THE DEVELOPMENT AND EVALUATION OF AN OUTCOME PREDICTIVE SCORE FOR A NEONATAL INTENSIVE CARE UNIT IN SOUTH AFRICA.

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I, the undersigned, hereby declare that the work contained in this dissertation is my original work and that I have not previously in its entirety or in part submitted it at any University for a degree.

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Summary

Background

The care of children is one of the cornerstones of social philosophy. In first world countries most children survive to adulthood. In South Africa the infant mortality rate is much higher than it should be, if compared to the gross capital income per person.

The ability to deliver neonatal intensive care (NIC) in South Africa has decreased in the past decade. Therefore it is necessary to choose which babies will receive care. This choice is mainly based on a birth weight (BW) of at least 1000 grams and or a gestational age (GA) of 28 weeks. The only other variable taken into consideration is antenatal care. International scoring systems, like the Clinical Risk Index for Babies (CRIB) score, have been found lacking in accuracy.

Aim:

The aim of this study was to devise a scoring system which could accurately predict outcome of individual patients before admission to the Neonatal ICU.

Patients and methods:

Data on the patients enrolled in the CRIB study (1992-1995) were collected retrospectively for the initial cohort (IC). Variables examined were:

Maternal risks like age, parity, type of delivery, prolonged rupture of membranes, syphilis and socio-economic status.

Neonatal risk factors like BW, GA, gender, ethnic group, ante natal visits, multiple gestations, place of birth, early or late admission to NIC and the one and five minute Apgar counts.

Outcome variables examined were mortality, length of hospital stay, duration of ventilation and the development of broncho-pulmonary dysplasia.

The scoring system was developed with data from the CRIB cohort. A prospective study obtained data for a validation cohort (VC) (1999-2002).

Statistical analysis:

Descriptive, parametric and non-parametric methods were used. Kaplan&Meier life tables, multivariate analysis and CART analysis were used.

Results:

The IC consisted of 455 babies with a mean BW of 1198g and mean GA of 30.3 weeks. The VC included 272 babies with a mean BW of 1169g and mean GA of 29.8 weeks. The mean maternal income had changed from R892 in the IC to R613 in the VC. These variables were all significantly different.

The mortality rate in the IC was 26.1 % and significantly less in the VC of 21.6% ($p<0.05$). Variables which were the most valuable in predicting outcome were the BW and GA, which were interchangeable. BW had a 63% predictive value for survival. The only outcome variable predictable was survival. BW, antenatal care, gender, place of birth and maternal income were important predictors. Maternal income of zero however nullified all other predictive variables of outcome.

In the Cart analysis of the IC the most important predictors were BW >1037g, maternal income of less than 1206 South African Rand, antenatal care and gender. Survival could be predicted in 94% of cases.

In the VC the predictive accuracy was 84% with the CART analysis. The alternative CART analysis was based on place of birth (babies from outlying areas did better), BW (<855g) and gender, but did not improve predictability.

Discussion

Babies admitted to the NICU in this study are chosen by means of non-validated variables. It remains difficult to identify a single prognosticating variable of outcome as the IC was already chosen and the variables are interdependent.

Comparable results were obtained in identifying prognosticators when using different statistical methods. The ranking of the variables differed, but the most important variables were similar.

Variables currently used to restrict access to the ICU like poor antenatal care and delivery in a peripheral hospital, are no longer justifiable, because babies with these variables did not have a poorer survival rate in this study. A birth weight of more than 855g has the same survival chance as a baby of 1001 grams, which is the current norm for admission.

In conclusion, a method by means of the CART analysis was devised that can predict individual survival by 84% or more which is much better than the 63% achieved by using BW.

Opsomming

Die versorging van kinders is die hoeksteen van sosiale filosofie. In eerste wêreld lande sal die meeste kinders volwassenheid bereik. In Suid Afrika is die kindersterfde koers baie hoër as verwag, gemeet volgens die per kapita inkomste.

Die vermoë om neonatale sorg in Suid Afrika te voorsien het in die afgelope dekade afgeneem. Daarom is dit nodig om die babas te selekteer aan wie sorg verskaf sal word. Die keuse word meestal gemaak op die baba se gestasie (G) (>27 weke) of die geboorte gewig (>1000g) (GG). Al ander veranderlikes wat in ag geneem word is of die moeder antenatale sorg ontvang het aldan nie. Internasionaal gevalideerde seleksiemetodes soos die CRIB score is getoets in Suid Afrika, maar is onakuraat.

Doel

Die doel van de studie was om 'n seleksiemetode op te stel wat akkuraat die uikomste van individuele babas sou kon voorspel voor die toelating tot die intensiewe sorg eenheid.

Pasiente en metodes

Data van die pasiente wat gebruik is in die CRIB studie (1992-1996), is retrospektief ontleed as die inisiële kohort (IK). Veranderlikes wat bestudeer is was:

Moederlike veranderlikes soos ouderdom, pariteit, tipe van verlossing, verlengde ruptuur van vliese, sifilis en moederlike inkomste

Neonatale veranderlikes soos GG, G, geslag, etnisiteit, voorgeboorte besoeke, veelvuldige gestasie, plek van geboorte, vroeë of laat toelatings, en die Apgar telling op een en vyf minute.

Uitkomstes wat bestudeer was is mortaliteit, lengte van hospitaal verblyf, lengte van ventilasie en die ontwikkeling van brongo-pulmonale displasie.

Die seleksiesisteem is op die gegewens van die inisieële kohort ontwerp en deur middel van 'n prospektiewe validasie kohort (VK) (1999-2002) getoets.

Statistiese analise

Beskrywende statistieke, parametriese en nie parametriese toetse is gebruik in die analise. Kaplan&Meier lewenstabelle, multivariaat analise en CART analises is gedoen.

Resultate

Die IK het uit 455 babas bestaan met 'n gemiddelde GG van 1198g en 'n gestasie van 30.3 weke. Die VK het uit 277 babas bestaan met 'n gemiddelde GG van 1169g en 'n G van 29.8 weke. Die gemiddelde inkomste van die moeders was 892 Suid Afrikaanse Rand (R) en R613 respektiewelik. Al drie hierdie veranderlikes was betekenisvol verskillend tussen die twee kohorte.

Mortaliteit in die IK was 26% en betekenisvol minder in die in die VK met 21%. Die veranderlikes wat die waardevolste was naamlik GG en G, kan mekaar vervang. Slegs oorlewing kon voorspel word. Veranderlikes wat die meeste gewig gedra het in die meeste analises was GG, voorgeboorte sorg, geslag, plek van geboorte en moederlike inkomste. Geen moederlike inkomste was die enigste faktor van belang in die voorspelling van oorlewing en het die ander faktore tersyde gestel.

Die CART analise van die IK het die vorspellers as geboorte gewig van meer a 1037g, sosio- ekonomiese status (>R1206), voorgeboorte sorg en geslag identifiseer. Die metode het oorlewing korrek voorspel in 94% van gevalle.

In die VK het die voorspelling oorlewing korrek identifiseer in 84% van gevalle. Die alternatiewe veranderlikes wat geïdentifiseer is in die validasie kohort was die plek van geboorte (babas gebore in die periferie het beter oorlewing), GG (>855g) en geslag maar die alternatiewe CART analise het nie beter gevaar as die oorspronklike nie.

Bespreking

Babas word op onwetenskaplike gronde gekies om intensiewe sorg te ontvang. Dit blyk onmoontlik te wees om een veranderlike te vind waarop die keuse gemaak kan word, aangesien die inisieële kohort reeds gekies was en die veranderlikes onderling afhanklik van mekaar is.

Eenderse veranderlikes is deur die verskillende statistiese modelle geïdentifiseer. Die rangordes het verskil, maar die belangrikste veranderlikes was dieselfde.

Al die veranderlikes wat tans gebruik om babas te selekteer vir intensiewe sorg is nie van waarde nie. Dit is duidelik bewys deur die CART analise. Veranderlikes soos voorgeboorte sorg en toelatings uit buite hospitale, wat tans in besluitneming gebruik word, penaliseer die babas volgens die ontleding onnodig. GG van meer as 855g skyn aanvaarbaar te wees in plaas van die huidige 1000g.

'n Wetenskaplike metode is met behulp van die CART analise ontwikkel wat die vermoë om die oorlewing van babas te voorspel, van 63% na 84% verbeter het.

Abbreviation	Meaning
ANC	Antenatal clinics
APACHE	Acute Physiology And Chronic Health Evaluation
BPD	Broncho-pulmonary dysplasia
CART	Classification and regression tree analysis
CPAP	Continuous positive airway pressure
CRIB	Clinical risk index for babies
DF	Degrees of freedom
FiO_2	Fraction of inspired oxygen
FN	False negative rate
FP	False positive rate
GA	Gestational age
GINI	Gini index for binary recursive partitioning
HIV	Human immunodeficiency virus
IC	Initial cohort
ICU	Intensive care unit
IMR	Infant mortality rate
LBW	Low birth weight
IPPV	Intermittent positive pressure ventilation
M:F	Male: female

Abbreviation	Meaning
MOU	Midwife Obstetric Units
MRC	Medical Research Council
N (n)	Number
NICU	Neonatal intensive care unit(s)
NTISS	Neonatal Therapeutic Intervention Scoring System
NVD	Normal vertex delivery
NPV	Negative predictor value
PPROM	Prolonged premature rupture of membranes
PPV	Positive predictor value
PRISM	Paediatric Risk of Mortality
PROM (PPROM)	Premature rupture of membranes
ROC	Receiver-operating curve
RPR	Rapid plasma reagent
RR	Relative risk
RSA	Republic of South Africa
SGA	Small for gestational age
Sig	Significance
SNAP	Score for Neonatal Acute Physiology
SNAP-PE	SNAP-Perinatal Extension
STD	Sexually transmitted disease
TBH	Tygerberg Hospital

Abbreviation	**Meaning**
UCT	University of Cape Town
USA	United States of America
VC	Validation cohort
VLBW	Very low birth weight babies

Afrikaanse afkortings

Afkorting	**Betekenis**
G	Gestasie
GG	Geboorte gewig
IK	Inisiële kohort
VK	Validasie kohort

CHAPTER 1

1 Introduction

1.1 Background

"There is no touchstone, except the treatment of childhood, which reveals the true character of a social philosophy more clearly than the spirit in which it regards the misfortunes of those of its members who fall by the way"[1] Thus quotes Knutsson in his book, which he calls: "Children: Noble Causes or Worthy Citizens".[2] The quest of many to right the rights of children can be found in all walks of society. The questions asked do not only involve the rights of children, but also touch on the definition of what a child is. The "survival of the fittest" and the extremely high mortality rate of newborns in medieval times has made way for the survival of babies (often damaged) at the extreme borders of viable prematurity.

This must be seen in the perspective of childcare through the ages. Knutsson quotes from de Mause's book on "the History of Childhood" that in the Greek city of Miletus, of the 79 families who gained citizenship in the time period of 228 to 220BC, there were 118 sons and 28 daughters."[3] This suggests the selective care that was given to male infants and that elective killing of female babies probably occurred. This changed somewhat in the Christian era[4], but even in the later periods of the fifth to the fourteenth century, it was customary practice to support all male infants and to restrict support to the first-born girl only. The French Revolution is considered a milestone in the recognition of human rights, but did not specify female rights.[3] The rights of women, children and the mentally insane started to feature only in the nineteenth century after the abolition of slavery. In 1889 the rights of children in England were adopted as part of the "same protection that we give under the Cruelty of Animals Act and the Contagious Diseases Act for Domestic Animals". During the previous century the perceptions regarding children, mostly in the Western world, have improved dramatically. The globalisation of these concepts have, however, not been embraced by all cultures. [5,6] Wars, famine, ethnic conflict and religious perceptions still today make the universal "happy childhood" a dream few children live.[7]

The crescendo of interest in newborn infants in the 1980s followed the development of appropriate equipment for their care, significant research into causes of abnormalities, and the presentation of evidence that even very-low-birth-weight infants could survive and be normal.[8] "If some could survive why not most all of them?" This statement of M E Avery in a neonatal textbook illustrates the quest for newborn care in South Africa.[9]
We should carefully examine this quote and ask whether these recommendations are followed. The infant mortality rate (IMR) in South Africa has always lagged behind the best international standards.[10] In the past decade the ability to deliver neonatal intensive care in South Africa has decreased.[11,12,13]

Is there appropriate equipment to treat every child, is there adequate support for research and what is the long-term outcome in survivors?

The answers to the first and second questions in South Africa, if we intend to serve the total population, are no.[14] We do know the good outcome of survivors in the limited number of neonates who had access to neonatal care.[15,16,17]

"As guardians of children's physical, mental, and emotional progress from conception to maturity, pediatricians are in the vanguard of social concern for children and their families. The caring qualities of any society may best be measured by the concerns it manifests for its aged, its disadvantaged (the dependent, handicapped, retarded, or incarcerated, for example), and its young. The young are often among the most disadvantaged." These words are taken from the opening paragraph of a leading textbook in paediatrics.[18]

The abovementioned principles are as applicable to neonatal care today, as in 1983 when they were formulated by the American Academy of Pediatrics. The demand for costly sophisticated medical care is constantly increasing.[19,20] It is increasingly important to measure the cost benefits of expensive treatment methods by quantifying the results.[21] At the same time there is the awareness of the need to provide evidence of the effectiveness of novel treatment options.[22] There is also an increasing demand for public knowledge about every treatment modality in most diseases, whether these treatment options have been adequately tested or not.[23] In a scenario of limited resources for health care, resources have to be largely allocated to where the greatest benefit will be achieved for the largest number of people in the most cost effective way.[24]

The quest for health in Africa is problematic.[25] In an era where most African countries have poor health services, South Africa is one of the countries which spends a substantial part of its gross national product on health care.[26] 11.2% of the 1998/1999 national budget was allocated to health.[27,12] The question of equality as well as the quality of care which is possible with the available resources is still debated.[28]

1.2 Managed health care

The ongoing debate in the United States of America (USA) about reform of the health care system has been focused more on access and cost than on the effectiveness of care. Yet, for the population as a whole, medical care appears to have only a modest effect on longevity or health.[29] Indeed, a major increase in the delivery of medical care produced almost no discernible improvement in the health status of adults during a large clinical trial to assess the benefits of providing free medical care.[30] The only improvement in outcome that has been found is in the supply of care to newborn babies.[30]

Cost is one of the main factors in determining the delivery of medical care. Even in the USA a young patient with leukaemia was denied a bone marrow transplant because of the costs involved.[31]

Premature infants are a subgroup of the pediatric population for whom medical care has undoubted effects on outcome. The mortality of premature infants has decreased dramatically during the past several decades. [32,33] The National Centre for Health Statistics, which estimates total years of life lost before age 65 from a large variety of causes, has reported that the largest recent reduction in total life-years lost from any cause has occurred among premature infants.[34] This is not necessarily the case in a developing country where more life years may be gained by a feeding programme, the immunisation of all babies or empowering women.[35] No comparative studies have been done in South Africa. The health policy decisions are mainly based on evidence from other countries and recommendations by bodies like the World Health Organisation, which may be inappropriate.[36]

The balance between supply and demand is even more problematic in developing countries. Due to the high birth rates the demand for neonatal care is higher, the available resources are less and the disease profile of the babies is often more complex than in affluent countries[37]. This is complicated by unsatisfactory systems to quantify disease severity and a lack of validated admission criteria to select neonates for admission to intensive care.[38] There is a great need for a revision of criteria for admission to intensive care as measured by morbidity and mortality. In the absence of adequate local studies decision criteria derived by research in developed countries have been used and found inappropriate.[19]

1.3 Neonatal intensive care: developing vs. developed world

In the developed world the supply and demand for neonatal care was at first revenue-driven. This has been the case in America since the Hill-Burton legislation in 1940[39] This caused a positive feedback cycle of ever increasing clinical research, increasing specialisation which lead to increased training, expanding mainly university based institutions and a greater public expectation for care[40] There was little if any attempt to limit this expansion or to quantify and qualify the process and the results.[41] An attempt to do this has only now started because health care business, both the public and private sector, are demanding accountability. The industry responded by introducing managed care which initiated a transition. The private sector in South Africa has followed suit.[42]

This process has not yet taken place in the public sector, which experienced a bloom period in development during the late seventies and early eighties followed by regression since the beginning of the nineties. Because of financial constraints, there has been a severe and steady loss of neonatal intensive care facilities for public sector clients in a time of increasing urbanisation.[43] This should be seen in the light of an article by Cooper, in which the need for extra neonatal beds in 1987 is discussed and in which he states that 133 babies could not be cared for in one year in the Metropolitan Witwatersrand area.[44]

The inappropriate care of newborns with a limited lifespan is questioned also internationally. Gunkel asked "how many starving children, who are healthy, could be helped internationally by refusing intensive care in Germany to a hopeless baby?"[45]

There is an increasing demand for tertiary care which is driven by better facilities in the primary health care arena and increased expectation of patients.[46] This raises questions about the rationale of allocating intensive care to selected neonates only. Firstly, this may be done to ensure the continuation of life if a good outcome is likely. Secondly, it can be allocated to benefit as many babies as is physically possible, as is the case in the South African public health sector. This does not relieve the government of its responsibility to maintain and upgrade health care facilities.[47] Wennberg believes that the key to the preservation of the fee-for service markets is not the micro-management of the doctor-patient relationship but the management of capacity and budgets.[31] Wainer, however, feels that the "unideal conditions under which doctors and nurses work in developing nations mandate resource allocation to be an integral component of NICU care".[48]

The facilities which are currently available are understaffed by international standards.[49] This causes the quality of care to lag behind that of developed countries, and that of the private sector in South Africa. This has an adverse effect on the training of registrars in pediatrics and neonatologists.[50]

All these factors have forced the public sector to select infants who qualify for neonatal intensive care.

1.4 Who chooses

In patient-related decision making in developed countries, the emphasis is mainly on the rights of the individual. These principles have to be reconciled with the dilemmas of autonomy, beneficence and justice. In the health care context, autonomy requires that persons be treated as self-determining and self-defining agents and that their wishes be respected whenever possible. Direct applicability to infants is problematic, because surrogate decision-making on their behalf cannot apply the now-preferred substituted judgement standard, which seeks to base all decisions on the expressed or inferred wishes of the patient. In the case of infants, parents bear the primary responsibility to exercise the rights of the child. In paediatrics, ethical decisions are often made according to the perceived best interests of the child. In terms of the newborn infant, the decision to treat has involuntary been made by the mother who receives her first antenatal care. Does it mean that the mother, who did not seek antenatal care, has made the decision not to have her baby treated? How does this influence the outcome of that baby? Traditionally these babies of mothers who did not seek antenatal care had to have a higher birth weight to qualify for NICU care. But is this not a question of cultural or social choice. The cost of antenatal care to the South African family has been reduced with the advent of free care by the public service for every mother and child. This has thus far made little impact on the percentage of mothers who deliver without antenatal care.[51] This finding has prompted an editorial by the editor of the South African Medical Journal in which he asks whether our limited resources should not be better used to improve survivability among the more moderate low-birth-weight infants, although he did not define the term “more moderate”.[52]

The attitude of mothers towards allocation of resources is vastly different to those of the medical personnel. In a South African study medical personnel based their criteria for admission and termination of care on a perceived bad (mainly neurological) outcome. The mothers, on the other hand, were against the termination of treatment, even though the expected outcome was extremely dismal. Neither did they think that the way of allocating the beds was fair if the best babies were chosen, or that babies were taken in on a first come first served basis. The biggest group of mothers felt that an additional bed should be found.[53]

1.5 "Best care"

The "best interest standard" respects and utilised the historical role of the primary care physician in assessing the patient's quality of life. The "best interest standard" rests on the ethical principle of beneficence, which exhorts physicians to first do no harm, to prevent and remove sources of harm, and to do good whenever possible. Ruark puts it even more strongly in saying: "The important relevant ethical principles include preservation of life, alleviation of suffering, nonmaleficence ("do no harm"), patient autonomy, and justice (fair allocation of medical resources)." [54]

In a developing country with limited health resources, ethical decisions are strongly influenced by the requirements of the community and not by individual needs. Issues of distributive justice, i.e. fair and equitable distribution of resources, of equal and appropriate access to basic-care services, and of affordability of health care services, have a special urgency when applied to seriously ill newborns. There is a dual medical care system in RSA with comprehensive access to all care, if medical insurance or the individual is paying the cost in mostly private hospitals, and restricted care if the state is the payee in state hospitals. This implicates a dual way of choosing whom to treat. Parents play a major role in the private care setting, and state-employed doctors decide on policy in state hospitals. This has lead to judiciary inquiries in a few cases on behalf of state hospital patients who were transferred to private hospitals and survived, and where the settlement of the medical accounts by the private hospitals was contested. [55]

Should the parents have the final say? A strong argument can be made for the parents as the final decision makers if we take into account that they have to live with the infant who may survive with a lifelong handicap. Silverman argues for balancing the interests of the infant, the family, and society, noting that "parents of a badly damaged baby often resent the implied demand that their family is required to pass a `sacrifice test' to satisfy the moral expectations of those who do not have to live, day by day, with the consequences of diffuse idealism. It is easy, some parents say, for others to demand prolongation of each and every new life that requires none of one's own resources to maintain that life later."[56]

1.6 Seeking Consent in the Early Neonatal Period

The goal of informing and involving parents appropriately in treatment decisions is of undisputable importance. Yet, this goal is often difficult to achieve, particularly during labour or shortly after delivery when decisions to forego or initiate neonatal intensive care are often made. If the baby was transported to a neonatal intensive care unit, the parents may be unavailable because they live in a distant community. Moreover, fathers are often not immediately available. About half of the mothers of infants weighing less than 1,500 grams at birth have undergone a caesarean section. Severe illness or narcotic medication may influence the ability of the mother to give consent. Virtually all parents experience considerable physical and emotional distress. Moreover, as discussed below, "adequately" or "fully" informed consent may be impossible even if the parents who are often young or poorly educated[57], are intensively involved in these discussions.

The right to choose may be arbitrarily divided into the three areas of expected excellent, expected hopeless and uncertain outcome. When a baby weighing more than 1250g, 32 weeks gestational age with respiratory distress syndrome (RDS) is born, the baby has such a good expected outcome that neither the doctor nor the parents can dispute the merits of treatment. In the case of a 250g baby born at 20 weeks gestation the same can be said but this time because of the uniformly dismal outcome of these babies. It is in the group in-between these two cases where ethical dilemmas occur.[19] In this group arbitrary recommendations can be made in a developed country, but in South Africa most state NICU units will not accept babies with a birth weight of less than 1000g for care.[12] It is difficult to reconcile these restrictions with the knowledge that the expertise is available in RSA to obtain the same results as in developed countries, given the same resources.[58] It may thus be necessary to refuse a baby with a good chance of a normal outcome when all the beds are occupied in a state NICU.

Tyson proposes that any baby with a 50% chance of death should receive mandatory (routine) care, those with a 51-75% chance of death should receive optional (dependant on caregiver) care and babies with a 76-95% chance of death should receive investigational care.[59] Those babies with an expected mortality of more than 95% should not be treated with a curative intent. At Tygerberg Children's Hospital we often cannot accommodate babies with a 60% expected chance of survival in the NICU. It may be helpful to estimate survival in different risk groups of South African babies.

At the Priorities in Perinatal Care Conference in South Africa in 1991 a policy was formulated not to treat babies less than 1000g in government hospital NICUs. These recommendations were made before surfactant therapy became available. The current survival rates of babies admitted to a NICU with birth weights of between 890 and 1000g are the same as those of babies more than 1000g birth weight in the era after the introduction of surfactant therapy.[60]

Having formal guidelines makes it both helpful and problematic.[61] A baby of 1001 g with severe congenital syphilis may thus be accepted for treatment and a "healthy" baby of 999g may be refused. Likewise a severely asphyxiated infant with irretractable convulsions may be admitted because the baby weighs 3 kg.

Selecting a specific baby for NICU care would be easy if all had a good outcome or if all died, but survival is not the only aspect that has to be taken into account. Survival with a lifelong disability has major implications for the family.[62] Even if the baby dies, morbidity and the cost have to be taken into account.[63] The ideal is a balanced approach that gives every potentially viable baby a chance to be treated.

One way of overcoming this problem is to treat all babies. This method is impractical in South Africa because of the insufficient available serviced beds and the problem of when and how to discontinue treatment.

Treatment in neonatal intensive care facilities is labour intensive, uses sophisticated technology and is expensive.[64] Expense seems to be the most important issue. Bowen asked: "Are inadequate levels of hospital services to sick newborns without private health insurance resulting in unnecessary suffering, disability or death?"[65] In an editorial, Chassins[66] defined "quality of care by quantity" in the following manner: overuse, where risks outweigh benefits; underused, where benefits outweigh risks; and misuse, where appropriate care is poorly provided. The concerns voiced by these authors are relevant in the South African setting where 80% of patients are cared for by the government health service. Since 1994 the government health policy has shifted the emphasis from tertiary to primary care, reduced the budget for tertiary care and reduced the number beds in NICUs. These circumstances make it essential that quality and rationing of care are carefully analysed and assessed. Cooper documented the quality of neonatal care in South Africa. He recommended "given the enormous improvement in survival of very low birth weight (VLBW) infants when there is good primary and secondary level care, and the excellent long-term prognosis of those who survive, the first priority should be to optimise such levels of care throughout the country".[67]

The comparison of outcome of patients managed by different NICU is problematic.[68] The differences in outcome could be explained by differences in the patients treated such as different degrees of disease, for example more extreme low birth weight babies, a higher incidence of congenital infections, a lower standard of antenatal care, or different treatment modalities (for example the frequency of using naso-pharyngeal continuous positive airway pressure (CPAP) instead of conventional ventilation), differences in the use of and indications for surfactant or different antibiotic protocols.[69]

1.7 Evidence based ethics:

It is accepted practice in medicine that the only mandatory interventions are those for which there is substantial proof that the benefits outweigh the hazards and burdens.[70] Evidence-based decision making[71,72]allows consideration of the level of care that is reasonable, based on the quality of evidence available; the identified benefits, hazards, and costs of treatment; and as is crucial in a pluralistic society, the values and preferences of the patient or surrogate.[73,36] Thus, medical reasonableness is a more broadly acceptable criterion than is futility for deciding whether to forego or administer neonatal intensive care.

1.8 What is the cause of death?

Ideally and simplistically all babies who die should die because of an untreatable "inborn error" or congenital defect. This assumption is too simplistic and may conceal co-morbidity factors. An in depth look at various possible reasons for and the time of death should be done. When for example a baby with RDS, who required ventilation, dies from a hospital-acquired infection, it is difficult to establish whether the cause of death was the RDS necessitating the admission or the acquired infection.

1.9 A South African perspective

In 1980 the Public Health Service in the USA adopted a document "Promoting health/preventing disease: objectives for the nation" (Washington DC). Even though these objectives were not achieved by 1990 and were replaced by the "Federal priority objectives for pregnancy and infant health"[74], at least it provided a written objective goal, and guidelines. In South Africa, no such written policy on the goals for infant care exists, and criteria for care differ in different settings and provinces.

The population pyramid of South Africa fits the non-industrialised model that is broad-based (proportionately more younger members than in an industrialised population). This means that a high proportion of the population is young with an expected high fertility rate.[75] In South Africa there is in addition a high prevalence of pre-term deliveries and a high proportion of small-for-date babies.[76] This places a high burden on neonatal health services.[77] Most of premature and small for date neonates in South Africa are born to the poorer socio-economic group,[78] who are dependent on the public health services for their care.

The providers of public health care in South Africa need to determine the requirements for neonatal care and to evaluate the performance of different neonatal care units.[79] This is difficult because there is no reliable factual database available for the estimation of the number of infants born or of the needs of these infants in South Africa.[80] This must also be seen in the context of the South African constitution of 1996, which is not clear in this regard. In Chapter 2 1(c) states that "every child has the right to basic health care services" and in 2.2 it states that "a child's best interest is of paramount importance in every matter concerning the child". This has to be seen in the light of the non-derogable rights to life that applies to all people. There is no definition of "child" or of "basic care".

Extremely small infants often have an extended stay in the NICU and frequently have a poor outcome.[83] Because of the high demand for access to state funded neonatal services most of the NICUs in state institutions only admit infants of more than 1000 g or 28 weeks gestation.[81] While not officially endorsed by the Ministry of Health, this policy was the result of a formal discussion at the 10th South African Conference on Priorities in Perinatal Care, which attempted to provide consensus and objective guidelines for neonatal care in South Africa. Most of the neonatal intensive care units in South Africa have written admission criteria.[82]

The NICUs in the private sector usually adhere to internationally accepted cut-off points, often a weight range of more than 600 g or at least 24 weeks gestation.[83] This is in line with policy at most West European and North American NICUs.[84,85]

In state funded units, the disease profile of most babies is often more complex than what can be ascribed to prematurity or growth retardation alone.[86] The burden of disease in the neonate is increased by other, often preventable factors such as peri- and post-natal infections. The incidence of syphilis in pregnant women was 8.2% at Tygerberg Hospital in 1993.[87] The Tygerberg NICU also admits infants transferred from outlying hospitals where the prevalence of syphilis in pregnant women at antenatal clinics reaches 20%. The official prevalence, as stated by the Department of Health, of syphilis in pregnant women in the Western Cape is 18%. [88]The population which we serve is a high-risk group for preventable perinatal acquired infections.[89]

Only an estimated 80% of eligible women in the Western Cape Province utilize the free antenatal care which is provided in clinics.[90] The remaining women either do not receive any antenatal care, or attend the clinic so late in pregnancy that many have to be referred to hospital for immediate delivery because of complications such as pre-eclampsia.[91] An inadequate patient transport system[92] is another reason why high-risk infants may be delivered at home or at a clinic, instead of at a hospital. These high-risk infants therefore receive sub-optimal care at a time when they need it most. The infant, who is admitted to a NICU with this type of history, cannot be expected to have the same chances of survival as a baby who was born under optimal circumstances.[93]

The level of care that is provided at different NICUs in South Africa also differs according to the clinical approach of a small number of trained individuals, and the available equipment. The two NICUs in the public service in the Western Cape region differ with regard to treatment modalities (personal communication Prof. D Woods, University of Cape Town and Dr J Smith, Stellenbosch University). Differences in the availability and use of surfactant in the Western Cape are just one example. There is a severe restriction in its use in some NICUs while it is relatively freely available in others. Formal antibiotic policy as well as surveillance of resistant organisms may also influence the mortality rates.[94]

The total number of neonatal intensive care beds available for the population is insufficient[95,96], and in many cases the babies are not even referred for care to these institutions. During a 36 months period 144 babies weighing between 750-1000 g were denied intensive care at Tygerberg Hospital during 1999, one of the public sector institutions (unpublished data Dr J Smith).

With such pressure on the NICU beds, there is a need for a system to assess the treatment and outcome of infants in specific units.[97] A reliable method for prediction may allow care for infants who, at present, do not receive NICU care because of the shortage of beds. The treatment of an infant with a hopeless prognosis could not be initiated or could be terminated and the treatment opportunity given to a neonate with a better chance. Lipman discusses the problem of lack of staff, lack of equipment and the need to choose which patients to admit and the difficulty of doing this without scientific data in the African context. [98] He described a case of three beds and five admissions in Windhoek, Namibia, and how decisions were made with little objective measurement.

It is clear that more objective and scientific means are needed to examine excellence of treatment in NICUs and to prognosticate outcome at individual level before a patient is admitted to the ICU. If it were possible to correct for disease severity, the different treatment modalities utilised in different NICUs could be compared. Clearer standards of excellence should be defined in order to compare different NICUs. These standards are important when planning multicentre research projects, as well as in the allocation of training facilities and research funding. These scoring methods have been devised and will be discussed at length in the next chapter.

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CHAPTER 2

1 Scoring systems

1.1 Scoring systems in intensive care units: their use and abuse

Severity of illness is an important factor when determining risk. A score can be used for systematic randomisation in research, to ensure fair allocation of resources and the to quantify the quality of care and outcome in different NICU settings. It may also be of value in predicting the length of stay, determining the extent of therapeutic interventions needed and to forecast outcome.[1]

With the development of neonatal care as a discipline, of better care of bigger infants and development of more sophisticated neonatal invasive therapies, there has been a gradual shift in emphasis towards the care for progressively smaller infants. The "old" scoring systems became obsolete as, for instance, it was physiologically impossible to obtain a 10 out of 10 Apgar score in these smaller infants. These smaller infants also consumed a greater amount of resources and occupied a disproportionate number of available NICU beds.[2,3] The need thus arose for a scoring system which could predict the course of disease and outcome in these small infants.[4]

At first birth weight and gestational age were used as predictors and the correlation between prediction and outcome was acceptable. The enthusiasm of the medical fraternity in caring for these small infants and the financial cost of these actions soon placed a question mark over the feasibility of ventilating and caring for these extremely small infants. The positive outcomes of these babies in some affluent centres placed a severe psychological strain on doctors in other centres which could not accept these infants for NICU care because of financial restrictions by administrators.[5,6] This was however an effective way of containing cost. According to Wennberg "we should limit the resources put into medical care in the form of hospital beds and expensive technology."[7] By limiting the capacity to treat patients the tendency for demand to expand in order to meet supply and the temptation of physicians to try anything to help their patients, is arrested. This is true in a system where enough beds exist to meet normal demands, but not when there are to few NICU beds for neonatal needs.

This led to the development of admission criteria to select the "best" infants to receive the available neonatal care. This is current practice in all the NICUs in the public sector in South Africa albeit without the official blessing of the Ministry of Health. This shifts the possible moral and ethical responsibility of selecting infants to doctors in the public service who are not responsible for the limitations in the health budget. Deviation from an institutional NICU's admission criteria are influenced by the clinician on duty's assessment of mortality risk.[8] Pressure to reduce neonatal intensive care beds in the public sector in South African NICUs is increasing because of the cost involved in these facilities[9] and since the emphasis in national health policy has shifted to preventative and primary health care which is less expensive.

It is dangerous to apply data collected in developed countries where statements like "medical care only makes a modest contribution to the health of a population, whether the outcome measure is mortality or disease prevalence" are proclaimed.[6] Although the overall neonatal mortality rates declined by 50% in the British National Health Service over the last 40 years, the decline was only 25% in the lowest social class.[10] Newborn infants are unable to fight their own cause and need advocacy.

Scoring systems have been devised to help the physician to evaluate the need for care and to classify a patient's initial disease status. These may then be used to evaluate different treatment regimes and the efficacy of different NICUs. Du Bois et al however found that there was little, if any, relationship between the variations in quality and differences in outcomes in different NICUs. The conclusion was made that the outcomes of outlier patients depended more on the degree of disease with outlying hospitals caring for sicker patients with poorer care.[11,12] It is important to realise that a predictor tool is not universally applicable, and may not be applicable to every patient in a population. It must be validated in comparable groups of patients and must improve clinical decision-making.[13]

The Score for Neonatal Acute Physiology (SNAP) was used by a health care provider in the United States to validate the performance of 3 of their NICUs.[14] If a scoring system could give an accurate prediction of outcome as measured by both morbidity and mortality, it would obviate the need for doctors to make stressful decisions on life or death in NICUs.[8]

1.2 Types of scoring systems

The introduction of scoring systems to evaluate the extent of disease and the development of tools to compare patients is not new. The Romans placed their newborns in a bucket of cold water, and those that emerged screaming were deemed fit for survival. Modern scoring systems were initiated in adult intensive care units (ICU) for the same research purposes as mentioned above.[15] The adult scoring system was revised and was followed by a Paediatric Risk of Mortality (PRISM) Score.[16] The need for a neonatal scoring system was addressed by the SNAP[17], the International Neonatal Network's Clinical risk index for babies (CRIB)[18] score developed in England in 1993, and a score developed by the National Institutes of Health Neonatal Research Network.[19] Meadow also examined the effect of clinical intuition in predicting the outcome of babies. He concluded that medical doctors were very good in predicting the outcome compared to the SNAP score on that specific day. They were, however better at predicting early deaths than late deaths.[20]

1.2.1 Apgar Score

This was the first of the internationally used scoring systems and was proposed in 1953 by Apgar.[21] It was intended to evaluate the need for resuscitation in newborn infants. This valuation is done at one, five and ten minutes after delivery, and is still done routinely on all infants delivered within a structured maternity system. During the fifties and up to the beginning of the seventies no neonatal intensive care was available, and the Apgar score was mostly used on bigger and mature infants. In these infants a good correlation was found between a low Apgar score and high mortality and morbidity. Both the morbidity and mortality increased with a low score at five and ten minutes, i.e. the time required to achieve a good Apgar score was indirectly proportional to the risk of a poor outcome.[22]

1.2.2 APACHE, APACHE II and PRISM scores

The APACHE[23](Acute physiology and chronic health evaluation) and its improved APACHE II[15] scoring system were introduced by anaesthetists in adult ICUs to predict mortality and morbidity. The PRISM score evolved out of these systems.[16] The abovementioned scoring systems are well validated[24] and widely used in adult and pediatric ICUs as a measure of disease severity and outcome.

1.2.3 SNAP score

This score was developed by Richardson et al.[17] to predict illness severity and not mortality. It measures 26 variables, which cover a wide range of clinical and physiological aspects, but may give a variable score, because some of the variables are only recorded if particular blood tests are done. Thus an enthusiastic or financially less constrained unit could record a different score than a more "conservative" unit for a similar infant. There are a number of studies that record the poor performance of this scoring method.[25] This has led to a perinatal extension of the SNAP score [17] in an attempt to make the predictions more reliable.

1.2.4 Other scoring systems

The SNAP score only measures morbidity. An improved SNAP score was developed, the SNAP perinatal extension (SNAP-PE)[17], that measures mortality as well as morbidity. This score depends on special investigations which are not routinely performed on every admission. A more enthusiastic (or unsure) doctor could influence the score by doing more tests and bringing in additional variables which may influence the score.

The National Research Network score measures fewer parameters, but was only developed in 1993, and has therefore not yet been widely validated in other NICU's.[19]

The National Therapeutic Intervention Scoring System (NTISS)[26] was developed on the basis of the Therapeutic Intervention Scoring System used in adult ICUs.[27] It assesses illness severity through the physician's therapeutic response to a patient, rather than through direct measurements of physiologic derangement. In a scoring method based on clinical judgement a host of variables are introduced, which may explain why the scoring method was not more widely used.

1.2.5 CRIB score

The CRIB score was developed as a means to quantify neonatal risk factors other than the time honoured birth weight-specific mortality. It was developed in tertiary care settings among high-risk infants and was used to assess the performance of tertiary and non-tertiary neonatal units. This scoring system was developed to measure not only the severity of illness, but also to measure morbidity and mortality. The CRIB score is a simple and easy way of measuring morbidity and mortality in a NICU, as well as making it possible to compare different NICUs.

1.3 The CRIB score

1.3.1 Introduction

The CRIB score was developed to predict mortality and morbidity. Its main aim was to develop a system by which different NICUs could be compared. Other risk factors, other than the time honoured birth weight-specific mortality, were evaluated. CRIB was developed in tertiary care settings among high-risk infants and was used to assess the performance of tertiary and non-tertiary neonatal units. The development and validation of this system was done by methods similar to those used by the PRISM score.[28]

During July 1988 to June 1990 the development cohort (812 infants) was collected in four tertiary NICUs in Britain by the International Neonatal Network.[18] The cohort included all babies without inevitably fatal congenital abnormalities who had a birth weight of less than 1501 g or were of a gestational age of less than 31 weeks. Data was collected on forty individual aspects of these babies and the results were analysed by means of uni- and multivariate methods.

The CRIB score was constructed by converting into integers the regression coefficients of independent ranges or categories of six routine clinical variables in a logistic model for hospital death. The score was then validated on a cohort of 488 high-risk infants with the same admission criteria admitted to four other tertiary NICUs during the same period.

The CRIB score differs from the SNAP score as it measures routine data of six variables collected within the first 12 hours of life. The six variables which remained independently associated with hospital death were birth weight, gestational age, the presence of congenital malformations, and three indices of physiological variation within the first 12 hours of life: maximum and minimum appropriate FiO_2 and the most acidotic base excess. A points system was allocated to each of these variables. Additional data, which could be collected, were: the five minute Apgar score, the admission temperature, the discharge date, the occurrence of intracranial haemorrhage and the days of additional oxygen required. The last two measurements were morbidity data.

The data was validated in a different cohort of babies and a prediction of mortality with a 51% sensitivity and a 95% specificity was found. The receiver-operating curve (ROC) was determined and an area under the curve of 0.90 was found for the CRIB score as a predictor of death before discharge. The area under the ROC curve, using birth weight as continuous variable, was 0.79.

1.3.2 Implementing the CRIB score

The variables used by the CRIB score are easily determined by the neonatologist. All the measurements can be readily obtained on all babies and most are measured routinely in all NICUs. No judgmental factors, except those regarding certain congenital abnormalities, are used. A list of lethal congenital abnormalities was not given by the developers of the CRIB score, but a points score was still required for such abnormalities. This raises a question mark on the validity of the point scored for these abnormalities. How did the researchers determine the presence of all invariably fatal congenital abnormalities before 12 hours of age?

1.3.3 Positive and negative aspects of the CRIB score

1.3.3.1 Positive aspects

1. The CRIB is a validated system of scoring.
2. Includes the most easily accessible physiological measures.
3. It is user friendly and relatively simple to use, even by untrained personnel.

1.3.3.2 Negative aspects

1. A prediction can only be made after twelve hours of age that could lead to termination of care, after it was initially decided to provide care.
2. No method of analysis is available if one or more scores are unobtainable.
3. Some variables require personal judgement or are treatment dependant.

The CRIB does not use the Apgar score that has been utilised since 1953 as a measurement of the need for resuscitation at birth.

1.4 Validity of the CRIB score:

After the initial publication of the CRIB score, the scoring method was debated by way of letters to the editors of various publications. Questions were raised on the validity of the score in comparing different NICUs without taking into account the staffing and expertise in these units.[29] The case mix comparing English to Canadian infants was also raised, as well as the fact that the CRIB score was only a slightly better predictor than birth weight in the original publication. In the August 1993 edition of the Lancet, Du Bow[30] questioned the validity of using mortality as a measure of excellence.

During 1994 and 1995 two publications examined the CRIB score in different settings. Rautonen et al[25] compared CRIB and SNAP scores retrospectively and found the CRIB superior to the SNAP, but commented that not all SNAP variables are routinely tested. This may have been the result of the retrospective design, but it also raised the same question asked by this investigator in the discussion of the SNAP score. De Courcy-Wheeler[31] found in 1995 that the CRIB was a better predictor of mortality than gestation and birth weight, but not as good for morbidity and quite useless for length of stay.

1.5 The Tygerberg CRIB score experience:

Data was analysed from 1992 to 1996 for the purpose of a masters degree by this investigator. During this period data was obtained on 458 babies of whom 109 died. The predictive accuracy of these babies was compared to the initial data used to devise the CRIB score. At Tygerberg Hospital the CRIB score was statistically less predictive of outcome in babies with a low score as well as in babies with a high CRIB score that Great Britain. These findings are illustrated in Figure 1. Furthermore, the CRIB score was only better in predicting outcome of babies in this cohort than gestational age. (Figure 2).

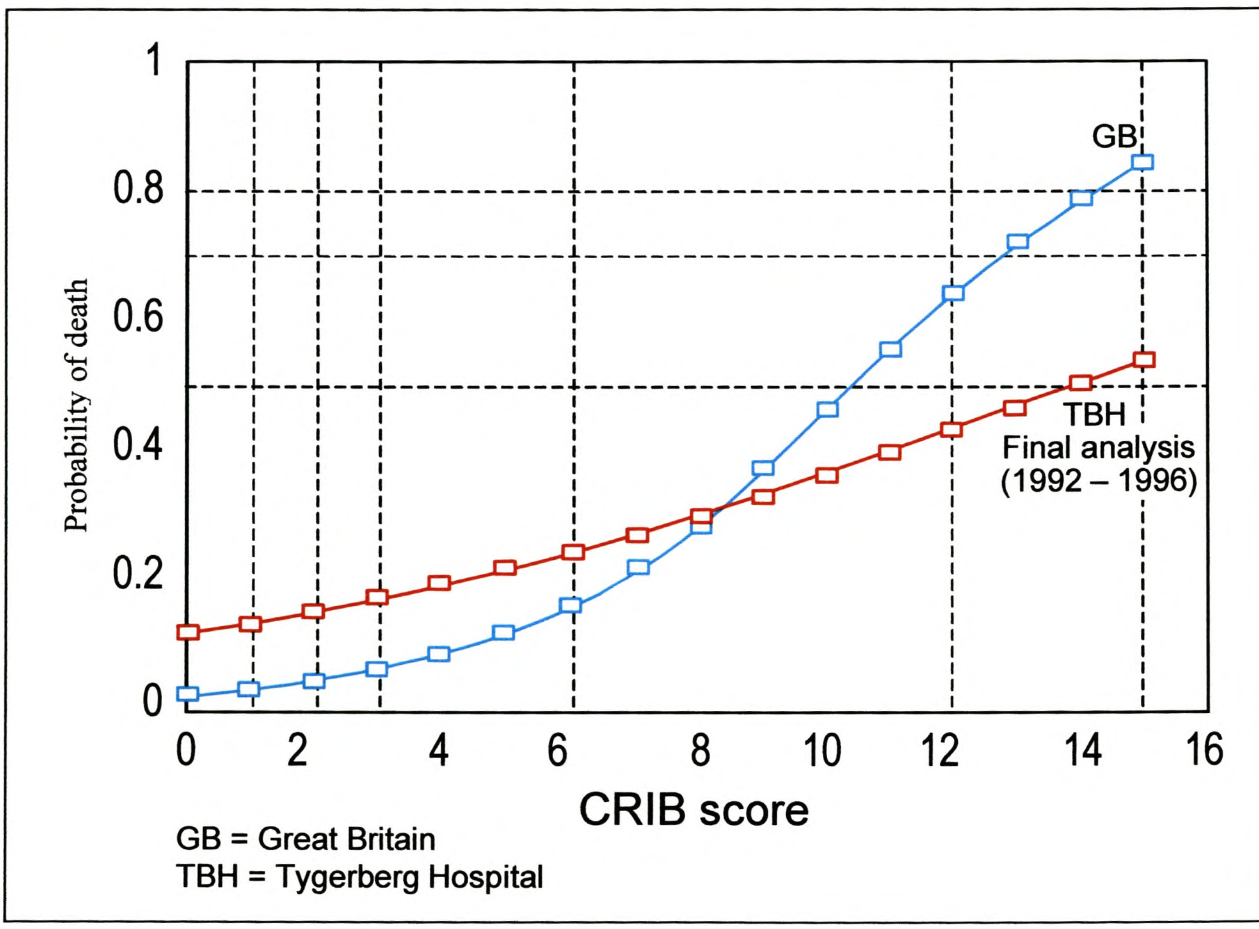
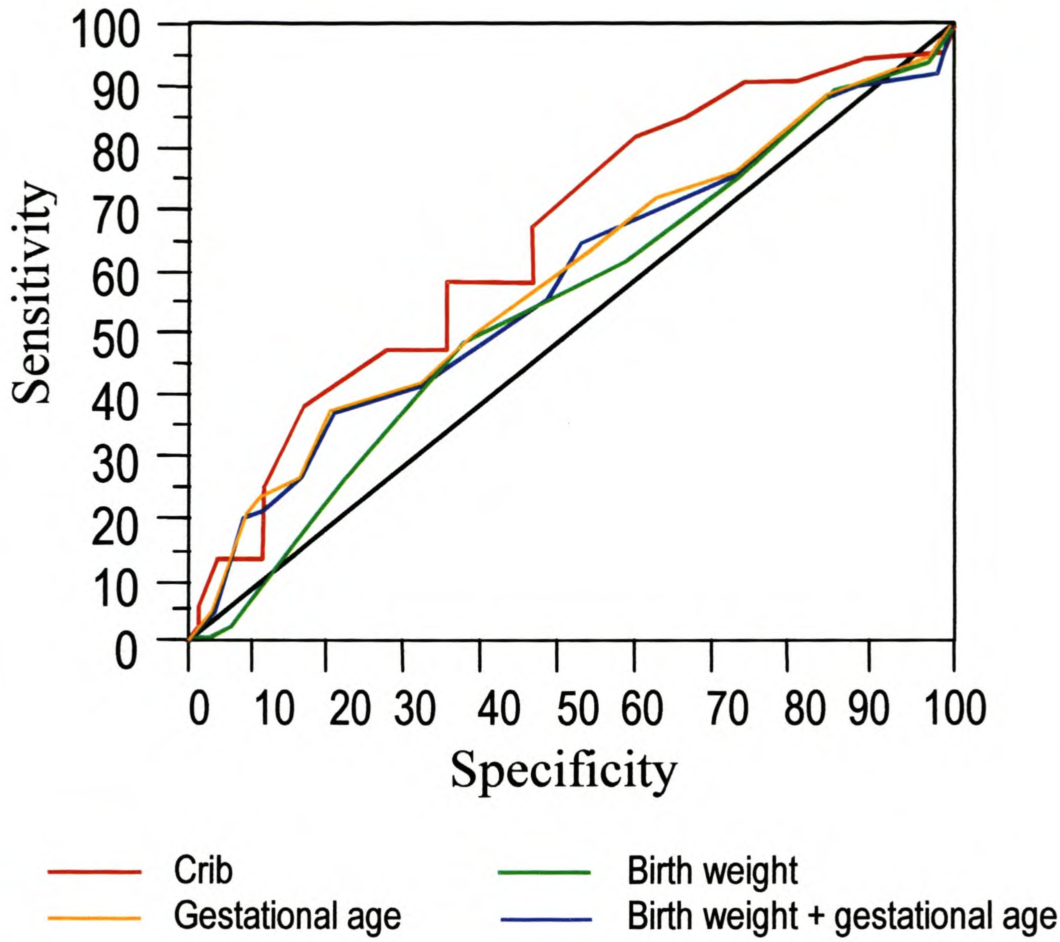


Figure 1: The CRIB score in relation to the birth weight and the gestational age.



Variable	ROC
CRIB	0.678
Birth weight	0.613
Gestational age	0.558
BW+GA	0.613

Figure 2: The predictive accuracy of the different parameters.

The only differences found between the ROC curves was between the CRIB score and gestational age with a p value of 0.008. This implies that the CRIB score, in its present formulation, does not add value to the prediction of outcome of babies born at Tygerberg Hospital.

2 Proposed new scoring method

2.1 Choice of a scoring "tool"

The choice of a measuring "tool" was not easy. The data collected had to be available at referral. Many referrals are done by nursing sisters from clinics which have no laboratory services or doctors available. The predictors are also needed to evaluate babies before transfer. For the present study it had to:

1. be a validated tool
2. be specifically designed for neonatal intensive care
3. include all possible neonates
4. be simple enough to implement with an acceptable margin of error
5. measure the morbidity and mortality of the babies.[32]

The review of the literature and our experience with the CRIB score implies that a scoring method should be devised which is appropriate for a developing country. A few basic principles must be satisfied when such a new scoring system is developed. It must

1. be applicable in a rural setting
2. have enough flexibility to accommodate missing data
3. not require any special investigations
4. be easy to provide on immediate request
5. need a minimum of training to perform

In setting up such a scoring system, the old and tried methods of prediction must be complimented by the current disease patterns. The population served and the disease profiles of the patients may influence outcome. Some risk factors, like congenital abnormalities, have a known or presumed relationship to mortality. Others may represent a vulnerability (gestational age, birth weight, gender), while others are proxies for other risks such as ethnic and socio-economic groups. Maternal obstetric risks are also cascaded to the baby, for example maternal infections, the type of delivery and maternal age.

The following factors were included in the original database to develop a new scoring system:

2.1.1 Maternal risk factors:

1. Age of mother
2. Parity of mother
3. Type of delivery
4. Prolonged rupture of membranes (> 24 hours)
5. RPR status
6. Maternal income

2.1.2 Neonatal risk factors:

1. Birth weight
2. Gestational age
3. Antenatal visits
4. Multiple gestation
5. Place of birth (TBH, MOUs or other)
6. Early (before 12 hours) or late admissions
7. Apgar count at 1 minute
8. Apgar count at 5 minutes
9. Gender
10. Ethnic group.

2.2 Individual parameters to be examined.

2.2.1 Maternal Risks:

1. **Age of mother**

A mother's age influences the outcome of the neonate. The two identified risk groups are teenage mothers and mothers who are older than 37 years. Their babies have a higher morbidity and mortality. [33,34]

The defined ages for "young" mothers as well as "older" mothers are not standardised, but were chosen for convenience because of previous studies with which comparisons could be drawn. Some investigators define 18 years, but the majority define 20 years as "young" and 37 to 40 years as "old" for mothers. In this study mothers < 21 years were categorised as "young" and mothers of ≥37 years as "old".

2. **Parity**

Parity was chosen above gravity because of concerns about the accuracy of the documentation of gravity. Parity is a more robust recording. [35]

3. **Type of delivery**

Different types of deliveries are associated with different risk profiles. A normal vertex delivery has a higher risk in extreme preterm babies. Premature babies born as breech deliveries also have a higher mortality. [36,37,38]

Deliveries were classified into normal vaginal deliveries, caesarean sections, breech deliveries and "other". Other was defined as vacuum extractions and forceps deliveries. Breech deliveries were classified separately as they are associated with worse outcome in premature babies. In some instances breech deliveries and other risk groups were combined because the numbers were small.

4. Prolonged rupture of membranes

An antepartum infection may lessen a baby's chance of survival. The risk of infection is increased with prolonged rupture of membranes. This is traditionally defined as 24 hours and was used as the cut-off in this study. Recent data record a higher incidence of infection after 18 hours.[39]

5. Syphilis serology

A baby born to a mother with syphilis has a higher morbidity and mortality. Even though most of the mothers diagnosed are treated for this disease during pregnancy, this group of babies are in many ways more at risk than the normal neonatal population. [40] Babies were therefore classified according to exposure (positive serology), and not according to the clinical presence of congenital syphilis. The serology which is routinely done in antenatal clinics is the RPR test. The RPR is a rapid plasma reagent test supplied by Omnimed®. Any positive titre was taken as positive for the purpose of this study.

6. Income of the mothers

The monthly income of the mothers is a marker for socio-economic grouping. This may identify an "at risk" group of babies who are more often born in rural areas and who may have limited access to medical care. [41,42]

As antenatal care and pregnancy related care is free in South Africa, there should be no reason for patients to declare an inaccurate income. Because a part of the study utilised retrospective data, the income as given by the mother was used as a marker of socio-economic status. The income was divided into no income, the basic minimal domestic worker's salary, and categories as suggested by the data obtained.

2.2.2 Neonatal risks:

1. **Birth weight and gestation**

It is widely accepted that birth weight[43,44] and gestational age are good predictors of outcome.[45,46] In many ways these indices are still used as the "gold standard" against which the newer scoring systems are measured. The first systematically documented birth weights in the world were done in the first and second quarter of the eighteenth century. They were used, as a measure of outcome, only after World War II.[47]

Gestational age was and remains more problematic. In developed countries antenatal ultrasound examinations in early pregnancy with accurate determinants of length of gestation is the rule, but in the developing world this is the exception. The recorded gestational age in our population is therefore not as accurate as that of developed nations. These variables, while better than selection by chance, have shortcomings. The predictive value of these measurements is lower than expected, mainly because other factors like growth retardation, which in itself may influence the outcome of these babies, are not taken into account.[48] Because these variables are time- honoured predictors of outcome, they are included in this study. The scales on which the babies were weighed were not checked for accuracy, as this is a field study. The gestational ages were obtained by the Ballard method[49] by preference, or from the records of the obstetrician.

2. Antenatal clinic visits

Mothers can attend antenatal clinics (ANC) free of charge since 1991. At these clinics the mothers are clinically examined, blood grouping and syphilis serology is done, and risk factors for this pregnancy are identified. On a second visit any abnormality is addressed. The majority of mothers attended the ANC at least twice. In this study mothers who never attended an ANC as "not booked", and those who had attended at least one clinic as "booked". [50,51]

3. Multiple births

The risk for premature delivery and its associated risk factors are increased in multiple pregnancies. The birthing order is also important as the second baby has a greater risk than the firstborn. Therefore both the fact that a baby is one of a multiple delivery as well as the birthing sequence are taken into account. [52,53]

4. Place of birth

There are vast differences in the expertise and in the type of health worker who assists deliveries in the three settings in which babies are born. At the tertiary hospital, all "at risk" babies are delivered under supervision of a consultant and mostly by doctors. Babies are resuscitated by paediatric registrars.

At the ANC nurses deliver the babies and resuscitate them. Their equipment and skills are at a lower level than that of a medical doctor.

Home deliveries are usually unattended and the ambulance paramedic may be the first person to help the mother and the baby. Therefore, in premature babies who need NICU care, the risk is vastly greater if they are born at home than at the ANC, where resuscitation is possible and where oxygen and heaters are available.

Compared to babies from a tertiary hospital, babies born at the ANC still have to be transported to a tertiary facility and are often intubated by ambulance paramedics. [54,55,56] Babies born in peripheral hospitals must have a higher gestation (2 weeks more) and a higher birthweight (200g more) than inborn babies to qualify for admission.

For study purposes the patients were classified by the place of referral or by place of birth.

5. **Early admission**

The time of birth to admission to the NICU has been recognised as a risk for survival in the CRIB study[18]. In developed countries, babies who were admitted later, had a different disease profile to early admissions. This may not be true for local babies, who are admitted late to the NICU, as it can take a long time to transport babies to the NICU.

Early admission was defined as an admission before the age of 12 hours.

6. **APGAR count**

The Apgar count at one minute is a reflection of the birthing process and the 5 minute Apgar is a measure of the length of asphyxia and the efficacy of the resuscitation. Both are taken into account in this study.

7. **Gender**

The fact that male babies have a higher mortality than female babies is well known and may influence the outcome of NICU stay. [57]

8. **Ethnic group**

The effect of the ethnic group on a patient may imply that a specific ethnic group has a higher mortality or morbidity, but it may also be an indicator of wealth and medical care. [58,59]

2.3 Outcomes:

The main outcomes for this scoring system are:

2.3.1 Mortality

This is also a time-honoured outcome, because at this point all is lost. Measuring the outcome by mortality is a very precise, but in many ways a crude method. It does not take into consideration the morbidity and ongoing medical care. In 1966 Segal remarked that the outcome as measured by the 28 day survival rate was very stable and unlikely to change, but that there was a great discrepancy between neonatal ICUs. He also felt that intact survival is of paramount essence.[60]

2.3.2 Length of NICU stay

This equates to the amount of expensive resources needed to obtain a good outcome. This is of importance in a developing country because tertiary NICU care is expensive and is of benefit to a limited number of infants.

2.3.3 Length of ventilation

The amount of time the baby spends being ventilated is a costing exercise. Ventilation is a primary function of tertiary care and is very expensive. The number of calendar days on which ventilation was provided is taken as the total time of ventilation.

2.3.4 Broncho-pulmonary dysplasia

The definition of broncho-pulmonary dysplasia (BPD) as being oxygen dependant at 28 days of life or at 36 weeks post conceptual age, is an international marker of morbidity. It defines a group of babies who need continuous medical care, often at tertiary level.

2.4 The rationale for choosing the abovementioned outcomes:

In this study only standard outcome measures are used. In neonatal care internationally recognised outcomes, like the survival and NICU stay, are well defined and comparable over different datasets.

Broncho-pulmonary dysplasia or necrotising enterocolitis as outcomes call for interpretation and varying definitions. A third group of outcomes may be even more interpreter sensitive like chest radiographs or the grading of intraventricular bleeds. Some outcomes, like long-term follow up, are time dependant and when the answer is found, the treatment options may have improved to the extend that the results are irrelevant. The diminishing number of deaths in developed countries has necessitated the introduction of outcomes for which no benchmarks exist, like weight gain at 28 days, or hypernatremia.

2.5 Study aims

Therefore the aim of this study was to develop a neonatal outcome based scoring method in a developing country and that would be applicable to local patients. This scoring method had to be simplistic as many babies were born in rural hospitals or clinics with no access to laboratory methods including blood gas analysis. Data must also be simplistic enough for midwives to be able to collect it.

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CHAPTER 3

Methods and patients

1 Methodology

1.1 Rationale for a severity index development:[1]

The development of a severity score index must fullfill certain criteria. These criteria include the following:

1) The information should be detailed and simple to gather.
2) The core information should be routinely available.
3) The score should be a multi-dimensional assessment. Scores which include only one or two variables may not adequately control for other factors which also influence outcome.
4) Methodology of development should be scientific and analysis of risk factors by different groups should yield comparable results.

The scientific methodology should satisfy three criteria:

1) It needs to be based on theoretical mathematical principles, i.e. the Bayesian theory or a multi-attribute theory.
2) The judgment of severity of clinical variables should be made by the best trained available health worker.
3) The method should be easy to understand and apply so that enough other users can learn and apply it.

The two major general approaches for developing indices are:

Empirical indexing approaches: using large databases and through cluster, factorial or decision tree analysis, the most important factors are correlated with outcome.

Judgmental approach: using the judgment of the attending physician to predict the outcome of the patient.

Both these indices have good and bad aspects. The problem with the empirical approach is that it utilizes factors that may not be consistently measured in all patients, for example a blood clotting profile, or it may be done on all patients indiscriminately by junior personnel. This may also influence the total score if some aspects are not scored or documented.

On the judgmental side, the judgment of patients may correlate more with the beliefs and experience of the person[2] attending than scientific fact, and may be influenced by the expertise of the scorer. It is important to evaluate lead-time bias in referred patients.[3,4] In most series this leads to a reduction of the risk score because of treatment instigated and thus correcting the physiological abnormal measurement, leading to a better than predicted outcome. In this study only the survivors or those deemed fit by the referring person would be admitted, which may improve the outcome of these babies. Their delivery history and the quality of care that the baby received in the referral hospital may, however, counteract this.

Based on the abovementioned criteria, a database will be developed by using the database of the TBH CRIB study done in 1992-1996 as a development cohort. Prospective data was collected from 1999-2002 to validate the score.

1.2 The development of the score:

The factors that will be measured are based on scientific facts as well as on the ability to withstand the rigors of data being provided by health personnel with wide ranging expertise. The factors that are to be measured must be available in all health care settings in South Africa. Factors which are not available for analysis must be taken into account and be adjusted for. A cut-off point must be found for available data, i.e. the least amount of variable that still makes the score acceptable. Alternatively substitute data points must be identified which can be used instead of the missing variables.

1.3 The setting for the score development

1.3.1 The Tygerberg NICU:

Tygerberg Hospital is the Tertiary referral unit for the Obstetric Unit of Tygerberg Hospital as well as the Metropolitan Midwife Obstetric Units (MOU). It serves a population of 3.9 million people according to the 1996 census data in the Metropole.[5] In addition, it serves most of the rural areas of the Western Cape except the George area. It is situated near Cape Town and is the academic teaching hospital of the University of Stellenbosch. The Tygerberg Hospital has a high care facility for pregnant women with obstetric problems. It provides obstetric care to a large geographic area of the Western Cape and serves the population who do not have private medical insurance. The attached maps illustrate the area.

The geographical areas of the Cape Metropole and the Western Province are illustrated in Figures 1 and 2.

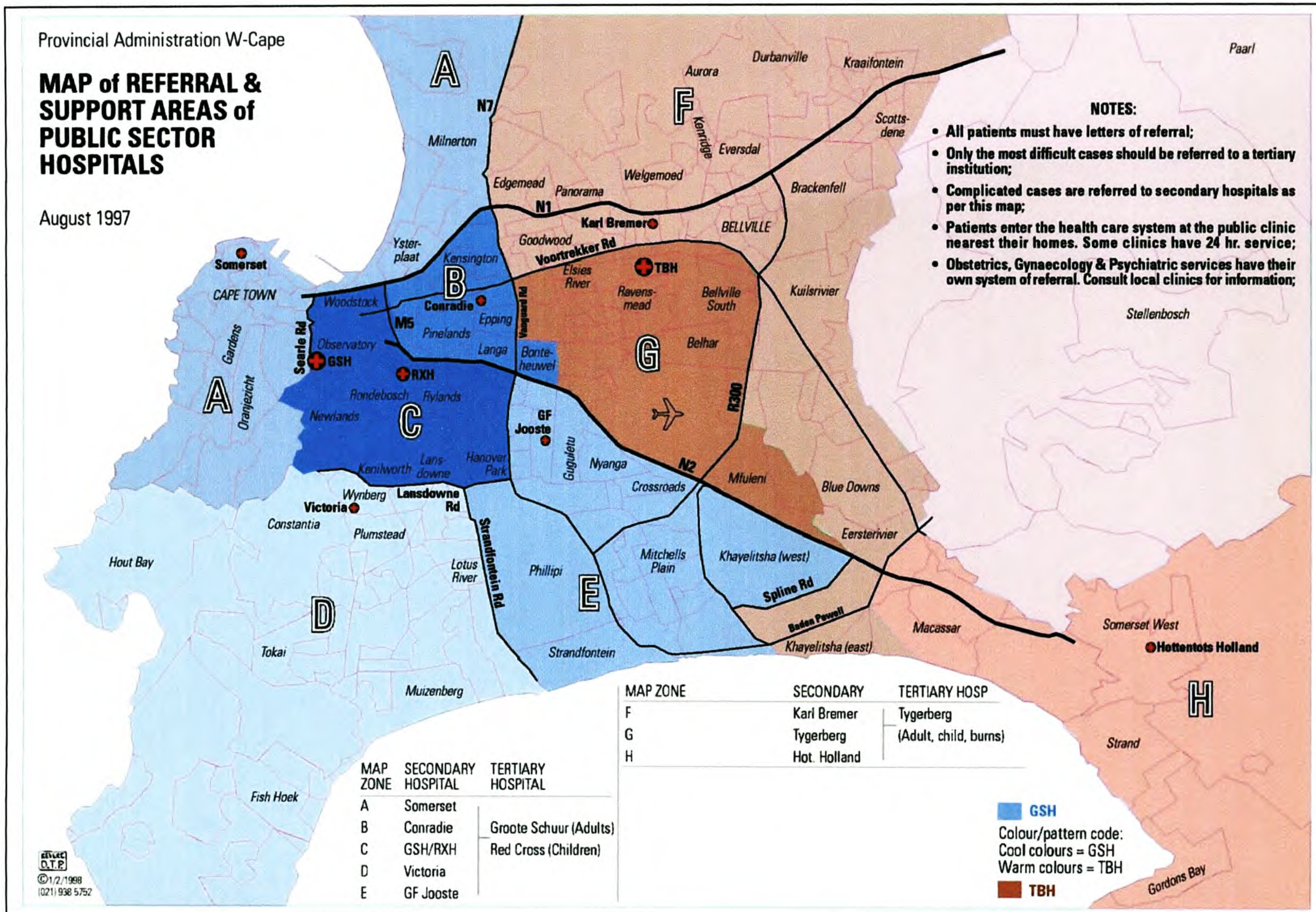

Figure 1: The area of drainage of the Tygerberg NICU-metropolitan area.

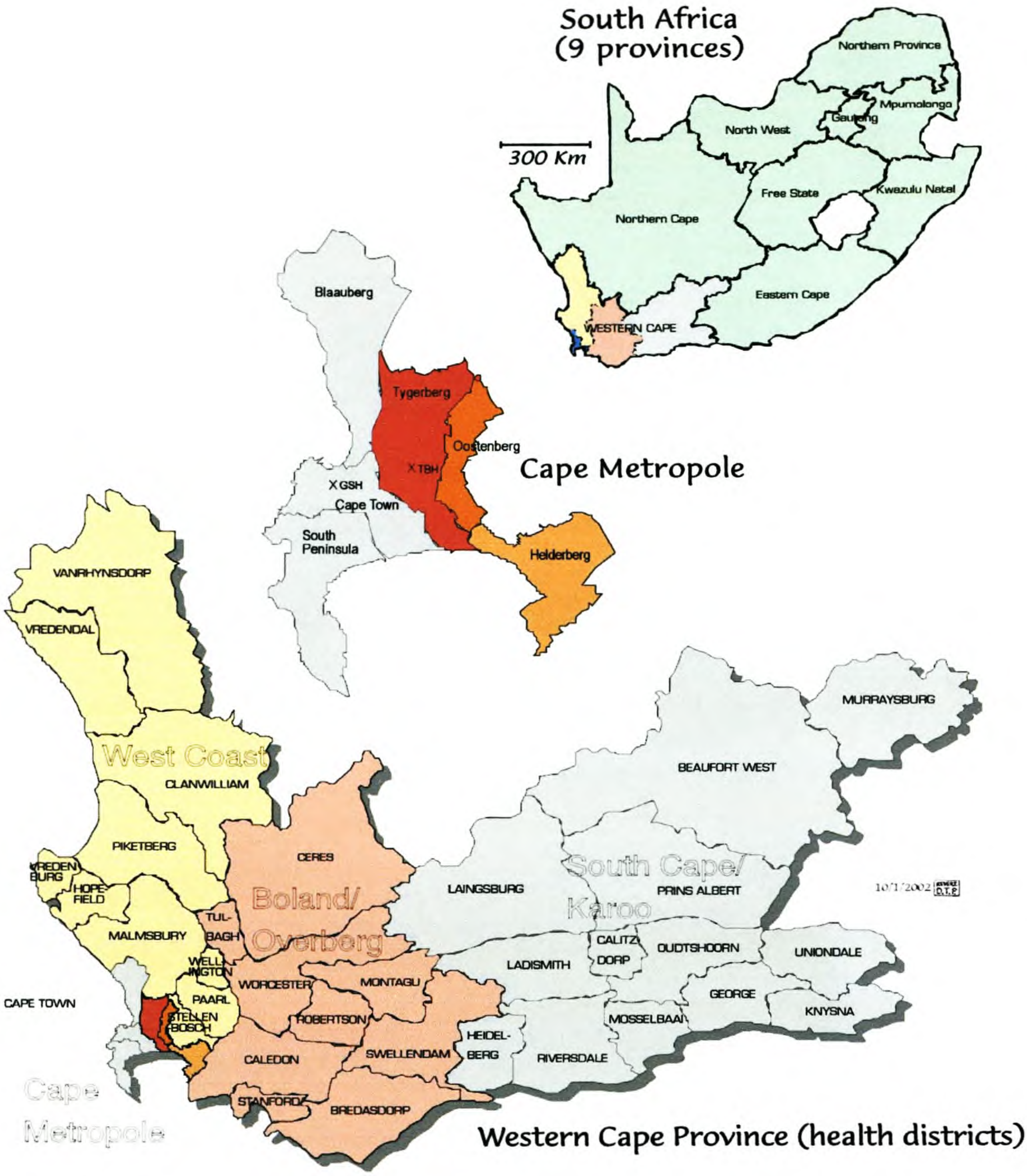

Figure 2: Drainage area of the NICU: Rural areas.

The TBH NICU has 12 beds and the medical staff consists of an attending full time neonatologist, two rotating registrars and one rotating junior doctor. The NICU is mainly a ventilation facility and few patients will be admitted to the NICU unless they need ventilation. High care is provided in a separate ward. Surfactant and nitric oxide are available. Standard volume cycled ventilators and oscillators are available. After weaning onto either a head box oxygen or continuous positive pressure (CPAP), the babies are discharged to the high care ward. Our policy for routine care has been recorded by Smith et al.[6] As soon as babies no longer require any total parenteral nutrition (if they are from a rural area) they are transferred back to the regional secondary hospital if in need of high care, or the referring hospital if normal care is adequate. Kangaroo mother care has been established in most rural hospitals, and breastfeeding is promoted in all mothers except in HIV positive mothers who can afford to buy formula feeds. HIV positive mothers who cannot afford formula feeds are advised to use pasteurised mother's milk.

Kangaroo mother care was developed by Rey and Martinez[7] in Bogota to address the high neonatal mortality rate in a developing country. The baby is placed between the mothers breasts and spends most of the day in this position. Exclusive breastfeeding is propagated and babies are fed either on the breast or by tube feeds.[8]

The TBH NICU has between 600 and 800 admissions a year with mortality rate of 18% for babies born at TBH. In babies weighing less than 1500grams, or younger than 32 weeks gestation, the mortality rate was 26% in 1992-1996. One third of NICU admissions are referred from rural areas and 15% from the metropolitan ANC. The remaining 59% are born at TBH.

Admission criteria for the NICU are as follows:

Inborn babies who are have received ante natal care will routinely receive NICU care if they are >999g birth weight and/or at least 28 weeks gestational age if a bed is available. Unbooked babies have to be 1200g birth weight or have a gestational age of at least 30 weeks. Babies of mothers with a poor obstetric history are often admitted even if they do not fulfil the abovementioned admission criteria. Babies are transported from other medical facilities by para-medics who are trained in neonatal care. Either an ambulances or a helicopter is used, depending on availability and prevailing weather conditions. Babies who need ventilation will mostly die if no NICU bed is available.

1.3.2 Ante Natal care

Antenatal care is provided mainly by antenatal clinics which are housed in a permanent building or a specially adapted vehicle (mobile clinic). Care to pregnant mothers in South Africa is free of charge. Despite this, many women do not attend the ANC until the onset of labour, or when problems arise. This may enforce the delivery of a premature baby who has had no antenatal care.

1.3.3 Delivery

Babies are delivered in many settings: a baby may be born at home, or in a rural clinic or primary hospital or even in a vehicle. If the mother presents early enough in labour, the mother will be transferred to a secondary hospital, which then would refer the mother and/or baby to the TBH. The delivery may have a birth helper with little or no medical education attending, but midwives or doctors deliver most babies. The quality of ante natal care during delivery may vary considerably.

1.4 Factors evaluated

Most models of performance of NICU's are based on the fact that all babies above a given birth-weight will be treated. With this comes the time honoured "angst" that the care of ever increasing premature babies will produce more damaged children.[9] Scores are then used to evaluate the quality and efficacy of care given to these infants. By correcting for severity of disease, it is possible to compare outcomes and treatment modules. This is, however, in stark contrast to the proposed use of the newly developed score for developing countries proposed by completing this research.

When there are not enough facilities to serve all babies, babies have to be selected. This can be done on a judgmental basis, as are the criteria used at TBH at this point in time. The criteria were developed 10 years ago by a caucus of experts in neonatology. The fact that only two aspects of the baby (i.e. birth weight and/or gestation) were used, made this an imperfect tool. The philosophy behind the inclusion and use of the factors in the new score is that most of the data required should be available at consultation per telephone. The shortage of NICU beds and the huge demand for care places a big responsibility on the service to give the best care to the most deserving patients. To base provision of care on one or two factors is not ideal. [1] It is therefore important to develop a scoring system which does not rely on special investigations, takes as many factors into consideration as possible and still is robust enough to give a good prediction of outcome.

Risk scores are most reliable if they are based on physiological measurements, and can be used when these measures are available, usually when active treatment has begun.[10] This is however not possible in our setting. It is morally easier to refuse treatment than to withdraw treatment, especially in a viable baby who would ultimately survive, but in the process maximally consumes resources and utilises an ICU bed for a long time. The question revolves more around the effective use of resources to benefit the majority and ensure fairness to most, than around the ultimate comparison of quality of care. Currently a baby of 1100 grams will be admitted to the NICU, regardless of whether the mother received antenatal care, has congenital syphilis and has a mother with 10 live children, whereas a 999g baby of a booked mother with no live children, will be refused if they have to compete for a bed and only one bed is available in the NICU.

The idea of choosing which baby to admit may be alien to international neonatologists, but adult ICUs have already adopted this method of utilizing scarce resources. Teres et al demonstrated that admission data is more reliable in predicting outcome in adult ICUs than 24 hour data.[11]

1.5 Data retrieval

The factors analysed in the evaluation of the 455 patients in the development database will be documented. The development database was based on all the patients who were admitted to the CRIB study. Many of these factors were prospectively documented for the CRIB study. Other potential risk factors will be retrieved from the patient files as well as the database of the hospital (for instances the RPR status). Data which is not available from the clinical patient-notes, will be obtained from the computer mainframe of the laboratory service. The four main outcome variables are: mortality, time (in days) spent in the NICU, time spent in Tygerberg Hospital (in days) and the development of BPD. These variables were chosen, as they have the biggest limiting effects on the availability of care to all infants.

A prospective dataset for validation purposes will be collected in 2000-2002. All babies admitted to the Tygerberg NICU during this period with a gestational age of less than 33 weeks and/or a birth weight of 1501 grams were enrolled. Patients excluded were all babies with lethal congenital abnormalities, although most of these babies would have been refused admission

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CHAPTER 4

1 Statistical evaluation

1.1 Statistical evaluation

The variables for evaluation on the 455 patients in the development database will be documented. Many of these variables were prospectively documented for the CRIB study, and the rest will be retrieved from the records as well as the databases of the hospital (for instance the RPR status). The main outcome variables are: mortality/survival, the time in days spent in the NICU as well as the time in days spent in Tygerberg Hospital and the development of BPD[1]. These outcome variables were chosen, as they are the ones limiting care to all infants. A Medical Research Council (MRC) statistician will analyse the data.

1.2 Statistical models

Various statistical methods and models will be used to evaluate the data. In keeping with standard practice the descriptive data will be presented first, analysed by para- and non-parametric methods as the data dictates. This will be followed by the Kaplan&Meier methods, multiple variant analysis and CART analysis. Receiver operator scores will be drawn and compared to chance as well as birth weight or gestational age. Finally the data will be presented as an epidemiological analysis. Probability or risk of mortality will be estimated for each baby. The score will then be validated on prospective data collected in 2000-2002.

1.3 General information

Data will be described as basic data comprised of means and standard deviations, ranges as well as medians where applicable. The data will be presented in tabular form for each tested variable.

Where applicable, the data will be subdivided into specific groups and presented as such. The data will be statistically interpreted using parametric as well as non-parametric tests, depending on the normal distribution of the data. The Student t test or Wilcoxon rank test will be used when comparing two groups (depending on the distributions). In comparisons of more than two groups the ANOVA methods (parametric or non-parametric) will be used. All tests will be done two sided except when specifically mentioned to be one sided. Data will be represented as tables, frequency tables and graphs, as necessary. Distribution normality will be tested by using the Kolmogorov-Smirnov test for normality for one sample tests with known means and standard deviations, and the Bartlett's test for homogeneity of variance when more than two groups are compared.[2]

Interferential statistics will be used to further analyse the data and to generalize the scoring method.[3] Firstly the variables will be tested for their predictive powers. Then the variables with the highest predictive powers will be given a score in keeping with their power of prediction.

The best predictor of outcome will also be determined and used for analysis purposes.

1.4 Kaplan&Meier, ROC and multivariate analysis

These statistical methods will be used to analyse the data in standard and time-honoured fashion. The significance and the confidence intervals will be determined for the variables. The data will be presented in tabular and graph format.

In the ROC analysis the predictive effect of individual variables are explored. Multivariate analysis will be performed using stepwise addition and removal of variables. During this process the most important variable is removed from the equation and the remaining variables are searched for other markers. As the variables are randomly inserted and removed this will influence the strength of the variables remaining in predicting outcomes.

1.5 Classification and regression tree (CART) analysis: strengths and weaknesses.

A CART analysis will be done to quantify the most important markers of outcome. CART analysis is used to classify observations on the basis of a large number of possible predictive variables.[4] CART analysis begins by selecting the single best predictor for separating patients into survivors and non-survivors. Each variable is considered at each decision point, regardless of whether it had been used earlier.

The CART analysis is a fairly new statistical model. It is ideally suited to the generation of clinical decision rules. Most statisticians have any or little experience with this model. The statistical model is extremely complex and a sophisticated computer is needed for the analysis. It is inherently a non-parametric method and therefore can use skewed data. CART does not require variables to be selected in advance, can handle datasets with complex structure, is robust to outliers and can handle continuous and categorical variables. It has however the ability to uncover complex interactions between predictors which are difficult or impossible to uncover using traditional multivariate analysis.

The CART analysis functions by means of a binary reclusive partitioning. This partitioning can be chosen. The one used in this dataset is the GINI index which classifies the data into the best 2 subgroups. This prior is altered by cost.[1] It "splits" data into two groups, with each having the possibility to be split into other subgroups. A "tree" is thus built which usually "overfits" the information contained. The tree is then "pruned", increasingly cutting off important nodes till an optimal tree is found which fits the information in the learning dataset without significant loss of predictive power. Misclassification costs and tree complexity parameters are empirically selected to generate a practical (ie, not overtly complex) decision tree with adequate sensitivity and specificity. This is achieved by using punitive measures included into the model when it makes wrong decisions.

The decision tree presented represents a balance between predictive power and simplicity. Confidence intervals have been omitted because the current version of CART does not provide the information necessary to calculate valid confidence intervals and because alternative means of calculating these intervals suggested an inaccurate measure of precision. According to Harrell [5] the number of predictors should be no more than $m/10$ where m is the number of uncensored event in the training sample. CART analysis can handle missing variables by identifying surrogate variables. It is able to learn with relative ease with limited input needed from the statistician.

The disadvantage of CART is its relative unknown and novel qualities. Some statisticians still mistrust the validity of CART given the poor performance of earlier tree analysis models. For clinicians, the CART analysis is easy to understand, makes inherent "logic" and tends to be more easy to implement in the clinical setting.

[1] Cost means that the program is penalized for patients who are wrongly classified as survivors because of a specific node or cut-off value.

All the patients will be used in this model as the training sample, and the validation cohort will be analysed to see whether the same nodes hold for a second independent sample

1.6 p-values used

The emphasis will be less on finding one outcome predictor that is of statistical importance, than on evaluating all the factors and finding a combination of predictors that are important. For the standard statistical methods like the Student t test and the Kaplan&Meier analysis a p value of 0.05 will be used. In finding predictor variables the p value is increased to 0.15 in keeping with standard statistical practice.[6] To emphasize the importance of different predictors and outcome variables, data will also be presented that may not be of specific statistical importance in this study, but which has been found relevant in other studies.

To measure the degree of accuracy, the model will be subjected to a series of comparisons:

1.7 Model excellence[7]

1.7.1 Calibration: (Goodness of fit)

This calibration is a measure of how well the predictor measures the outcome. To do this the Hosmer- Lemeshow goodness of fit test will be done.[8]

1.7.2 Discrimination [9]

The physician usually likes to know if a test is positive or negative. It is just as important to know the sensitivity and specificity of the predictor. When analysing a great number of variables the chances are increased to make a Type 1 error. The area under the ROC curve illustrates the predictive value more accurately.

Therefore the area under the curve will be described for certain variables to compare individual predictors with outcome. These variables can be compared as they measure the same outcome.

1.7.3 Data reliability:

Data is entered by 2 persons only. A sample of the data will be drawn by the investigator and examined for possible faults in either the collection or the registration of data. Computerisation will all be done by the main investigator.

Accuracy and reliability of data are crucial to any effort to make fair comparisons. The consistency model will be tested on the data collected during the years 2000-2002. According to Richardson, the data should be collected prospectively and be error free. The association between risk and outcome can change as new technology emerges. Thus the score must be recalibrated regularly to maintain its predictive power, validity and reliability. No power analysis will be done on this study.

1.8 Development of the score:

The score will be used to set up a statistical method of allocating a computer-based probability of a specific outcome. This will not form part of this thesis.

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CHAPTER 5

Statistical analysis of the initial cohort

1 Descriptive data

1.1 Maternal data

The data on 455 babies was analysed. The data on the mothers is presented in Table 1 and the babies' data in Table 2.

Table 1: Maternal data

Variable	Number	Mean	SD	Range
Age of mother (years)	435	27.06	5.88	14-44
Parity	450	2.7	1.53	1-9
Income (Rand per month)*	453	892.3	1180.19	0-8500

* 1US$=8 South African Rand

The mean age of the mothers was 27 years and for the majority it was not the first pregnancy. "Young" mothers (<21 years) constituted 11.2% of mothers and 1.3% of mothers were 40 years or older. The income of "young" mothers was nil in 61% of cases. In the remaining 39% of "young" mothers this income exceeded R800 in only 13%.

The mean income of all mothers of R890 per month was just more than the official minimal wage of R800 for domestic employees. A total of 122 mothers had no formal income at all and a further 148 earned less than R800 per month. The mean income (of those who had an income) was R1098.

1.2 Neonatal data

The neonatal data is illustrated in Table 2.

Table 2: Neonatal data

Variable	Number	Mean	SD	Range
Birth weight (gram)	545	1198.7	196.28	655-1625
Gestational age (weeks)	454	30.3	2.13	25-36
1 min Apgar	437	5.04	2.83	0-10
5 Min Apgar	436	7.22	2.11	0-10

The babies had a mean weight of 1198g. The mean gestational age was 30.3 weeks. The mean weight for gestational age is just above the 10th centile on the growth charts[1], indicating that the majority of babies were small for gestational age.

1.3 Delivery data

The delivery data is illustrated in Table 3.

Table 3: Delivery data of babies

Variable	Total number	Positive (%)	Negative
Booking status	449	365 (81%)	84
Syphilis serology	433	26 (6%)	407
Admission time (<12 hours of birth)	455	360 (79%)	95
Prolonged rupture of membranes	396	36 (9%)	360
Gender (M:F)	455	238 (52%)	217
Multiple births	455	60 (13%)	395

Fifty-seven babies were part of twins and 3 babies were part of a set of triplets. The type of delivery was normal vertex vaginal in 251 cases, breech delivery in 3 cases, caesarean section in 173 cases and instrumental (suction or forceps) in 28 cases (Table 4). When babies were delivered vaginally, 85% were vertex deliveries. Assisted deliveries accounted for 15% of vaginal deliveries. The mortality in normal delivered babies was 25%, in forceps delivered 33% and 40% of breech deliveries.

Table 4: Number of deliveries by type and survival

Type of delivery	Total	Non-survivors	% Deaths
Caesarean	251	64	25.4
Vaginal: Normal	173	43	24.8
Forceps	3	1	33.3
Breech	28	11	39.2

In babies born by caesarean section the most important indication was fetal distress (42%) with a mortality of 24%. Pre-eclampsia was the indication for 32% with a mortality of 24% (Table 5).

Table 5: Indication for caesarean sections and survival

Indication for caesarean sections	Total	Non-survivors	% Deaths
Pre-eclampsia	79	21	26.5
Eclampsia	4	0	0
Fetal distress	101	24	23.7
Multiple pregnancy	20	2	10
Other	40	15	37.5

378 babies were born at Tygerberg Hospital and 21 at the ANC service in the rural areas. There were 336 survivors and 119 (26%) deaths occurred before discharge from hospital.

(Table 6). The mortality rate was 21.5% for infants of "young" mothers. Infants of "older" mothers had a mortality rate of 33%, but the numbers were small. The mean age of primigravidas was 22.1 years.

1.4 Outcome data

The outcome data is illustrated in Table 6.

Table 6: Outcome data

Variables	N	Mean	SD	Range
IPPV duration (days)	455	8.48	11.8	0-100
CPAP duration (days)	209	1.05	1.77	0-10
Days oxygen (days)	455	20.98	42.01	0-630
Length of stay (days)	454	13.19*	14.75*	1-632

* 1 patient with a stay of 632 days was excluded from analysis.

The babies required a mean time of 8.5 days of ventilation. Hundred and seventeen babies (26%) needed CPAP after ventilation.

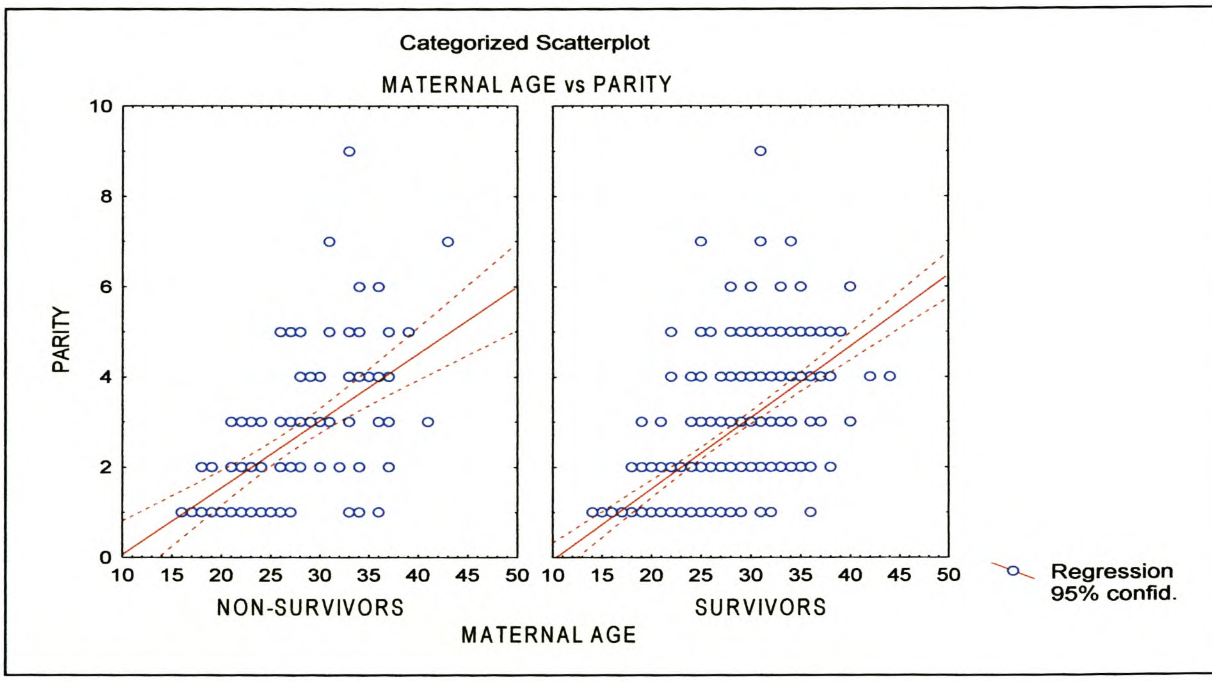
The relation of survival analysis to maternal data is listed in Table 7.

Table 7: Maternal data: Survival analysis

	Survivors		Non-survivors		P value
Variable	Mean	SD	Mean	SD	
Age of mother (years)	27	5.84	27.23	6	>0.10
Parity	2.62	1.46	2.73	1.7	>0.10
Income (Rand)	**958.68**	**1267.77**	**706**	**867.28**	**<0.05**

There was no difference in either age or parity, but mothers of survivors had a higher income (Figure 1). The mean income of mothers was very low, but the standard deviation in the survivors and non-survivors was large. There was no higher mortality found in the mothers who had less than 3 babies or the mothers who were grand multipara.

The association of the mother's age, parity and survival is illustrated in Figure 1.



Each circle represents a patient

Figure 1: Comparison of maternal age, parity and outcome.

As expected a higher age correlated to a higher parity. There is an increase in the numbers of babies surviving in the lower aged mothers of higher parity.

The comparison of survivors and non- survivors by birth weight, gestational age and Apgar count is presented in Table 8.

Table 8: Neonatal data: Survival analysis

	Survivors		Non-survivors		P value
Variable	Mean	SD	Mean	SD	
Birth weight (grams)	**1223.33**	**182.24**	**1129.16**	**217.55**	**0.001**
Gestational age (weeks)	30.43	2.1	29.9	2.2	0.10
1 min Apgar	5.06	2.82	4.96	2.87	0.10
5 Min Apgar	7.26	2.04	7.11	2.32	0.10

The mean gestational age and Apgar counts did not significantly differ in the survivors and non-survivors. There was however a significant difference in the birthweight between the survivors and non-survivors. Even though the absolute difference is small at 94 grams the effect of this possibly combined with the half-week increase in gestational age made all the difference.

Other variables measured in babies are listed in Table 9.

Table 9: Other neonatal variables: Survival analysis.

	Survivors		Non-survivors		
Variables	Positive	Negative	Positive	Negative	p-values
Booking status	**262**	**72**	**103**	**14**	**0.023***
Syphilis serology	18	303	8	104	0.55
Admission time (<12 hours)	266	70	94	25	0.92
Prolonged rupture of membranes	258	25	87	11	0.61
Gender (M:F)	**166**	**170**	**72**	**47**	**0.048#**
Multiple births	41	295	19	100	0.37

* OR 2.02 (CI 1.05-3.39) # OR 1.57 (CI 1-2.46)

There were no differences in the booking status RPR results or admission time of the two groups. More boys than girls were admitted, and more boys died.

Details of ventilation, oxygen requirements and duration of stay are illustrated in Table 10.

Table 10: Duration of ventilation and hospital stay.

	Survivors		Non-survivors		
Variables	Mean	SD	Mean	SD	p-value
IPPV duration	7.98	10.77	9.87	14.2	0.081
CPAP duration	1.09	1.8	0.85	1.64	0.48
Days oxygen	21.37	45.95	19.89	28.12	0.56
Length of stay	13.15	14.5	13.3	15.49	0.97

There was no difference in the length of ventilation, the duration of CPAP, the days on oxygen therapy or the length of stay in the NICU in the two groups. Babies who died did not use more resources compared to survivors.

The mortality rates for different maternal age groups and parity are illustrated in Table 11.

Table 11: Mortality rates for maternal age groups and parity.

Variable	Survivors	Non-survivors	Mortality rate (%)
Age <21 years	50	13	20.6
Age 21-39 years	270	98	26.6
Age >39 years	4	2	33.3
Primigravidas	94	33	25.9
Parity 4-6	72	20	21.7
Parity >7	**4**	**5**	**55.5***

* p<0.05   Data on parity 2-3 not demonstrated

Mothers with advanced parity of more than 7 babies had a significant higher mortality. The number of mothers in the age groups less than 21 years and more than 39 years were too small to enable statistical comparison with the age group 21 to 39 years.

1.5 Small for gestational age

Morley found that the ratio of birth weight divided by the mean birth weight for the specific gestational age corresponds to a 10^{th} centile when the ratio is 0.8.[2] Babies with a ratio of less than 0.8 are classified a small for dates. There were 89 babies with a birth weight to normal weight for gestational age ratio of less than 0.8. Of these, 26 died. Their mortality rate of 29.2% (n=26) was higher than the 25.4% in the normal weight group, but did not reach statistical significance.

1.6 Maternal income

Seventy three percent of mothers with no income delivered at in Tygerberg Hospital. Twenty percent (25 mothers) of the women with no income delivered outside of the Tygerberg Metropole, compared to seven percent who delivered in the Metropole ANC. Women who earned less than R800 per month constituted 13 % of deliveries outside of the hospital catchment area.

If a cut-off point of R1030 is used, 29% of babies born to mothers under this income died, compared to 19% in the higher income group. The odds of this happening is 1.89 (CI 1.13-3.15) with a RR=1.62 (CI1.11-2.37) (p=0.013). In this (<R1030) group 30% of women did not attend antenatal care, compared to 9% in the higher income group. The incidence of a positive RPR was also much higher at 8% in the lower, compared to 0.04% in the higher income group. More of the lower income babies were admitted at a later age. The incidence of BPD at 36 weeks was higher in the all income groups compared to BPD measured at 28 days. (Table 12)

Table 12: The incidence of BPD

Income	% BPD at 28 days of life	% BPD 36 weeks post conception
Low (<R1030)	27%	33%
High (>R1030)	18%	29%

Odds Ratio 1.73 (CI 1.06-2.83) RR=1.13 (CI 1.01-1.27).

If, however, the number of babies who died is added to the number who developed BPD, the percentages are similar at 47% for the low-income group and 45% for the high-income group. This suggests that the higher income babies have a lower prevalence of deaths, but a higher prevalence of BPD.

2 Statistical methods of data analysis

The data obtained constitute two groups: firstly there are the patient's variables (like birth weight or gender) that could predict a specific outcome and secondly there are different outcomes (like survival or length of stay) that can be measured. The data was analysed by means of life tables to identify potentially significant parameters which could be used to correlate patient parameters with outcome parameters.

3 Kaplan&Meier life tables

This method was used to evaluate the parameters in relation to neonatal deaths and time spent in the NICU. Each variable that could influence these two outcomes was individually analysed. The possibility that any single variable would indicate both the outcome of time spent in the NICU as well as survival, is small. The search for all possible indicators of outcome necessitates that not only statistically significant variables are researched. All variables with a p value of less than 0.15 are given.

3.1 B irth weight

The birth weight of the babies was divided into quartiles. The results of the Kaplan & Meier (K&M) analysis are illustrated in Figure 2. The log rank statistic was 7.1 with 3 degrees of freedom and a significance of 0.0687.

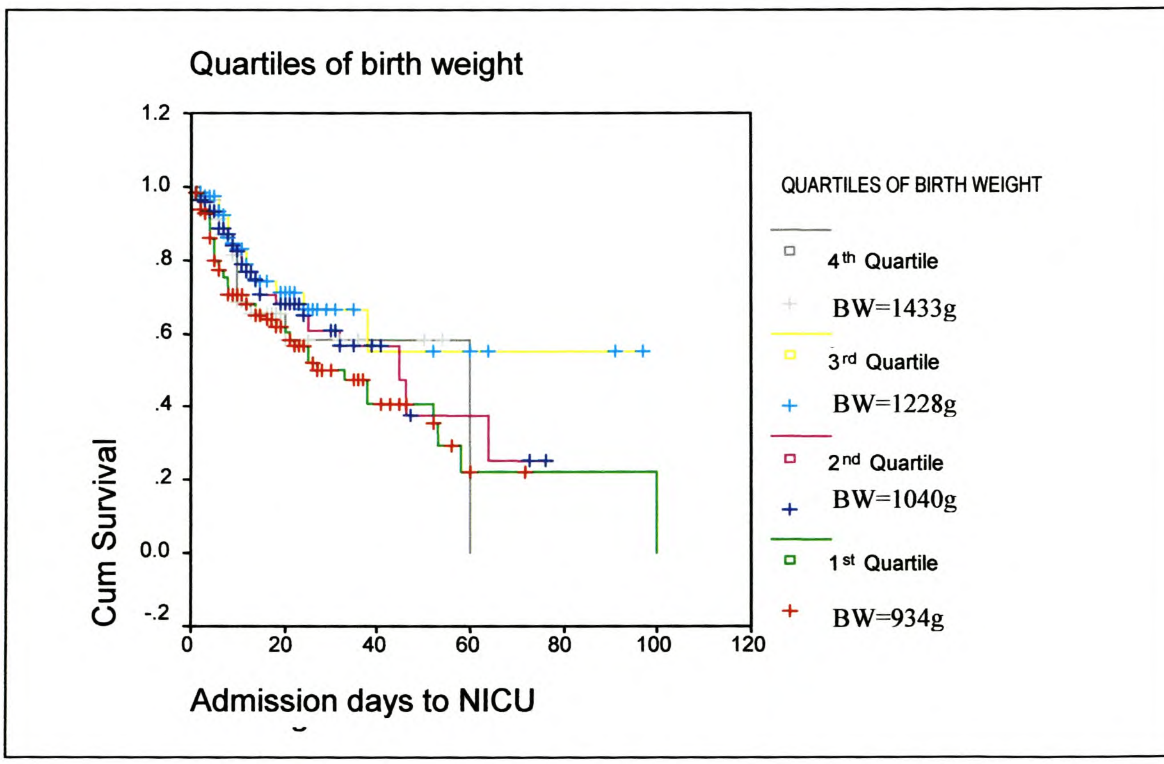


Figure 2: Comparison of birth weight in quartiles to length of stay in NICU and survival. The birth weight was divided into four quartiles

There were no differences in the survival and length of stay in babies if divided into quartiles.

3.2 Birth weight in 50th centiles.

The K&M analysis for birth weight divided into 2 groups divided at the median is seen in Figure 3. The log rank statistic was 3.03 with 1 degree of freedom and a significance of 0.0818.

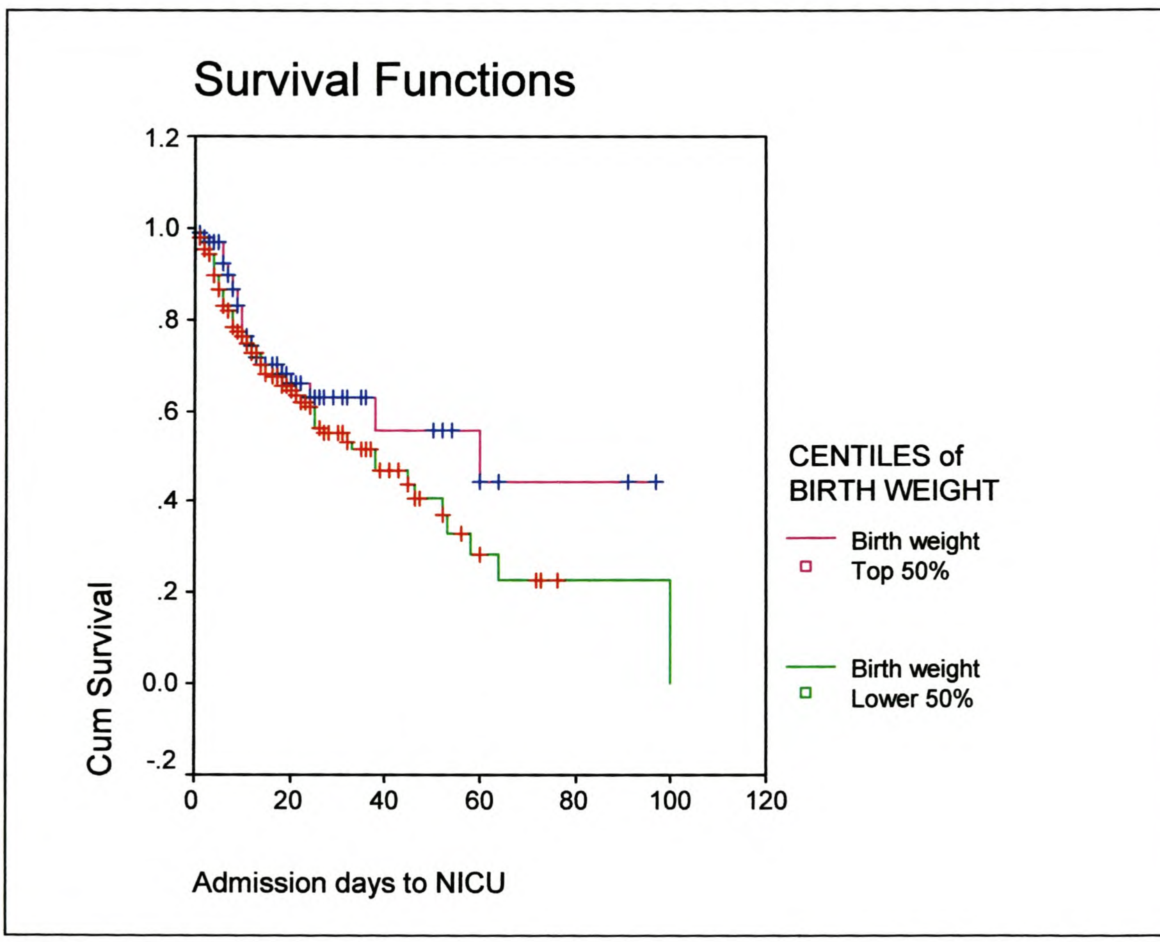
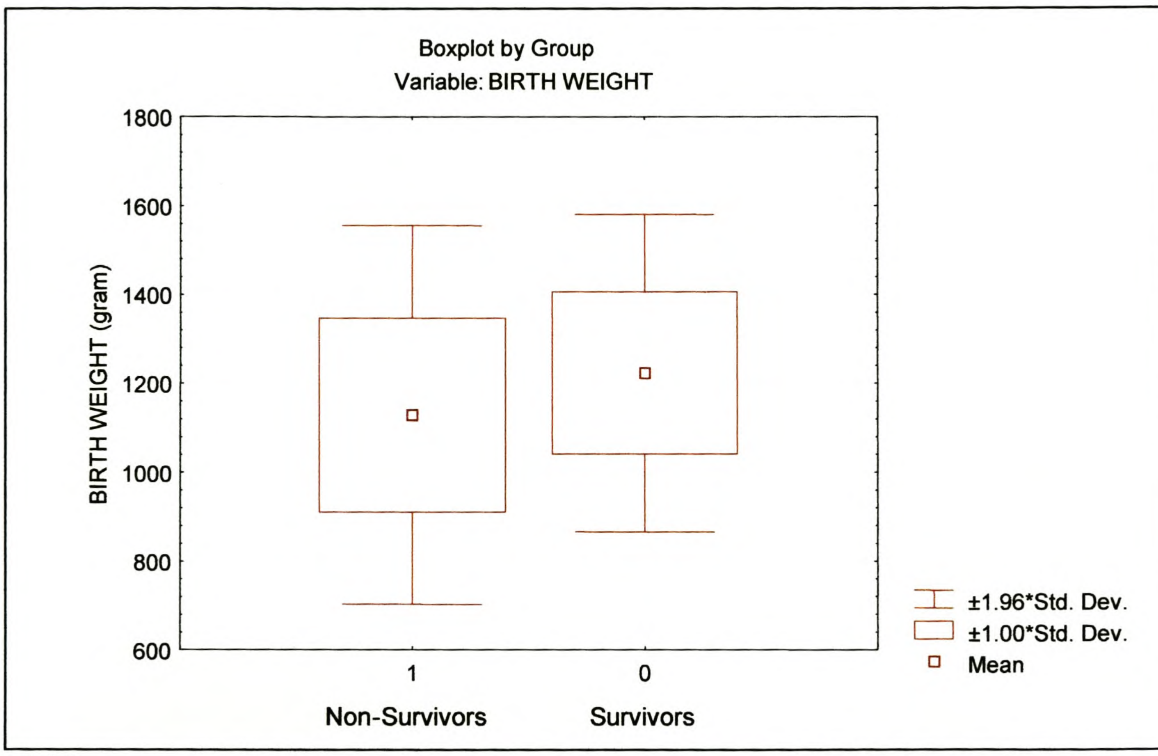


Figure 3: Comparison of birth weight in 50^{th} centiles to length of stay in NICU and survival.

When babies were divided into two groups according to their birth weight there was no statistical difference in outcome or length of stay.

The association of birth weight with survival is illustrated in Figure 4. The non-survivors had a significant lower weight than the survivors, although in real terms this number is small.



$p<0.05$

Figure 4: Box plot of birth weight of survivors versus non-survivors.

The birth weight of the survivors was significantly higher in this analysis. The difference in real terms was however small.

3.3 The booking status

The K&M analysis for booking status (receiving antenatal care) is illustrated in Figure 5. The log rank of this graph is 3.13 with 1 degree of freedom and a significance of 0.0767.

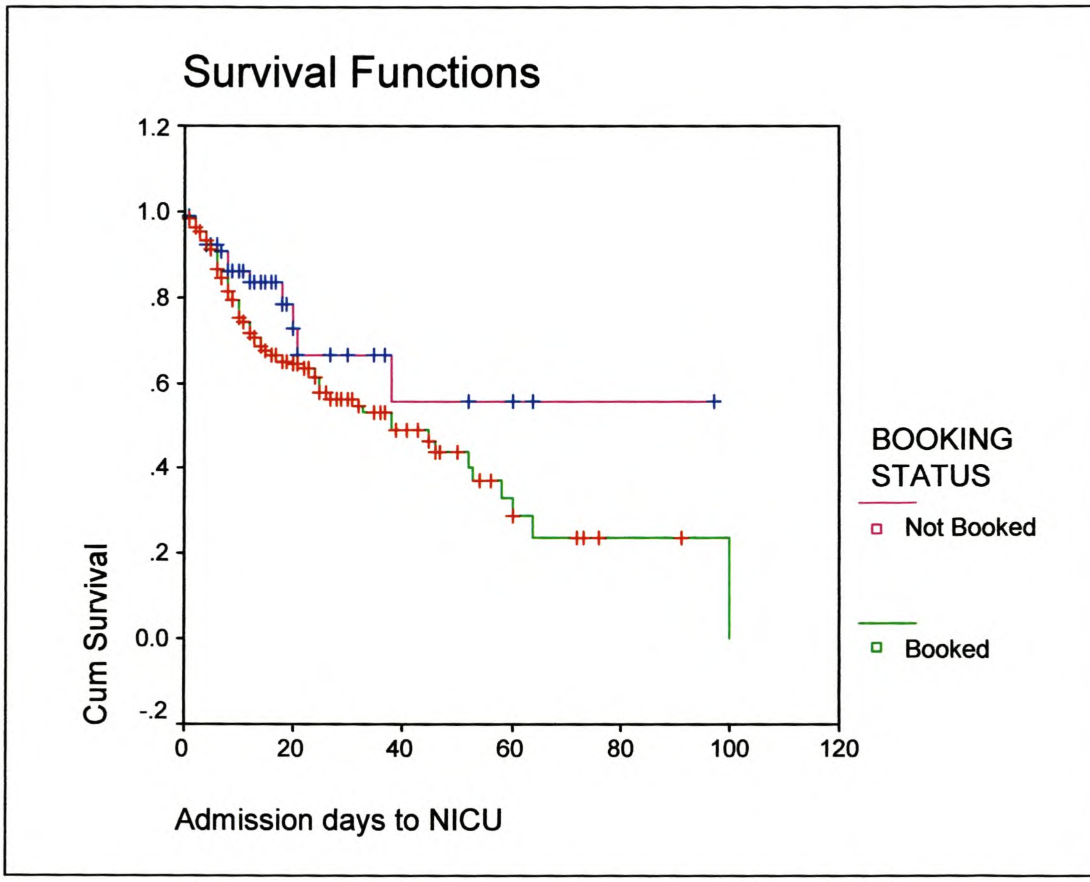


Figure 5: Comparison of booking status to length of NICU stay and survival.

Even though there was no overall difference in the survival of booked compared to unbooked patients, the survival of the unbooked patients was higher. This was also evident in the CART analysis of the validation cohort in which this was one of the nodes.

The difference in the booking status between survivors and non-survivors is illustrated in Figure 6.

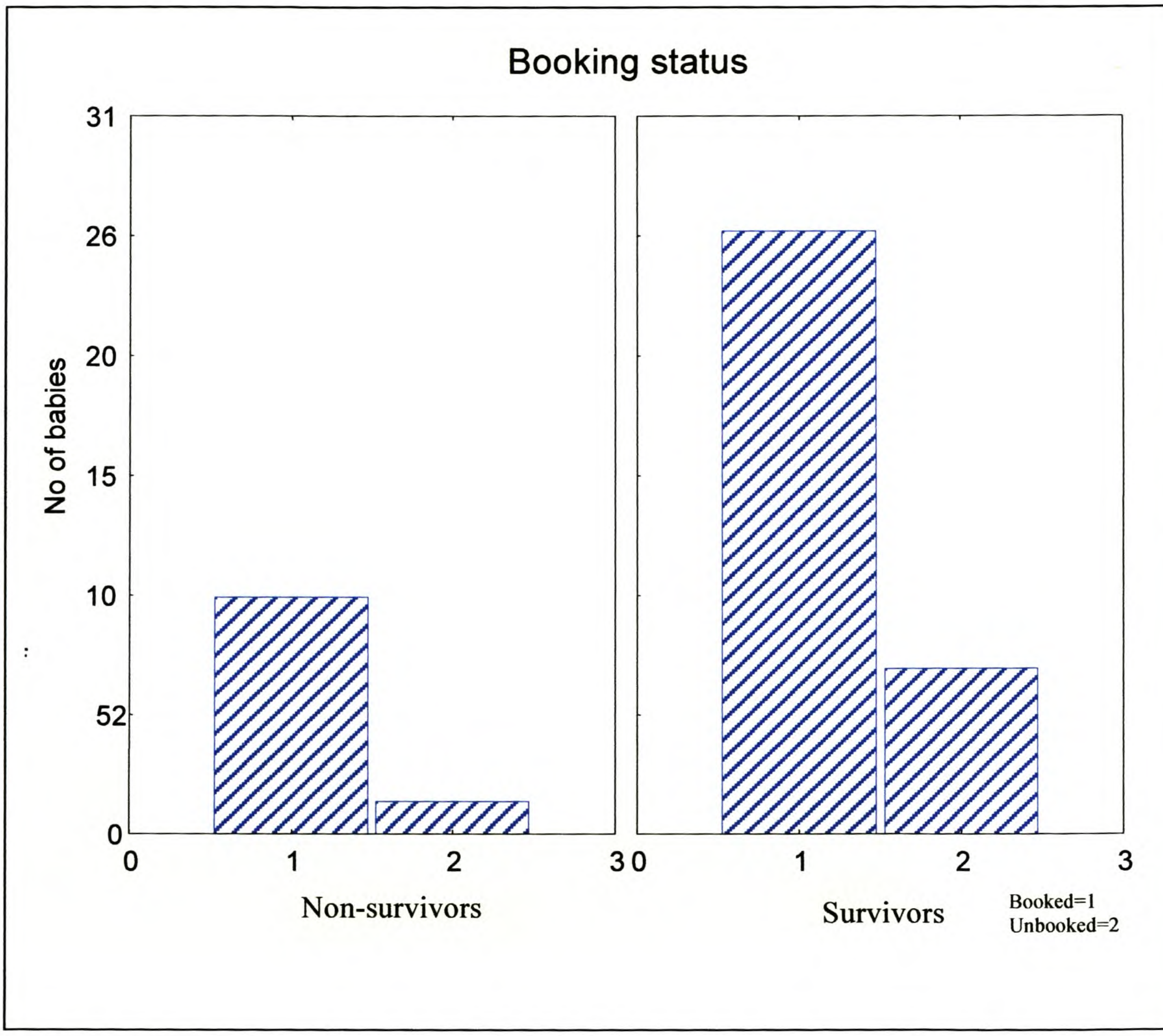


Figure 6: Histogram of the association of booking with survival.

There was no difference in the outcome of booked versus unbooked patients ($p>0.10$).

3.4 The variable of multiple births

The function of twin or triplet births on the outcome of the babies is illustrated in Figure 7. The log rank of this analysis was 0.19 with 1 degree of freedom and a significance of 0.662.

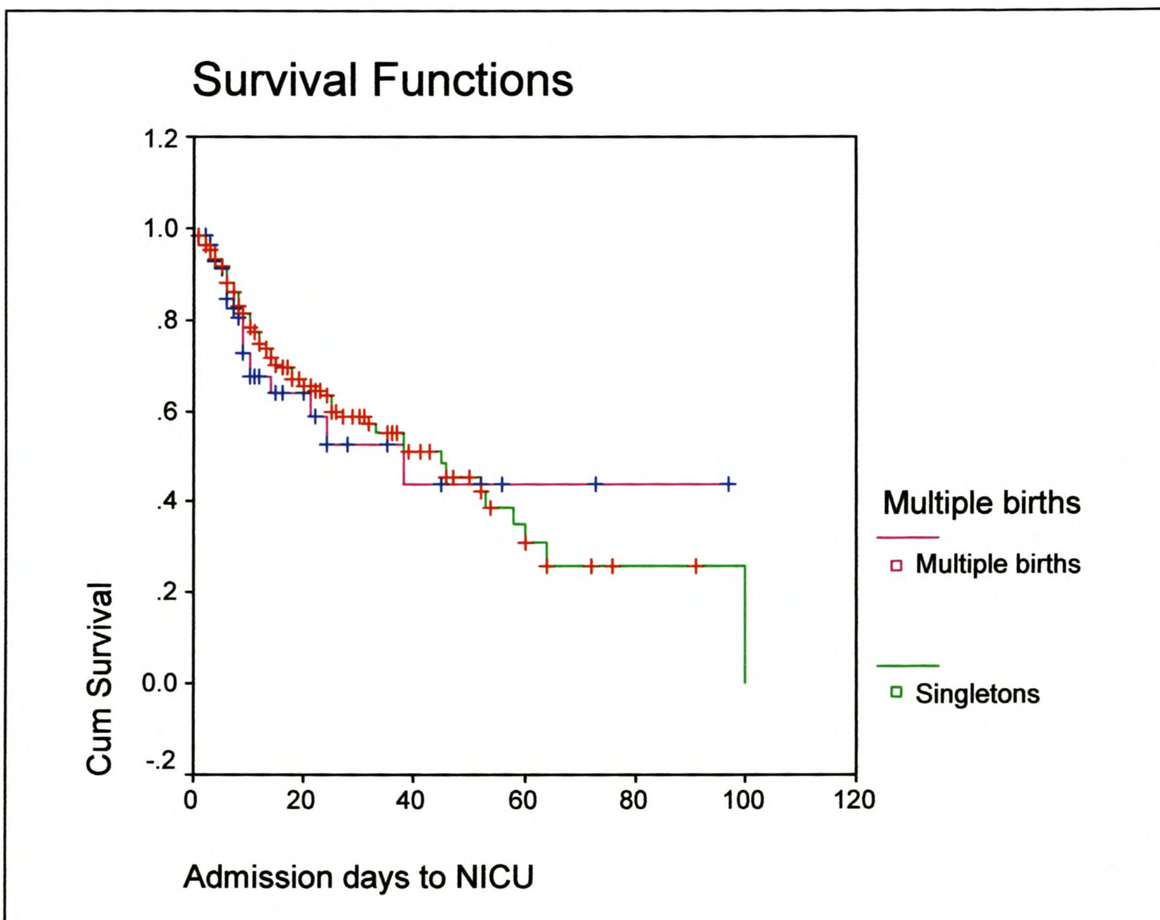
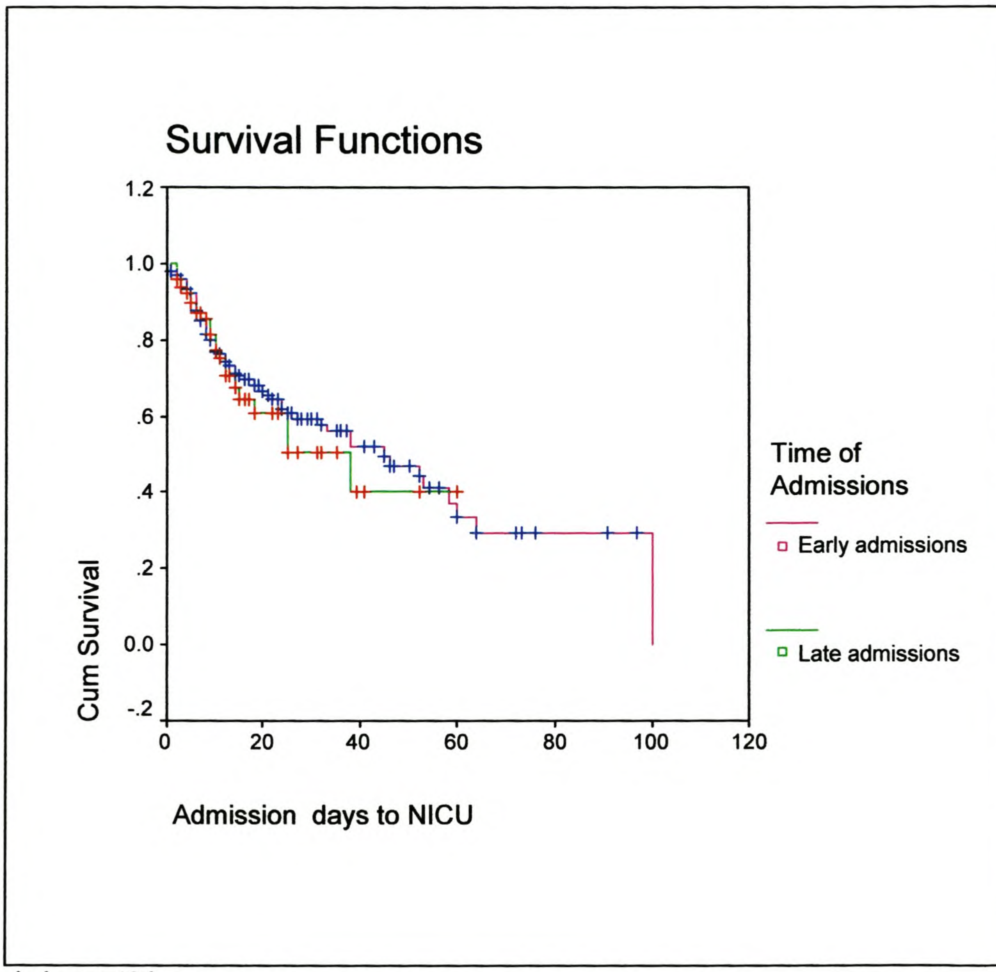


Figure 7: Comparison of being part of a twin or triplet pregnancy to length of NICU stay and survival

There was no difference in the outcome of singleton pregnancies compared to twin or triplet pregnancies.

3.5 The effect of time of admission on outcome

The effect of the time of admission on the K&M analysis is illustrated in Figure 8. This variable was not significant with a log rank of 0.26, 1 degree of freedom and a p =0.609.



Early admissions < 12 hours

Figure 8: Comparison of time of admission to NICU as a function of length of stay and survival

No difference was found between babies who were admitted before 12 hours of age compared to those admitted after 12 hours of life.

3.6 The place of birth

The way in which the place of delivery related to the outcome is illustrated in Figure 9. The statistics on this analysis showed a log rank of 4.4, 2 degrees of freedom and with a p=0.111.

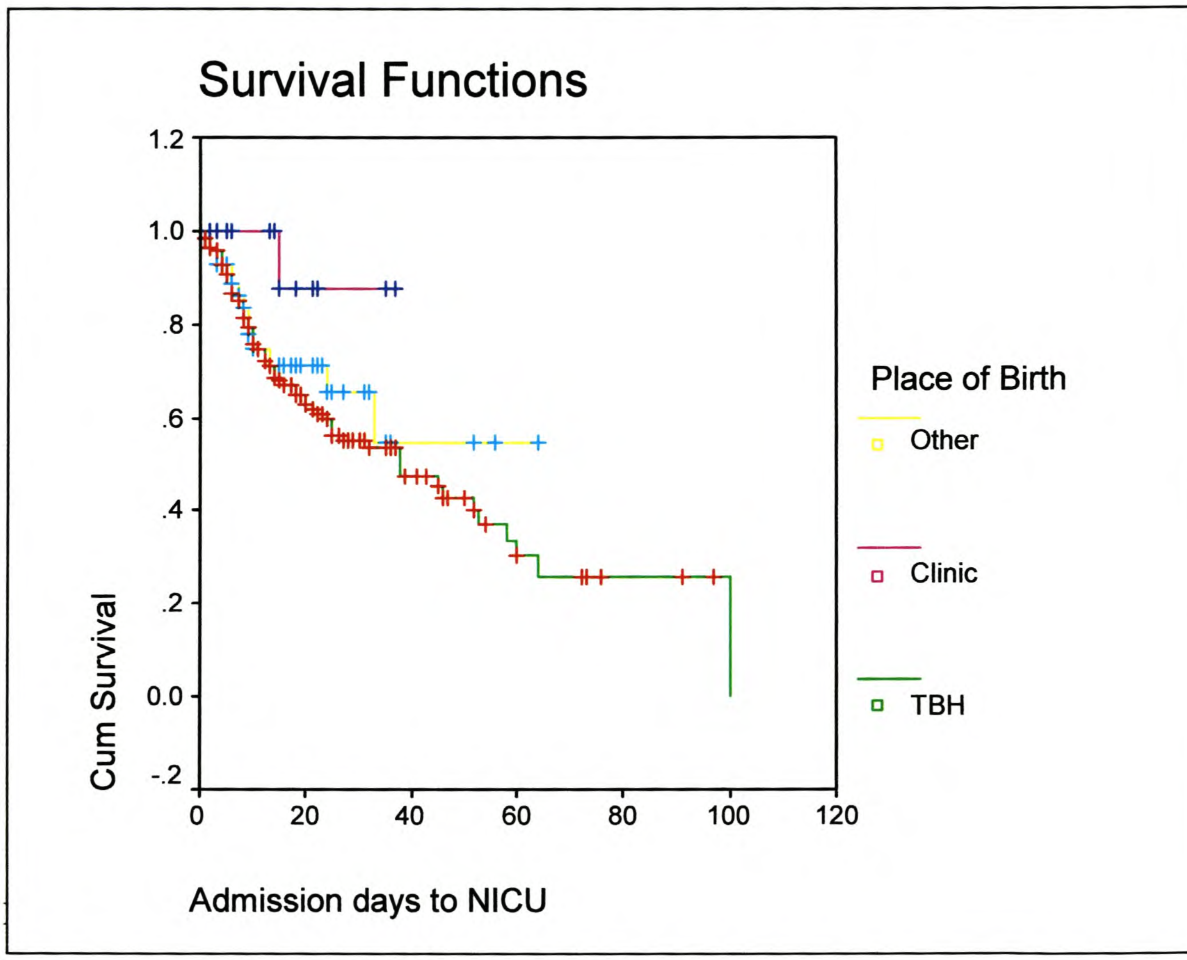


Figure 9: Relationship of place of birth to length of stay and survival

The babies who delivered in the clinics did better than the others, mainly because all the babies who fall into the high-risk group will be immediately transferred to the hospital before delivery. This group constitutes those babies who were delivered before transfer could be achieved or where the delivery was not perceived as problematic.

3.7 The method of delivery

The method by which the baby was delivered also did not impact significantly on the mortality of the baby. This can be seen in Figure 10 (log rank 4.49, 3 degrees of freedom with a p=0.2129).

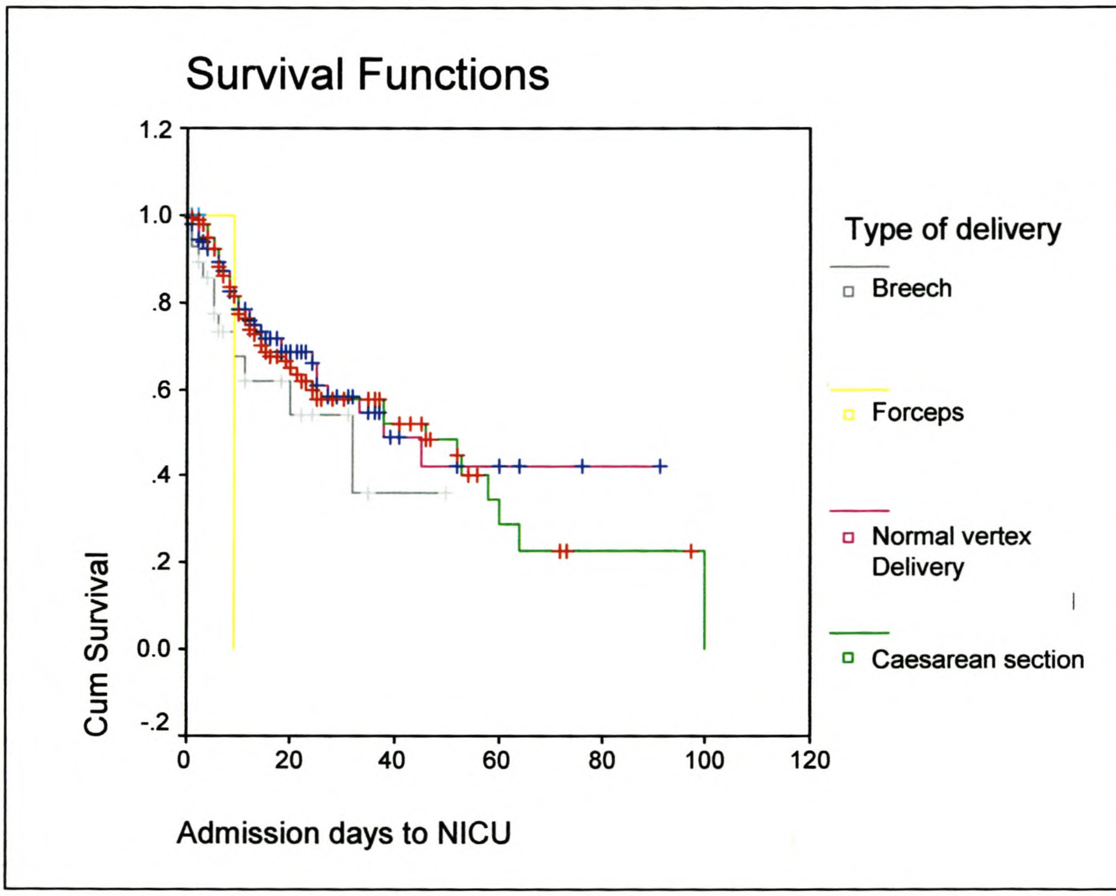


Figure 10: Comparison of the type of delivery, length of NICU stay and survival.

The babies who were delivered by means of a forceps delivery did worse than the rest, but the numbers were small.

3.8 Prolonged rupture of membranes

This risk variable did not change the outcome significantly as illustrated in Figure 11. The log rank was 0.49, 1 degree of freedom with a p=0.4833.

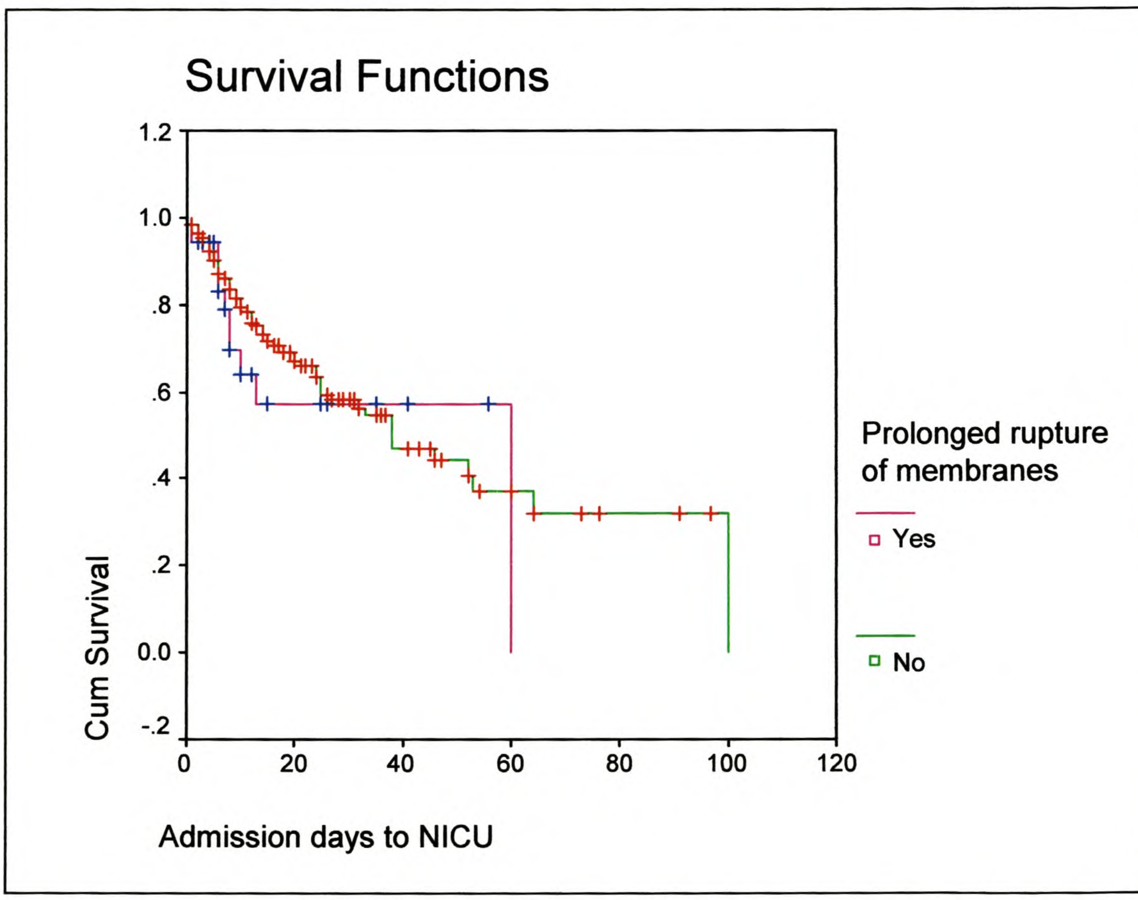


Figure 11: Association of premature rupture of membranes with length of stay and survival

No difference was found between babies who had prolonged ruptured membranes (PPROM) compared to those who did not. There was a trend for those babies with PPROM to have a shorter survival initially.

3.9 Syphilis serology

The effect of a positive RPR test is illustrated in Figure 12. The log rank of this fact is 1.64 (1 degree of freedom) with a non-significant p=0.1998.

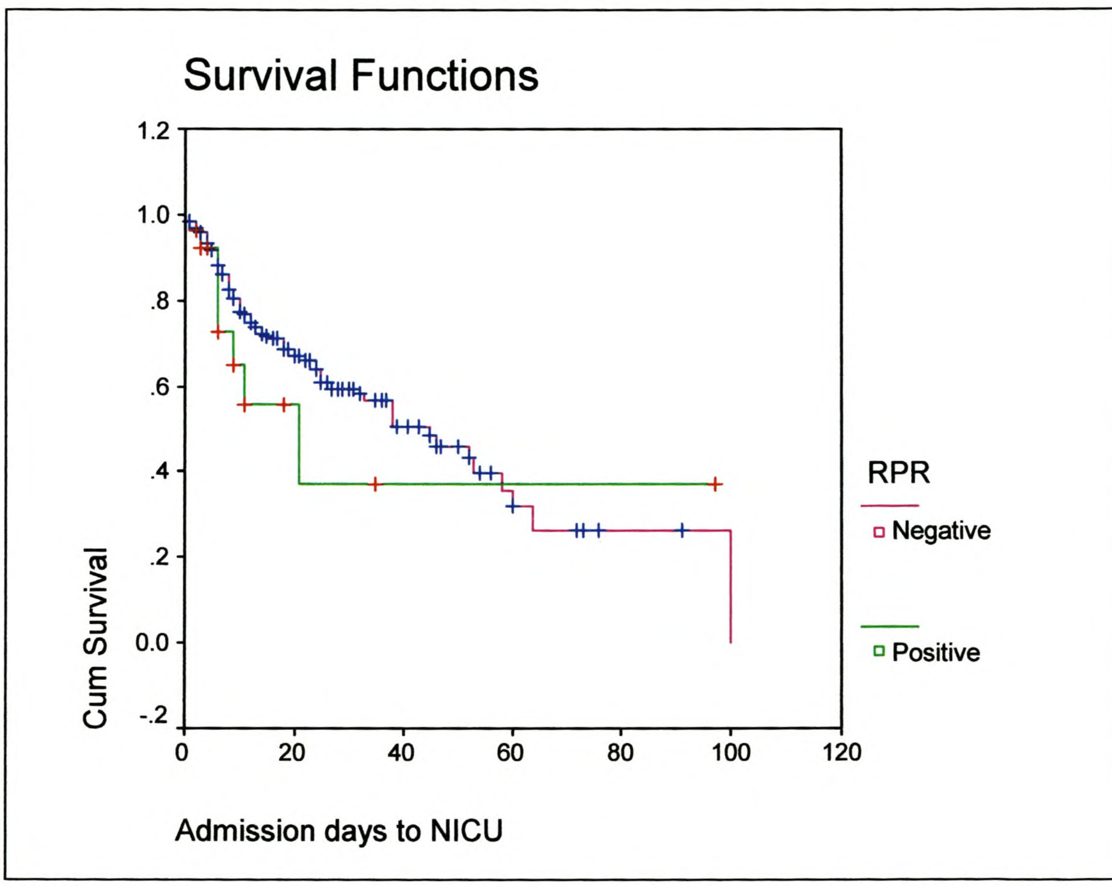


Figure 12: Association of a positive RPR test with length of NICU stay and survival.

Babies who were infected by syphilis during pregnancy had similar outcomes as the babies who had no infection.

3.10 The association of gender and outcome

The effect of gender on the outcome is illustrated in Figure 13. The log rank of this data is 0.14 (1 degrees of freedom) and a p=0.7131.

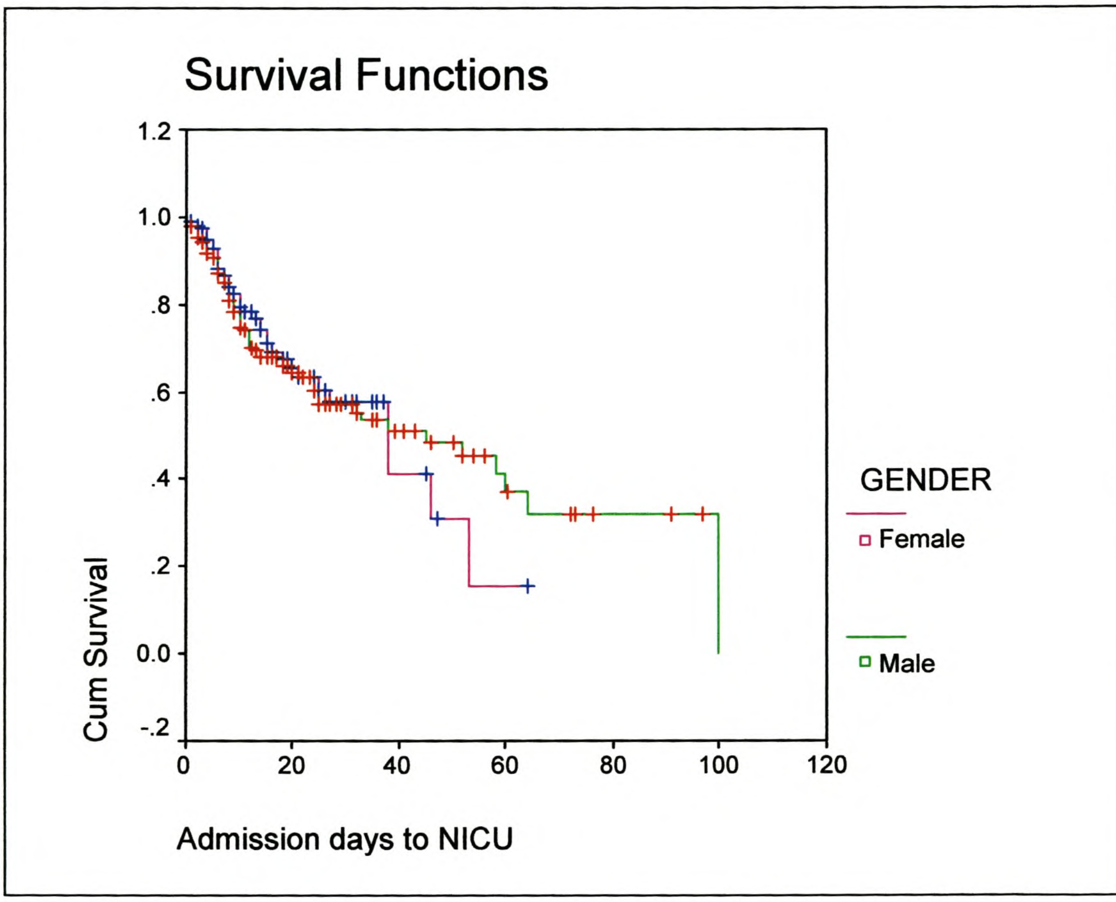


Figure 13: Association of gender with survival and length of NICU stay.

According to this K&M evaluation there was no difference in outcome as classified by gender.

3.11 Ethnic group

The association of ethnicity with the outcome of babies is illustrated in Figure 14. The log rank was 3.45, 2 degrees of freedom and a p=0.1781.

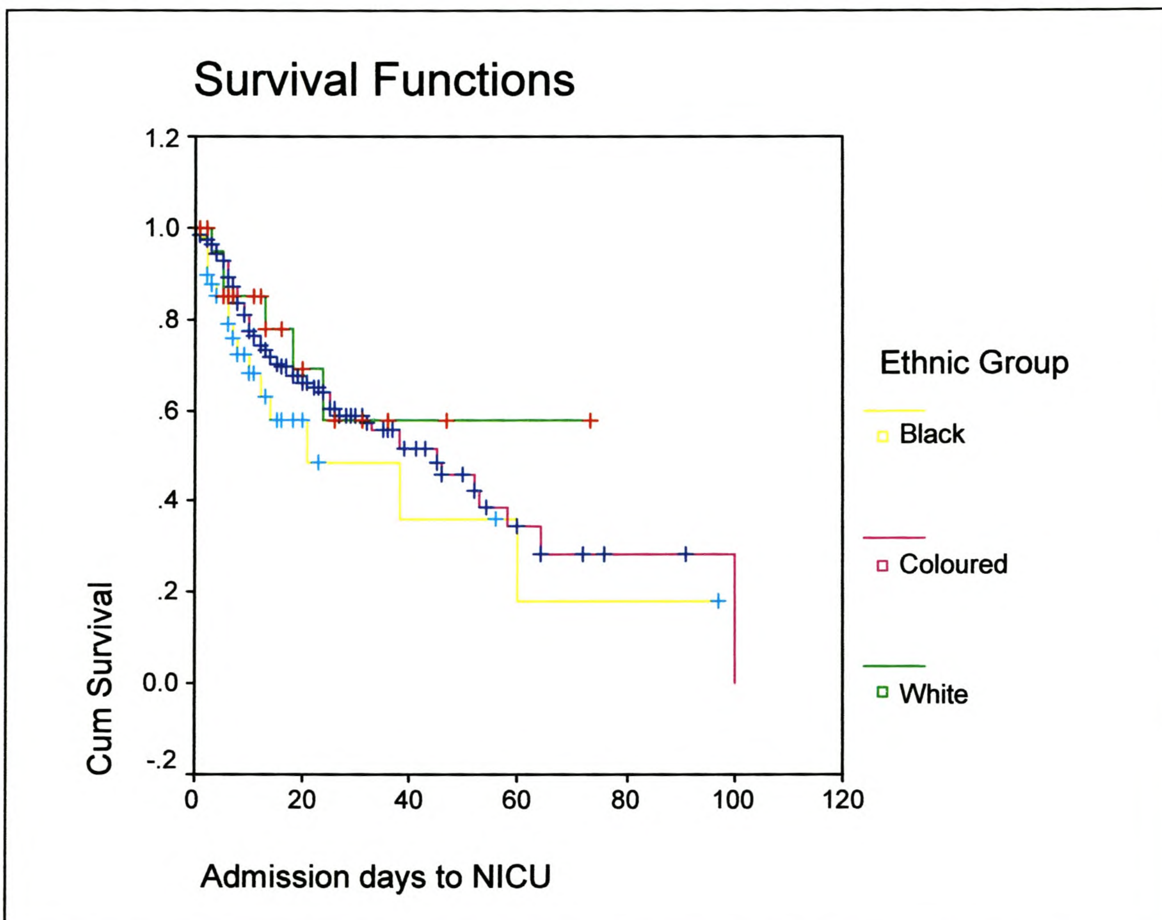


Figure 14: Association of ethnic group with survival and length of stay in NICU.

There was no difference in outcome of different ethnic groups.

3.12 The association of the development of BPD on the length of stay and survival

The predictive effect of the subsequent development of BPD on long-term outcome is predictable because the baby has to survive to 36 weeks post conceptual age and be oxygen dependant to be classified as having BPD. This is, however, an indicator of late deaths in this population and can be expected, as the baby has to survive 28 days to be classified as having developed BPD. This K&M analysis demonstrates statistically significant differences (Figure 15).

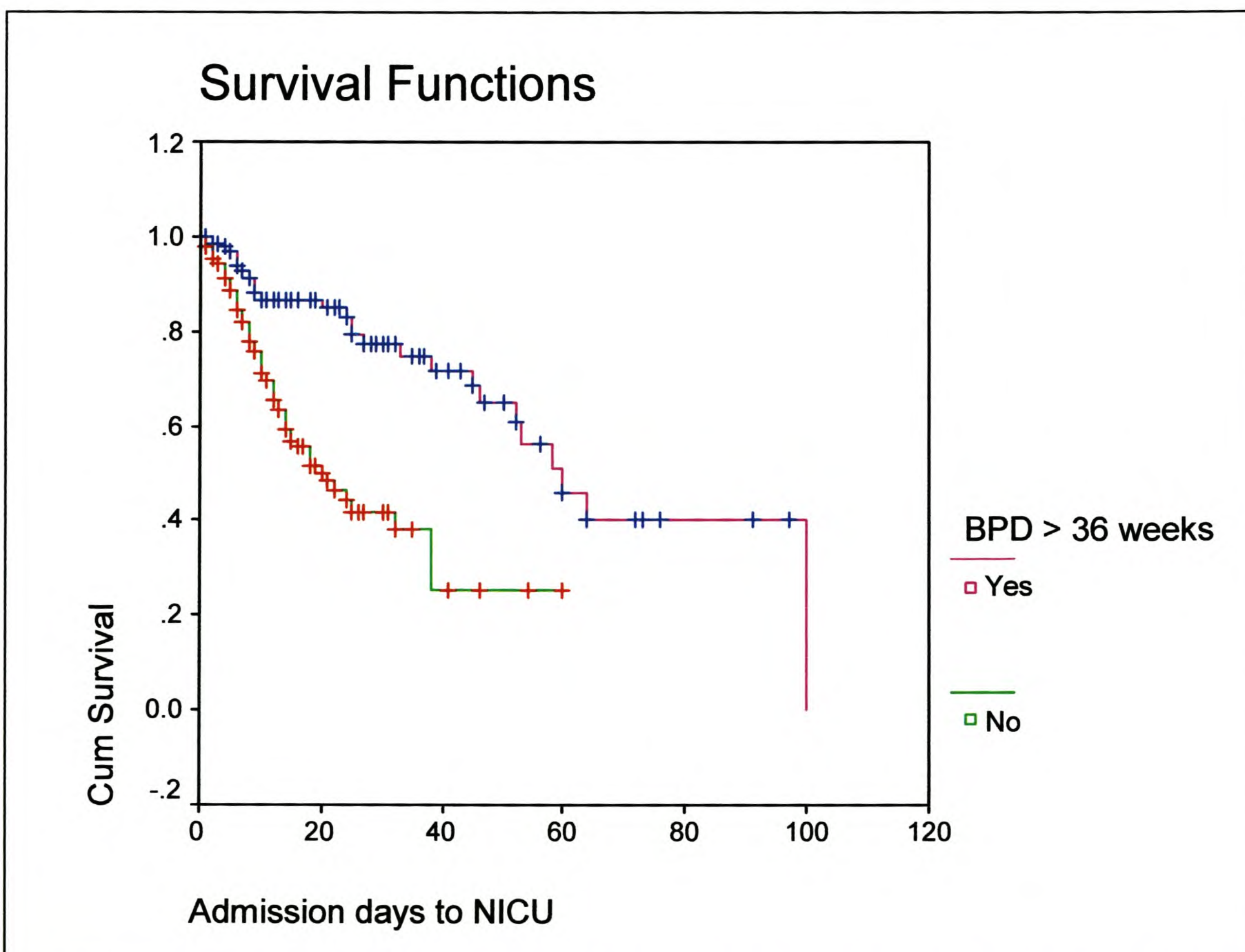


Figure 15: Association of subsequent development of BPD with survival and length of NICU stay.

3.13 Maternal income

The income of the mothers is an accepted social marker for disease profiles. The income of the mothers is illustrated in Figure 16.

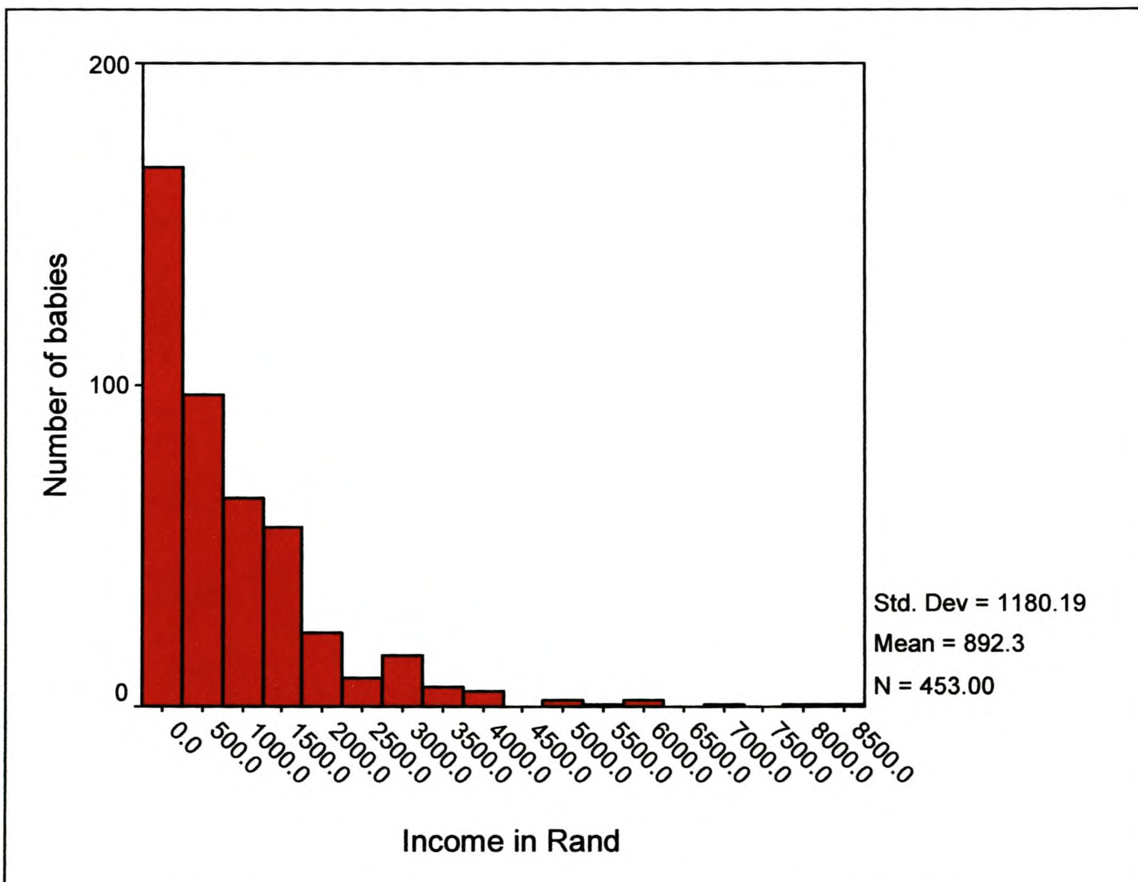


Figure 16: Histogram of the mothers' income.

The majority of mothers with an income had a very low income, with an exceptional few in the income group of more than R2000. The majority had no income at all.

The distribution is skewed with a high percentage of mothers with no income at all. There is a clustering of babies who died in the low birth weight, low-income area of Figure 17. The prognostic effect of the birth weight is nullified in the mothers who had no income, but remained the most important marker in babies of the mothers who had any income. This effect is currently without explanation and warrants further research.

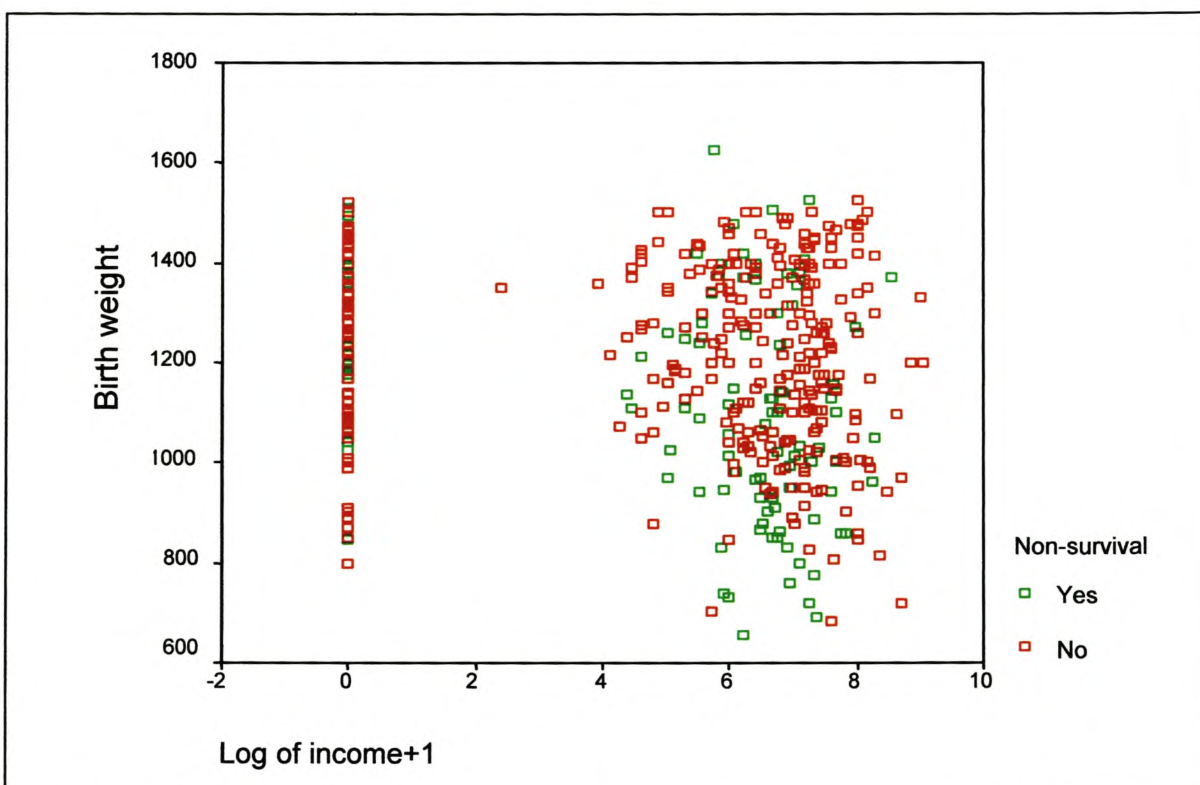


Figure 17: Income of mothers and survival.

The histogram of the differences in income and survival are illustrated in Figure 18.

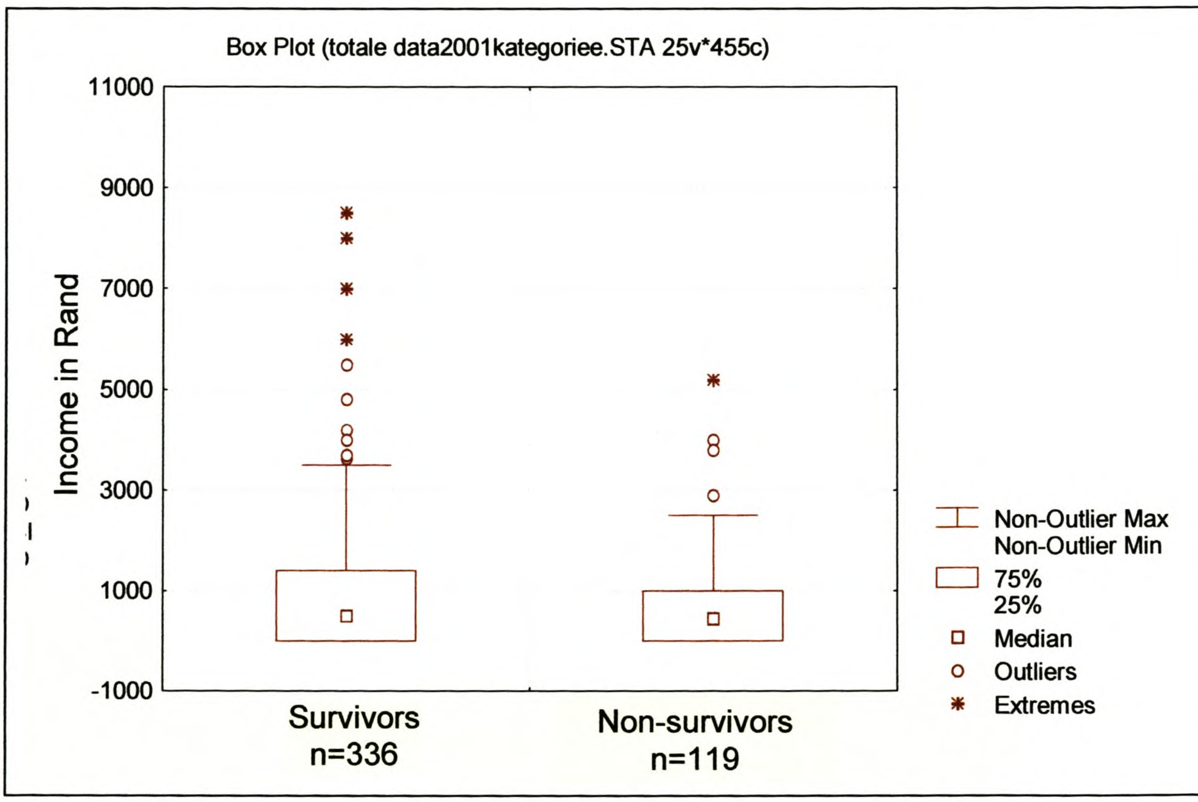


Figure 18: Box plot of income of mothers compared to baby's survival.

There was a significant difference in the outcome of the mothers with a higher income in this analysis ($p<0.05$). Babies of mothers with a very high income also did better as illustrated in Figure 18.

The differences in outcome in relation to the mothers with an income of more and less than R1030 is illustrated in Figure 19.

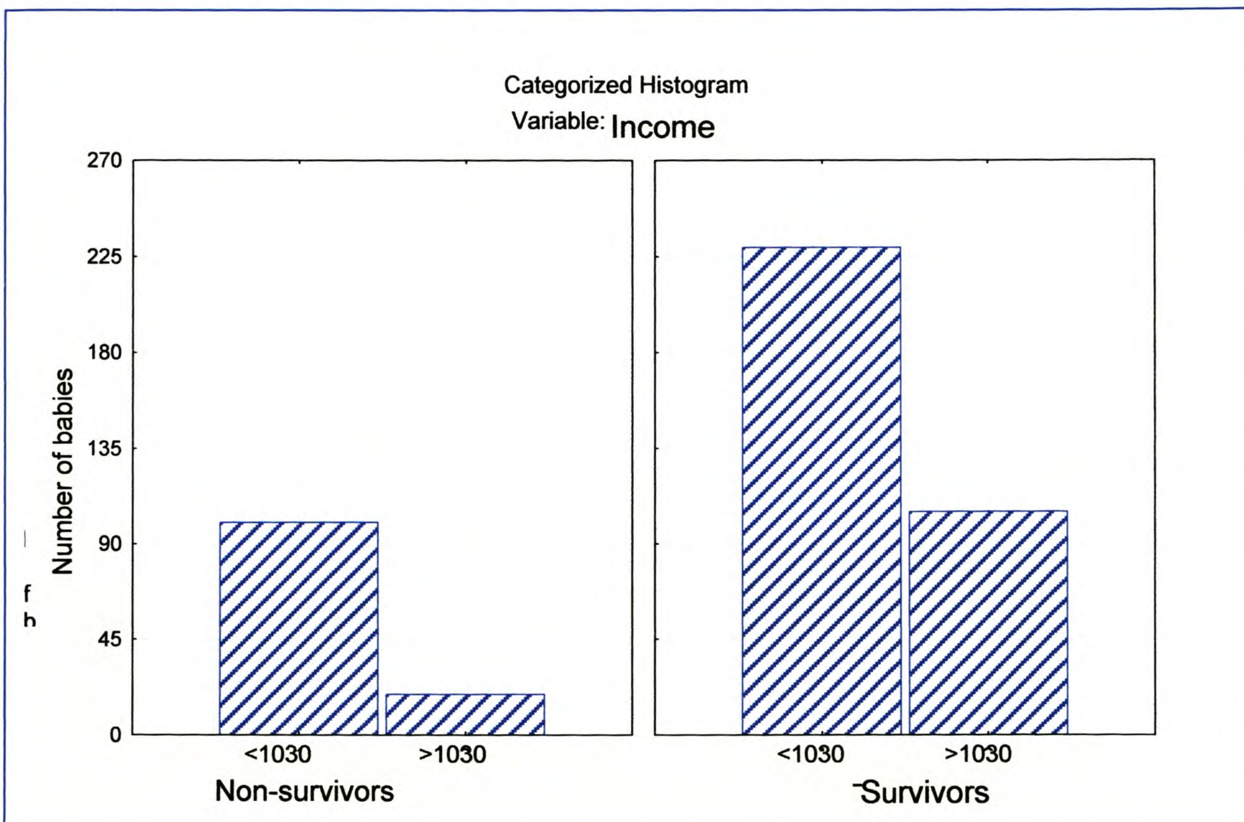


Figure 19: Income divided into more or less than R1030 per month, and survival.

Only 22% of non-survivors earned more than R1030 compared to 25% of survivors. Thirty percent of babies with a maternal income of less than R1030 died compared to 19% of the higher income group.

4 95% Confidence intervals of the K&M graphs:

The 95% confidence intervals of the quartiles of birth weight are illustrated in Figure 20 and the confidence intervals of the different quartiles in Figure 21.

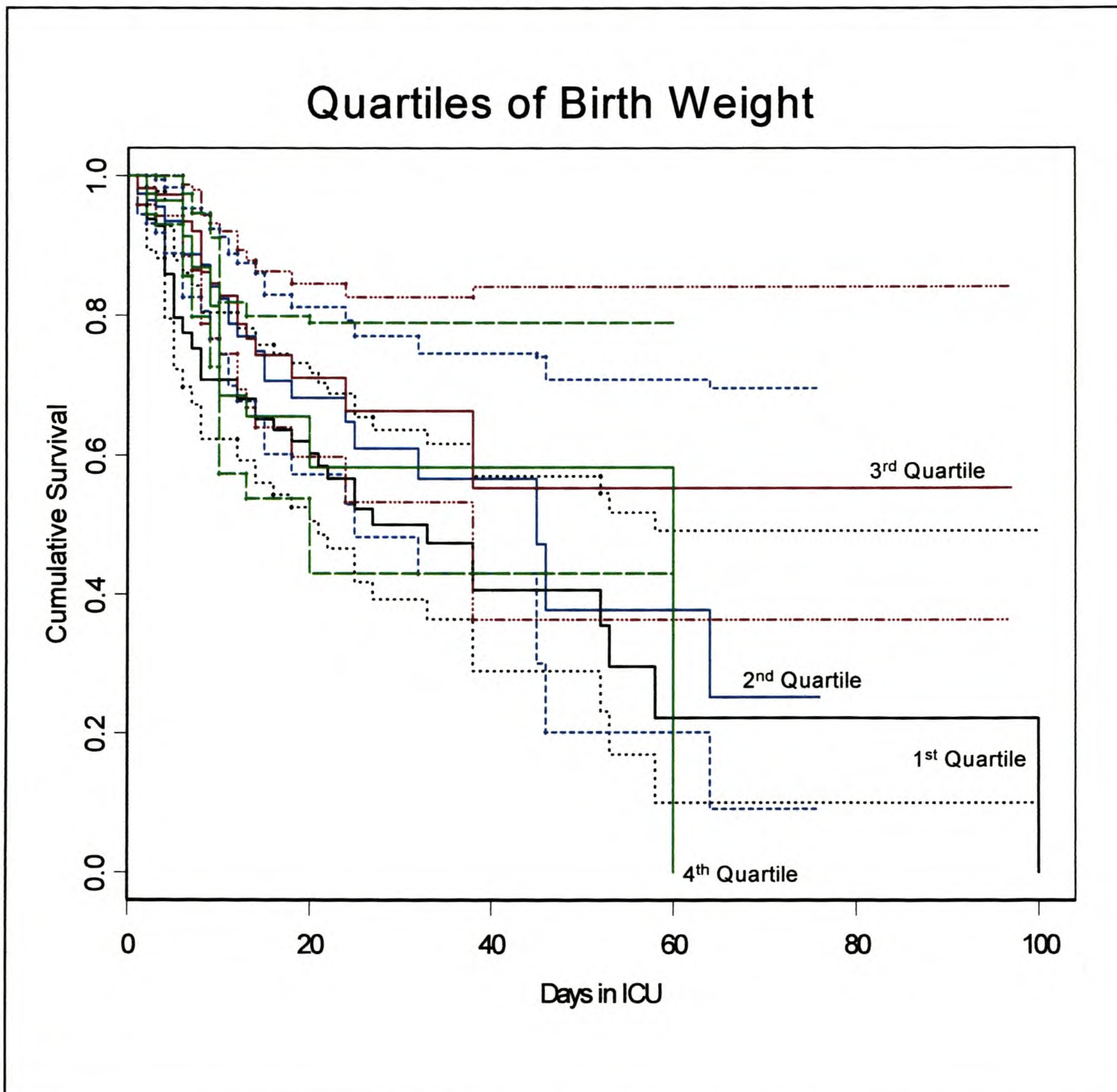


Figure 20: The 95% confidence intervals of the quartiles of birth weight.

Individual confidence intervals are illustrated in Figure 21. The solid lines of individual colours are the mean and the dotted lines in the corresponding colour the confidence intervals.

To simplify interpretation of the confidence intervals the individual quartiles and their confidence intervals are presented in Figure 21.

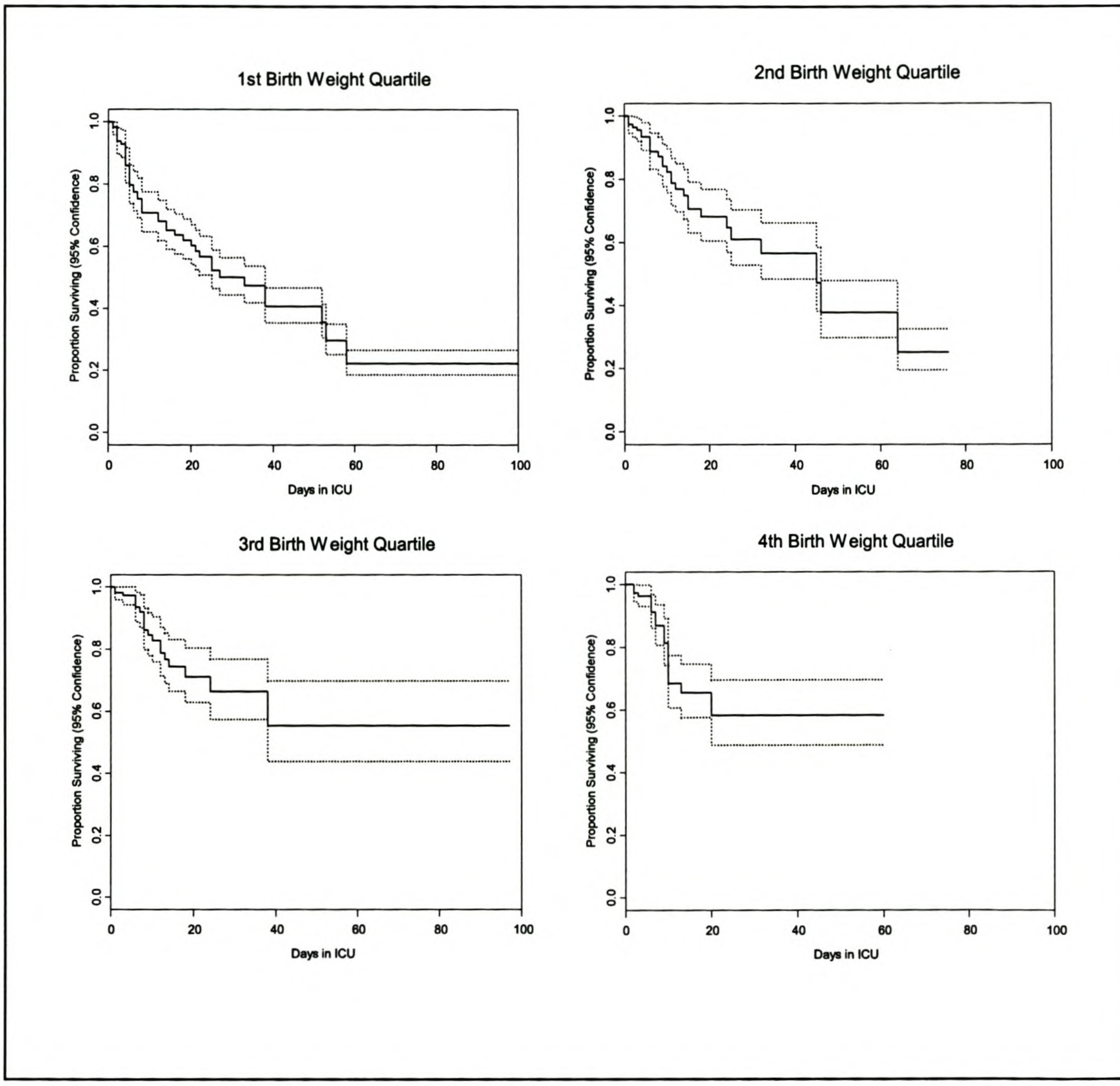


Figure 21: The 95% confidence intervals of the birth weight quartiles plotted individually.

The confidence intervals of the birth weight halves are illustrated in Figure 22.

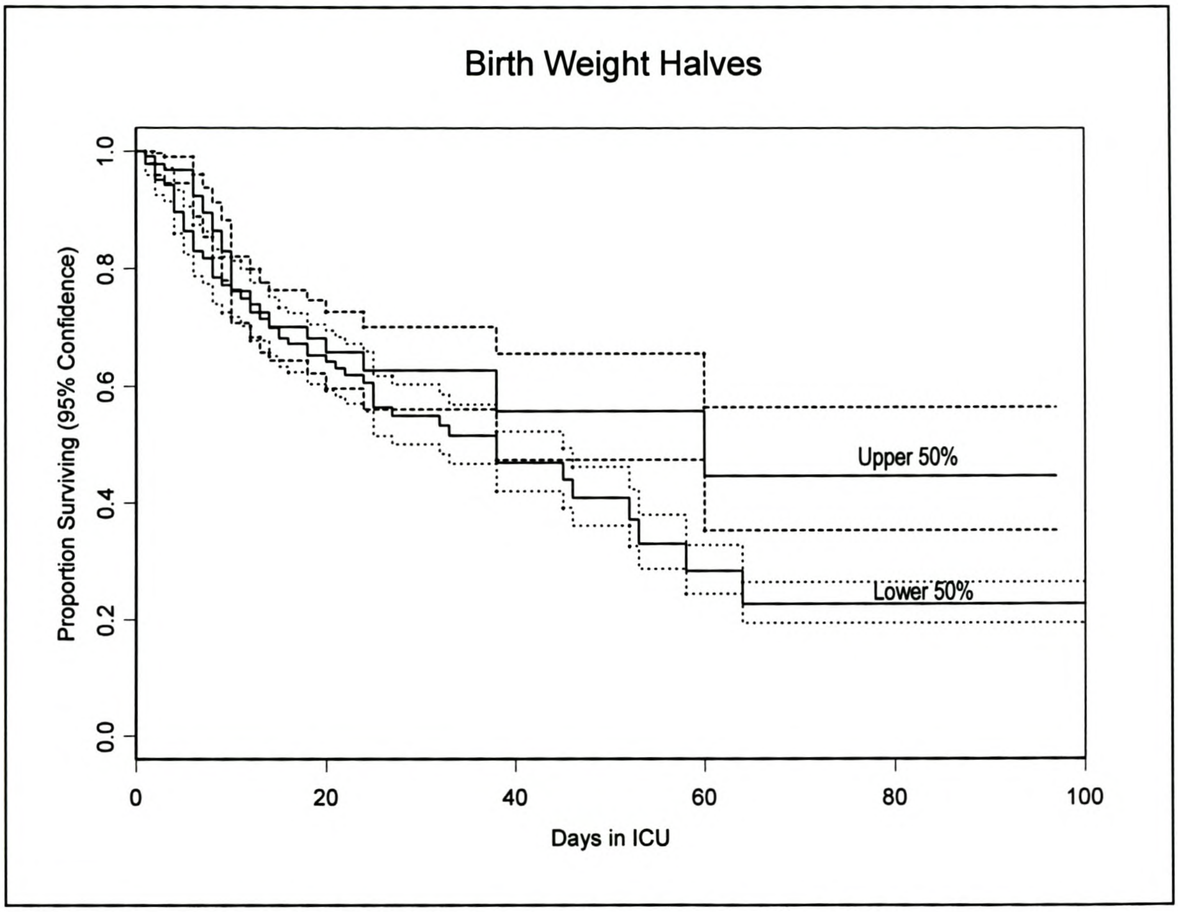


Figure 22: The 95% confidence intervals of the birth weight halves.

There was no difference in outcome when comparing the higher birth weight babies to the lower birth weight babies.

The 95% confidence intervals of the place of birth is presented in Figure 23.

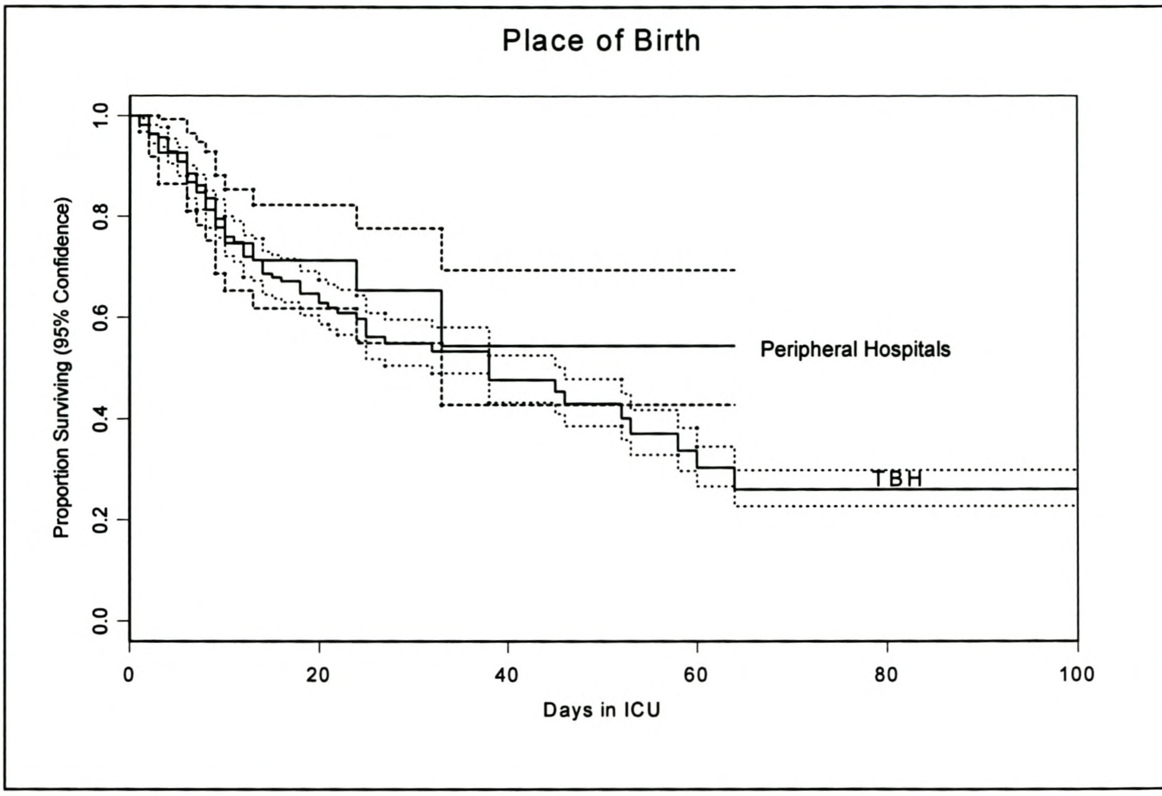


Figure 23: The 95% confidence intervals for place of birth.

There was no difference in the place of birth in admitted babies with regard to the number of survivors.

The illustration of the confidence intervals of the booking status is presented in Figure 24.

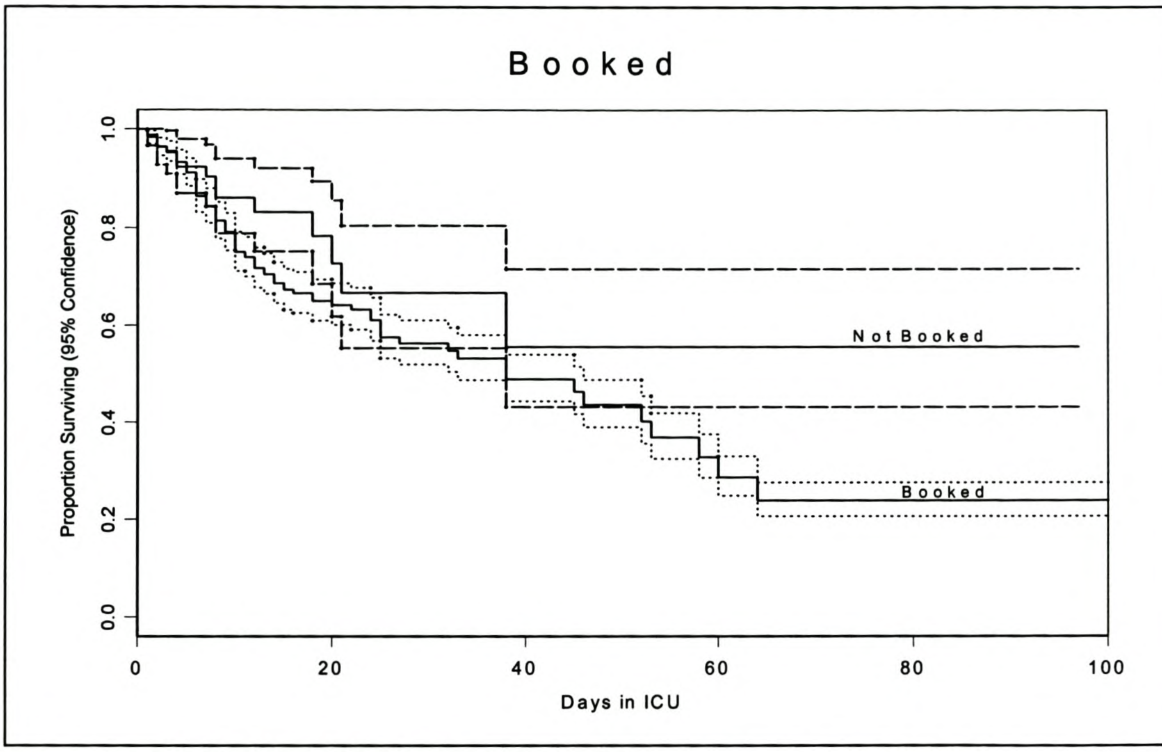


Figure 24: The 95% confidence intervals of booking status

No significant difference was found in the babies who had received antenatal care compared to those that did not, although the babies who did not receive care died earlier. This may be the effect of more stringent admission criteria for these babies.

The confidence intervals for the effect of multiple births is illustrated in Figure 25.

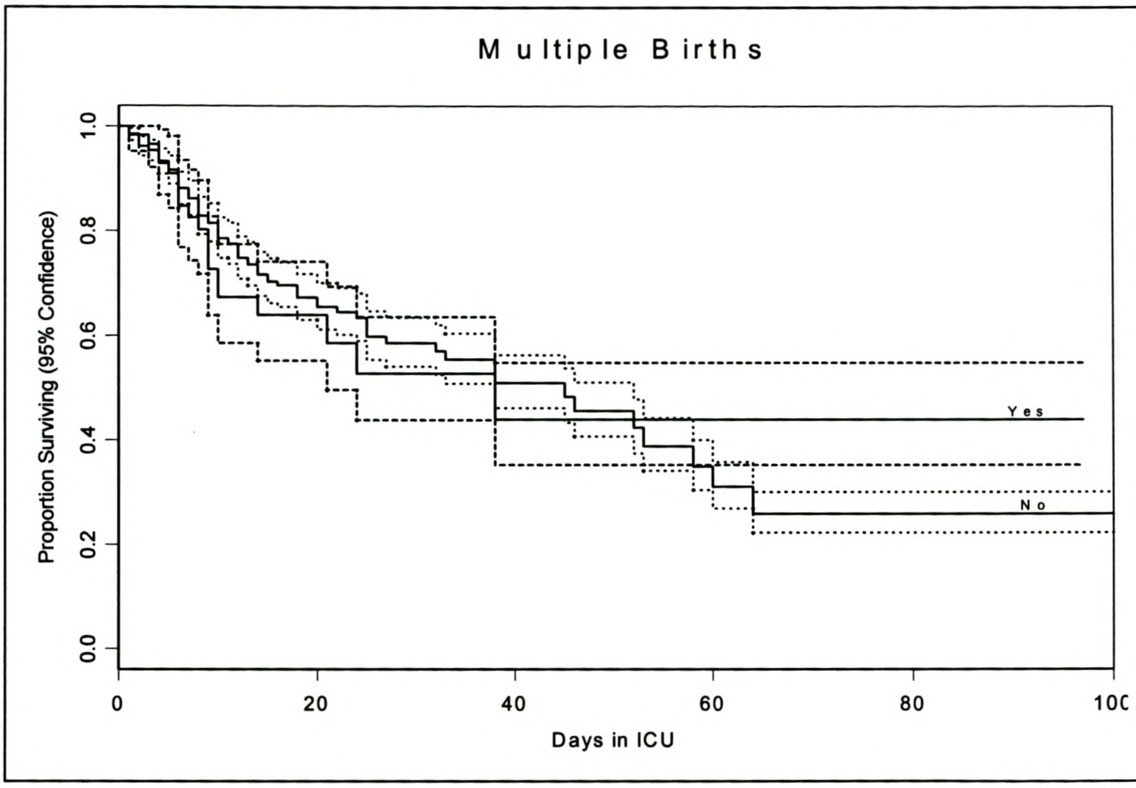


Figure 25: The 95% confidence intervals of multiple births

Babies who were one of twins or triplets had a similar outcome than singletons.

The confidence intervals for time of admission is illustrated in Figure 26.

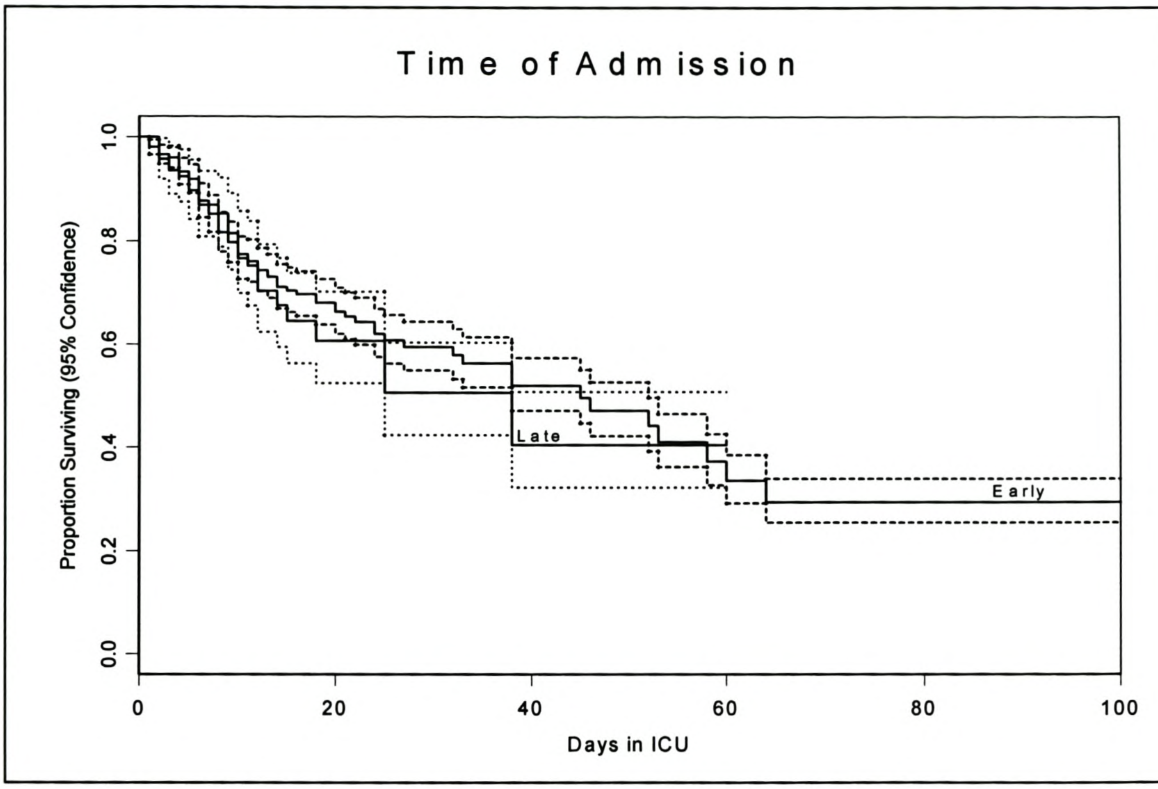


Figure 26: The 95% confidence intervals of admission status

There was no difference in babies who were admitted before 12 hours of age compared to the babies who had to wait for transfer and were admitted at a later age.

The confidence interval of the differences in way the baby was delivered is illustrated in Figure 27.

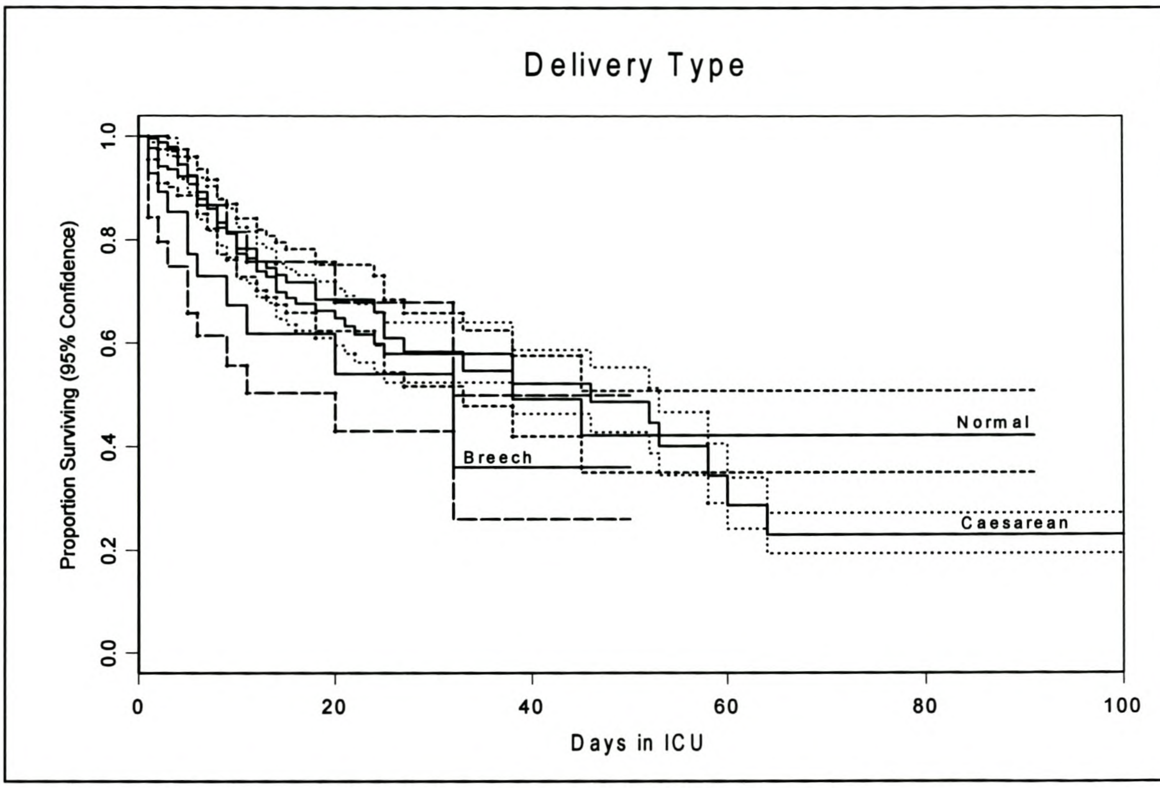


Figure 27: The 95% confidence intervals of type of delivery

Babies born by means of breech did worse than babies who either had a normal vertex delivery or were born by caesarean section.

The confidence intervals for the effect of prolonged rupture of membranes is illustrated in Figure 28.

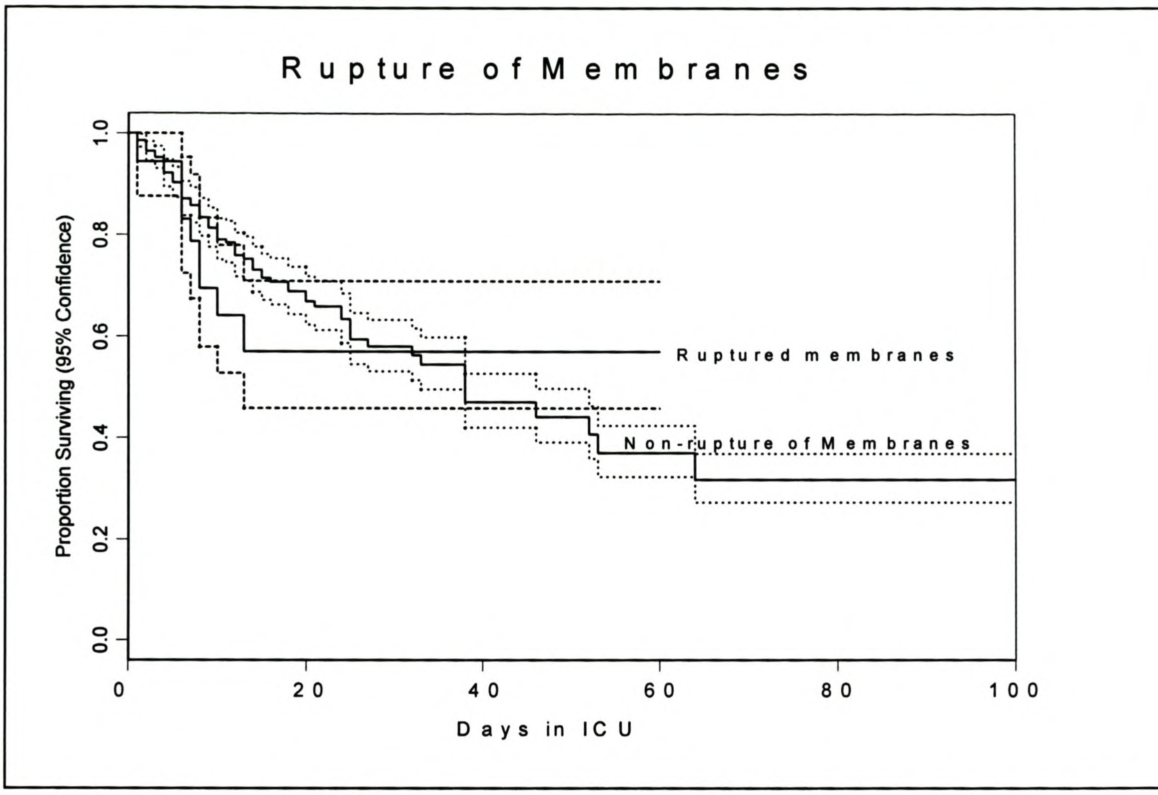


Figure 28: The 95% confidence intervals of rupture of membranes

Although PROM is generally seen as a bad prognostic factor, it had no influence on the outcome or length of stay.

The confidence interval of the association of a positive RPR test with survival is illustrated in Figure 29.

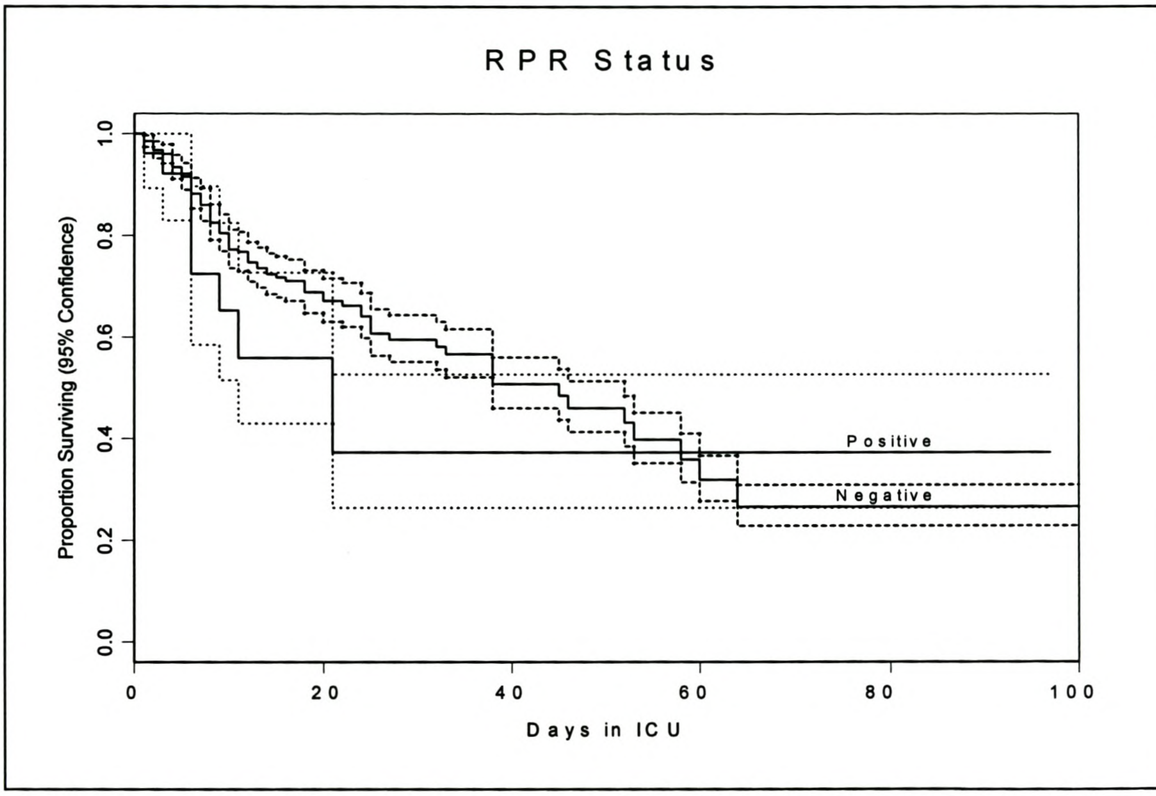


Figure 29: The 95% confidence intervals of RPR status

Whether babies were seropositive for syphilis or not did not influence their survival.

The confidence interval of the effect of gender on survival is illustrated in Figure 30.

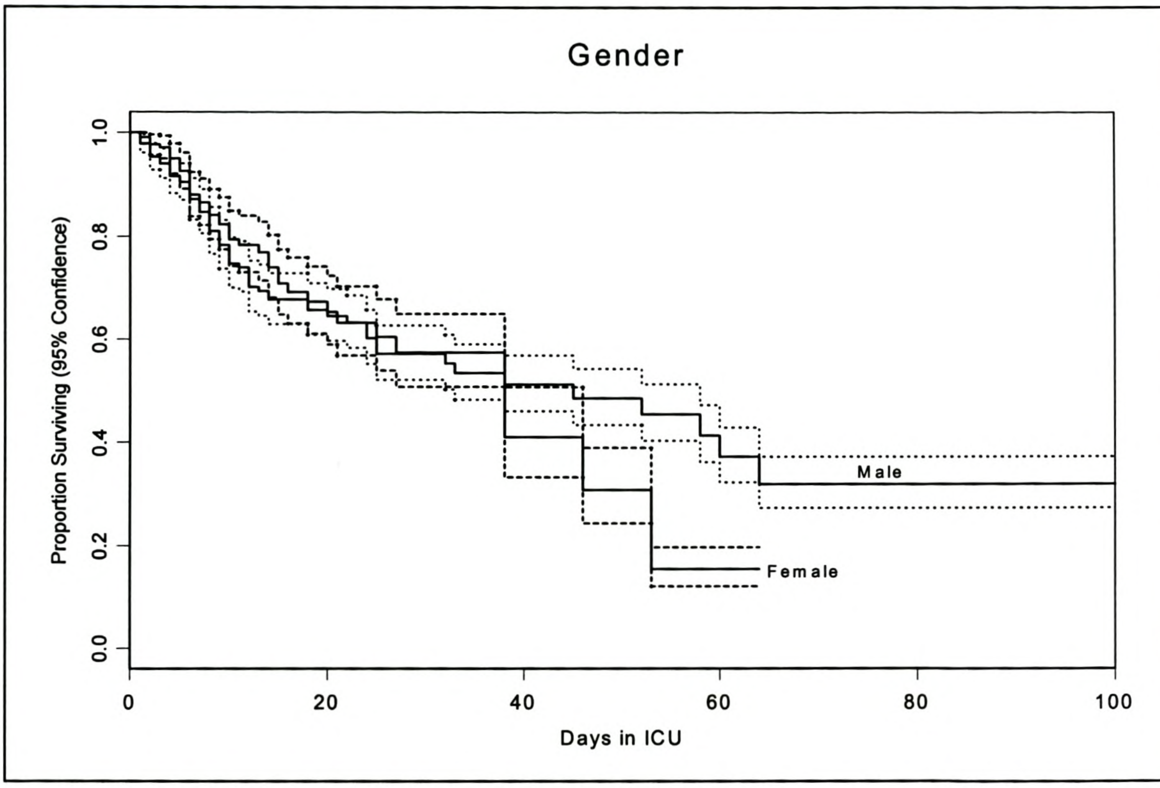


Figure 30: The 95% confidence intervals of gender

The female babies spend less time in the NICU. There was no difference in outcome between males and females in this analysis.

The 95% confidence interval of the association of ethnic group with outcome is illustrated in Figure 31.

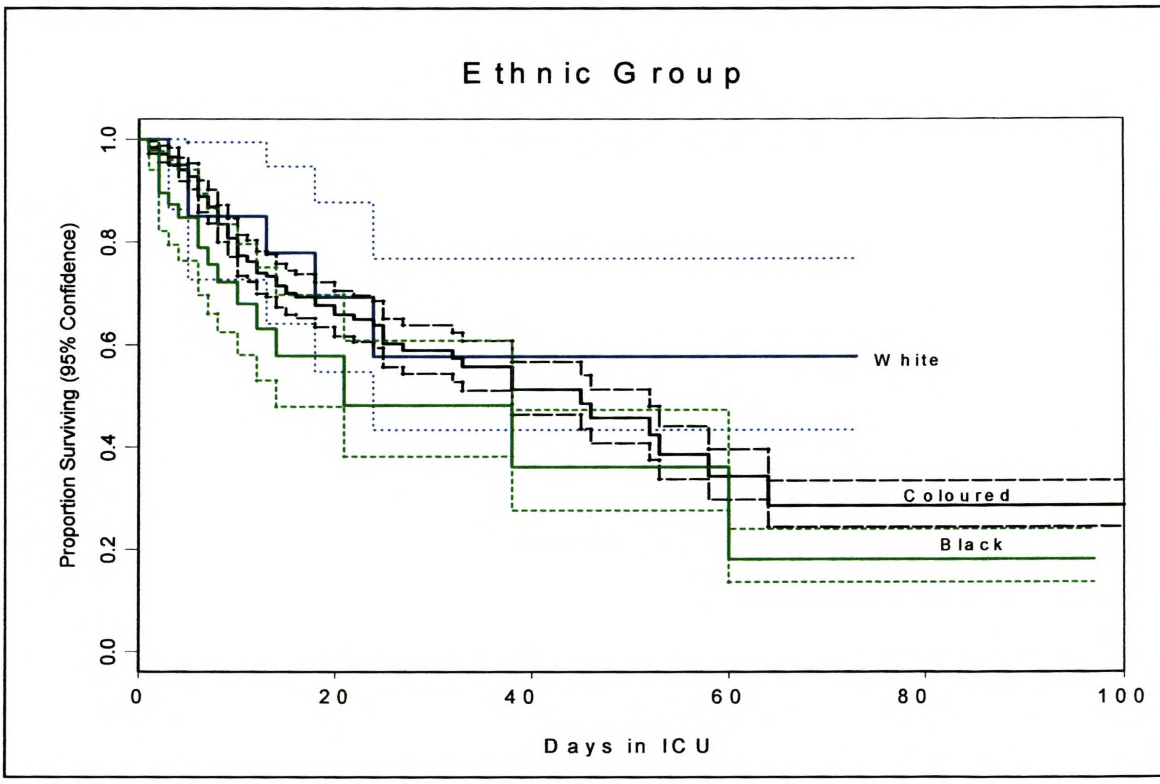


Figure 31: The 95% confidence intervals of ethnic group

Figure 31 illustrates the differences, although not significant, in survival between white and other ethnic groups.

The association of the development of BPD with length of stay and the 95% confidence intervals for this variable is illustrated in Figure 32.

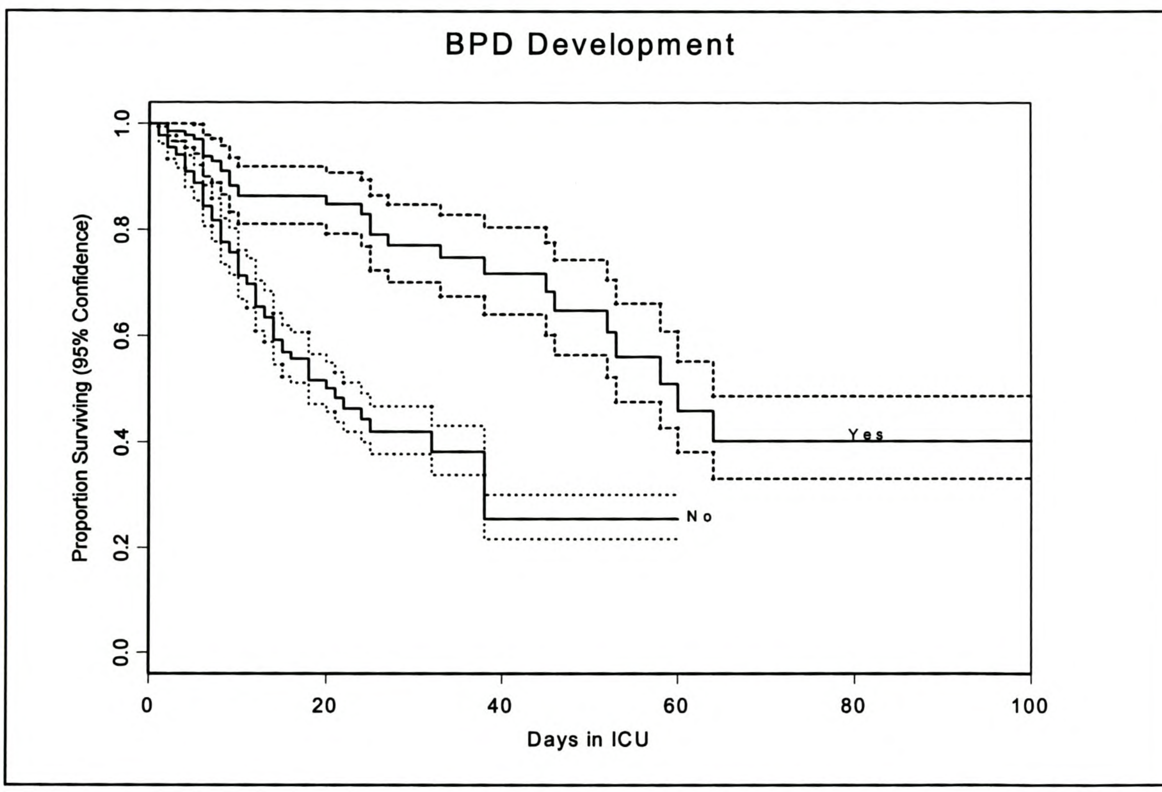


Figure 32: The 95% confidence intervals of development of BPD

Babies who develop BPD have a prolonged stay in the NICU. They also tend to die at a later age than the babies who do not develop BPD.

5 Multiple logistic regression analysis:

The data was analysed with the logistic regression method. Logistic regression modelling was done in two ways: firstly by the addition of variables, and secondly by the removal of variables. The variables were removed if the p value was more than 0.15.

The variables used in the forward regression were as follows (Table 13)

Table 13: Variables used in the forward regression analysis.

Variables	Score	Df	Sig.
Centiles of birth weight	**8.348**	**1**	**.004**
Multiple pregnancy	1.382	2	.501
Firstborn	1.335	1	.248
Second born	.348	1	.555
Ethnic group	1.072	1	.301
Gender	1.990	1	.158
Place of birth (all babies)	3.752	2	.153
Place of birth Tygerberg	1.623	1	.203
Place of birth: ANC	**3.579**	**1**	**.059**
Apgar 1 min	.129	1	.720
RPR status	.024	1	.877
Booking status	**5.623**	**1**	**.018**
Age of mother	.240	1	.624
Apgar 5 min	.567	1	.451
Early admission	.310	1	.577
Maternal income	1.954	1	.162

Residual Chi-Squares are not computed because of redundancies.
The variables most strongly associated with survival are printed in bold.

The logistic regression model with replacing variables:

The variables used in the backward stepwise method are presented in Table 14.

Table 14: Variables in the equation

Variables*	B	S.E.	Wald	df	Sig.	Exp(B)
Centiles of birth weight	**.724**	**.253**	**8.178**	**1**	**.004**	**2.063**
Multiple pregnancy			1.196	2	.550	
Firstborn	-.451	.427	1.115	1	.291	.637
Second born	-.272	.596	.209	1	.648	.762
Ethnic group	.279	.318	.771	1	.380	1.322
Gender	**.414**	**.242**	**2.929**	**1**	**.087**	**1.512**
Place of birth (all babies)			.290	2	.865	
Place of birth Tygerberg	-.081	.492	.027	1	.869	.922
Place of birth clinic	-5.974	11.507	.270	1	.604	.003
Apgar 1 min	.038	.058	.430	1	.512	1.039
RPR status	.006	.530	.000	1	.991	1.006
Booking status	**.777**	**.382**	**4.125**	**1**	**.042**	**2.175**
Age of mother	.007	.021	.131	1	.717	1.007
Apgar 5 min	-.069	.075	.851	1	.356	.933
Early admission	-.044	.337	.017	1	.895	.956
Maternal income	**.000**	**.000**	**2.611**	**1**	**.106**	**1.000**
Constant	-2.132	1.217	3.068	1	.080	.119

The variables most strongly associated with survival are printed in bold.. B=Regression coefficient, S.E.=standard error of B, df=Degrees of freedom, Sig.=significance, Exp(B)= expected value of B.

The order in which the variables were removed from the model is:

a Variable(s) removed on step 2: RPR status.

b Variable(s) removed on step 3: Early admission

c Variable(s) removed on step 4: Age of mother

d Variable(s) removed on step 5: Multiple pregnancies

e Variable(s) removed on step 6: Min Apgar

f Variable(s) removed on step 7: 5 Min Apgar

g Variable(s) removed on step 8: Ethnic group

The complete table for variables predicting survival is seen in Table 15.

Table 15: The most important predictors for survival.

Model if Term Removed

Variable	Model Log Likelihood	Change in -2 Log Likelihood	df	Sig. of the Change
Centiles of birth weight	**-219.950**	**8.531**	**1**	**.003**
Multiple pregnancies	-216.265	1.160	2	.560
Race	-216.069	.769	1	.381
Gender	**-217.170**	**2.971**	**1**	**.085**
Place of birth	**-218.107**	**4.844**	**2**	**.089**
1 Min Apgar	-215.901	.432	1	.511
RPR status	-215.685	.000	1	.991
Booking status	**-218.000**	**4.631**	**1**	**.031**
Age of mother	-215.750	.131	1	.717
5 Min Apgar	-216.110	.850	1	.357
Early admission	-215.693	.018	1	.895
Maternal income	**-217.148**	**2.927**	**1**	**.087**

Based on conditional variable estimates

The variables most strongly associated with survival are printed in bold.

The final variables which are the most predictive of survival are listed in Table 16.

Table 16: The most important predictors for survival using backward stepwise methods.

Variable	Model Log Likelihood	Change in -2 Log Likelihood	df	Sig. of the Change
Centiles of birth weight	-221.013	7.596	1	.006
Gender	-218.672	2.915	1	.088
Place of birth	-219.688	4.947	2	.084
Booking status	-219.766	5.103	1	.024
Income of mother	-219.473	4.517	1	.034

Therefore, the variables that were of relevance in the Kaplan Meier curves, i.e. centiles of birth weight and booking status, are repeated in this model.

To further illustrate the importance of a combination of variables, and to try and define the at risk population, it was found that survival for the combination of gender and booking status was significantly higher in the booked group, but did not differ in the unbooked group. In booked patients the OR for survival was 0.56 (CI 0.34-0.92) with a RR of 0.85 (CI 0.75-0.97). For unbooked patients the gender did not influence the outcome.

In analysing income and gender separately it is of importance to note that the highest mortality was found in the lower income groups, with a disproportionate increase in the group of babies who had an income of between R800 and R1030, although the numbers are small. The percentages and numbers of patients are illustrated in Table 17.

Table 17: The data of patients by income and survival.

Monthly income in Rand	Total number	Survivors	Non-survivors	% Deaths
0	124	92	32	25.8
1-799	147	102	45	30.6
800-1029	36	21	15	41.6
1030-1999	88	71	17	19.3
>2000	58	48	10	17.2

The number of patients per income group is presented in Figure 33.

The groups were:

1= no income

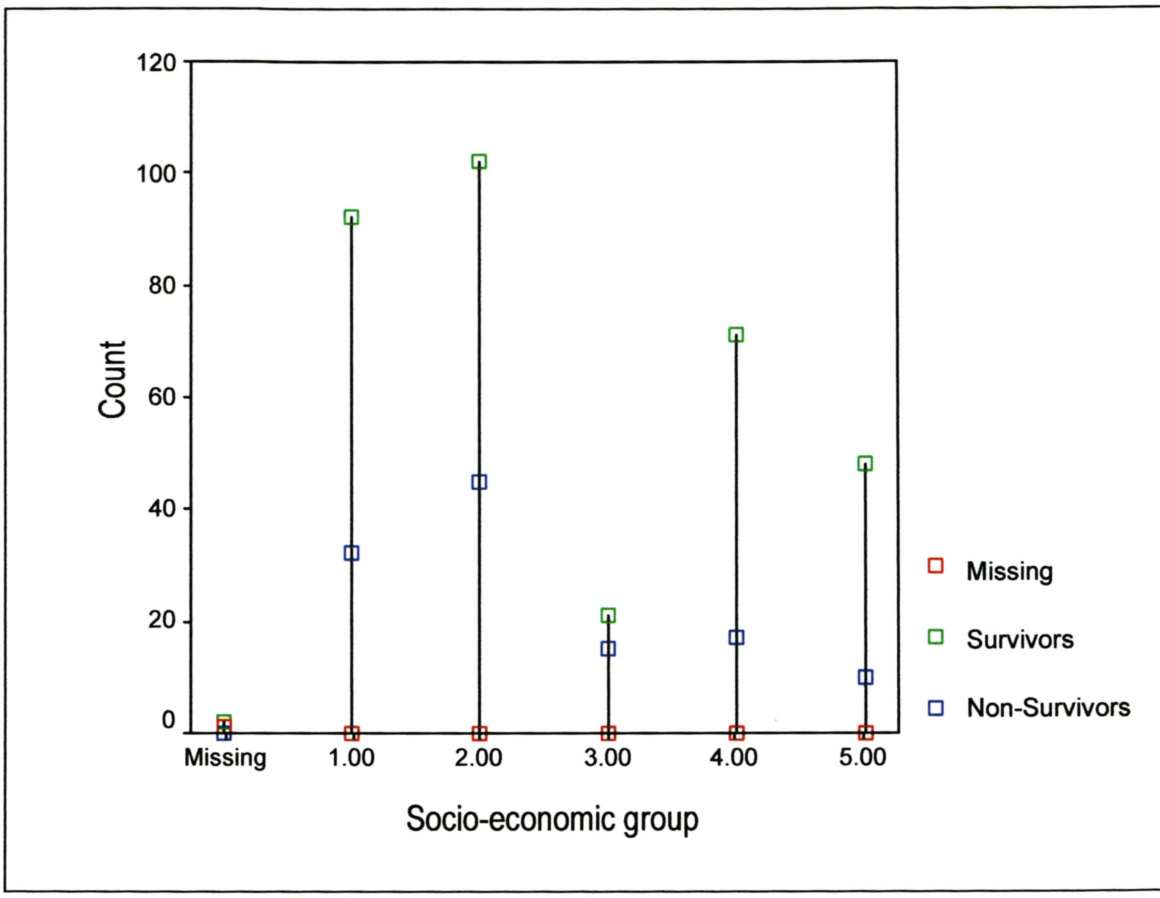
2= less than R800

3= R800-R1029

4=R1030-R1999

5=>R2000

Abovementioned cut-off points were used on the basis of R800 being the minimum wage and R1030 the CART analysis node identified..



The codes represent:

1= no income   2= less than R800   3= R800-R1029

4=R1030-R1999   5=>R2000

Figure 33: Code of income compared to survival

6 CART analyses

Using the statistical program CART analysis, there were clear prognosticators when the outcomes length of ventilation days in the NICU, or the development of BPD were used as endpoints

Individual nodes

Nodes are the values which divide the data into two distinct groups.

6.1 Birth weight

The most important prognosticator for survival was birth weight (0.03). The first node was found at a birth weight of 1037 grams. Variables that could be used as a substitute are normal vaginal delivery with an association of 0.921 and improvements of 0.026. Competitor variables were income (0.017), place of birth (0.01), booking status (0.008) and gender (0.006).

6.2 Maternal income

The second most important predictor for survival was the income of the mother. This node had a first split at 2374 South African Rand and a second split at 1206 South African Rand. The first split had an improvement of 0.011 and a surrogate in the type of delivery at an association of only 0.051 with no improvement. Surrogate variables were 5 minute Apgar (0.004), birth weight, 1 minute Apgar and age of mother all at 0.003.

The second split was at 1206 South African Rand with an improvement of 0.016 and no substitutes. Surrogate variables were booking status and gender at 0.008 and birth weight and place of birth at 0.006 and 0.005 respectively.

6.3 Booking status

This seemed to be the third prognostic variable. It had an improvement of 0.011 and competitors were gender at 0.011and birth weight and type of delivery at 0.004. Place of birth and 1 minute Apgar score improved it by 0.003.

6.4 Gender

The next important split occurred whether the baby was male or female. This improved the model by 0.015. This node had surrogates in birth weight (0.003), 1 minute Apgar, place of birth and 5 minute Apgar (less than 0.002). Competitor variables were birth weight (0.008), age of mother and syphilis status (0.003) as well as gravity of mother and normal delivery (0.002).

The schematic drawing of the individual nodes is presented in Figure 34:

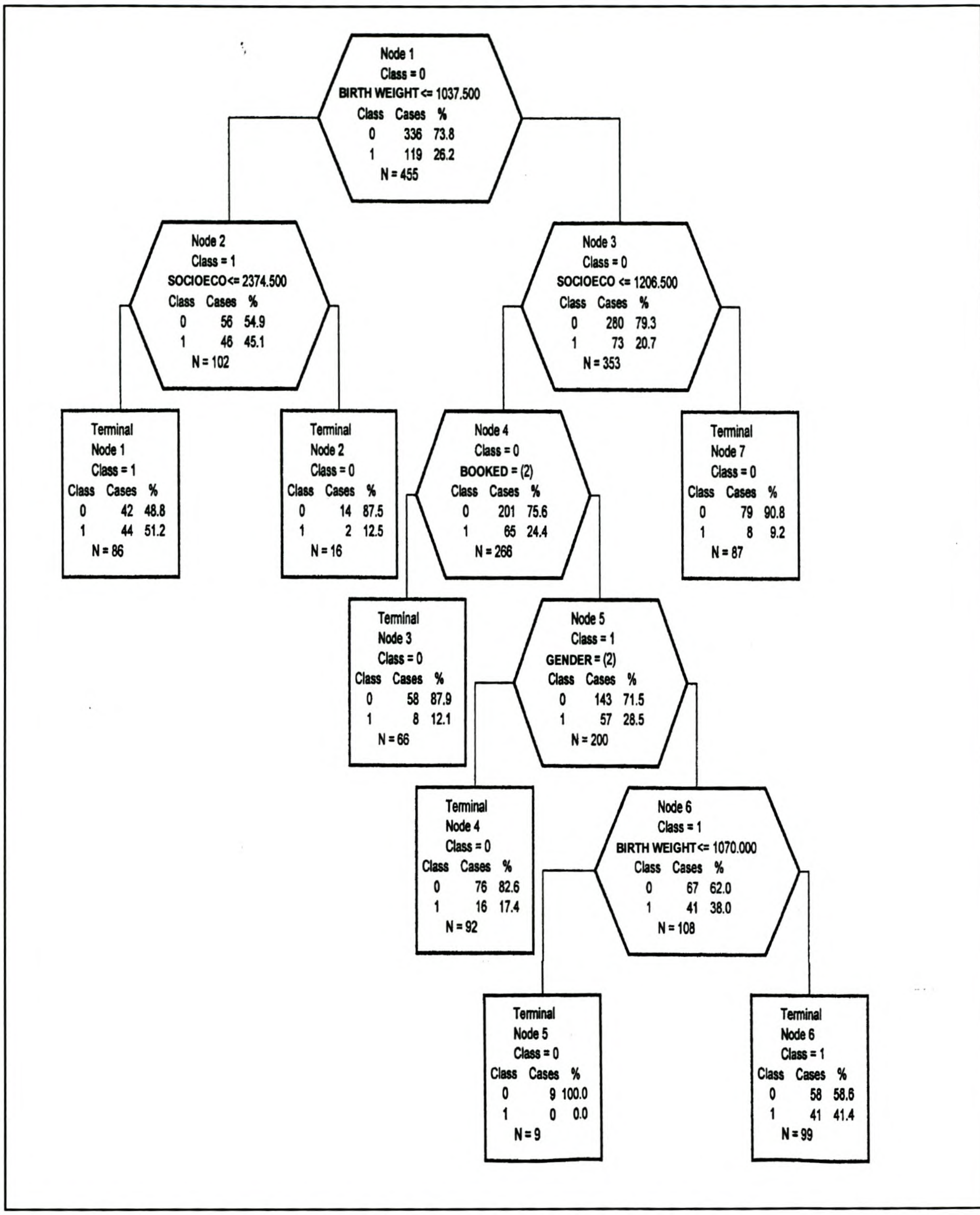


Figure 34: The schematic presentation of the nodes in the CART analysis.

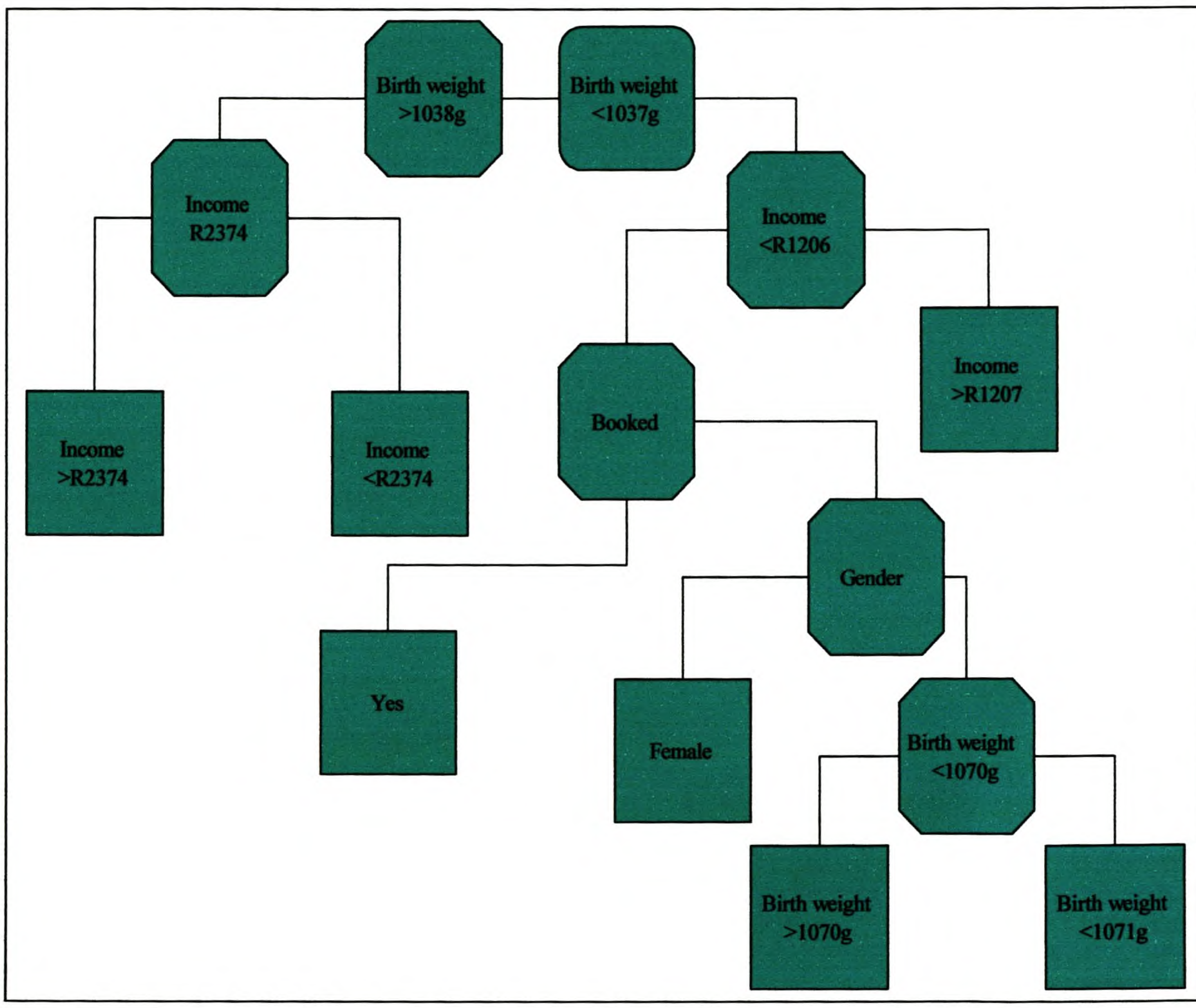


Figure 35: Schematic presentation of the discretionary nodes

In Figure 35 the schematic discretionary nodes and their respective values are illustrated. The square boxes represent the final node and the hexangular boxes the nodes which can still be subdivided. This is a practical method without using computerisation to divide babies into risk categories.

7 Validation of data:

Validation of data can be performed by using the area under the curve as well as sensitivity analysis. The higher the area under the curve, the better the predictive value of the variable.

7.1 Sensitivity and specificity

After 10 sets of sub-samples the model had a sensitivity of 0.64 and a specificity of 0.672 with an 80% correct prediction of survival. At testing the model had a 90% probability of predicting survival but only a 41% probability of predicting death.

7.2 Regression analysis

The four most important predictors (i.e. birth weight, income, booking status and gender) were re-analysed with the Wilks' lambda regression analysis. This method showed a false positives rate (FP) of 16% and a false negative rate (FN) of 62% with a positive predictor value (PPV) of 84% and a negative predictor value (NPV) of 38%. Compared to this the tree analysis had a FP of 13% and a FN of 54% with a PPV of 70% and a NPV of 71%. This makes the tree analysis a better instrument of prediction as a logistic as well as a discriminating model.

The results of the receiver operator curve (ROC) of the different variables are illustrated in Figure 36.

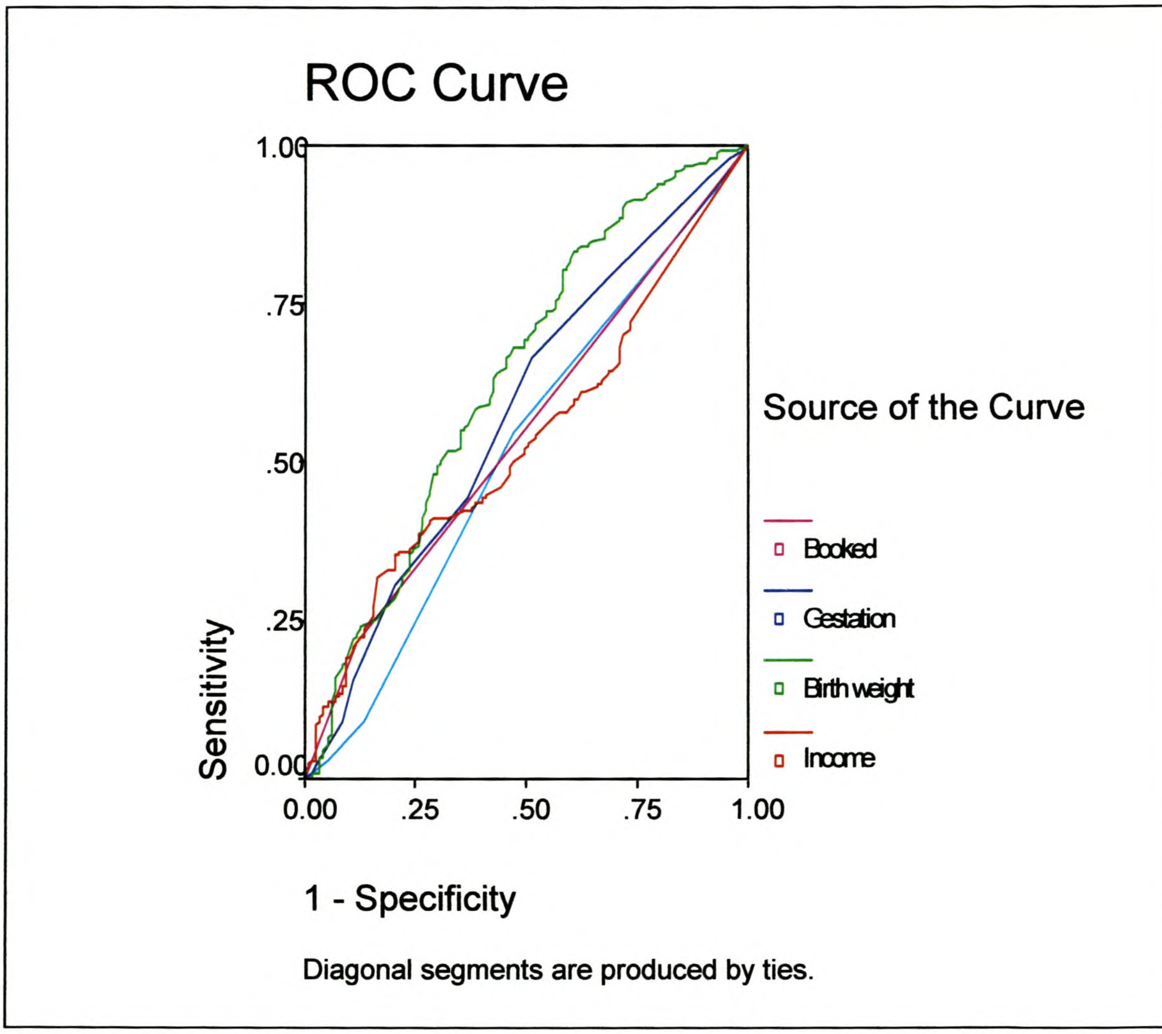


Figure 36: The results of the ROC of the different variables

Figure 36 explores the low predictive value of single variables on survival. Each of the variables improved the estimation of variables by little more than chance.

The significance of the different variables is illustrated in Table 18.

Table 18: Areas under the curve

Variable(s)	Area under the curve
Birth weight	0.634
Gestation	0.579
Booking status	0.547
Monthly income	0.535
Gender	0.520

The probability of predicting outcome as measured by survival by using gender, income, booking status or gestation is hardly better than chance. Birth weight is a slightly better predictor at 63.4% but still very close to 50%. This makes these variables unsuitable for predicting outcome.

7.3 Multiple variables as predictors of outcome

Figure 37 illustrates the relationship between income, gender, birth weight, ethnic group and outcome.

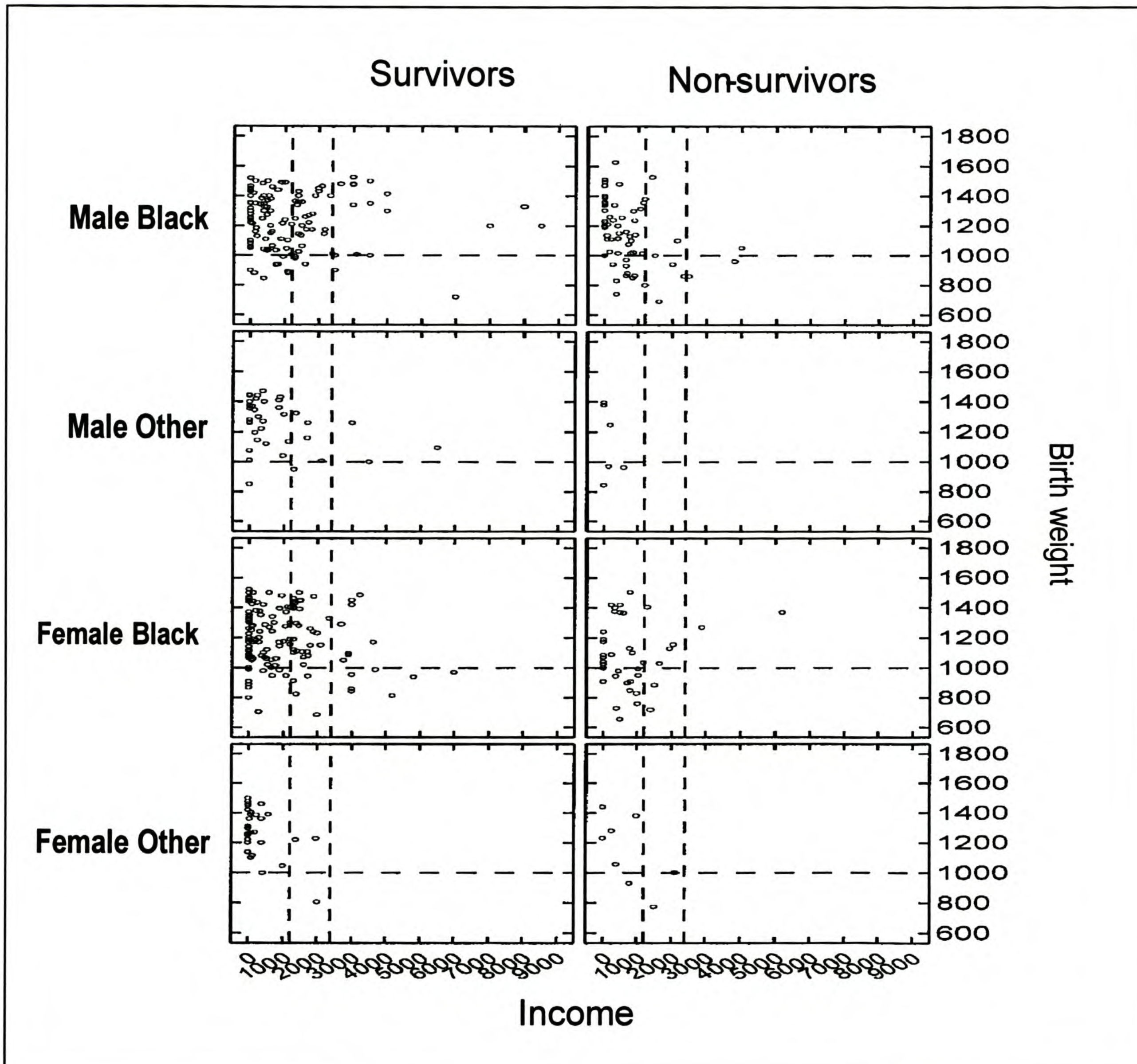


Figure 37: The comparison of birth weight, income and gender to survival.

In Figure 37 combined effect of lower income and higher mortality in black male population is illustrated. There are only 2 babies who were black males who died in the income group of over R1030.compated to none in the other ethnic groups. This was not evident in the female group

The relationship of increasing birth weight to gestational age is illustrated in Figure 38.

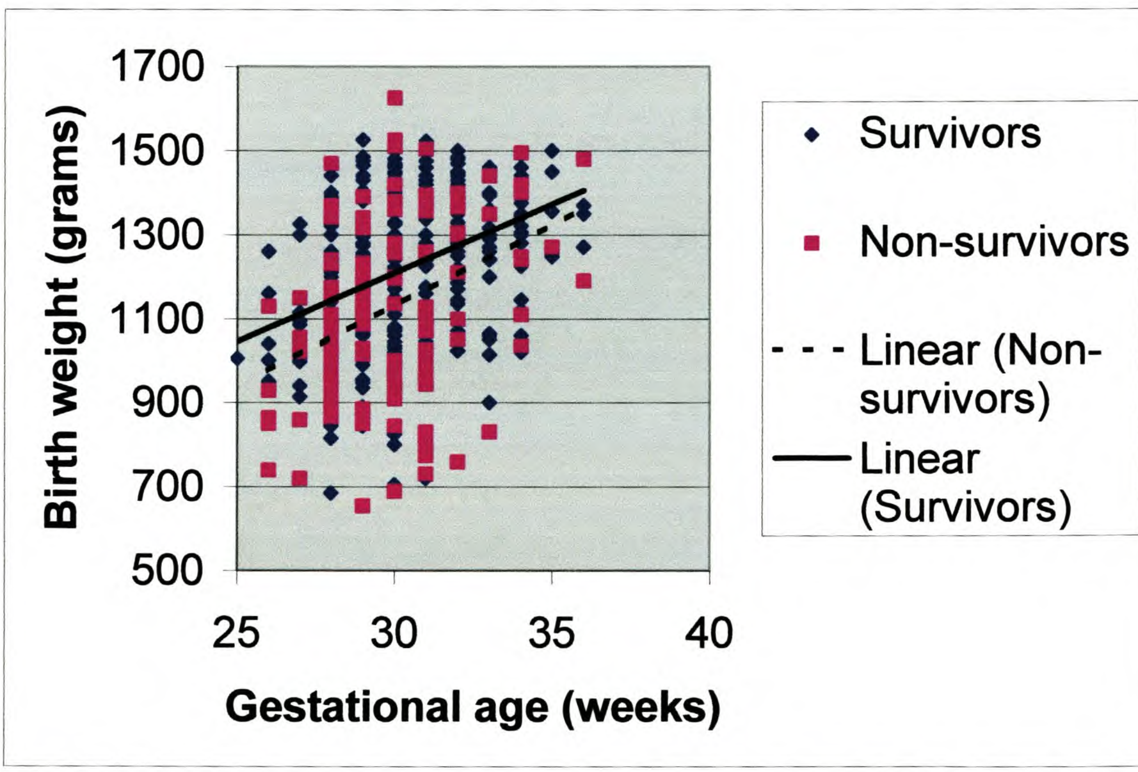


Figure 38: Gestational age and birth weight divided into survivors and non-survivors

It is of interest to note that the non-survivors had a lower birth weight than the survivors for the lower gestational age, but that this relationship was diminished in the higher gestational age babies with a tendency of survivors to be smaller for gestational age. The relative importance of specific groups of patients is illustrated in Table 19.

8 Epidemiological data

The data was also analysed by epidemiological methods to demonstrate the relative importance of each variable. These comparisons are made by describing the relative risk of the variable and the individual confidence intervals.

The risk of death in babies with a birth weigh of less than 1299g or more is significantly different. When babies are unbooked there is also a increase in survival, but this is a function of more stringent admission criteria. None of the other variables evaluated were significant.

Table 19: Relative risks of death in specific variables.

Variable		% Deaths	RR	CI of RR
Birth weight	**<1300**	**44/97**		
	>1299	**75/358**	**2.17**	**1.61-2.91**
Booking status	**Booked**	**103/365**		
	Unbooked	**14/86**	**1.73**	**1.04-2.88**
Place of birth	TBH	104/378		
	District	1/21		
	Other	14/56	1.2	0.66-2.19
Gestational age	<28	10/27		
	>27	109/427	1.45	0.86-2.44
Mother's age at delivery	<21	13/63		
	12-39	96/366		
	>39	2/6	1.05	0.72-1.52
Parity	Primigravida	33/127		
	2-6	80/314		
	>6	5/9	1.34	0.75-2.41
Type of delivery	NVD	43/173		
	C/S	64/251		
	Other	12/31	0.92	0.69-1.4

Table 19: Continued

Variable		% Deaths	RR	CI of RR
Gender	Female	47/217	1.3	0.94-1.81
Apgar 1 min	<4	43/153		
	4-6	72/280	1.23	0.82-1.85
Apgar 5 min	<4	10/25		
	4-6	39/150	1.04	0.76-1.43
RPR	Positive	8/26		
	Negative	104/407	1.2	0.66-2.19
Ethnicity	White (W)	6/23	W:B 1.36	0.62-2.98
	Coloured (C)	96/384	C:B 0.71	0.46-1.07
	Black (B)	17/48	W:C 1.04	0.51-2.12
Income class	1	32/124		
	2	49/154		
	3	28/121		
	4	10/54	0.92	0.66-1.27
Time of admission	Early	94/360		
	Late	25/95	1.01	0.69-1.47

The most important predictors are presented in bold.

There is an admission bias in the number of admissions and the survival rate in the variable "place of birth". Babies are selectively admitted from rural areas depending on the availability of NICU beds and the referring doctors opinion on the chances of the individual survival.

References

[1] Theron GB, Thompson ML. A centile chart for birth weight for an urban population of the Western Cape. S Afr Med J 1995; 85: 1289-1292.

[2] Morley R, Brooke OG, Powell R, Lucas A. Birthweight ratio and outcome in preterm infants. Arch Dis Child 1990; 65: 30-34.

CHAPTER 6

1 Statistical analysis of the final cohort

1.1 Descriptive data:

The data of 727 babies were analysed, 455 in the initial cohort and 272 in the validation cohort. The data on the mothers is presented in Table 1 and the babies' data in Table 2.

Table 1: Maternal data

Parameter	Total cohort				Validation cohort			
	Number	Mean	SD	Range	Number	Mean	SD	Range
Age of mother (years)	691	26.96	6.06	14-44	256	26.8	6.3	15-41
Parity	718	2.6	1.55	1-11	268	2.52	1.58	1-11
Income (Rand per month)*	725	787.6	1222	0-8500	272	613	1272	0-7400

*p=0.001 between initial and validation cohort.

The mean age of the mothers was 26.8 years and for the majority it was not the first pregnancy.

The mean income of the mothers was R787 per month that is now less than the official minimal wage of R800 for domestic employees. A total of 313 mothers had no formal income at all of whom 31% of their babies died. A further 168 had less or equal to R800 per month, of whom 31.5% of the babies died. The mean income (of those who had an income) was R1386.02.

Table 2: Neonatal data

	Total cohort				Validation cohort			
Parameter	Number	Mean	SD	Range	Number	Mean	SD	Range
Birth weight (grams) *	**727**	**1169.1**	**206**	**575-1700**	**272**	**1119**	**214**	**575-1700**
Gestational age (weeks)*	**725**	**29.8**	**2.08**	**24-36**	**275**	**29.2**	**2.08**	**24-36**
1 min Apgar#	670	5.24	2.75	0-10	233	5.63	2.56	0-10
5 Min Apgar	668	7.27	2.10	0-10	232	7.31	2.08	0-10

* p<0.001, # p=<0.05 between initial and validation cohort.

The babies had a mean weight of 1169g. The mean gestational age was 29.2 weeks, which was significantly lower in the validation cohort when compared to the initial cohort.

The data on the deliveries of these babies is presented in Table 3.

Table 3: Delivery data of babies

	Total cohort			Validation cohort		
Parameter (p values)*	Total number	Positive	Negative	Total number	Positive	Negative
Booking status (p=0.080)	727	549	178	268	216	52
Syphilis serology (p=0.17)	692	51	641	259	25	234
Admission time (<12H) After birth (p=0.32)	619	581	138	272	212	59
Prolonged rupture of membranes (p=0.0008)	**637**	**49**	**588**	**255**	**13**	**243**
Gender (M:F)* (p=0.08)	727	398	329	272	160	112
Multiple births (p=0.29)	727	91	636	272	31	241

*p between initial and validation cohort

Eighty seven babies were part of twins and 4 babies were part of sets of triplets. The type of delivery was normal vertex vaginal in 290 cases, breech delivery in 56 cases, caesarean section in 376 cases and instrumental (suction or forceps) in 3 cases. The mortality in normal delivered babies was also 24.7% but 33.3% of forceps delivered babies died and 32.1% of breech deliveries died as illustrated in Table 4. There were significantly less babies with premature rupture of membranes and less females were admitted in the validation cohort.

The survival of babies by type of delivery is illustrated in Table 4.

Table 4: Number of deliveries by type and survival

	Total cohort			Validation cohort		
Type of delivery	Survivors	Non-survivors	% Deaths	Survivors	Non-survivors	% Deaths
Caesarean	283	93	24.7	96	29	23.2
Vaginal: Normal	226	64	22.0	96	21	17.9
Forceps	2	1	33.3	0	0	0
Breech	38	18	32.1	21	7	25

Deliveries at Tygerberg Hospital constituted 605 cases, deliveries in the district services 33 cases and 89 cases delivered in the rural areas. There were 549 (24.4%) survivors and 178 deaths occurred before discharge from hospital. In the initial cohort the mortality was 26.1% and in the validation cohort it was 21.6%.

2 CART analyses:

The validation cohort fared worse than the initial study cohort in the prediction of survival when the initial CART model was used. The CART analysis on the validation cohort was able to predict survival in 83% of cases compared to 94% in the initial cohort.

The value of prediction of the individual nodes is illustrated in Table 5.

Table 5: Predictive value of individual nodes

Node number	Nodes	Outcome	Probability	Number of non-survivors	Correct
1	BW <1037g	1	0.313	85	0.282
2	Income>R2374	2	0.051	14	0.786
3	Income< R1206	2	0.143	39	0.795
4	Booked	2	0.154	42	0.857
5	Gender	2	0.033	9	0.889
6	BW<1070	1	0.213	58	0.223
7	Income >R1206	2	0.092	25	0.840

Outcome: 1=Death 2=Survival

The predictive value of death in the validation cohort is poor at 28% and 22% respectively for nodes 1 and 6. The prediction of survival, however, is much better at between 79% and 89%.

In Table 6 the comparison of the initial cohort and the validation cohort across the 7 nodes is illustrated.

Table 6: Comparison of the initial and validation cohort.

	Terminal nodes								
Initial Cohort	Nodes	1	2	3	4	5	6	7	N
	N	86	16	66	92	9	99	87	455
	Prop.	.189	.035	.145	.202	.019	.218	.191	1.00
	Died(%)	**51.2**	**12.5**	**12.1**	**17.4**	**0.0**	**41.4**	**9.2**	**26.2**
Validation Cohort	Nodes	1	2	3	4	5	6	7	N
	N	85	14	39	42	9	58	25	272
	Prop.	.313	.051	.143	.154	.033	.213	.092	1.00
	Died(%)	**28.2**	**21.4**	**20.5**	**14.3**	**11.1**	**22.4**	**16.0**	**21.6**
	Correct	28.2	78.6	79.5	85.7	88.9	22.4	84.0	52.9

Nodes :1= BW <1037g 2= Income>R2374 3=Income< R1206 4=Booked 5=Gender 6=BW<1070 7=Income >R1206

There is a difference between the distributions across the 7 nodes for the two cohorts. This is the case for nodes 1 and 7. Another difference is the lower overall prevalence of deaths in the validation cohort (21.6%) compared to 26.2% in the initial cohort. The difference between the death prevalence in the 7 nodes explains the poor performance of the tree model to predict the deaths in the validation cohort.

Of the 59 deaths, 37 are predicted correctly (62.7%) and of the 213 survivors only 107 babies were correctly classified (50.2%). The false negative proportion is 17.1% and the false positive proportion is 74.1%. From the model the accuracy in the survivor nodes (2,3,4,5,7) is reasonable but in the death nodes (1,6) the accuracy is poor. The prevalence of deaths in these nodes for the validation cohort is only half of that of the learning cohort. The inverse is also true for the survival nodes where higher prevalence of deaths were observed.

The survival prevalence in the validation cohort is just below 80%. This means that the tree model does not add much to predict babies who will die, but performs better in predicting babies who will survive.

A different set of nodes were identified when doing a CART analysis on the validation data compared to those who were identified in the initial cohort.

2.1 Individual nodes of the validation cohort:

2.1.1 Place of birth

The place of birth was the most important marker of survival in the validation cohort. Babies born outside of the Tygerberg Hospital complex had the best chance of survival. This is caused by the more stringent admission criteria for this group of babies. Surrogate markers were birth weight at 1650grams with an improvement of 0.001.

2.1.2 Birth weight

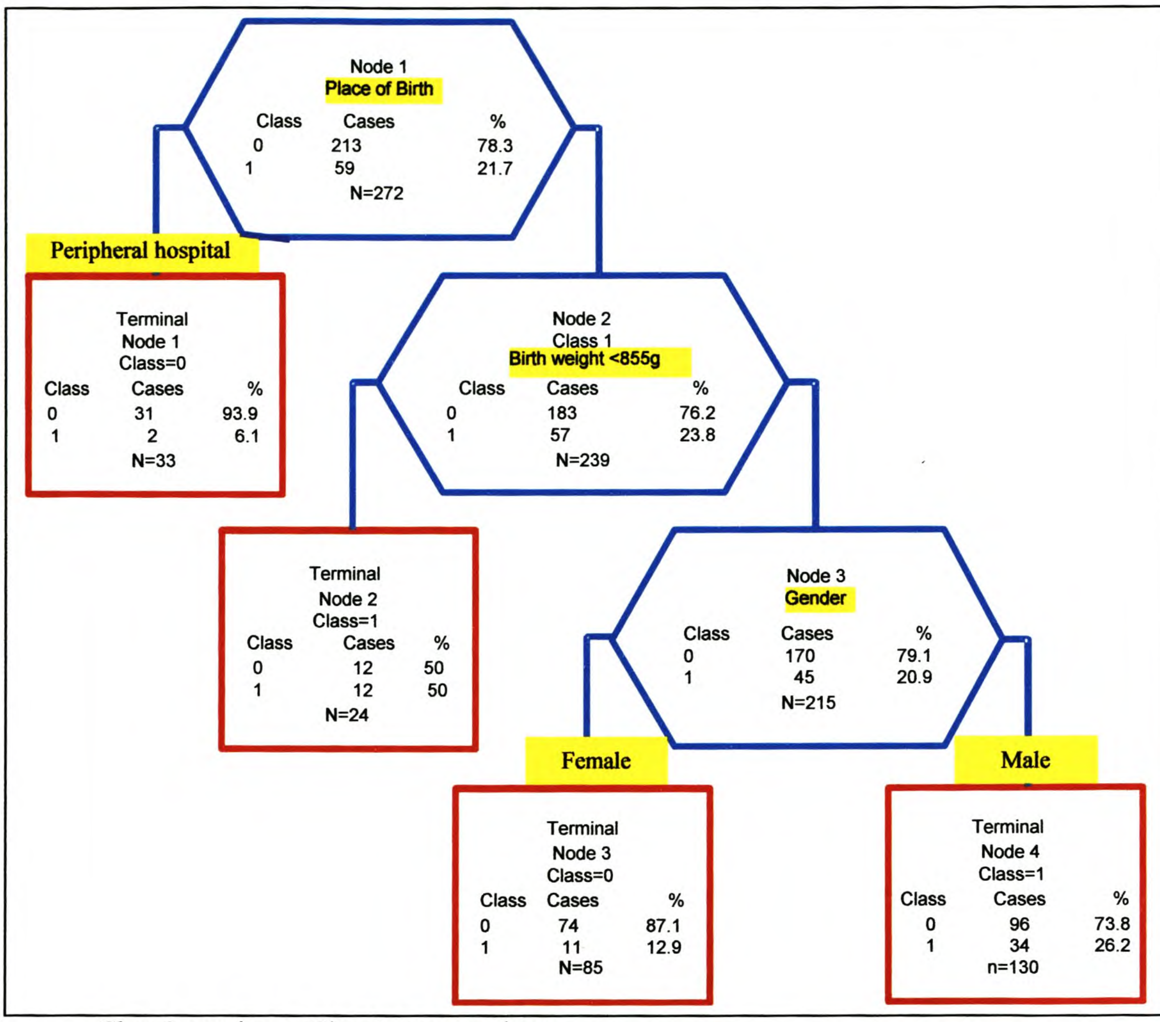
The second most important prognosticator for survival was birth weight (0.019). The first node was found at a birth weight of 855 grams. Competitor factors were Gestational age at 0.013, gender at 0.011 as well as multiple births at 0.009.

2.1.3 Gender

The gender of the baby was the third most important marker of outcome. Female babies had a marked better survival. Surrogate markers were gestational age at 0.001 and birth weight at 0.00077. These were also the competitor markers.

The differences in the terminal nodes in the two cohorts is illustrated in Table 5.

The schematic drawing of the individual nodes is presented in Figure 1.



Class 0=survivors Class 1= non-survivors

Figure 1: The schematic presentation of the nodes.

The nodes identified by the validation cohort, however, did not improve the overall predictability of the model as identified by the initial cohort. Therefore the model as devised by the initial cohort is validated by the validation cohort.

CHAPTER 7

1 Discussion

The aim of the current study was to devise a simple and easy way of prognosticating the outcome of a specific baby. The aim of the research was to find the best prognosticators as well as to identify the best outcome modality, which could be predicted. In the first part of the current study the objective was to identify the best variables and outcomes and to develop a score. In the second part this scoring method was validated.

After analysing the development cohort with different methods it was proven that the survival of babies admitted to the NICU could be predicted by using their birth weight/gestational age, their mother's socio-economic status, booking status and the baby's gender with an accuracy of 94%.

In the validation cohort the same variables showed an accuracy of 83% to predict survival. The validation cohort had systematic differences when compared to the initial cohort in that the babies were significantly smaller and of a lower gestation, and that 6% more babies survived in the initial cohort than in the validation cohort. This effect of systematic differences can be expected as treatment methods and expertise change, and therefore the analysis must be regularly updated with continuing research.

This change in the frequency of outcome compromised the CART analysis. The reason for this increased survival could possibly be explained in two ways: Firstly by virtue of the fact that the babies were chosen more effectively and that this ensured a better outcome. This is improbable as the birth weight and the gestational age were both lower, favouring a higher mortality rate. The second possible reason may be the improved service and expertise of the unit. The rigorous implementation of breastfeeding in all premature babies may have been one of the key factors, as has been recorded by Kirsten et al.[1]

1.1 Risk factors:

The effect of risk factors on neonatal outcome is in many ways interlinked. Most studies evaluating risk factors find similar factors in varying degrees of importance depending on the population, the sample size and the statistical methods, and most find more than one factor of importance.[2]

Some factors may be preventable, like lack of antenatal care but some, like gender, are a given fact. Most risk factors however, can be used as substitute markers for other variables and cannot be examined on their own: lack of antenatal care goes hand in hand with poor socio-economic populations who have a poorer health status, are more prone to substance abuse and have less access to health care. Thus finding one determinant is intricately woven into many other problem areas.

1.2 Maternal risks

1.2.1 Age of mother

Increasing age of the mother has been associated with increased risk of maternal as well as neonatal mortality and morbidity.

1.2.2 Teenage pregnancies

The risk of teenage (alternatively "young mothers") pregnancy and the associated long-term effect this has on the parents, as well as the family, has prompted a statement by the American Academy of Pediatrics.[3] They see the event of adolescent pregnancy as "a complex and perplexing issue for families, health professionals, educators, government officials and youth themselves". Historically the highest rates of teenage pregnancy were seen during the period 1950-1960 before the legalization of abortions. The rate in the USA then decreased until 1986, followed by a subsequent increase until 1991. The rate in 1996 was still higher (54.7/1000) than in 1980.

It is currently legal to obtain a termination of pregnancy in South Africa by choice. The effect of this legislature on the amount of teenage pregnancies is not yet documented. Of the 172,494 abortions performed in South Africa in 1997-2001, 5% were performed on women younger than 18 years.[4] If these legal terminations of pregnancy are added to the finding that 35% of women have already been pregnant by the age of 19 years it is clear that teenage pregnancy is a major problem in South Africa.[5]

When analysing international trends, these young women frequently have a lower educational level, a higher rate of substance abuse and a lower socio-economic status.[6] Our mothers come from a mostly rural background in the poorer regions of South Africa. There was a higher trend of teenage pregnancies in rural black and coloured girls.

The pregnancy risks have prompted another statement by the American Academy of Pediatrics clearly putting this group of mothers into a high-risk group.[6] This is a potentially increasing group of patients as the numbers of adolescents grow, especially in a developing country where 50% of the population is aged less than 15 years. These mothers are at increased risk for poor weight gain, anaemia and pre-eclampsia. They are also more prone to be of low socio-economic status and more prone to domestic violence.[3] They are more likely to be single mothers and less likely to finish school. Even though their use of addictive substances decreases during the pregnancy, there tends to be a major increase in the use in the first 6 months after delivery, according to the American Academy of Pediatrics.[6]

Rip recorded that 13.3% of black mothers and 13% of coloured mothers were teenagers in his population based study in Cape Town in 1990.[7] Teenagers were defined as less than 20 years. His study population constituted 1324 black and 1964 coloured teenagers.

In the present study 11.2% of mothers were teenagers if defined as less than 21 years of age. The neonatal mortality in this subgroup was 21.5%, which was lower than the general mortality of 26%. They also represent a very low income group. Thirty one

(61%) of these mothers had no income, and only35% had an income of exceeding the minimum wage. Family members or the father of the child may have contributed to the income of these mothers. Low maternal age by itself was nevertheless not a risk factor for neonatal death as an outcome in the current study.

The only difference found was that teenage mothers had bigger babies with a mean weight of 1267g, compared to 1193g for older mothers. According to the most important node in the CART analysis, this is the most important outcome indicator.

1.2.3 Older mothers:

At the other end of the spectrum are the older mothers.[62] Even though there is no universal accepted definition of age for this group, they represent a higher risk group. This seems to be the case whether the mothers are multiparous or when they have knowingly decided to postpone their childbearing.[8] These mothers have a higher incidence of pre-eclampsia, low birth weight, preterm delivery and multiple pregnancies. They also have higher incidences of maternal concurrent illnesses and fetal congenital abnormalities.[29] There is a higher induction rate, lower Apgar scores and higher caesarean section rate for fetal distress.[9,10]

Some older mothers may also have long-term health problems. [11] More mothers have underlying hypertension and also have more sequelae after the pregnancy. Studies that have assessed the influence of advanced maternal age on LBW, preterm, and small for gestational age (SGA; <10th percentile) deliveries among primigravidas have provided conflicting and inconclusive results. Although some studies have shown that advanced maternal age is associated with LBW [12,13,14,15,16] and preterm delivery,[17,18,19]other studies have found no increased risk of these adverse pregnancy outcomes with increasing maternal age.[20,21] Some researchers have also demonstrated a significant increase in SGA births among elderly primigravidas.[10,22,23]

The infant mortality rate for South Africa for the period 1988-1998 was approximately 42/1000 for women of 40 years or younger and a markedly higher 74.5/1000 for women older than 40 years.[24] Similar international results were found by Rip with 11.8% of black mothers in his study being older than 35 years.[7] In Zimbabwe however, no effect of maternal age on outcome was found.[25]

The increased risk in older mothers was confirmed in the current study. There were only six mothers (1.3%) in this age group in the current study but they had a higher infant mortality at 33%. They also had a low income with 5 mothers earning less than R800.

Epidemiologically speaking, South Africa is a developing country with a pyramid shaped population distribution with 50% of the population aged less than 15 years and a relatively high female fertility rate. It is generally found that the mothers in such a population start their families early and continue to have babies to a high age. Despite the high proportion of teenage mothers, the median age of the mothers was 27 years. This is probably explained by the fact that the mean parity was 2.7. The mean age of mothers who had their first pregnancy was 22.1 years (n=123).

1.2.4 Parity of mother

The concern about a possible increased risk of poor outcome with increasing parity has been debated for decades. Some investigators found an association[26,27] and others not.[28] Goldman however found that with good antenatal care the risks for neonates of these mothers were nullified. Grand multiparas had a significantly higher age than controls and that this could be the reason why more of them had risk factors like diabetes mellitus.[29]

There is an association between low socio-economic status and multigravity. Bai recorded a linear increase in risk with increasing parity.[29] This is underlined by the South African statistics of 1988-1998 which gives an under 5 mortality rate of 55/1000 for firstborns, 68.7/1000 for 4-6 births and 97.5/1000 for >7 births.

The current study had a mortality rate of 259/1000 admissions for firstborns, 217/1000 admissions for 4-6 births and 444/1000 admissions for >7 births. These figures are much higher than the population figures in the RSA for 1988-1999 but it must be appreciated that our cohort consisted of very high-risk babies.

In the current study there was no difference in the outcome of firstborns and mothers who had between 4 and 6 pregnancies. Mothers who had more than 7 pregnancies however had a significantly higher neonatal mortality. The socio-economic status is also intertwined with these results as the number of mothers earning less than R800 in the survivors (1 of 4 mothers) in the > 7 parity were much higher than the non-survivors (3 of 5 mothers). Rip found an incidence of 18.3% of mothers older than 35 years. In our study these mothers only constituted 8.9% of our deliveries[7].

The only at risk group found in our study were the mothers with a parity of more than 7.

1.2.5 Type of delivery

The best method to deliver a very low birth weight baby is still debated. Some studies demonstrate that vaginal delivery is associated with a higher incidence of intraventricular bleeds[30,31,32] but others claim that other predisposing factors are more important than the type of delivery in the causation of intraventricular bleeds.[33,34,35]

Larimore states in his article on "keeping normal labour normal" that labour mostly does not need to be interventionally managed. In the current study group of babies the choice of the type of delivery was dictated by maternal and neonatal factors. Fifty-five percent of babies were born because of caesarean sections, of whom 25% died, which is a disproportionally high figure compared to deliveries in all birth weight groups. The accepted normal caesarean section rate is between 15-25%.[36] Our high rate is however in keeping with good obstetric practice. Nassar found that induction of labour in mothers with severe pre-eclampsia remote from term, resulted in 48% of babies born vaginally.[37]

The babies who were delivered vaginally in our study (45%) were mostly normal vertex deliveries. Assisted deliveries accounted for 15% of all vaginal deliveries. The mortality in normal vaginal delivered babies was 25%, but 33% of forceps delivered babies died and an alarming 40% of breech deliveries died. These numbers are small but could indicate the need for a possible change in obstetric practice. Bakos also recorded a poorer neonatal outcome in breech delivered infants.[38] This was confirmed in Harare, Zimbabwe, where breech delivered babies had a mortality of 11.3% for all admissions, regardless of birth weight.[25]

In babies born in our study by caesarean section, the most important indication was fetal distress (42%), with a mortality of 24%. In 32% the indication for a caesarean section was pre-eclampsia with a mortality of 24%. Other indications for caesarean sections were a minor group and the numbers too small to draw valid conclusions.

Therefore, in our study, the main risk factors for death as outcome were forceps and breech deliveries. Multiple pregnancies, even though the numbers were small, had a lower mortality at 10%.

1.2.6 Prolonged rupture of membranes (>24 hours)

Prolonged premature rupture of membranes (PPROM) is associated with a large increase in mortality. It occurs in 2-4% of all pregnancies and 30-40% of premature deliveries are complicated by premature rupture of membranes.[39] Premature rupture of membranes may increase the occurrence of chorio-amnionitis depending on the number of vaginal examinations and the length of time of ruptured membranes.[40]

The published definition of PPROM differs from 18 to 24 hours. The definition for the current study is 24 hours and more. Premature rupture of membranes also occurs in one third of premature deliveries, of whom 75% deliver within one week of rupture. PPROM in association with the absence of neonatal care increased the mortality risk to 1.3 times of those mothers who had received care.[41] Vintzileos recorded a mortality rate in babies with PPROM who received antenatal care of 20.3% compared to 48.8% in those who did not .[62] The incidence of Group β haemolytic Streptococcal disease is also increased after 18 hours of PPROM.[41]

In our study the prevalence of PPROM in survivors was 8.8%, compared to 11.2% in non-survivors. Although the prevalence was higher in non-survivors it was not statistically significant.

1.2.7 Syphilis status

The effects of syphilis on the outcome of pregnancy is well documented. Gray recently recorded that the empirical treatment of sexually transmitted disease (STD) in adults with unconfirmed but suspected STD lowered not only the incidence of infant ophthalmic infections, but also significantly lowered the perinatal mortality and low birth weight rate.[42]

In the current study, the prevalence of deaths in the RPR positives was higher (7.1% compared to 5.6% in RPR negatives) but did not reach significance.

There are no published data on the association and the effect of HIV status on these results. It is accepted that the mothers who are RPR positive have a higher chance of being HIV positive as well. The effect HIV in the current study could not be assessed because the prevalence of RPR mothers was low at 6%, and HIV testing was not routinely performed.

1.2.8 Socio-economic status

The social status of the mother or family has profound influence on the outcome of the infants. Social status is measured in different modalities, like occupation, family income, maternal and paternal education, etc. Not only do poor children have a higher mortality,[43] they also have a higher long-term morbidity. The incidence of handicaps, dental caries, visual and hearing impairment is much greater.[44]

The problems associated with neonatal outcomes are exacerbated by low socio-economic status. McCormick states that the outcome in mothers with low socio-economic status involves at least three dimensions: The severity of disease on admission, the medical response to interventions and the presence and sequela of the abovementioned at discharge. In a group of very low birth weight babies 18.5% had moderate to severe problems at 8 years of age, and 54.5% of them came from parents with low educational levels, compared to 8.7 % in children of mothers with high educational attainment. The birth of a low birth weight baby can have profound and ongoing effects on the family, the healthcare and the educational system.[45]

In our study we only recorded the maternal income as index of socio-economic status. The income of the mothers was the second most important marker of outcome. In the group of mothers with no income this factor becomes so important that it removes the predictive value of the other markers like birth weight, gender and place of birth as the only marker of outcome. This is in keeping with Hollingsworth[46] who said that the degree of equality of outcomes in health is influenced primarily by the total structure of the society. This study done on health care in England over 80 years ago concluded that it is not the equal access to medical care or the quality of care that makes the difference. The level of education more than the income leads to a higher use of medical services but also lead to a healthier lifestyle. This study also underlines the fact that the poorest people have the highest health needs. He found that persons in the lowest income level needed twice the amount of medical care than persons in the highest income group. This remained fairly constant over a study period of 35 years. These findings emphasise the increased requirements for medical care of the lower socio-economic group, which is served by the public sector in the RSA. It therefore also underlines the need for a method of allocating scarce resources to those babies with the best predicted outcomes.

In the Cape Metropole the only comparative data are from studies by Kirsten in 1995 where 69% of mothers earned less than R1000 per month[107] and Thompson et al in 1993, where 79% of mothers had a low income.[47] It will be of interest to examine the effect of the new legislature on minimum wages for domestic and farm workers on the maternal income in subsequent babies.

Income was used in the current study as a marker for social status and literacy. Because the first cohort was partly analysed retrospectively, data on literacy and social status could not be obtained. Income can be used as an equivalent substitute marker for socio-economic status and literacy.[48] In the initial cohort the income was the second most important marker of survival, second only to the birth weight. In the no-income group this variable was the only marker of outcome and nullified all the other variables. The effect of inflation on the actual value of the South African Rand during the study period is illustrated in Appendix 1. It is of great concern that the actual income in mothers in the validation cohort has dropped. This drop is marked if compared to the value of the Rand.

In the validation cohort maternal income was not a marker in the alternative CART analysis, but this could be due to the fact that only 4 markers were identified. The new CART analysis did not perform better than the initial CART analysis

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1.3 Neonatal risk factors:

1.3.1 Birth weight

It is widely accepted that birth weight and gestational age are good predictors of outcome.[47,49] In many ways these are still used as the "gold standard" against which newer scoring systems are measured. These variables, however, while being better than selection by chance, do have shortcomings. The predictive value of these measurements is lower than expected, mainly because of other factors like growth retardation, which in itself may influence the outcome of these babies, are not taken into account.[50] Low birth weight and preterm delivery are the most important determinants of neonatal mortality and of infant and childhood morbidity. Lower birth weights in developed countries are mainly due to premature infants and in developing countries due to growth retardation.[92,95]

LBW for gestational age contributes to approximately 65% to 75% of neonatal deaths. [51,52] High-risk infants (preterm, LBW, multiple gestation) may have persisting health problems after hospital discharge and higher rates of re-hospitalizations than full-term peers.[53] Infants who weigh 1500 to 2499g are twice as likely to be hospitalized as those who weigh 2500g or more, and those who weigh <1500g are approximately 4 times as likely to be hospitalised. [54]

McCormick found that the mortality rates in the USA have decreased rapidly, with the highest decline in infants who were of low birth weight. The reason for this was intensive, hospital based management.

In Harare, Zimbabwe, the mortality of babies with a birth weight of 500-999g was 91.6%. The overall mortality rate was 19.3% with a mortality rate in the under 2500g group of 26.9%. The mortality rate in the 1000-1499g group exceeded 40%.[25]

In the current study the babies with a lower birth weight did worse than the babies with a higher birth weight. The effect of a higher mortality rate in babies of lower birth weight was lost in babies with a higher gestational age. The birth weight was the most consistent marker of outcome in all the cohorts and in the different methods of analysis. This was also found to be the main reason why the mortality of teenage mother's babies did not differ from the rest.

1.3.2 Gestational age

As birth weight and gestational age are highly correlated, there is statistical evidence to include only one in the analysis.[55] In both CART analyses the gestational age was found to be a direct substitute for birth weight.

1.3.3 Small for gestational age

Morley found a ratio of birth weight to mean birth weight for gestational age of less than 0.8 to be indicative of a birth weight under the 10th centile. He also demonstrated a linear correlation between this ratio and the requirement for mechanical ventilation. He however found no correlation between outcome and size for gestation.[56] This was contradicted in a study by Lackman, who recorded a 5-6 fold greater risk of perinatal death for both preterm and term fetusses with intrauterine growth restriction.[57] Sciscione documented that other factors that determine birth weight like ethnicity, weight gain by the mother, parity, etc made the prediction of outcome of babies who were born with a birth weight of less than the 10^{th} centile more accurate.[58] The mortality in SGA babies was found by Lee to be even higher in the most severe intrauterine growth retarded group, with a 77% survival to NICU discharge.[59]

In the current study the 29.2% mortality of SGA babies was higher than the 25.5% in normal weight for gestational age babies, but this did not reach significance. This was however, similar to the findings of Lee.[59]

The occurrence of low birth weight was also increased in teenage mothers. Of babies born to mothers of less than 17 years old, 33% were SGA in a study by Rees.[60] This was not the case in the current study where none of the mothers aged less than 17 years had SGA babies.

In some aspect the SGA babies have a better outcome. Cooper found in a South African cohort that the SGA babies had a lower incidence of respiratory distress syndrome but this did not improve overall survival.[61] The mortality rate for SGA babies (born between 30 and 32 weeks) in Cooper's study was 32.4% and the rate for the normal grown babies was 27.8%, which closely corresponds to our own overall mortality rates of 29.2% and 25.5% respectively.

1.3.4 Booking status

Lack of prenatal care (booking) is associated with increased neonatal death rates and carries a relative risk of 1.3 (CI 1.1-1.5)[62] This is true for all population groups.[50,63] Even though antenatal care for mothers and babies up to 6 years of age is provided free of charge in South Africa, 18.7% of mothers did not attend an antenatal clinic.

Rip recorded a comparable occurrence of 17.9% in black, and 9.5% in coloured mothers who did not receive antenatal care in the Cape Metropole in 1990.[7] Menown recorded a survival rate of 82% in booked and 60% in unbooked black South African babies .[64] Amini recorded that unbooked mothers, who did not have al least 3 clinic attendances, had babies of lower birth weight, lower Apgar scores and were mostly black, poor and unmarried. The lower birth weight was unrelated to the gestational age. Babies of unbooked mothers had a worse neonatal outcome measured by length of stay, and obstetric complications.[63]

In the current study the prevalence of unbooked patients was 21.3% in survivors and 11.9% in non-survivors. This is a surprising finding in view of the generally accepted fact that antenatal care reduces mortality.

The reason for our discrepant findings may lie in our admission criteria for the NICU. The current study was done on all babies admitted to the NICU over a given time, and had been "chosen" with a set of criteria, one of which was the booking status. Babies of mothers who had not attended an ANC, were required to have a higher gestational age and/or birth weight to be admitted to the NICU. Ideally this research should have been done on a group of babies with no restrictions on weight, gestational age or number of babies who needed admission. The current study thus underwrites the admission criteria, but whether this apparent better outcome in unbooked patients was a factor of the booking status, or of the higher gestational age and birth weight, remains to be investigated.

1.3.5 Multiple gestation

The risk incurred by twin or triplet gestations is far higher than that of singleton pregnancies. Twins make up only 2-3% of live births[65], but they account for 10-15% of adverse neonatal outcomes.[66] There is a marked increase in multiple pregnancies in the United States.[67] Preterm delivery, low birth weight and very low birth weight occur more frequently and contribute to higher rates of mortality, morbidity and long-term adverse neurological outcomes. Many of these pregnancies are also the result of in vitro fertilization. Fetal wastage was also high among these multiple pregnancies, as was the higher registration of babies born at the limit of viability. [68]

In babies of less than 1500g, the place of delivery increases the risk of mortality in twin pregnancies, whether the mother is a teenager and/or has not received antenatal care. Hospitals with a high number of deliveries fare better.[69] The risk for mono-chorionic twins is even greater, with a perinatal mortality rate of as high as 70% in some studies.[70]

Triplet pregnancies present additional risk factors: The increase in the babies' weight at 24 weeks as well as the parity of the mother seems important. If the mother is nulliparous or if the babies do not grow sufficiently, the risk is increased.[71] Suri found no differences in higher order multiple births compared to lower order twin pregnancies, except for a longer hospital stay, but did mention that these pregnancies were closely monitored by a sub-specialist team at one institution.[72]

The prevalence of multiple births in the current study was 12.2% in survivors and 15.9% in non-survivors. This difference did not reach statistical significance.

However, more babies who were born as the second twin, died than the firstborn twin (11 babies versus 8). In the current study multiple births had a lower mortality than singleton pregnancies. There is however a problem with the interpretation of these results, as not all twins were both admitted to the NICU, and it is not known if one twin had died before or during the delivery, or before admission to the NICU.

1.3.6 Place of birth

The impact of the place of delivery on the neonatal outcome of low-birth weight babies has been documented mostly in developed countries. The USA has developed "Guidelines for Perinatal Care" which recommend that babies with very low birth weight and babies of lesser than 32 weeks gestation be delivered in a level 3 hospital.

In a study on the implementation thereof, in South Carolina, USA, a higher mortality was recorded amongst babies born in level 1 and 2 hospitals. The ethnic group-adjusted mean length of stay was increased in level 1 and 2 hospitals. This adjustment was made to reduce the confounders of race on severity of illness and outcome. In level 1 and 2 hospitals the leading cause of death was respiratory distress, whereas the leading cause of death in the level 3 hospital was congenital malformations. The effect of transporting the baby on outcome is difficult to assess. Many babies who are deemed too sick to travel may be kept in a secondary hospital, whilst these may be the babies who would had a better outcome in a tertiary facility.[73]

Chien documented an improved outcome of preterm babies born in a tertiary setting. This was true even when risk adjustments were made for perinatal risks and severity of disease.[74] Changes that may occur during transport, like the development of hypothermia, may also influence outcome.[75] Truffet recorded a protective effect of being born in a tertiary centre, irrespective of the quality of transport. He also found that the higher mortality in smaller babies (<28 weeks) in the tertiary centres was similar to the mortality in babies of greater gestational age in other centres, underlining the effect of choosing to transport small babies to tertiary centres who are not deemed viable.[76]

Self referral is also a confounder. Many patients in our province migrate from a rural area to the metropolitan area for health care. The relatively effective "blocking" of tertiary hospitals to self referrals, does not prevent the self referrals to attend MOUs, which are affiliated to these tertiary hospitals. These effects are found in most countries.[77]

In France the place of delivery resulted in differences in outcome in all weight categories. The best results were found in tertiary referral hospitals. This was ascribed to the attitude of the obstetrician and the fact that babies were transported to influence the outcome.[78] Again the effect of a higher degree of disease and a lower physician competence increased the mortality in the rural hospitals.

In the current study the best results were seen in babies who were born in the district MOUs of Tygerberg Hospital. One baby died in this group of 21 babies (4.7%), compared to 27.5% of babies born in Tygerberg Hospital, and 25% born in the district. This is a reflection of the local medical care system where all premature deliveries are not managed at the clinic but are primarily referred to Tygerberg Hospital. The slightly lower mortality in out-born babies may be a reflection of a sifting process and of admission criteria, as well as the method of delivery, as caesarean sections are not performed by MOUs.

In the validation cohort the babies who were admitted from outside the Cape Metropole did better, and the place of birth was the most important marker. This may be explained by the more stringent admission criteria that are placed on babies born in peripheral hospitals.

1.3.7 Early (before 12 hours) or late admissions

There was no difference in the outcome of early and late admissions with a mortality rate of 26.3% in late admissions and 26.1% in early admissions. The effect of transport on the babies was not measured. This is a confounding factor in many of the late admissions as well as in babies born outside Tygerberg Hospital. Berman classified transport as one of the reasons for varied outcomes in similar babies.[79] Infant transport is a key component in neonatal-perinatal care. This remains a problem when resources are limited. With a limited amount of ambulances available it is often perceived that a newborn who is already receiving care in a hospital albeit at a lower level of expertise, is better off than a patient at home. It may take as much as 15 hours from the time of referral to transport a sick baby to the Tygerberg NICU over a distance of 5 kilometres. The impact of this delay in transport on outcome is unknown. Patients who are referred are often those who are perceived by the referral hospital as having a good chance of survival. Therefore when measuring the time to referral, quite a few confounders which may make the outcome of these babies better or worse, may come into play.

In the current study there was no difference noted in outcome of early and late admissions.

1.3.8 Apgar count

This scoring method has been in use since 1953[80]. The 1 minute Apgar score is a function of the baby's antenatal state and birthing process. The 5 minute score is in many ways influenced by the competence of the resuscitator. Both have a predictive effect on mortality as well as morbidity.[2,81] The effect of resuscitation training was demonstrated by Patel in Illinois where he showed a dramatic improvement on the 5 minute Apgar score after training personnel, but no effect on the 1 minute score.[82] In a study by Moster an Apgar score of less than 3 at 5 minutes was associated with a 8 fold increase in deaths (neonatal as well as infant) and a doubling of the number of babies with cerebral palsy.[83] The predictive effect of Apgar scores on pre-term babies has been extensively investigated.[84,85,86,87] Although the score is generally lower in pre-term babies, it still remains the best tool for identifying babies who are in need of cardiopulmonary resuscitation. The risk of mortality for pre-term babies with low one minute Apgar scores is 115 times higher if the baby has an Apgar score of 0 to3 and 5.9 times higher if the score is 4 to 7.[88]

In the current study 28.1% of babies with a 1 minute Apgar count of less than 4 died, compared to 26.3% with a score of higher than 7. Forty percent of babies with a 5 minute Apgar count of less than 4 died compared to 26.6% in the higher than 7 Apgar count. A low Apgar score at 5 minutes was, as recorded in the literature, associated with death in nearly half the babies. The effect of resuscitation techniques could not be taken into consideration in the current study as the responsible pediatric registrars change constantly. There is an active program of teaching of resuscitation techniques for all new members of staff who have to perform the resuscitations. The registrars, who were on duty for all the babies in the current study, may have had varying degrees of experience and skills. Truffet did not find any positive effect on the outcome whether a paediatrician was in attendance at the delivery or not. [76]

Neither the 1 nor the 5 minute Apgar count had any significant prognosticating value in the current study.

1.3.9 Gender

In the period 1988-1998 the under 5 mortality rate for boys in South Africa was 65.9/1000 compared to 47.9/1000 for girls, and the neonatal mortality was 23.7/1000 and 14.6/1000 respectively in boys and girls.[89] Copper recorded a higher survival rate in female than in male pre-terms.[54]

The same effect of gender was observed in the current study. Female babies represented 47.6%, and male babies 52.3% of patients. The mortality rate of 21.6% in females and 30.2% in males, underlines the vulnerability of male babies. This difference in gender outcomes was not observed in Zimbabwe. The high overall mortality in the low birth weight group in Zimbabwe may have masked the finer determinants of outcome.[25]

In the current study there was a direct correlation between maternal income and survival in males. In male babies whose mothers had no income the mortality was 33%, compared to 21% in the high income group. This difference was small in females with 18% mortality in the no income group and to 20% in the high income group. This may be explained by the lower number of female admissions.

Female babies are recorded to have a significant higher 1 minute Apgar count at birth than boys[81]. In the current study this difference was also present with an Apgar count of 4.7 in males and 5.3 in females (p=0.051).

1.3.10 Ethnic group

Neonatal mortality rates differ in different population groups. Vintzileos found that African Americans had a higher mortality than whites irrespective of whether there were high risk factors complicating the pregnancy.[68] The mortality rates were 2.7/1000 versus 1.5/1000 for high-risk pregnancies and 10.7/1000 versus 7.9/1000 for absence of antenatal care. Lack of antenatal care was also associated with increased relative risk of mortality of 1.3 fold in African Americans and 1.4 fold in white infants. Kleinman recorded the death rates for blacks were twice as high as whites in both singleton and twin births. He also noted a higher prevalence of low birth weight in black infants.[90] Differences in nutritional status between black and white women did not account for the differences in outcome and there was a higher incidence of low birth weight and small for gestational age babies in the black population.[91]

The equivalent figures for South Africa are a neonatal mortality rate of 11.4/1000 for whites, 9.6/1000 for coloured and 20.6/1000 for black neonates.[89] This may be skewed as most whites and a high proportion of coloureds have private health care. The second confounder is that a high proportion of coloureds and whites live in the Western Cape, which has the best recorded overall neonatal outcome in South

Africa.[24] Stein recorded that a low birth weight baby born to an "African" mother had a 73% chance of being small for gestational age of whom 39% were male and 61% female. These infants were measured according to the centiles of Battaglia and Lubchenco. This may have caused errors because the centiles of normal for the indigent population at risk should be used. He also recorded a 26% incidence of twin pregnancies in his cohort, who have different growth patterns compared to singletons.[92]

The discrepancies between ethnic groups may be more indicative of social class and address than of real differences. Menown ascribed the higher mortality rate in blacks to ignorance and poverty, and states that the effect of literacy is even more important than poverty per se. Another comment was that receiving antenatal care itself could not explain the better outcome of the booked babies as most of these babies were low-risk. [64]

The effect of ethnicity on the outcome of babies is present in this study. Black babies, although small in number, had a 34% mortality rate in males and 37% mortality rate in females. This was higher than in other ethnic groups and also represented a higher mortality rate in females.

In the coloured population the mortality rate is 29.8% in males and 20.2% in females. In the small number of white babies it was 26.6% in males and 25% in females.

There may be another explanation for the above findings. Berman found that the African-American babies in her study were less sick than their European controls. She is of the opinion that this may be because of genetic differences or the effects of unmeasured antenatal factors.[79] White South African premature babies needed more ventilation because of respiratory distress syndrome than other ethnic groups but had a much better survival of 11.7%.

The effect of adding another risk factor to ethnic group, for instance teenage pregnancies, was investigated by Boult. Singleton teenage black mothers lacked antenatal care, often delivered significantly lower birth weight babies that controls, and also had a higher incidence of anaemia.[93]

The effect of ethnic group may also be explained by other confounders such as acts of racism and violence.[94] The discrepancy in outcome cannot be explained by socio-economic factors alone. David et al found a paradox in that mothers, who had recently immigrated to the United States, had higher birth weight babies in spite of a lower socio-economic status, than women of colour who had been born and raised in the States. This belies the theory of genetics and socio- economic status being the cause of low birth weight.[96]

Rich-Edwards postulates the difference being the constant experience of fear and violence to be a major contributing factor.[95] She quotes the incidence of 25% of sexual abuse,[96] 33% of physical and sexual abuse[97] and 3% of women being severely physically abused by their husbands in any given year.[98] This increased to 16-20 % in urban public clinics in America.[99]

In our study, however, black infants had a worse outcome than coloured infants if measured by mortality. The best outcome was in white females, but the numbers are small.

2 Outcomes

2.1 Length of stay

Using length of stay as an outcome is justified as this is a factor which can be used to calculate cost. If the number of available beds does not keep up with the demand it is important to take the length of stay into consideration. Even though a 25 week gestational age baby may survive without long-term damage, he/she may occupy a bed for 4 months in which time 10 or more other babies with a higher gestation could have been treated. The mean length of stay in the NICU for a term baby is 2.7 days according to Liu.[100] Most of the babies born with a birth weight of >2500g are discharged before 5 days of age.[101]

St John found an exponential increase in length of stay when comparing the gestational age with the length of stay. The length of stay varied from babies of 34 weeks who stayed 7.9 days, 28 week gestational aged babies who stayed 57.6 days, and 24 week gestational aged babies who needed 98.7 days of care.[102] Cooper recorded that ventilating one baby of less than 1000g may take the same ventilator time as two babies of more than 1000g.[103]

The problem of length of stay in the ICU is confounded by other aspects. In our hospital, traditional NICU care like Nasal CPAP and TPN are given in a high care neonatal ward and babies have to stay longer in the NICU because of lack of space in the neonatal wards. This may influence the sensitivity of the length of stay as a marker of outcome. It is also universally found that babies who die, do so within the first few days of life. These babies thus do not use many resources before death.

In our study the length of stay was equal in survivors compared to non-survivors.

2.2 Mortality

Verma initiated a morbidity score for babies.[104] The comment by the author on why a morbidity and not a mortality outcome is used, was that the prevalence of mortality was low. This was also the reason why Wilson used length of ventilation as a marker of outcome, commenting that as mortality rates drop, other markers are needed for outcome.[56] This is unfortunately not true in the current study with an overall mortality rate of 26%. In Canada the mortality rate was recorded as 5% in the weight group 1000-1500g and 24% in the weight group 750-999g. [105] The second factor is that rankings of scores may differ from year to year because of changes in management. Thirdly, the morbidity scores may be skewed as not all parameters are scored in each baby.

The survival of a specific baby, was found to be the most stable predictable outcome in the current study. This is an ideal finding for South Africa where limited resources need to be allocated to the patient with the best chance of survival. Morbidity data is of less relevance because of an existing policy of terminating curative treatment in babies who have an expected very bad long-term prognosis. Babies with a grade 4 intraventricular bleed (IVH) for example will be discussed by an ethics committee, and active ventilatory treatment of these babies will be stopped although they will still receive supportive care. The majority of babies with BPD will however remain on ventilation for as long as necessary.

The reason for including markers of morbidity in this study is twofold. They firstly are internationally recognised markers and will be of use as soon as the local mortality rates are so low that they no longer are useful predictors. Secondly, they also mark an unfavourable outcome, which is associated with accumulating cost of treatment for these survivors. The same can be said for the length of NICU stay. Because of the high mortality rates in our population, the development of IVH and/or BPD were not the most useful predictors.

It is important to realise that the mortality does not stop at hospital discharge. An additional 12-14% mortality in the first 18 months of life was documented in a South African cohort of very low birth weight infants.[106]

In the initial cohort of this NICU the mortality was 26%. In an earlier "pre-surfactant era" group of patients with the same weight, the mortality was 28%.[107] In the validation cohort the mortality has fallen to 20%. There was little change in the consultant staff or the treatment options, except that the validation cohort was mostly breastfed. Breastfeeding was the reason given by Stein for the low rate of necrotising enterocolitis low birth weight babies in Baragwanath Hospital in Johannesburg, RSA, in 1980 compared to other studies.[108] The incidence of necrotising enterocolitis dropped from 10% during the IC to 2.8% in the VC in our patients.

2.3 Cost

The bottom line in neonatal care for small and sick babies is cost. The cost saving by preventing a baby of 1000g being born was calculated to be $58 000 per survivor in a study by Rogowski in 1998.[109] The effect of this amount is lost when the small number of these babies is taken into account in the total health budget of a country.

We calculated in 1999 that it would cost 0.001% of the national health budget to treat all infants below 1000g in South Africa.[110] Capacity to treat and ventilate small babies can be "bought". Rothberg also underlined the fact that "for many years South African Neonatologists have been forced to make choices such as limiting assisted ventilation to EBLW babies, because of limited resources".[111] His proposal on the method to minimise the gap between the private and public neonatal care facilities was to "impose severe rationing in the private sector".

In a meta-analysis of costing the fact that all units use different ways of costing was a problem. In addition, methodological flaws in all studies made it impossible to ascertain the real cost of neonatal ICU care.[112]

3 Interdependent variables

It is clear that the variables, whether they are maternal or neonatal, are interdependent. In the CART analysis the inter-dependence of the variables can be seen in the many ways in which substitute variables can be used in the place of missing variables. Birth weight and gestational age are equal in predictive value and using both does not add to the accuracy of predicting outcome. This substitution of variables nullifies the problem of missing data which is a problem in other scoring systems.

The other important aspect of the CART analysis is that it gives a probability of survival for individual patients. It is a "learning" database and therefore should improve with a growing database size. The efficacy of care in the South African NICUs must still be evaluated in further studies. Given the simplicity of the data this should not pose an insurmountable problem.

4 Factors not evaluated.

The impact of Human Immune Deficiency Virus infection (HIV) status on the outcome of these babies was not measured. The current study was partly done retrospectively, and started at a point in time when the prevalence of HIV in South Africa at antenatal clinics was 2.69% and in the Western Cape 0.66%.[113] In 1999 the prevalence of HIV in the Western Cape had increased to 7.1%. Although there are suggestions that babies of HIV positive mothers are more susceptible to infections, we feel that the current incidence of this disease in our population is too low to have a major impact. It is, however a factor that may become of high importance, especially if the predictions of a future incidence of 60% in 25 year old mothers proves to be true.[114]

There are other limitations to this study. A large number of cases are needed to identify predictors without making alpha and betha errors. No power analysis was performed. Even though this study had 727 cases this is deemed small in epidemiological terms. Another problem which arose in the validation cohort is the fact that less babies died, making it harder to predict the outcome.

5 Conclusion

The main objectives of the study have been achieved. The statistical model has been validated, was specifically designed for the Tygerberg NICU in a developing country, included all possible neonates even if data was missing and was easy enough and robust enough to be able to be implemented with a margin of error. It also performed markedly better than the other existing models in predicting outcome. The data which were required were easily accessible and could be obtained per telephone prior to admission.

It was possible to devise a method by which the survival of individual patients could be predicted in 83-94% of cases by using sophisticated statistical methodology. This is a major improvement on the predictive capability of birth weight only, which is 63%. The next step should be the development of a computer-based program and to test this predictive score in other neonatal ICUs, in South Africa and possibly later in other developing countries. It is now possible to allocate scarce resources to babies with the best outcome, based on scientific evidence.

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Chapter 8

Conclusions and recommendations

This study has developed a scientific method to assist with the allocation of available NICU beds to the babies with the best prognosis. The method uses easily obtainable data, has substitute variables for unobtainable data and has a much higher predictive value than birth weight or gestational age only. The method also has the advantage of "learning" as more data becomes available, as well as the possibility to add new markers of outcome like HIV status.

This computer based scoring method will reduce the stress on medical personnel, who can now make life-threatening decisions based on well documented data. The method was developed in the local population, making it more relevant than methods devised in developed or other developing countries.

This study was done in one NICU. The study has to be extended out to other NICUs in South Africa and the efficiency documented in these settings. It may also be evaluated internationally in countries that have the same limited resources as South Africa. Continuing re-evaluation, as the database grows, will ensure the continuing validity of the scoring method.

Implementing this method in countries will also underwrite the WHO strategy. They state that the health community has limited effect for action outside of the health sector and has limited credibility. Therefore the WHO feels that the major impact may be achieved by focusing the energy on the efficient delivery of powerful interventions provided by medical science.[1] They also advise governments to set broad policy directions, create an appropriate regulatory environment and to supply finance. They should diversify the sources of service provision and select interventions that will provide maximum gains in health levels and their most equitable distribution.[2] What can be more effective that allocating scarce resources to patients with the best outcome?

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Appendix 1

To calculate the present values of money in the past:

Example

Year	Current value	Inflation index for that year	Present value of money (in 2002)
1999	R 100	94.9	R 121.60
2000	R 100	100	R 115.40
2001	R 100	105.7	R 109.18
2002	R 100	115.4	R 100.00

Thus, R100 in 1999 will have the same value as R121.60 in 2002.

Medical question:

Year	Current value	Inflation index for that period	Present value of money (in May 2003)
1992-1995	R 892.00	64	R 1,711.53
1999-2002	R 613.00	104	R 723.81
May-03		122.8	

Thus, R892 in the period 1992 - 1995 will have a present value in May 2003 equal to R1 711, 53.

R613 in the period 199 - 2002 will have a present value in May 2003 equal to R 723, 81