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S. W. Ryan
J. Nycyk
B. N. J. Shaw

Prediction of chronic neonatal lung disease on day 4 of life

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S. W. Ryan (✉) · J. Nycyk · B. N. J. Shaw
Neonatal Intensive Care Unit,
Liverpool Women's Hospital,
Crown Street, Liverpool L8 7SS, UK
Tel.: 0151-702-4093/1
Fax: 0151-228-2024

Abstract Clinical parameters, available on day 4, were collected for 204 ventilated neonates < 32 weeks gestation. Logistic regression was used to identify factors significantly and independently associated with chronic neonatal lung disease (CNLD) at 36 weeks postconception, which developed in 29% of neonates. At 36 weeks birth weight, peak inspiratory ventilator pressure and requirement for assisted ventilation on day 4 were such factors. The logistic regression equation for this association was applied to each infant resulting in a value between 0 and 1. By knowing which neonates developed CNLD, the discriminatory ability of this value was assessed. A receiver-operator characteristic curve for this value had an area under the curve of 0.97 (SE 0.03) in an unrelated population. A logistic equation value > 0.4 had a sensitivity of 90% and a specificity of 88% in predicting CNLD at 36 weeks.

Conclusion Use of logistic regression to identify factors independently associated with chronic lung disease at 36 weeks postconception, allowed accurate prediction of this disorder. This would allow reduction in size of randomised trials of early intervention in chronic lung disease.

Key words Chronic neonatal lung disease · Prediction · Preterm neonate

Abbreviations *CNLD* chronic neonatal lung disease · *LV* logistic value · *ROC* receiver-operator characteristic · *SE* standard error

Introduction

We have previously shown that using simple clinical and radiographical information, it is possible to predict which neonates are at high risk of chronic neonatal lung disease (CNLD) [9]. On that occasion logistic regression was used to identify factors independently and significantly associated with CNLD. The value from the logistic regression equation which described this association ("the logistic value") was used as the basis of a predictive test. The value of this equation, calculated for individual infants, lies between 0 and 1. By arbitrarily choosing a single cut off value and by knowing which infants developed CNLD, it was possible to assess the discriminatory ability of this value as a test for CNLD.

The effectiveness of this process over the whole range of values (0–1) was assessed by receiver-operator characteristic (ROC) curves [2, 4, 5]. The area under such a curve has a maximum value of 1, which represents a perfect test. A test with no discriminatory value has an area of 0.5. The previous predictive test of CNLD at day 28, predicted at day 7, had an area under the ROC curve of 0.92. The combination of logistic regression and ROC curve generation have now been used in other fields to predict outcomes [8].

We felt that the predictive test needed further development before being implemented prospectively. The previ-

ous test was developed before the introduction of surfactant and before the recent resurgence in the use of antenatal corticosteroids and it was important to validate the technique in babies receiving these treatments. The previous test was limited to neonates < 1500 g birth weight and therefore missed some preterm neonates with a higher birthweight who developed CNLD. Using a gestation cut off (< 32 weeks) would incorporate most such neonates developing CNLD.

The original test was used at 7 days and predicted CNLD at 28 days of age. We wished to predict CNLD at 4 days of age, so that corticosteroids could be used early in the course of cellular inflammation [1] and protease/antiprotease imbalance [6] from which CNLD follows. Oxygen dependency at 36 weeks postconception is a more important outcome than oxygen dependency at 28 days of age since it more accurately predicts later lung abnormality [10].

One possible weakness of the previous test was the use of variables which may have a subjective element to their value. Inspired oxygen concentration and ventilator pressures are both determined by the underlying disease process and the medical staff's reaction to it. Use of alveolar to arterial oxygen ratio as a variable would overcome this problem. Therefore a new predictive test was developed to take these factors into account.

Patients and methods

Patients

Two hundred and four neonates surviving for 4 or more post-natal days, < 32 weeks gestation who were ventilated and sequentially cared for on the Neonatal Unit at Liverpool Maternity Hospital in 1991 and 1992 were identified. Neonates with major malformations were excluded from the analysis. Data values from these neonates were used to develop a predictive test. Their case notes and intensive care record charts were reviewed. We also reviewed 47 neonates < 32 weeks gestation born in 1993 to assess the reproducibility of the test.

Methods

Likely explanatory variables were selected based on those significantly associated with CNLD in the previous study, together with surfactant and steroid administration, the use of both of which had increased since the previous study. Variables recorded were birth weight (g), gestation (completed weeks), use of surfactant, use of antenatal corticosteroids, peak inspiratory ventilator pressure, days of intermittent positive pressure ventilation, patent ductus arteriosus before day 4 (detected clinically and requiring a change in management), inspired oxygen concentration on day 4 and alveolar/arterial oxygen ratio on day 4.

The outcome variable CNLD was defined as: (1) the need for supplemental oxygen to keep blood oxygen saturation > 92% as measured by an Ohmeda Biox pulse oximeter either on day 28 or at 36 weeks postconception and (2) an abnormal chest X-ray. Neonates who died after 4 days of age were not included in the CNLD group, since the causes of death were heterogenous and since deaths always occurred before the 28th post-natal day.

All of the explanatory variables were entered into a logistic regression (SPSS Release 4.0, SPSS Inc, Chicago) with CNLD as the dependent variable. Explanatory variables not independently significantly associated with CNLD were removed from the model, starting with the least associated variable. After its removal the logistic regression was repeated until only significantly related variables remained. This regression equation for this final analysis produces a logistic value between 0 and 1. By selecting a single cut-off value, for example, 0.5, it was possible to divide the neonates into two groups, one with probability values < 0.5 and one with probability values > = 0.5. The most discriminatory cut-off value cannot be determined prior to this analytical process, since it will depend on the relative proportion within the population of babies at low and high risk of CNLD. Knowing the CNLD status for each infant then allows the discriminatory capacity of each logistic value to be calculated. It is then possible to plot the sensitivity and specificity for a range of logistic values. A plot of sensitivity against 1-specificity is called a receiver-operator characteristic (ROC) curve. A ROC curve provides an alternative to single sensitivity and specificity values, allowing examination of a test's discriminatory capacity across a full range of cut off values [2, 4, 5, 8].

Results

Of 204 neonates < 32 weeks gestation surviving 4 days and ventilated, 63% had received antenatal corticosteroids and 74% had received surfactant. Two babies with lethal malformations were excluded from the study. Median birth weight (range) was 1160 g (512–2300). Median gestation was 28 weeks (23–31). Within the 1st week 8.7% of neonates developed a patent ductus arteriosus detected clinically resulting in a change in medical management. Of the neonates 42% had developed CNLD at 28 days of age and 25% had CNLD at 36 weeks postconception. After day 4 seven (3%) infants had died and they were included in the non-CNLD group for the purpose of analysis.

At day 4 weight, ventilation status, and the clinical presence of a patent ductus arteriosus were significantly and independently associated with CNLD at day 28. The logistic regression equation for this relationship was:

$y = 3.453 - 4.990 *$ weight (kg)
$+ 2.923$ if ventilated on day 4
$+ 2.634$ if patent ductus arteriosus present before day 4

This equation can produce a logistic value (LV) for CNLD by inserting y into the equation:

$LV = e^y/(1 + e^y)$
(e = base of natural logarithms)

The area under the ROC curve for this data was 0.92 (SE 0.033).

Weight, peak inspiratory pressure and the need for ventilation on day 4 were significantly and independently associated with CNLD at 36 weeks postconception. The logistic regression equation for this relationship was:

$y = -0.609 - 3.470 *$ weight (kg)
$+ 0.096 *$ peak inspiratory pressure (cm H_2O)
$+ 1.610$ if ventilated on day 4

Table 1 Sensitivity and specificity of different cut-off values from the logistic regression equation, predicting at 4 days of age, chronic neonatal lung disease at 36 weeks postconception. Similar values for the validation group are also shown

Cut-off logistic regression value								
0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Predicting CNLD at 36 weeks postconception								
Sensitivity								
92	84	82	72	52	40	32	10	0
Specificity								
61	72	79	84	87	93	98	100	100
Validation of prediction in 47 neonates								
Sensitivity								
100	100	95	90	76	52	29	14	0
Specificity								
69	81	84	88	96	100	100	100	100

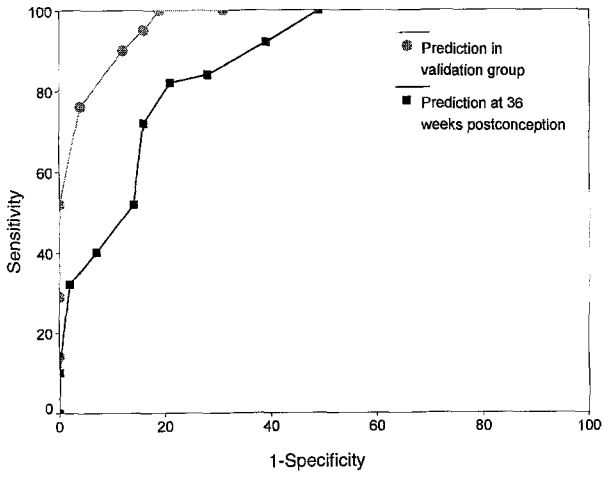

Fig. 1 ROC curves comparing predictive tests for CNLD at 36 weeks postconception and for a cohort of 47 neonates in which the test was validated

The area under the ROC curve for this test was 0.85 (SE 0.032). Table 1 shows the sensitivity and specificity for the full range of logistic cut off values in predicting CNLD at 36 weeks postconception. Figure 1 shows the ROC curve for the separate group of babies born in 1993, showing how closely it overlies the ROC curve for the neonates born in 1991/1992. The area under this ROC curve was 0.97 (SE 0.032).

Discussion

This predictive test for CNLD has several advantages over the previous test [9]. It can be undertaken at 4 days of age, so that intervention to prevent the development of CNLD can begin earlier in the course of abnormal healing from hyaline membrane disease. There is evidence of an excess inflammatory response at this time [6] and the early use of corticosteroids has been suggested as a potential strategy [11] to improve outcome. Later use of corticosteroids has not produced benefits in long-term outcome despite improvements seen in the short-term [3]. The potential risks of corticosteroid treatment are well described [7], and include serious and life threatening complications.

Another difference from the previous prediction, is that neonates who died after 4 days of postnatal age are not included in the group with CNLD, but classified along with neonates surviving without CNLD. This is because the causes of death were heterogenous and additionally could not be classified as CNLD until the infant reached the age of 28 days; all such deaths occurred between 4 and 28 postnatal days. Since the main purpose of this prediction is to select neonates for randomisation within controlled intervention trials of the prevention of CNLD, such interventions would not be aimed at such heterogenous causes of death. The outcome measure of such a study would be oxygen dependency at 36 weeks post-conception and this is therefore reflected in the outcome chosen for this study.

It is important that early corticosteroid trials are targeted as closely as possible at those who are likely to derive maximum benefit. This means identifying those neonates who will develop long-term CNLD. Based on this study, if one were to randomise a cohort of neonates < 32 weeks gestation who had been ventilated, only 31% would develop CNLD at 36 weeks postconception (including those who died before this time). A proposed trial with a β of 0.8 and an α of 0.05 would require 1078 patients to detect a 25% reduction in the incidence of CNLD. Of those treated 69% were never destined to get CNLD.

The use of the prediction test developed here with a cut off value of 0.4 and a specificity of 88% and a sensitivity of 90% would produce a trial cohort with an incidence of CNLD of 86% (Table 1). To detect a similar reduction in CNLD with similar performance would only require 114 patients.

Despite the earlier use of the test on this occasion, its ability to predict CNLD at 28 days was only slightly decreased, as measured by the area under the ROC curve. The area in this study was 0.92 compared to 0.94 in the previous study [9]. The incidence of CNLD was also similar to that in our previous study, although that study looked at infants < 1500 g birth weight and this study was of infants < 32 weeks gestation.

The more frequent use of antenatal corticosteroids and surfactant (63% and 74% respectively) has also probably changed the nature of the prediction equations. Most notably peak airway pressure, classically associated with CNLD is significantly associated with CNLD at 36 weeks in this study. Interestingly antenatal steroid use and surfactant were not themselves significantly associated with CNLD. This lack of association might be because the ef-

fect is diluted by those babies who died before day 4 and who were not entered into the study, since both interventions are heavily associated with improved survival. Also the lack of association may be because the contribution of these interventions to variability in some other parameter, such as ventilation status, which has a stronger overall association.

The use of a subjective measure of lung disorder – the alveolar arterial oxygen ratio was not successful for the simple technical reason that at 4 days of age neonates were frequently without arterial lines. Hence an accurate estimate of the ratio could not be made in the majority.

It was possible to predict CNLD at 36 weeks, although this resulted in a reduced area under the receiver operator characteristic curve (0.906). Despite this the ability to predict a more important outcome outweighs this disadvantage. We now aim to use the prediction formula for CNLD at 36 weeks postconception to identify neonates for a trial of early corticosteroid treatment.

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