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CRITICAL CARE

Factors associated with poor prognosis in very-low-birth-weight infants

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Objective. To evaluate predictors of poor outcome, including the CRIB (Clinical Risk Index for Babies) score, in a local population of very-low-birth-weight (VLBW) infants, in order to provide guidelines for selection of these babies for expensive tertiary care.

Subjects. Two hundred and thirty-one neonates born at less than 31 weeks' gestation and/or weighing between 1 001 g and 1 500 g, enrolled prospectively as part of a multicentre study evaluating the CRIB score.

Design. Univariate analysis (chi-square/*t*-tests) and multivariate analysis (stepwise logistic regression) on the above sample to determine predictors of poor outcome.

Setting. Neonatal Unit, Johannesburg Hospital.

Outcome measures. Death or impairment (namely oxygen therapy > 28 days, grade 3 or 4 intraventricular haemorrhage, or ventricular enlargement).

Results. Poor outcome was predicted by birth weight, lowest oxygen requirement in the first 12 hours (which are two components of the CRIB score), and maximum partial arterial carbon dioxide pressure ($PaCO_2$) in the first 72 hours. Other factors, including the full CRIB score, were not predictive of outcome.

Conclusions. One method of selection of infants for expensive tertiary care is on the basis of predicted outcome. Birth weight remains a reasonable basis for this selection, but the inclusion of other factors, such as oxygen requirement, would improve accuracy. The CRIB score was not a suitable means to select infants in the local context, but may be of value in international comparisons.

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Severely limited health resources necessitate the selection of patients for expensive tertiary care, including admission to the neonatal intensive care unit (NICU). For this reason, a birth weight cut-off of 1 000 g was recommended as a criterion for admission to the NICU (10th Conference on Priorities in Perinatal Care, Eastern Transvaal, 1991). As pressure on tertiary facilities grows owing to burgeoning patient numbers, the tendency is simply to increase the required birth weight or NICU admission. Birth weight alone, however, only predicted mortality in our neonatal population with an accuracy of about 60%.[1] Severity of illness has been shown to be a powerful independent predictor of neonatal mortality and to improve on prediction by birth weight alone.[2]

Several scores of severity of illness have been developed recently, including the NTISS (Neonatal Therapeutic Intervention Scoring System),[3] SNAP (Score for Neonatal Acute Physiology)[4] and CRIB (Clinical Risk Index for Babies).[5] Both the NTISS and SNAP are cumbersome and require special investigations, whereas the CRIB is simple and easy to apply. The CRIB score[5] is a measure of initial risk and illness severity. This score predicts mortality risk and was not developed to predict impairment, although it may do so on a limited basis (W. Tarnow-Mordi — personal communication). Scores such as the CRIB have been used to compare outcome between different units and not as a means to select individual patients for tertiary care. Furthermore, these scores were developed in First-World units with practices and standards of care different from those in South Africa. The CRIB score[5] is heavily weighted towards very small babies (< 1 000 g), who are not usually ventilated in state hospitals in South Africa.

If a severity of illness score is to be used for selecting neonates for tertiary care, it should be specifically developed and tested for that purpose in our own neonatal population. As an initial step, this study evaluated various predictors of poor outcome (in terms of death alone and death or impairment) in the very-low-birth-weight (VLBW) neonates at Johannesburg Hospital.

Subjects and methods

Subjects were a cohort of infants prospectively enrolled from the neonatal admissions at the Johannesburg Hospital as part of a large collaborative study using the CRIB score (International Neonatal Network, W. Tarnow-Mordi, Dundee). Inclusion criteria were birth weight below 1 501 g and/or gestational age less than 31 weeks. Infants weighing less than 1 000 g were excluded because they are not routinely ventilated and would therefore bias the analysis. The study was conducted between 1 September 1992 and 1 September 1994. Data collected for the first 12 hours included birth weight, gestational age, 5-minute Apgar score, place and mode of delivery, presentation, the use of antenatal steroids, highest, lowest and earliest appropriate oxygen requirements[1] (defined as the highest, lowest and earliest fractional inspired oxygen concentration (FiO_2) in the first 12 hours of life needed to maintain a partial arterial oxygen pressure (PaO_2) of 50 - 80 mmHg, or arterial saturation of 88 - 95% on pulse oximetry), base deficit and congenital malformations. Subsequent data included the need for ventilation, maximum partial arterial carbon dioxide pressure ($PaCO_2$) in the first 72 hours, duration of ventilation

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and oxygen therapy, presence of hyaline membrane disease (HMD), incidence of pneumothorax, presence of intraventricular haemorrhage (IVH) or periventricular leucomalacia (PVL), and outcome in terms of death or death/impairment. Since long-term follow-up was not planned, impairment was defined as grade 3 or 4 IVH (Papile *et al.*[6]), PVL, ventricular enlargement[7,8] or oxygen therapy for more than 28 days.[9] The CRIB score was determined from birth weight, base excess, earliest, highest and lowest appropriate oxygen requirements, and congenital malformations. Where infants were well enough not to require blood gas measurement a value of zero was given for base deficit when determining the CRIB score.

Statistical analysis was conducted by the Centre for Epidemiological Research in Southern Africa. The data were analysed twice for different outcomes — once for death and again for death/impairment. Initially, univariate analysis was conducted to test for association and difference in the outcome measurements, with regard to all the independent variables; the chi-square test was used for categorical data and *t*-tests, with confirmation by the Mann-Whitney *U*-test, for continuous variables. Multivariate analysis was then performed using stepwise logistic regression, since the dependent variable was binary.

Results

The study sample comprised 231 neonates, whose basic characteristics are shown in Table I. Fifty per cent were male. Antenatal steroids, including incomplete courses, had been administered to 17% of mothers in preterm labour. Most infants (80%) were inborn, 32% were delivered by caesarean section, and 13% were products of a multiple pregnancy. The primary diagnosis in 59% of cases was HMD, and 69% of the total sample was ventilated. Surfactant was administered to 78 of 159 ventilated babies (49%) and pneumothorax occurred in 8 of 159 ventilated infants (5%). The majority of infants (84%) survived. Information regarding cranial ultrasound findings is shown in Table II. Twenty-three per cent of infants were considered too well to have cranial ultrasonography performed.

Table I. Characteristics of the study sample

	Mean	SD
Birth weight (g)	1 286	152
Gestational age (wks)	30.9	2.2
5-min Apgar score	7.5	2.04
Admission age (h)	2.7	12.65
$FiO_2(1)$*	0.56	0.28
$FiO_2(2)$†	0.43	0.22
$FiO_2(3)$‡	0.59	0.3
Base deficit (N = 159)	10.2	4.5
CRIB	4.24	3.8
Max. $PaCO_2$ (mmHg)	43.2	9.3
Duration of ventilation (d) (N = 159)	8.8	8.8
Duration of O_2 requirement (d)	14.4	17.4

* Earliest appropriate oxygen requirement in first 12 hours.
† Lowest appropriate oxygen requirement in first 12 hours.
‡ Highest appropriate oxygen requirement in first 12 hours.

Table II. Cranial ultrasound findings

	No.	%
No cranial ultrasound done	53	23
No IVH	70	30
IVH grade		
1	4	2
2	83	36
3	11	4.7
4	10	4.3
Dilated ventricles	19	8
Periventricular leucomalacia	12	5

When considering death as the outcome variable, chi-square tests showed significant associations between pneumothorax, congenital malformation, Apgar score, gestational age, oxygen requirements, base excess, CRIB score and maximum $PaCO_2$ and the outcome measurements (Table III). However, on stepwise logistic regression analysis, only the lowest appropriate FiO_2 in the first 12 hours (a component of the CRIB score) and maximum $PaCO_2$ (< 72 hours) were associated with death. A good fit was obtained for the model:

logit (P) = –5.149 + 0.0292 max. $PaCO_2$ + 0.0354 FiO_2, where P is the probability of death (goodness of fit χ^2 P = 0.98).

Table III. Comparison of continuous variables for survivors v. non-survivors

	Died		Survived		
	Mean	SD	Mean	SD	P
Birth weight (g)	1 247	158	1 290	149	NS
5-min Apgar score	6.7	2.4	7.6	2.0	0.055
Gestational age (wks)	30.0	1.7	31.0	2.2	0.0033
Admission age (h)	9.9	31.0	1.4	2.5	NS
$FiO_2(1)$*	0.71	0.28	0.54	0.27	0.0049
$FiO_2(2)$†	0.61	0.27	0.41	0.20	<0.0001
$FiO_2(3)$‡	0.77	0.27	0.57	0.29	<0.001
Base deficit (N = 159)	11.9	4.6	9.8	4.4	0.05
CRIB (N = 217)	7.03	3.91	3.89	3.6	< 0.001
Max. Co_2 (N = 159) (mmHg)	46.7	11.9	42.6	8.8	0.09

Footnotes as for Table I.

Re-analysing the data using death/impairment as a single outcome variable gave similar results. Univariate analysis showed congenital malformations, the need for ventilation, presence of HMD, pneumothorax, surfactant administration, birth weight, Apgar score, gestational age, oxygen requirements in the first 12 hours and the CRIB score to be significantly associated with the outcome variable (Table IV). However, stepwise logistic regression only revealed birth weight and lowest FiO_2 in the first 12 hours (both components of the CRIB score) to be predictive of death/impairment. The fit was equally good for the model:

logit (P) = 1.71 – 0.3117 x 10^{-2} birth weight + 0.3613 x 10^{-1} FiO_2, where P is the probability of death/impairment (goodness of fit χ^2 P = 0.976).

Table IV. Comparison of continuous variables with death/impairment as the outcome

	Death/impairment		Normal		
	Mean	SD	Mean	SD	*P*
Birth weight (g)	1 235	162	1 312	138	0.0005
5-min Apgar score	6.9	2.8	7.8	1.9	0.0048
Gestational age (wks)	29.5	1.9	31.4	2.2	< 0.001
Admission age (h)	5.4	21.2	1.3	1.5	NS
$FiO_2(1)$*	0.69	0.28	0.49	0.26	< 0.001
$FiO_2(2)$†	0.54	0.25	0.37	0.18	< 0.001
$FiO_2(3)$‡	0.72	0.28	0.51	0.28	< 0.001
Base deficit ($N \approx 159$)	10.3	3.9	10.1	4.9	NS
CRIB ($N = 217$)	6.19	3.78	3.23	3.4	< 0.001
Max. $PaCO_2$ ($N = 159$) (mmHg)	44.9	9.6	41.9	9.0	NS

Footnotes as for Table I.

Hence, the significant predictors of either death or death/impairment were the lowest appropriate FiO_2 within 12 hours, birth weight and maximum $PaCO_2$. Certain variables identified on univariate analysis, such as pneumothorax and congenital malformation, could not be included in the logistic regression owing to very small numbers.

Discussion and conclusions

One way to select neonates for expensive tertiary care is on the basis of prognosis in terms of function and survival. An objective assessment of initial severity of illness would assist in this process. The CRIB score[5] has been developed to assess initial severity of illness in neonates and could possibly be used for this purpose. The best predictors of poor outcome in the present analysis included birth weight, lowest appropriate FiO_2 (< 12 hours) (two of the six components of the CRIB score) and maximum $PaCO_2$ (< 72 hours), while the full CRIB score was not independently predictive of outcome. Certain other variables, such as pneumothorax and congenital malformation, which were associated with poor outcome on univariate analysis, could not be included in multivariate analysis owing to small numbers.

Some traditional risk factors for VLBW infants such as gender, place of birth and Apgar score were not predictive of outcome in this analysis. Although Apgar score achieved significance on univariate analysis, actual differences were small and were not significant on multivariate analysis. Other variables were interrelated and hence lost significance on multivariate analysis; e.g. HMD, ventilation and surfactant administration were closely related to oxygen requirement. The use of antenatal steroids was infrequent during the study period and therefore did not predict outcome. There are some methodological limitations with this study. In particular, neonates below 1 000 g birth weight were excluded because they are not routinely ventilated. In addition, a few infants who were moribund on entry to the admission ward were treated conservatively and not considered as admissions. It is therefore possible that some of the sickest babies were selected out of the sample and hence biased the analysis. These numbers were small, however.

The failure of some traditional risk factors to predict outcome is similar to the findings of Tarnow-Mordi *et al.*[10] They found that the mean level of oxygenation in the first 12 hours of life was more strongly associated with death than four traditional risk factors (birth weight, short gestation, male sex and the diagnosis of respiratory distress syndrome). Furthermore, mean pH in the first 12 hours was as strongly associated with death as was birth weight. Previous research in our neonatal population showed that maternal booking status, an assumed predictor of poor outcome, was an invalid criterion for admission to the NICU.[11] This emphasises the need to evaluate prognostic factors properly in the local context before implementing admission policies based on such information.

This study also brings into question the appropriateness of the CRIB score in our population. The complete CRIB did not predict outcome on multivariate analysis, whereas two of the individual CRIB components, viz. birth weight and lowest appropriate FiO_2 requirement, were strongly associated with outcome. Thus oxygen requirement and birth weight appear to be the most important components of the CRIB score in our VLBW neonates. Although the full CRIB score was not independently predictive of death/impairment in this study, it may be in a larger local sample and remains of value for international comparisons.

As shown in this study, birth weight remains a reasonable basis for selection of NICU patients. Given the limited number of NICU beds in our area,[1] a birth weight cut-off of 1 000 g for ventilation appears to be appropriate to our situation. The inclusion of additional factors such as oxygen requirement would improve the accuracy and flexibility of this selection process. In this particular study, oxygen requirement was determined during the first 12 hours of life, which makes it impractical as an admission criterion. It could, however, be used in decisions to limit aggressive therapy. The use of predictors of poor outcome such as this in deciding to withdraw treatment is controversial; the authors who developed these scores strongly argue against it. Klaus,[12] however, feels that this could be useful to both health care workers and parents in deciding on the further management of small neonates. An objective assessment of prognosis would provide a rational means of both selecting patients for admission and deciding to withdraw therapy. Although such an assessment does not provide absolute answers for an individual patient, it does allow expensive care to be limited in that group of patients who are *most likely* to have a poor outcome. Whatever method is used to limit care (including birth weight), there will always be individual patients who would have done well. This, unfortunately, is the consequence of insufficient health resources.

Further research needs to be conducted to establish predictors of poor outcome in our own VLBW population. An admission score could then be derived from such data. It may be appropriate to include other factors such as initial response to therapy in such an assessment. It is to be hoped that such a score would assist doctors in the difficult decisions regarding selection of neonates to be treated.

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