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Factors Associated with Increased Mortality in Surgical Neonates Admitted to a Neonatal Intensive Care Unit in Johannesburg, South Africa

Degree Project in Medicine

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List of abbreviations

GBD	Global Burden of Disease
LMIC	Low and middle-income countries
HIC	High-income country
NICU	Neonatal intensive care unit
NEC	Necrotising enterocolitis
ARM	Anorectal malformation
ICU	Intensive care unit
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
LBW	Low birth weight
VLBW	Very low birth weight
ELBW	Extremely low birth weight
EOS	Early onset sepsis
LOS	Late onset sepsis
MRSA	Methicillin-resistant Staphylococcus aureus
CRE	Carbapenem-resistant Enterobacteriaceae
ESBL	Extended Spectrum Beta-Lactamase
SD	Standard deviation
IQR	Interquartile range

Abstract

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Introduction: Globally, the neonatal mortality is decreasing but still remains high in low and middle-income countries. The main causes of death in neonates are premature birth, birth asphyxia, and sepsis. However, surgical conditions such as congenital malformations and necrotising enterocolitis are also contributing to the neonatal Global Burden of Disease.

Aims and objectives: This study's hypothesis suggests that there are identifiable risk factors contributing to mortality in surgical neonates and the aim was to investigate if birth weight, place of birth, site of surgery, congenital malformations, duration of invasive ventilation and the development of necrotising enterocolitis or sepsis increase the mortality.

Methods: A retrospective study was conducted in Johannesburg, South Africa, at Charlotte Maxeke Johannesburg Academic Hospital using data gathered from surgical patients admitted to the neonatal unit between 1st of January 2016 to 31st of December 2018. A multivariate logistic regression model was used to investigate factors associated with increased mortality in surgical neonates. Primary outcome was measured as survival to discharge.

Results: Of the 278 surgical patients admitted, 85 (30.6%) died during the hospital stay. The multivariate logistic regression analysis demonstrated that being born at the hospital, having a low birth weight, having a congenital anomaly or developing necrotising enterocolitis were independently associated with a significantly increased mortality.

Conclusion: This study suggests that there are identifiable factors associated with increased mortality in surgical neonates and emphasises the importance of keeping neonatal surgery in mind when developing health policies which aim to reduce the neonatal mortality.

Key words (3-5)

Neonatology; Surgery; Mortality; Global Health

1. Background

1.1 Global Burden of Disease

The Global Burden of Disease (GBD) is the study of diseases and risk factors leading to early death, loss of health or disability in different countries and the world as a whole (1). When countries develop from being low and middle-income countries (LMIC) to a high-income country (HIC), there are not only economical and infrastructural challenges but also an epidemiological transition of diseases resulting, paradoxically, in a greater burden of disease. As a country develops, a new disease panorama with non-communicable diseases – such as cardiovascular diseases, trauma and cancer – becomes more prevalent. However, several LMICs are still battling communicable diseases and malnutrition (2). This creates a double burden of disease which can slow the socioeconomic development. Therefore, one can understand that neonatal surgery might not be the top priority for public health systems in LMICs, even if the surgical conditions are treatable and contribute to a high burden of disease, if left untreated. For numerous surgical conditions, the initial care is crucial (for example, children born with congenital anomalies). If not treated, the disease can lead to lifelong disabilities, or death that could otherwise have been prevented (3).

In 2015, the United Nations adopted the Sustainable Development Goals with a vision to improve health, create sustainable peace and preserving the global environment. The third goal aims to reduce all preventable neonatal (first 28 days of life) and under age of five deaths across the globe by 2030 to a maximum of 12 and 24 death per 1,000 live births respectively (4). As of 2018, the global mortality for neonates was 18 deaths per 1,000 live births and 39 deaths per 1,000 live births for children under-5 years. The mortality rates are gradually decreasing and have done so since 1990 with a 52 % and 59 % reduction respectively. (5) However, the distribution of deaths is not spread evenly across the globe. The under-five mortality remains the highest in Sub Saharan Africa; it contributes 52 % of the world's under-five mortality, followed by Central and Southern Asia where 29 % of all under-five deaths occur. The United Nations recognises the first month of life as the period with greatest risk of dying and neonatal mortality as one of the greatest contributors to the under-five mortality rate, accounting for 47 % of the total (5). To summarise, neonatal mortality rates are decreasing but remain high in LMICs (6).

1.2 Neonatal causes of death

Globally, the main causes of death for neonates can be summed up in three categories (7). Firstly, premature birth (<37 completed weeks of gestational age) is a risk factor with both short-term and long-term consequences. Premature neonates have their own disease panorama where some conditions are associated with poor prognosis. Examples of these diseases are necrotising enterocolitis (which almost exclusively occurs in prematures), neonatal jaundice and bronchopulmonary dysplasia (8). Low gestational age and low birth weight are closely connected to neonatal mortality rate. The lower gestational age or birth weight a baby is born with, the higher the risk of dying is (9). Birth weight is categorised as low (< 2500 g), very low (< 1500 g), or extremely low (< 1000g). Gestational age can be divided into prematurity (< 37 completed weeks), very premature (< 32 weeks), and extremely premature (<28 weeks). These two factors are not mutually exclusive but rather enforce one another. Therefore, babies born as small for gestational age in regards to birth weight are most at risk (6). Secondly, being exposed to hypoxia during birth (perinatal asphyxia) due to prolonged labour can result in direct damage to the brain or long-term morbidity such as cerebral paresis or seizures (10). Lastly, the risk of infections and the development of sepsis increase the neonatal mortality, where premature babies are once again more vulnerable (11).

1.3 Surgical conditions

In the Sub-Saharan African countries, the spectrum of surgical diseases among neonates mainly contain different types of congenital malformations and the inflammatory disease necrotising enterocolitis (NEC) (12). A short description of these conditions follows below.

Anorectal malformation (ARM) occurs in 1 of 4000 births (13) and is discovered through a clinical examination or when the child presents with distended abdomen, vomiting, and electrolyte deficiency, all signs of intestinal obstruction. ARM is classified as low, intermediate, or high depending on the level of obstruction and treatment varies with classification. For low ARM, the surgical correction is performed 24 – 48 hours after birth. For higher obstructions, there are different surgical techniques and a temporary colostomy is usually done before definitive surgery. ARM is associated with other congenital malformations in 50-60% of the cases which include urogenital, skeletal, and cardiac systems. Another congenital malformation presenting with bowel obstruction in neonates is intestinal atresia. Jejunal or ileal atresia are more common than duodenal and occurs in 1 of 1 500 – 2 000 births. If nasogastric tubes and total parenteral nutrition is available, the condition can be surgically corrected during day two or three of life (14). Lastly, oesophageal atresia is a congenital anomaly where parts of the oesophagus are malformed or missing. The global prevalence of oesophageal atresia is 2.99 per 10 000 births. It can be combined with a tracheoesophageal fistula where an abnormal communication between the oesophagus and the trachea develop. The anomalies are classified according to the Gross classification depending on if both the atresia and fistula are present and where the anomalies are located anatomically. The surgical treatment consists of ligating the tracheoesophageal fistula and repairing the atresia by anastomosis (15).

Gastroschisis and omphalocele are two diagnoses with different pathological genesis which involve a defect closure of the abdominal wall. Omphalocele is a larger (4 – 8 cm) defect in the abdominal wall covered by an amniotic membrane sac which may contain both the liver, small and large intestines. Gastroschisis is a smaller (2 – 4 cm) defect where the small intestine can herniate but is not covered by a sac. Both diagnoses can be found during the antenatal period through ultrasound and are treated after birth with immediate wrapping of the organs outside the defective wall to avoid dehydration and later on surgical closure of the abdominal wall (14).

Apart from the congenital malformations, a great burden of disease treated with surgery is represented by NEC which is an inflammatory process in the abdomen causing damage to the intestines. The cause of NEC is multifactorial and yet not completely understood. Low birth weight and prematurity have been identified as risk factors for the development of NEC. Newborns with NEC usually present with feeding intolerance, distended abdomen, and bloody stool. NEC can be divided into three categories where Grade 1 is suspected NEC (non-specific radiographic findings), Grade 2 is definite NEC (with pneumatosis intestinalis), and Grade 3 is advanced NEC (intestinal perforation). Grade 1 is treated medically whereas Grade 2 and 3 can be treated with medical or surgical interventions. The surgical options depend on the severity of the disease and varies from peritoneal drainage to laparotomy with bowel resection (16).

1.4 Challenges in LMICs

Mortality rates for neonatal surgery remain high in Sub-Saharan Africa and the patients most at risk are the neonates undergoing surgery during the first week of life (17). Some issues associated with a high mortality have been identified and are presented below.

In LMICs, not all babies are born at a hospital. Instead, many of them are born at home. This can contribute to a delayed presentation of diseases that might not obvious at first, such as gastrointestinal malformations, NEC and complications due to asphyxia. Related to the late presentation is the issue of poor transportation services. For many families it can take several days to reach a hospital. These two factors contribute to a worsened condition when the newborns are referred to surgical facilities than if they would have been born at a hospital with resources to diagnose and correct the diseases earlier (12).

Another main concern regarding mortality in surgical neonates is the lack of resources. This includes both the low availability of neonatal intensive care units (NICUs), as well as the shortage of equipment such as ventilators and incubators. Another issue is the absence of trained personnel, which includes both paediatrics surgeons and neonatologists (17). The mortality in NICUs remains high, a phenomenon partly explained by the limited amount of resources but also by the patients' characteristics, since most patients admitted to a NICU have a high risk for comorbidities. Nevertheless, the survival rate for neonates increases if they are admitted to a paediatric or neonatal ICU instead of a general ICU (18).

Lastly, neonates, especially premature neonates, have a unique physiology with an immature immune system that makes them more susceptible to infections. The surgical neonate also has an additional risk of developing sepsis due to the invasive procedures and the exposure to organisms in hospital environments. This leads to sepsis being a significant contributor to neonatal deaths (11). In a study on neonatal emergency surgery in a LMIC, 56 % of the postoperative complications were infections and a majority of these occurred after surgery in the gastrointestinal area (19).

1.5 The need for additional research

Previous studies have described some risk factors associated with poor prognosis in surgical neonates in LMICs such as; being born outside of the hospital, the development of sepsis, premature birth, and the need for resuscitation after birth including the use of inotropic agents such as adrenaline (12, 20). In LMICs, knowledge about the outcome of intensive care among neonatal surgical conditions is scarce, which makes identifying factors associated with increased mortality difficult (21). This study is conducted to examine the hypothesis that there are identifiable factors affecting the mortality in surgical neonates. This study aims to explore the risk factors for surgical neonates at a tertiary hospital in Johannesburg, South Africa – a LMIC. This could provide the local hospital with additional knowledge on mortality for surgical neonates, enabling decision making when resources are limited and information about outcome has been lacking. From a wider perspective, the study also tries to emphasise the importance of neonatal surgery and its impact on the GBD, especially in LMICs.

2. Aim and objectives

2.1 Hypothesis

There are identifiable risk factors which contribute to the mortality in surgical neonates.

2.2 Aim

The aim of the study was to identify risk factors that contribute to a high mortality in surgical neonates, in a research setting where information about outcome is scarce, to enable knowledge-based decision making and improve the neonatal intensive care.

2.3 Objectives

The aim was achieved by retrospectively comparing risk factors in neonates who underwent surgery with outcome in terms of survival using local data from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in South Africa.

Specific objectives

1. Evaluate the overall survival in surgical neonates admitted to CMJAH between 1st of January 2016 to 31st of December 2018 and provide accurate information about outcome and risk factors.
2. Investigate if birth weight, place of birth, site of surgery, congenital malformations, duration of invasive ventilation and the occurrence of sepsis or NEC affect mortality in surgical neonates.

2.4 Specific research question

Will being born outside of the hospital, having a low birth weight, undergoing gastrointestinal surgery, having a congenital malformation, the duration of invasive ventilation and the development of sepsis or NEC increase the mortality in surgical neonates?

2.5 Significance of the study

When resources in a LMIC are limited and priorities must be made, knowledge about survival and risk factors which contribute to poor prognosis may be of value to assess patients most at risk and enable decision-making regarding neonates who undergo surgery.

3. Material and Methods

3.1 Research setting

South Africa is classified as an upper middle-income country (22) and has 58 million inhabitants, with Johannesburg as the largest city. 85% of the population enjoy the public health care and 15 % have access to the private health care through private insurances (23). CMJAH is a public referral and teaching hospital for the University of Witwatersrand. The hospital has a combined paediatric and neonatal intensive care unit with 14 ventilator beds and has been lacking policies about admission to the facility (18).

3.2 Study design

This was a retrospective study on surgical neonatal patients admitted to the NICU at CMJAH between 1st of January 2016 to 31st of December 2018. Primary outcome was measured as survival to discharge. The work of collecting, sorting and analysing data was done at the University of Witwatersrand in Johannesburg, South Africa, with support from a statistician and continuous contact with two supervisors at the University of Witwatersrand. The writing of the scientific report was mainly done with the help of two supervisors at Gothenburg University in Sweden.

3.3 Definitions

Neonatal patients were defined by age from birth to 28 days of life. Birth weight was measured in grams and was categorised into low birth weight (LBW) < 2 500g, very low birth weight (VLBW) < 1 500g, and extremely low birth weight (ELBW) < 1 000g. Gestational age was measured in weeks and prematurity was defined as being born before 37 completed weeks of expected pregnancy (6). Place of birth was divided into inborn and outborn, were inborn was defined as being born at CMJAH while outborn considered babies born at home or any other medical facility than CMJAH. Surgical neonates were defined as a neonate requiring surgical procedures and postoperative care in the neonatal intensive care unit, which excludes minor surgical procedures such as establishing a central vascular access. The surgical interventions were categorised by anatomic site-specific codes according to the Vermont Oxford Network (VON) database. For patients with multiple surgeries, each surgery was counted in its category respectively, leading to more surgeries observed than patients. Congenital anomalies were also defined through specific codes in the VON database (24). Sepsis was defined as positive blood culture of significant organisms and classified as early onset (EOS) within 72 hours or late onset (LOS) if presenting after 72 hours. Drug resistant bacteria included MRSA (methicillin-resistant Staphylococcus aureus), CRE (carbapenem-resistant Enterobacteriaceae), and ESBL *Klebsiella* (Extended Spectrum Beta-Lactamase).

3.4 Variables

Primary outcome was survival to discharge where patients discharged or transferred home, to another department or hospital were considered survivors. Data on death after discharge was not available. Variables analysed are displayed in Table 1.

Table 1: Variables included in the statistical analyses divided into pre-, peri- and postoperative factors.

Preoperative factors	Perioperative factors	Postoperative factors
Place of birth	Surgery due to congenital anomaly	Length of stay
Birth weight	Surgery due to NEC	Requiring ventilation
Gestational age	Head & Neck surgery	Duration of ventilation
Head circumferences	Thorax surgery	Age at outcome
Age on admission	Gastrointestinal surgery	Weight at outcome
Gender	Urinary or genital surgery	Bacterial sepsis
Resuscitation at birth	Central nervous system surgery	Gram positive or negative bacteria
Apgar score at 5 minutes	Musculoskeletal surgery	Drug resistant bacteria
Congenital anomaly		Fungal sepsis
Abnormal cranial sonar finding		Metabolic acidosis
Bacterial sepsis		Blood transfusion
Gram positive or negative bacteria		Conventional mechanical ventilation
Drug resistant bacteria		
Fungal sepsis		

3.5 Inclusion and exclusion criteria

Patients included were neonates admitted for the first time to the neonatal intensive care unit who had undergone a surgical intervention. Patients born at the hospital or admitted to the hospital were included. Patients with insufficient data were excluded from analysis. Patients admitted after day 28 of life were also excluded.

3.6 Data collection

Information about the patients from the neonatal unit at CMJAH was gathered at discharge from the patient records, handwritten in English. Forms that summarise the essentials about the patient's demographics, clinical conditions, and outcome relevant for clinical research were filled out for each patient. There were two different forms, one for patients with a birth weight < 1500 g and another one for patients > 1500 g. The information in the forms was then entered on to the REDCap ® (Research Electronic Data Capture) database, hosted by the University of Witwatersrand (25). Data from the relevant dates was then extracted to two Excel (Microsoft, USA) documents, one for patients with a birth weight < 1500 g and one for the patients weighing > 1500 g at birth. The variables in the different spreadsheets were then compared and merged into one spreadsheet used for the statistical analysis.

3.7 Statistical analysis

Extracted data was analysed using SPSS 26 (IBM, USA). Only valid cases were analysed. For descriptive statistics, mean and standard deviation (SD) were used for normally distributed continuous data while median and interquartile range (IQR) were used to report skewed continuous variables. Categorical variables were presented with frequencies and percentages. Primary outcome was measured as death or survival to discharge. To conduct the statistical analysis, a univariate binary logistic regression analysis was first performed where a two-sided p-value < 0.05 was considered statistically significant. Since there were missing data in some variables, the total number of observations varies among variables and therefore the total number is reported for every categorical variable. To investigate correlations between variables, Spearman's rank correlation coefficient and crosstabs were used. For variables in the primary analysis, a multivariate logistic regression model was built according to backwards selection (26). The final model with significant variables was reported.

4. Ethical considerations

The degree project was integrated in a study approved by the Human Research Ethics Committee of the University of Witwatersrand, Johannesburg, with clearance certificate number M160338 (Appendix A). Since the study was retrospective, consent from each individual patient was not required. Data sheets only displayed a database number; personal information about patients was stored in a separate database in a different location only available to supervisors of the study. The study was conducted according to the World Medical Association (WMA) Declaration of Helsinki (27).

5. Results

5.1 Descriptive results

During the studied period, 5061 patients were admitted to the neonatal unit at CMJAH. Out of these, 287 patients underwent a surgical procedure. Three patients were excluded since critical data, such as information about outcome, was missing. Another six patients were excluded since they had been admitted after day 28 of life. 278 patients met the inclusion criteria and were included in the analysis (see Figure 1).

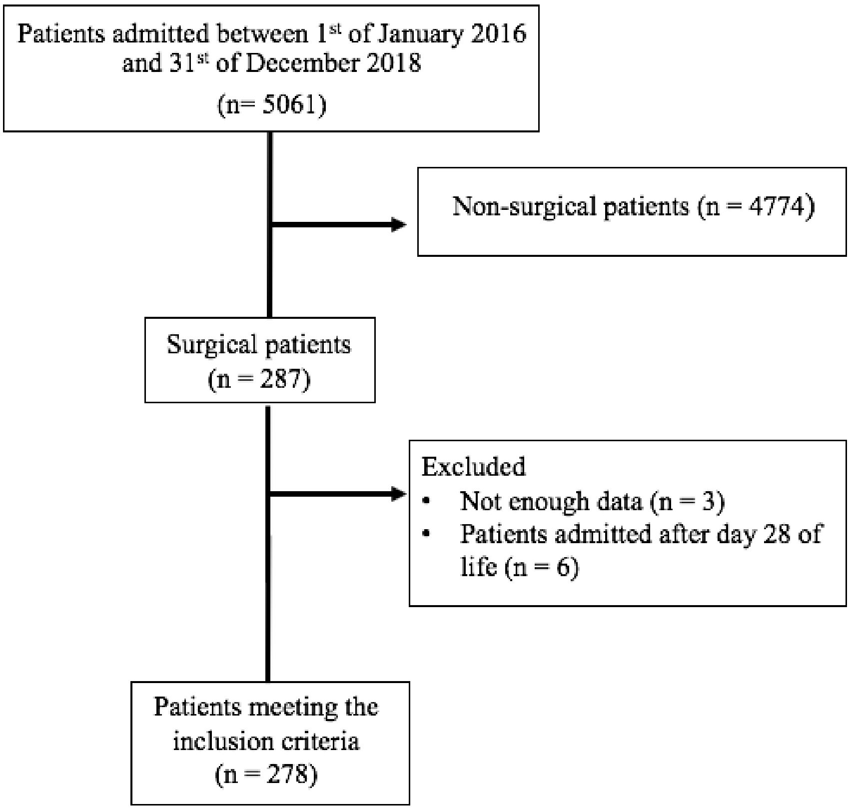

Figure 1: Patient selection process for neonates with surgical diagnoses admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2016 – 31 December 2018.

Clinical characteristics for the surgical neonates are shown in Table 2 (below). A majority of neonates included were male (151/278, 54.3%). Most of the patients were outborn (169/260, 60.8%). The median birth weight was 1962 g (IQR 1376 – 2700) and gestational age 34 (IQR 31 – 39) weeks. 78/278 (28.1%) of the neonates were exposed to HIV, however, none of the children tested positive for HIV.

Table 2: Clinical characteristics for neonatal patients with surgical diagnoses admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2016 – 31 December 2018.

Clinical characteristics	Neonates with surgical diagnosis (n=278)
Birth weight in grams Median, [IQR]	1962 [1376 – 2700]
Gestational age in weeks Median, [IQR]	34 [31 – 39]
Head circumferences at birth in cm Mean, (SD)	30.9 (4.3)
Age on admission in days Median, [IQR]	1 [1 – 7]
Length of stay at hospital in days Median, [IQR]	15 [5 – 37]
Duration of ventilation in days Median, [IQR]	2 [1 – 8]
Age at outcome in days Median, [IQR]	18 [9 – 37]
Weight at outcome in grams Median, [IQR]	2100 [1655 – 2800]

Data was reported as median and interquartile range (IQR) or mean and standard deviation (SD).

Regarding the maternal characteristics, the mean age was 28.3 (SD 5.8) years. The median parity was 1 (IQR 0 – 2) and gravidity 2 (IQR 1 – 3). For those neonates in which the mode of delivery was recorded, normal vaginal delivery (85/173, 49.1%) was almost equivalent to caesarean section (84/173, 48.6%).

Out of the 278 neonatal patients admitted with a surgical diagnosis, 193 (69.4%) survived to discharge and 85 (30.6%) died during the hospital stay. Overall, surgery in the gastrointestinal area was the most common (224, 80.6%). Of these 224 surgeries, 100 (44.6%) were due to a congenital anomaly such as intestinal atresia or gastroschisis, and 83 (37.0%) due to NEC Grade 2 or 3. After gastrointestinal surgery, surgery in the thoracic area was the second most common (26, 9.4%) with a majority being oesophageal atresia with or without tracheoesophageal fistula. The types of surgeries are displayed in Table 3.

During the hospital stay, 7/278 (2.5%) of the surgical neonates were diagnosed with EOS and 138/278 (49.6%) with LOS. Out of the 138 babies who developed LOS, 57 (41.3%) had a drug resistant bacterium where ESBL *Klebsiella* was the most common.

Table 3: Types of surgeries performed on neonatal patients admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2016 – 31 December 2018.

Type of surgery	Number of patients n (%)
Gastrointestinal	224 (80.6%)
Thorax	26 (9.4%)
Genital or urinary	10 (3.6%)
Central Nervous System	8 (2.9%)
Musculoskeletal	7 (2.5%)
Head & Neck	5 (1.8%)
Open heart	1 (0.4%)

5.2 Univariate logistic regression analysis

To analyse the relationship between risk factors and outcome, a univariate logistic regression analysis was performed. Results of a primary analysis with variables included in the specific research question are shown in Table 4 and additional factors that might be interesting are shown in Tables 5 and 6.

Table 4: Primary analysis of risk factors and outcome (Died vs Survived) for surgical neonates admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2016 – 31 December 2018.

Variable	Died	Survived	p-value	OR (95% CI)
Birth weight Median, [IQR]	1500 [1144 – 2115]	2090 [1465 – 2800]	0.001*	0.99 (0.99 – 0.99)
Place of birth (Inborn) n (%)	37/84 (44.0)	54/176 (30.7)	0.036*	1.78 (1.03 – 3.04)
Gastrointestinal surgery n (%)	75/85 (88.2)	149/193 (77.2)	0.026*	2.22 (1.09– 4.88)
Congenital anomaly n (%)	40/85 (47.1)	98/193 (49.2)	0.739	0.917 (0.54 – 1.52)
Duration of ventilation Median, [IQR]	4.0 [1.0 – 11.5]	2.0 [1.0 – 6.0]	0.014*	1.03 (1.00 – 1.05)
EOS n (%)	5/85 (5.9)	2/193 (1.0)	0.035*	6.01 (1.26 – 42.65)
LOS n (%)	53/85 (62.3)	85/193 (44.0)	0.005*	2.10 (1.25– 3.57)
NEC n (%)	42/85 (49.4)	44/193 (22.8)	<0.001**	3.27 (1.90– 5.67)

*Data was reported as median and interquartile range (IQR) or number (n) of total valid number of observations and percentages (%). OR = Odds Ratio. CI = Confidence interval at 95%. NEC = necrotising enterocolitis. EOS = early onset sepsis. LOS = late onset sepsis. * p < 0.05. ** p < 0.001.*

Table 5: Secondary analysis of continuous variables and outcome (Died vs Survived) for surgical neonates admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2016 – 31 December 2018.

Variable	Died	Survived	p-value	OR (95% CI)
Gestational age Median, [IQR]	32 [29 – 36]	35 [31 – 40]	<0.001**	0.89 (0.84 – 0.95)
Head circumferences Median, [IQR	29.0 [26.0 – 34.0]	31.5 [29.0 – 34.8]	0.032*	0.89 (0.80 – 0.99)
Age on admission Median, [IQR]	0 [0-5.0]	2.0 [0-8.0]	0.099	0.97 (0.92 – 1.01)
Length of stay at hospital Median, [IQR]	13.0 [6.0– 31.0]	16.0 [5.0 – 39.5]	0.137	0.99 (0.98 – 1.00)
Age at outcome Median, [IQR]	15.0 [7.5 – 31.0]	20.0 [10.0 – 40.0]	0.126	0.99 (0.98 – 1.00)
Weight at outcome Median, [IQR]	1680 [1300 – 2400]	2200 [1842 – 2897]	<0.001**	0.99 (0.99 – 1.00)

*Data was reported as median and interquartile range (IQR) or number (n) of total valid number of observations and percentages (%). OR = Odds Ratio. CI = Confidence interval at 95%. * p < 0.05. ** p < 0.001.*

Table 6: Secondary analysis of categorical variables and outcome (Died vs Survived) for surgical neonates admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2016 – 31 December 2018.

Variable	Died n (%)	Survived n (%)	p-value	OR (95% CI)
Gender (male)	43/85 (50.6)	108/193 (56.0)	0.518	0.85 (0.50 – 1.41)
Apgar score at 5 minutes < 6	7/49 (14.3)	9/94 (9.6)	0.404	1.57 (0.53 – 4.51)
Resuscitation at birth	21/85 (24.7)	24/193 (12.4)	0.013*	2.31 (1.19 – 4.44)
Abnormal cranial sonar finding	28/85 (32.9)	37/193 (19.2)	0.014*	2.07 (1.15 – 3.68)
Surgery due to congenital anomaly	35/85 (41.2)	97/193 (48.7)	0.247	0.74 (0.43 – 1.23)
Surgery due to NEC	41/85 (48.2)	42/193 (21.8)	<0.001**	3.35 (1.94 – 5.81)
Metabolic acidosis	35/85 (41.1)	15/193 (7.8)	<0.001**	8.48 (4.36 – 17.19)
Blood transfusion	57/85 (67.1)	96/193 (49.7)	0.007*	2.06 (1.22 – 3.54)
Conventional mechanical ventilation	75/85 (88.2)	167/193 (77.7)	0.033*	2.15 (1.06 – 4.74)
Sepsis				
Gram-positive bacteria, EOS	4/85 (4.7)	1/193 (0.5)	0.021*	9.48 (1.38 – 186.88)
Gram-positive bacteria, LOS	25/85 (29.4)	54/193 (27.9)	0.827	0.94 (0.53 – 1.67)
Gram-negative bacteria, LOS	38/85 (44.7)	58/193 (30.1)	0.019*	1.88 (1.11 – 3.19)
Drug resistant bacteria, EOS	17/85 (20.0)	40/193 (20.7)	0.890	1.05 (0.56 – 2.01)
Fungal sepsis	15/49 (30.6)	24/84 (28.6)	0.803	0.91 (0.42 – 1.98)

*Data was reported as median and interquartile range (IQR) or number (n) of total valid number of observations and percentages (%). OR = Odds Ratio. CI = Confidence interval at 95%. NEC = necrotising enterocolitis. EOS = early onset sepsis. LOS = late onset sepsis. * p < 0.05. ** p < 0.001.*

The was a significant difference in outcome whether the patients were born at the hospital or outside of the hospital. For inborn patients, the odds ratio for death was 1.78 (95% CI 1.03 – 3.04, $p = 0.036$) compared to the outborn patients. Regarding birth weight and gestational age, there were statistically significant differences in odds ratio between the two groups where newborns with a higher birth weight (OR 0.99, 95% CI 0.99 – 0.99, $p = 0.001$) and gestational age (OR 0.89, 95% CI 0.84 – 0.95, $p < 0.001$) had a lower risk of dying. However, there was no significant difference in outcome regarding gender, Apgar score at 5 minutes, or age on admission. If the patient had an abnormal cranial sonar finding within the first 28 days of life, the odds ratio for death was 2.07 (95% CI 1.15 – 3.68, $p = 0.014$) compared to if the patient's cranial sonar finding within 28 days was normal.

Receiving initial resuscitation in the delivery room was significantly associated with poor prognosis with an odds ratio of 2.31 (95% CI 1.19 – 4.44, $p = 0.013$). However, there was no significant differences between the degrees of resuscitation, such as endotracheal intubation, chest compressions, or receiving adrenaline. Receiving invasive conventional mechanical ventilation was associated with poor prognosis as well as a longer duration of ventilation during the hospital stay was associated with higher odds ratio for death (OR 1.03, 95% CI 1.00 – 1.05, $p = 0.014$).

Regarding the anatomical site of surgery, gastrointestinal surgery was significantly associated with poor prognosis with an odd ratio for death of 2.22 (95% CI 1.09 – 4.88, $p = 0.026$). No other surgical site was significantly associated with a difference in outcome. In the univariate analyses, neither congenital anomaly nor surgery due to congenital anomaly were significantly associated with mortality. There was a significant difference in survival for patients with the diagnosis of NEC. For patients with NEC undergoing any type of surgery, the odds ratio of death was 3.27 (95% CI 1.90 – 5.67, p < 0.001), associating NEC with poor prognosis.

Both EOS and LOS were associated with a higher odds ratio for death. The odds ratio for death was 6.01 (95% CI 1.26 – 42.65, p= 0.035) for patients with EOS. For LOS, there was a significant difference in death with an odd ratio of 2.10 (95% CI 1.25 – 3.57, p = 0.005). There was no significant difference in death associated with drug resistant bacteria (including MRSA, CRE and ESBL *Klebsiella*) nor fungal sepsis.

5.3 Multivariate logistic regression analysis

For variables in the primary analysis, a multivariate logistic regression model was built according to backward selection. The results of the final model are shown in Table 7.

Table 7: Multivariate logistic regression analysis on primary variables and outcome (Died vs Survived) for surgical neonates admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2016 – 31 December 2018.

Variable	p-value	OR (95%CI)
Place of birth (Inborn)	0.016*	2.11 (1.152 – 3.899)
Congenital anomaly	0.001*	5.51 (2.157 – 16.580)
NEC	< 0.001**	6.83 (2.704 – 19.940)
Birth weight	0.017*	0.99 (0.991 – 0.999)

*OR = Odds Ratio. CI = Confidence interval at 95%. NEC = necrotising enterocolitis. * p < 0.05. ** p < 0.001.*

The multivariate logistic regression model showed that being born at the hospital, being born with a congenital anomaly, development of NEC, and a low birth weight were all factors that independently increase the risk of dying. However, duration of ventilation, gastrointestinal surgery, and late onset sepsis were not significant in the multivariate logistic regression analysis.

6. Discussion

6.1 Key findings

This study suggests that having a low birth weight, being born at the hospital, having a congenital anomaly, or developing NEC are all independently associated with increased risk of mortality in surgical neonates. Furthermore, the study shows that there was no significant difference in mortality regarding gastrointestinal surgery, developing sepsis, or for how long the patient was ventilated.

In this study, close to a third of the patients with surgical diagnoses died. The mortality is similar to other studies conducted in the same region (19, 28). Surgical neonates who died had a statistically significant lower birth weight and gestational age, results that align with previous research (6, 29). Even though there were statistically significant results for these two variables, the observed effect (OR 0.99, 95% CI 0.99 – 0.99 and OR 0.89, 95% CI 0.84 – 0.95 respectively) might be too small to have a clinical significance.

Regarding place of birth, this study suggests that there is a greater risk of dying if the patient is born at the hospital. Previous research on how birthplace impact mortality is inconclusive (30).

Some studies suggest that being born outside of a tertiary hospital (at home or a smaller health facility), is associated with increased mortality. Inborn babies are theorised to enjoy better access to surgical and intensive care. Furthermore, delivery at a tertiary hospital rather than at home reduce the need for transportation of critical ill newborns should complications arise (31-33). Yet, other studies have not been able to establish a statistically significant correlation between place of birth and mortality (34, 35). There are several possible explanations for these indecisive results, which makes it difficult to draw any generalised conclusions. Firstly, numerous studies research specific surgical diagnoses but few examine a whole group of surgical neonates. The importance of place of birth might differ depending on the surgical diagnosis. Furthermore, large multicentre studies are often conducted in HICs and results might not always be applicable in a LMIC.

In order to interpret the results of this study appropriately, attention should be paid to the type of hospital at which the data was collected. CMJAH is a large referral centre to where both high-risk pregnancies and high-risk babies born are transferred to from smaller health facilities. This could mean that babies with identified risk factors during pregnancy are overrepresented in the data on hospital deliveries. Additionally, there is also a possibility that babies with very poor prognosis born at home might not make it to the hospital alive at all. Thus, there might be a selection bias where more babies delivered at the hospital have a poorer prognosis. However, this study's sample size was relatively small and factors contributing to mortality are many, which means that one should be cautious about drawing any definite conclusions from these results. Even though there is no consensus about the effect of place of birth, many studies recognise that neonatal mortality is a complex and multifactorial phenomenon and that place of birth could play an important role for outcomes in surgical neonates (13, 30, 34). Therefore, a future study focusing on associated socioeconomic factors could be of value to gain greater understanding of how place of birth and mortality interact in the local setting of Johannesburg.

Gastrointestinal surgery was the only surgical site significantly associated with increased mortality in the univariate analysis. This could be related to the sample size, since a larger number of gastrointestinal surgeries were performed compared to other types of surgery and that there were not enough observations in the analysis for other types of surgery. Another possible explanation, supported by previous research, is that gastrointestinal surgery is extensively invasive with a high risk for complications or death (13).

Furthermore, the underlying reason why gastrointestinal surgery was performed should also be addressed. For example, the incidence of NEC is high among premature babies, a patient category already at risk of high mortality due to their immature development, which also makes them more susceptible for developing sepsis (29). NEC surgery usually includes laparotomy and resecting parts of the bowel if necessary (36). A combination of a diagnosis with poor prognosis (such as NEC), undergoing major gastrointestinal surgery, coupled with the development of sepsis is likely to put the baby at higher risk for additional comorbidities or death. Similarly, some congenital malformations, such as gastroschisis and diaphragmatic hernia, which may require gastrointestinal surgery, are also associated with high mortality and morbidity (31, 37). In the multivariate analysis, being diagnosed with NEC or having a congenital malformation were both independently associated with increased mortality. This could be explained by severity of the diagnoses since the remaining most common diagnoses in the gastrointestinal category involved correction of malrotation, small bowel resection, and gastrostomy which are not as severe and have a better prognosis. The results indicate that babies with NEC or a congenital malformation have a poorer prognosis for survival which should be considered when making risk assessments in the clinic.

Consistent with previous studies (11), the development of bacterial sepsis was significantly correlated with increased mortality in the univariate analysis, but could not be isolated as a significant factor in the multivariate analysis. There was also no significant difference in outcome regarding sepsis caused by drug resistant bacteria such as CRE, MRSA, or ESBL *Klebsiella*, nor fungal sepsis. MRSA has previously been demonstrated as a risk factor for developing sepsis in surgical neonates (38). A possible explanation for the differences in results between this study and previous research could be that the number of observations for sepsis and drug resistant bacteria are relatively low. Information on which antibiotics were given and when in correlation to outcome was unavailable but would be interesting to investigate in further research.

6.2 Methodical considerations

The study was conducted with a retrospective design which was suitable for the time frame given. Analysing locally collected data is valuable since the results can be converted into applicable and relevant knowledge for clinical use. Nonetheless, performing a retrospective study also comes with limitations. Firstly, the dataset suffered from instances of missing data. This led to both that it was not possible to analyse all variables available, and that a few patients had to be excluded. A prospective study could have resulted in more exhaustive data collection and in turn support a more accurate analysis. However, if a prospective study would have been conducted, the study's sample size would have been considerable smaller during the given time frame.

A second limitation concerns the patient selection, since only neonates admitted to neonatal units were included. Essentially, this means that neonates who bypass the neonatal unit after surgery but are admitted directly to the surgical wards were not included in the sample. The number of babies not included because of this is unknown. This could be a possible selection bias and an improvement would have been to include these patients as well.

Lastly, some variables which would have been useful to analyse were not available. Originally there were two separate databases; one for VLBW and one for babies born > 1500 g. The two databases' variables where not identical and some of them had to be excluded because of this. Moreover, options in the variables were sometimes interpreted in different ways. For example, in the VLBW database, the options in a variable were "checked" or "unchecked" where the latter one included both "negative" or "not known", whereas the other database had the options "positive", "negative", or "not known". This makes interpretation of the variables more difficult and may have affected the results. Nevertheless, it is still important that gathered information, although incomplete, can be analysed and results could still be of value at the local hospital to support decision-making.

A multivariate logistic regression model was chosen to analyse the variables in the study. There is a strength in being able to not only compare variables to outcome separately, but also study how they interact with each other and affect the outcome. However, the sample size was too small to gain a high statistical power to adjust for a large number of confounding factors. To improve the study, one could have extended the study to observe a longer period of time to include more patients.

Due to the lack of population-based studies in South Africa, there is also a limitation regarding generalisability. One factor that contributes to this is that South Africa is a resource limited country and large studies might be hard to conduct. The incidence of different diseases is often unknown, which makes findings in small studies difficult to apply on the whole population. However, it is of great value to conduct studies in LMICs to contribute to a larger amount of research which can be used in the future.

Lastly, CMJAH is a large referral centre where critically ill patients are admitted in a larger extent. The reported mortality rates at the hospital could be higher than the actual mortality rates in the population in South Africa. Therefore, the results might not be as representative enough to draw population-based conclusions from. However, since CMJAH is a referral hospital it was possible to gather a larger sample size than if the study would have been conducted in a smaller facility. In the future, it would be interesting to see population-based studies be conducted in South Africa and see if the results differ.

To summarise, the main limitations of this study were its retrospective character, missing data, and a relatively low sample size. Nevertheless, it is important to conduct studies in countries where research is scarce, and retrospective studies also contributes to wider understanding of the local challenges which can be of clinical use in the future.

7. Conclusions

In conclusion, the survival rate for surgical neonates during the studied period of time was 69.4%. This study suggests that being born at the hospital, having a low birth weight, being born with a congenital anomaly, and developing NEC are all factors that independently increase the risk of dying in surgical neonates. This information could provide to a clearer risk profile for surgical neonates at CMJAH in Johannesburg and might be valuable for decision making in the neonatal unit. A suggestion for future studies in the same research setting would be to also focus on how socioeconomic factors contribute to an increased mortality in surgical neonates, to gain a deeper understanding on the causes of mortality.

These results also emphasise the importance of keeping neonatal surgery in mind when the global community aims to improve neonatal care. To reach the Sustainable Development Goal of reducing the neonatal mortality to 12 deaths per 1000 live births, surgical conditions should be addressed and taken into consideration when developing new health policies both nationally and globally.

Populärvetenskaplig sammanfattning

Riskfaktorer för död hos nyfödda som genomgått kirurgi

Barnadödligheten hos nyfödda barn sjunker i världen och har gjort så de senaste 30 åren. Det finns dock stora skillnader mellan länder, och i låg- och medelinkomstländer är denna dödlighet betydligt högre än i höginkomstländer. De främsta orsakerna till varför nyfödda (specifikt de första 28 dagarna i livet) barn dör globalt sett är att vara född förtidigt, att drabbas av syrebrist under förlossningen eller att få blodförgiftning. Dessa utmaningar är välkända och hålls i åtanke när länder implementerar nya riktlinjer för att förbättra vården av nyfödda. Ett mindre prioriterat område är de nyfödda barn som behöver opereras, vilket också kan bidra till en ökad risk för död. I låg- och medelinkomstländer har logistiska faktorer, som för att vara född utanför sjukhuset samt begränsad tillgång till intensivvård och utbildad personal, identifierats som utmaningar att förbättra för att dessa kirurgiska patienter ska överleva i större utsträckning. Det finns också medicinska aspekter att ta hänsyn till som kan påverka dödligheten, till exempel om man är född med en missbildning, om man drabbas av infektioner efter operationen eller om man är född med en låg födelsevikt.

Målet med denna studie var att undersöka om några av dessa tidigare identifierade riskfaktorer ökar risken för död hos kirurgiska patienter samt att visa på att kirurgi hos nyfödda är ett viktigt område att prioritera för att bidra till en minskad barnadödlighet. Studien utfördes med data samlad under 3 år på en intensivvårdsavdelning för nyfödda barn i Johannesburg, Sydafrika, där riskfaktorer analyserades mot huruvida barnen överlevde eller dog.

Av de 278 kirurgiska patienterna som studerades överlevde 193 (69.4%) stycken och 85 (30.6%) dog. Liknande siffror på överlevnad har man sett i närliggande länder också. Barnen som dog var i större utsträckning födda förtidigt än de som överlevde. Studien lyckades isolera låg födelsevikt, att vara född på sjukhuset, att vara född med en missbildning och att drabbas av den inflammatoriska tarmsjukdomen nekrotiserade enterokolit som riskfaktorer som var för sig ökar risken för död hos de kirurgiska patienterna.

Studiens resultat är användbara på flera olika sätt. Först och främst finns det ett behov av mer forskning från låg- och medelinkomstländer. Att använda resultaten från lokalt samlad information kan vara fördelaktigt när beslut ska fattas om hur vården ska förbättras på sjukhuset som studien gjordes på. Ur ett större perspektiv kan resultaten i framtiden bidra till att riskfaktorerna hos nyfödda barn som opererats uppmärksammas i större utsträckning och prioriteras när nya beslut fattas i arbetet för att minska barnadödligheten.

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Appendix A

R14/49 Dr Robin Terence

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160338

NAME: (Principal Investigator)	Dr Robin Terence
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	An Analysis of Neonates with Surgical Conditions Admitted to the Neonatal Intensive Care Unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2015
DATE CONSIDERED:	01/04/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/06/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in March and will therefore be due in the month of March each year.

Principal Investigator Signature ____________ Date ____________

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES