubation reported a combined incidence of BPD of 32.4 - 34.0% for CPAP and intubation respectively (18). The included studies though were performed in infants born < 32 weeks of gestation in which the total incidence would be expected to be lower. The incidence of BPD and the duration of mechanical ventilation would be expected to decrease in

the future with the recent application of new modes of surfactant delivery such as less invasive surfactant administration (19) and the application of systems such as closed loop oxygen delivery.

It is interesting that the duration of mechanical ventilation had a higher predictive ability for BPD and need for home oxygen compared to the gestational age. This is in agreement with Laughon et al who reported that, although for the first three days of life the gestational age was the strongest predictor for BPD, from seven days of life onwards the type of respiratory support had the highest predictive ability (20). The explanation for this might lie in that, in extremely preterm infants, the duration of mechanical ventilation possibly acts as a composite index for demographics as well as for postnatal events such as infection, NEC and PDA which are also associated with increased incidence of BPD (21).

In order to maximise the completeness and reliability of our data, we took a pragmatic approach in defining our outcomes and potential confounders and might not have captured all neonatal pathology with a very high granularity. We included PDA ligation as a definition of PDA as a complete course of pharmacological treatment and its effect might not have been entered consistently in the database. Gastrointestinal pathology in the form of isolated bowel perforation was also not included in the model as it is often an indistinguishable entity to NEC in extreme premature infants that underwent an operation. We selected to use the definition of BPD that corresponds to moderate/severe BPD as per the Jobe and Bancalari 2001 definition (13) as mild BPD in infants that were breathing room air by 36 weeks PMA but were previously treated with supplemental oxygen were not captured by the national registry. More recent definitions of BPD have been introduced (22, 23) but they chronologically followed our study period and were not in use for the largest part of our study.

Our study has obvious clinical applicability. Early identification of infants that will require home oxygen offers the logistical advantage of an early initiation of the process of the evaluation for home suitability and establishing a safe home set-up for oxygen therapy without unnecessarily delaying discharge from the neonatal unit.

Our study has strengths and some limitations. This was a whole population study with more than eleven thousand extremely preterm infants in a recent five year period. Despite the retrospective nature of our study, the number of the included infants allowed us to make multiple comparisons and multiple regression corrections in our analysis, as BPD is a disease with multiple interrelated etiological factors (22). Our population was also relatively homogeneous as all infants were cared by the same health system and the definition of BPD was uniform and collected via a central software. The ability of the duration of invasive ventilation to predict a later diagnosis of BPD or need for home oxygen had a sensitivity and specificity in the region of 70% for predicting both conditions. This might be due to that a number of factors that are associated with BPD and need for home oxygen cannot be easily quantified. Such factor is perinatal and postnatal systemic or respiratory infection whose firm diagnosis is often elusive with frequent blood culture negative sepsis and chorioamnionitis that can be reliably diagnosed with histological examination of the placenta which is difficult to implement at a whole population level.

In conclusion we have reiterated that extremely preterm infants that develop BPD and are discharged on home oxygen are ventilated for longer periods than their counterparts without BPD or home oxygen. We have demonstrated that the duration of invasive support can be used to predict BPD and need for home oxygen with moderate sensitivity and specificity.

References

1. Islam JY, Keller RL, Aschner JL, Hartert TV, Moore PE. Understanding the Short- and Long-Term Respiratory Outcomes of Prematurity and Bronchopulmonary Dysplasia. *American journal of respiratory and critical care medicine* 2015; 192 2:134-56.
2. Santhakumaran S, Statnikov Y, Gray D, Battersby C, Ashby D, Modi N, et al. Survival of very preterm infants admitted to neonatal care in England 2008-2014: time trends and regional variation. *Archives of disease in childhood Fetal and neonatal edition* 2018; 103 3:F208-F15.
3. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *Jama* 2015; 314 10:1039-51.
4. Kallapur S. Updates on neonatal chronic lung disease. Waltham: *Elsevier*, 2019.
5. Collaco JM, McGrath-Morrow SA. Respiratory Phenotypes for Preterm Infants, Children, and Adults: Bronchopulmonary Dysplasia and More. *Annals of the American Thoracic Society* 2018; 15 5:530-8.
6. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *Bmj* 2012; 345:e7976.
7. Lapcharoensap W, Bennett MV, Xu X, Lee HC, Dukhovny D. Hospitalization costs associated with bronchopulmonary dysplasia in the first year of life. *Journal of perinatology : official journal of the California Perinatal Association* 2020; 40 1:130-7.
8. Lagatta J, Clark R, Spitzer A. Clinical predictors and institutional variation in home oxygen use in preterm infants. *The Journal of pediatrics* 2012; 160 2:232-8.
9. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. *Birth defects research Part A, Clinical and molecular teratology* 2014; 100 3:145-57.
10. Jobe AH, Ikegami M. Mechanisms initiating lung injury in the preterm. *Early human development* 1998; 53 1:81-94.
11. Bose CL, Laughon MM, Allred EN, O'Shea TM, Van Marter LJ, Ehrenkranz RA, et al. Systemic inflammation associated with mechanical ventilation among extremely preterm infants. *Cytokine* 2013; 61 1:315-22.
12. Jensen EA, DeMauro SB, Kornhauser M, Aghai ZH, Greenspan JS, Dysart KC. Effects of Multiple Ventilation Courses and Duration of Mechanical Ventilation on Respiratory Outcomes in Extremely Low-Birth-Weight Infants. *JAMA pediatrics* 2015; 169 11:1011-7.

13. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *American journal of respiratory and critical care medicine* 2001; 163 7:1723-9.
14. Brazier M, Archard D, Campbell A, Franck L, Green B, Haimes E, et al. Critical care decisions in fetal and neonatal medicine: ethical issues. In: Bioethics NCo, editor. London Latimer Trend & Company Ltd; 2006
15. Wright CM, Williams AF, Elliman D, Bedford H, Birks E, Butler G, et al. Using the new UK-WHO growth charts. *Bmj* 2010; 340:c1140.
16. Hunt KA, Dassios T, Ali K, Greenough A. Prediction of bronchopulmonary dysplasia development. *Archives of disease in childhood Fetal and neonatal edition* 2018; 103 6:F598-F9.
17. Escobar V, Soares DS, Kreling J, Ferrari LSL, Felcar JM, Camillo CAM, et al. Influence of time under mechanical ventilation on bronchopulmonary dysplasia severity in extremely preterm infants: a pilot study. *BMC pediatrics* 2020; 20 1:241.
18. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *Bmj* 2013; 347:f5980.
19. Herting E, Hartel C, Gopel W. Less invasive surfactant administration (LISA): chances and limitations. *Archives of disease in childhood Fetal and neonatal edition* 2019; 104 6:F655-F9.
20. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *American journal of respiratory and critical care medicine* 2011; 183 12:1715-22.
21. Trembath A, Laughon MM. Predictors of bronchopulmonary dysplasia. *Clinics in perinatology* 2012; 39 3:585-601.
22. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al. Bronchopulmonary Dysplasia: Executive Summary of a Workshop. *The Journal of pediatrics* 2018; 197:300-8.
23. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. *American journal of respiratory and critical care medicine* 2019; 200 6:751-9.

Table 1: Characteristics of the included infants

	Median (IQR) or *N* (%).
Maternal age (years)	31 (26 – 35)
Antenatal corticosteroids	10,409 (88.2)
Gestational age (weeks)	26.0 (24.9 – 27.1)
Birth weight (kg)	0·81 (0.67 – 0.96)
Birth weight z-score	-0.38 (-0.88 – 0.01)
Apgar score at 5 minutes	8 (6 – 9)
Male sex	6,371(54.0)
Surfactant administration	10,558 (89.7)
Duration of invasive ventilation (days)	10 (3 – 26)
BPD at 36 weeks postmenstrual age	6,264 (57.5)
Postnatal corticosteroids	2,350 (19.9)
Operated for necrotising enterocolitis	674 (5.7)
Surgical ligation of patent ductus arteriosus	464 (3.9)
Intraventricular haemorrhage grade 3-4	1,864 (25.9)
Periventricular leucomalacia	445 (7.4)
Treated for retinopathy of prematurity	1,368 (11.7)
Death before discharge from neonatal care	2,391 (20.3)
Age at death (days)	7 (2 – 24)
Discharged on home oxygen	3,477 (29.4)
Postmenstrual age at discharge (weeks)*	39.5 (37.6 – 42.1)
Weight at discharge (kg)*	2.68 (2.26 – 3.25)

**Data for the alive at discharge only*

Table 2: Comparison of the characteristics of infants diagnosed with BPD versus no-BPD and infants discharged on home oxygen versus not discharged on home oxygen. Data excluding infants that died before discharge from neonatal care.

	BPD *N*=6,105	No BPD *N*=2,389	p value	Home oxygen *N*=3,464	No home oxygen *N*=4,944	p value
Antenatal steroids	5,477 (89.7)	2,170 (90.8)	0.15	3,116 (90.0)	4,456 (90.1)	0.102
Gestational age (weeks)	26.0 (24.9 – 27.0)	26.9 (26.0 – 27.4)	<0.001	25.9 (24.7-26.9)	26.7 (25.7-27.4)	<0.001
Birth weight z-score	-0.44 (-0.95 – 0.01)	-0.23 (-0.68 – 0.19)	<0.001	-0.45 (-0.96 - 0.02)	-0.28 (-0.73 – 0.15)	<0.001
Apgar at 5 minutes	8 (6 – 9)	8 (7 – 9)	<0.001	7 (6 – 9)	8 (7 – 9)	<0.001
Male sex	3,390 (55.5)	1,140 (47.7)	<0.001	1,914 (55.3)	2,503 (50.1)	<0.001
Surfactant administration	5,610 (91.9)	2,026 (84.8)	<0.001	3,195 (92.2)	4,261 (86.2)	<0.001
Duration of ventilation (days)	18 (7 – 35)	4 (2 – 10)	<0.001	19 (7 - 35)	6 (2 – 16)	<0.001
Postnatal corticosteroids	1,726 (28.3)	145 (6.1)	<0.001	1,037 (30.0)	895 (18.1)	<0.001
Operated for necrotising enterocolitis	387 (6.3)	87 (3.6)	<0.001	286 (5.7)	112 (3.2)	<0.001
Surgical ligation of patent ductus	402 (6.6)	17 (0·7)	<0.001	252 (7.3)	346 (4.1)	<0.001
Treatment for retinopathy of prematurity	1,147 (18.8)	136 (5.7)	<0.001	616 (17.8)	505 (10.2)	<0.001
Intraventricular haemorrhage grade 3-4	855 (14.0)	229 (9.6)	<0.001	433 (12.5)	569 (11.5)	0.057
Postmenstrual age at discharge	40.8 (39.0 – 43.4)	37.8 (36.8 – 39.2)	<0.001	40.6 (38.7-43.0)	38.6 (36.9-40.9)	<0.001

Legend to figures

Figure 1: Flow diagram of the included infants. Data were missing in 921 infants.

Figure 2: Duration of mechanical ventilation in all included infants that survived to discharge from neonatal care (*N*=8,494)

Figure 3: Receiver operator characteristic curves for duration of mechanical ventilation to predict bronchopulmonary dysplasia (a) and need for home oxygen (b). AUC: area under the curve.

Abbreviations

AUC: area under the curve

BPD: bronchopulmonary dysplasia

CI: confidence intervals

GA: gestational age

HRA: Health Research Authority

IQR: interquartile range

NEC: necrotising enterocolitis

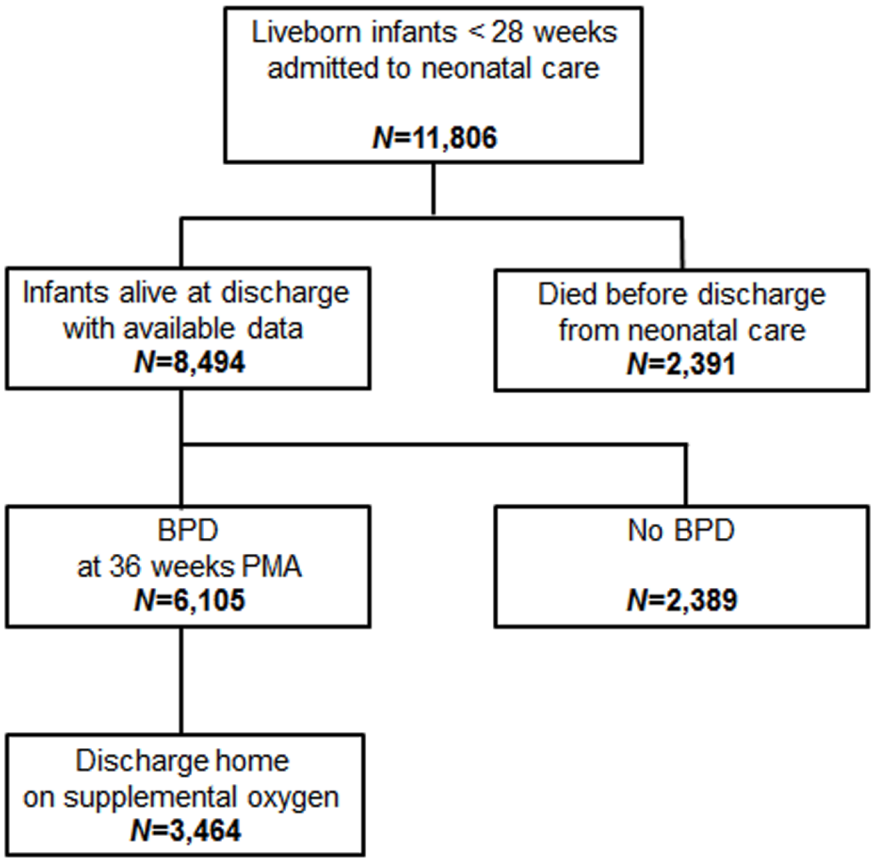
NHS: National Health Service

NNRD: National Neonatal Research Database

PDA: patent ductus arteriosus

PMA: postmenstrual age

REC: Research Ethics Committee



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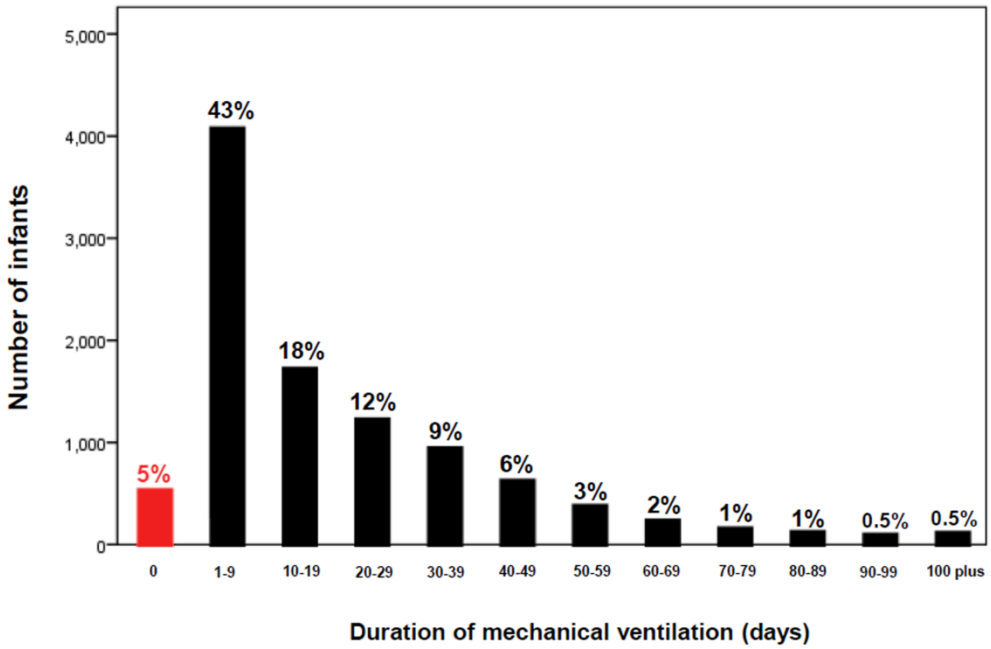

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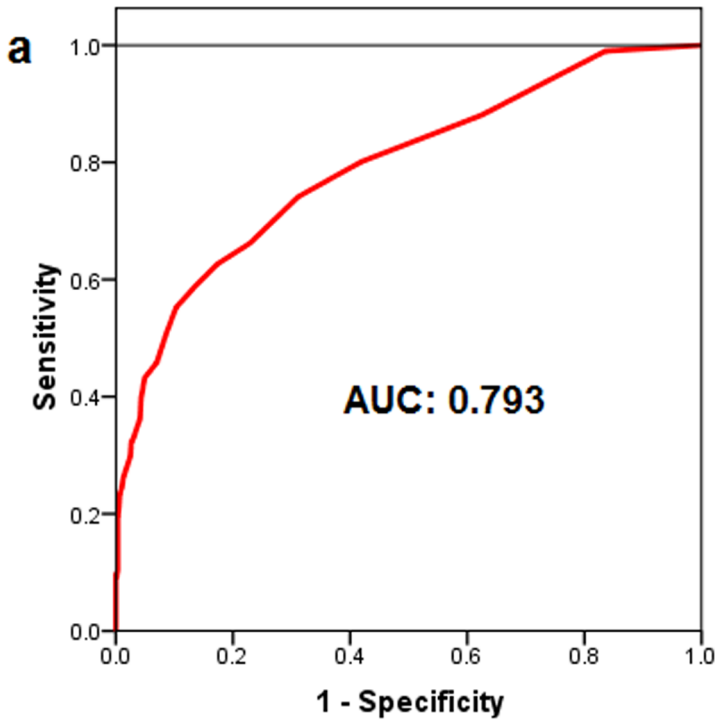

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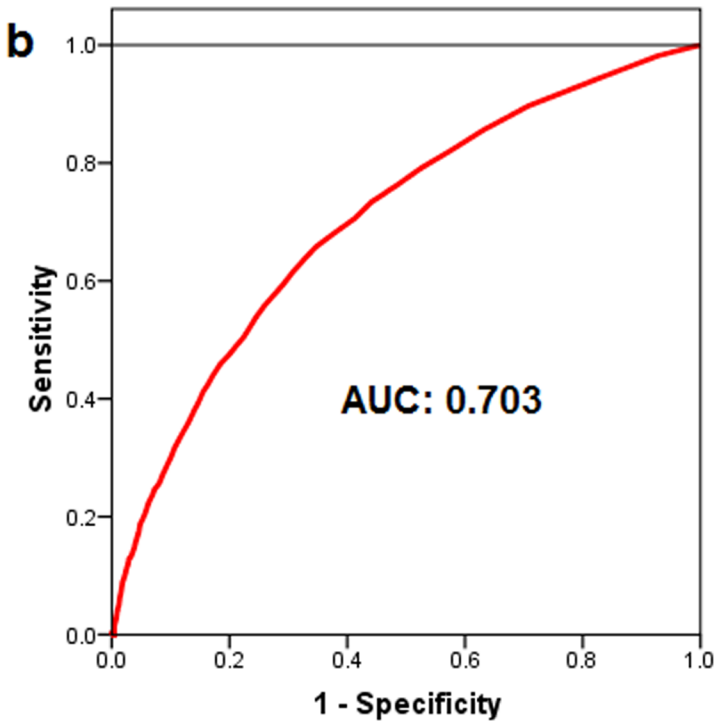

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