

An analysis of neonates with surgical diagnoses admitted to the neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, South Africa

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Background. The burden of neonatal surgical conditions is not well documented in low- to middle-income countries (LMICs). These conditions are thought to be relatively common, with a considerable proportion of neonates admitted to the neonatal intensive care unit (NICU) requiring surgical intervention.

Objectives. To review neonates with surgical conditions admitted to the NICU in our hospital setting.

Methods. This was a retrospective, descriptive study of neonates with surgical conditions admitted to the NICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), South Africa, between 1 January 2013 and 31 December 2015. The characteristics and survival of these neonates were described using univariate analysis. The NICU at CMJAH is combined with a paediatric intensive care unit, to a total of 15 beds, and serves as a referral unit.

Results. Of 923 neonates admitted to the NICU, 319 (34.6%) had primarily surgical conditions. Of these 319 neonates, 205 survived (64.3%). There were 125/319 neonates (39.2%) with necrotising enterocolitis (NEC), 55 of whom survived (55/125; 44.0%), making the presence of NEC significantly associated with poor outcome ($p < 0.001$). Other significant predictors of poor outcome were the patient being outborn ($p = 0.029$); the presence of late-onset sepsis ($p < 0.001$), with Gram-negative organisms ($p = 0.005$); and lesser gestational age ($p = 0.001$) and lower birth weight ($p < 0.001$). Major birth defects were present in 166/319 neonates (52.0%). The abdomen was the most prevalent site of surgery, with 216/258 procedures (83.7%) being abdominal, resulting in a mortality rate of 76/216 (35.2%).

Conclusions. Neonates with major surgical conditions accounted for one-third of NICU admissions in the present study. The study highlights the considerable burden placed on paediatric surgical services at a large referral hospital in SA. Paediatric surgical services, with early referral and improvement of neonatal transport systems, must be a priority in planned healthcare interventions to reduce neonatal mortality in LMICs.

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The burden of neonatal surgical diseases in Africa is not well documented. Neonatal surgical conditions are thought to be relatively common, with a considerable proportion of neonates admitted to the neonatal intensive care unit (NICU) requiring surgical intervention.^[1,2] A survey among paediatric surgeons practising in Africa indicated that neonatal surgery comprised 10 - 20% of their paediatric surgical workload.^[1] There are no specific data on the number of surgical admissions to NICUs in South Africa (SA), resulting in inadequate planning and delivery of neonatal surgical services.

The World Health Organization estimates that ~10% of all neonatal deaths in sub-Saharan Africa and South Asia are due to congenital malformations, many of which are only amenable to operative intervention.^[1] In Africa, it was found that congenital malformations accounted for more than a quarter of paediatric surgical admissions and nearly half of emergency procedures.^[3,4]

Common surgical problems encountered in Africa include necrotising enterocolitis (NEC), congenital diaphragmatic hernia, anorectal malformations, Hirschsprung's disease, omphalocele, gastroschisis, oesophageal atresia and tracheo-oesophageal fistula (TOF), intestinal atresia and intestinal perforation.^[1]

Resources for neonatal surgery vary widely between high-income countries (HICs) and low- to middle-income countries (LMICs).^[3] There is variability with regard to conditions resulting in admission to hospital, as well as contributing to the neonatal surgical workload, in Africa.^[1] These differences can be attributed to a number of factors, such as availability of antenatal diagnosis, primary healthcare and transport facilities, distance, poverty, cultural methods of treatment, time of presentation, death before arrival, access to paediatric surgery, intensive care and neonatal anaesthesia, and genetic predisposition in the various populations.^[1,4]

In HICs, much progress has been made in the management of neonatal surgical conditions, resulting in a decrease in neonatal surgical mortality rates from >50% in the 1950s to <5% in recent years.^[1,5,6] However, in Africa multiple challenges leading to high morbidity and mortality remain, with mortality figures between 16% and 45% being reported.^[1,4,5]

A major postoperative complication is the development of sepsis, which results in serious morbidities and mortality. Surgical interventions have been shown to have a strong association with the development of infection, with the risk rising as the number of

interventions increases.^[2,7,8] Infections may be septicaemia, related to supportive interventions (e.g. ventilator-associated pneumonia, urinary tract infections, central line-associated sepsis), or localised to the surgical site.

Neonates who need surgical intervention require mechanical ventilation for longer periods than their non-surgical counterparts and have increased duration of hospitalisation. The site of surgery determines the site of infection: laparotomies (generally considered to be a contaminated procedure) have a higher rate of surgical site infection than thoracic surgeries (generally considered to be a clean procedure).^[2] Notably, very-low-birth-weight (VLBW) neonates as well as neonates who have undergone gastroschisis closure are at the greatest risk of developing surgical site infection.^[2]

Many hospitals in sub-Saharan Africa do not have paediatric surgical facilities or neonatal intensive care units, and neonates with surgical conditions are therefore referred to central hospitals. The impact of neonatal surgical patients on the limited neonatal intensive care facilities available is not known.

Objectives

To review neonates with surgical conditions admitted to the NICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a large referral hospital in SA.

Methods

This was a retrospective, descriptive study of neonates (<28 days) admitted to the NICU at CMJAH with surgical diagnoses between 1 January 2013 and 31 December 2015. Neonates with incomplete records were excluded. Outcome was defined as death or survival to discharge.

The NICU at CMJAH is combined with a paediatric intensive care unit, to a total of 15 beds. Neonates with surgical conditions admitted to the CMJAH NICU are managed by neonatologists in conjunction with paediatric surgeons. Owing to limited resources, the NICU essentially functions as a ventilator unit – neonates who require intensive observation are not routinely admitted.

Neonates with surgical conditions admitted to the NICU and treated by paediatric surgeons were included in the analysis. Neonates with surgical conditions who were admitted to high-care wards, e.g. those with minor conditions (such as circumcision) and those who underwent surgical procedures in the high-care wards, including insertion of central catheters, were not included. A neonate who had more than one surgical condition or congenital abnormality (e.g. TOF and a cardiac defect) was included in all the respective categories.

During the study period, patent ductus arteriosus ligations were performed by paediatric surgeons, and so were included in the analysis. All other forms of congenital heart defects were repaired by cardiothoracic surgeons in a separate unit and were therefore excluded from the analysis. Myelomeningocele were repaired by neurosurgeons in a separate unit and were excluded from the analysis of surgical procedures, but because these patients were admitted to the NICU postoperatively, they were included in the analysis of the frequencies of major birth defects. Head and neck surgery was performed by ENT surgeons in a separate unit and was excluded from the analysis.

Major birth defects included lethal or life-threatening anomalies as defined in the Vermont Oxford Network database (www.vtoxford.org). Sepsis was classified as culture proven only, with onset within 72 hours of birth being classified as early-onset and after 72 hours as late-onset sepsis. Grades 2 and 3 NEC (diagnosed both clinically and radiologically according to the modified Bell's staging criteria) were included in the NEC variable.^[9] Neonates were deemed to have a low 5-minute Apgar score if they had an Apgar score ≤ 5 at 5 minutes.

Database

The neonatal records at CMJAH are stored on the REDCap (Research Electronic Data Capture) database, hosted by the University of the Witwatersrand.^[10] REDCap is a secure web-based programme that aids data capture for the purposes of clinical audit and quality improvement. Upon discharge of patients, data were captured onto the REDCap database. The information was verified at several stages of collection. The following data were collected from the database: (i) maternal data – demographics, antenatal care (ANC), place of delivery and mode of delivery; and (ii) infant data – gestational age, birth weight, sex, 5-minute Apgar score, NEC, other surgical conditions, duration of ventilation, late sepsis (occurring after 72 hours) and outcome at discharge (death or survival). The information regarding surgery was correlated with a corresponding surgical database.

Statistical analysis

An Excel spreadsheet, version 16 (Microsoft, USA), was used to enter the data, which were then imported into the statistical software package SPSS version 23 (IBM, USA). Frequencies and percentages were used to describe categorical variables. Means and standard deviations (SDs) were used to describe normally distributed continuous variables, and skewed continuous variables were described using medians and interquartile ranges (IQRs). For the purposes of analysis, survivors were classified as neonates who were transferred out to other hospitals and those who were discharged from the NICU. Neonates who died were compared with those who survived with regard to characteristics, surgical diagnoses and interventions, using univariate analysis. The characteristics of survivors v. non-survivors were compared using univariate analysis. Chi-square tests were used to compare categorical variables, and continuous variables were compared using unpaired *t*-tests (for those that were normally distributed) and non-parametric tests (for those with skewed distribution). A *p*-value <0.05 was considered significant. Only valid cases were analysed for each variable (i.e. cases with missing data were excluded from the analysis).

Ethical considerations

The Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, granted ethics approval for the study (ref. no. M160338).

Results

During the study period, 5 320 infants were admitted to CMJAH, of whom 923 were admitted to the NICU; 319 neonates fulfilled the inclusion criteria and were included in the analysis (Fig. 1).

The clinical characteristics of neonates admitted with surgical diagnoses are presented in Table 1. The majority were male ($n=178$; 55.8%). For neonates whose mode of delivery was recorded, normal vaginal delivery was most common (115/202; 56.9%). The majority of neonates with surgical conditions were outborn (196/299; 65.6%).

The majority of mothers were black (287/319; 90.0%), and 176/210 (83.8%) had attended ANC. Most mothers were multiparous (81/128; 63.3%). The mean (SD) maternal age was 27.8 (7.1) years.

Maternal demographics, ANC attendance and mode of delivery were not significant when comparing survivors with non-survivors. The infant's sex and presence of a low 5-minute Apgar score were also not significant when comparing the two groups.

The overall survival rate was 64.3% (205/319). Prematurity and low birth weight were significant risk factors for death, both with *p*-values <0.001 (Table 2).

The significant variables relating to survival are summarised in Tables 2 and 3.

There were 125 neonates with NEC (39.2%), 55 of whom survived (55/125; 44.0%), making the presence of NEC significantly associated with poor outcome ($p < 0.001$). The majority of neonates with NEC

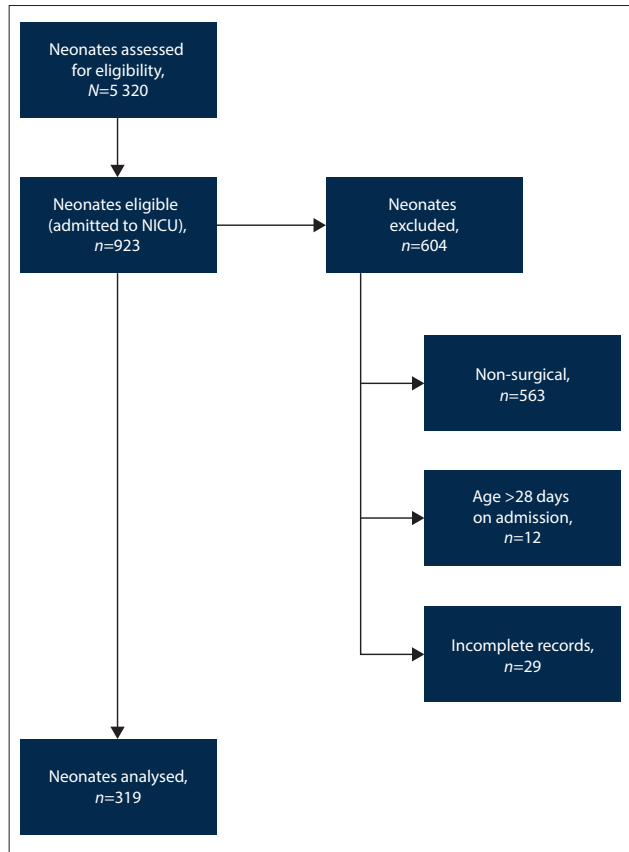


Fig. 1. Process of exclusion of study participants in an analysis of neonates with surgical diagnoses admitted to the NICU at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2015. (NICU = neonatal intensive care unit.)

Table 1. Clinical characteristics of neonates with surgical diagnoses (N=319) admitted to the neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2015

| Characteristics | |
|--|-------------|
| Gestational age (weeks), mean (SD) | 34.2 (4.7) |
| Birth weight (g), mean (SD) | 2 028 (801) |
| Head circumference (cm), mean (SD) | 29.3 (3.2) |
| Age at admission (days), median (IQR) | 1 (1 - 5) |
| Duration of ventilation (days), median (IQR) | 5 (1 - 10) |
| Length of stay in NICU (days), median (IQR) | 13 (1 - 29) |
| Age at outcome (days), median (IQR) | 19 (1 - 28) |

SD = standard deviation; IQR = interquartile range.

(72/125; 57.6%) underwent surgery, of whom 34/72 survived (47.2%). Patients requiring surgery for NEC had a mortality rate of 52.8% (38/72) despite surgery. There were 200 neonates (62.7%) with other surgical diagnoses, 6 of whom had concurrent NEC. Forty-six neonates in the study did not undergo surgery (46/319; 14.7%). Most of these had NEC (34/46; 73.4%).

Duration of ventilation was not significantly different between survivors and non-survivors (median (IQR) 5 (8.5) days v. 4 (12) days; $p = 0.549$). Likewise, length of stay was not significantly different between survivors and non-survivors (median (IQR) 13 (31.5) days v. 12 (21.8) days; $p = 0.155$).

The presence of sepsis within the first 72 hours of life was not significantly different between survivors (3/205; 1.5%) and non-survivors (2/114; 1.8%) ($p = 1.000$), whereas the presence of sepsis after 72 hours was significant (survivors 82/205 (40.0%) v. non-survivors 70/114 (61.4%); $p < 0.001$). Within the late-sepsis variable, a number of other factors were analysed: the presence of septicaemia was significant ($p < 0.001$), but the presence of wound sepsis was not ($p = 1.0$). Regarding septicaemia within late sepsis, infection with Gram-negative organisms was significant ($p < 0.001$), yet infection with Gram-positive organisms ($p = 0.525$), multidrug-resistant organisms ($p = 0.016$) or fungal organisms ($p = 0.479$) was not.

A total of 258 patients underwent surgical procedures, with a mortality rate of 32.9% (85/258). The vast majority of surgical procedures were abdominal (216/258; 83.7%), with a mortality rate of 35.2% (76/216). Surgery for NEC was the biggest contributor to mortality, with 38/72 patients dying (52.8%).

Surgery to repair intestinal obstruction (oesophageal, duodenal, jejunal, ileal, large-bowel atresias) made up 47 cases, with a mortality rate of 8.5% ($n = 4$). Surgery to repair abdominal wall defects comprised gastroschisis repair ($n = 36$) and omphalocele repair ($n = 13$). Gastroschisis repair had a mortality rate of 50.0% (18/36).

Other abdominal surgery included laparotomy for other causes, ileostomy and colostomy placement or reversal, anorectal malformation repair, congenital diaphragmatic hernia repair, and pyloroplasty.

The predominant surgical procedure conducted in the thorax was TOF repair, accounting for 23/33 cases with a mortality rate of 13.0% (3/23). The remainder included patent ductus arteriosus ligation, aortopexy, congenital cystic adenomatoid malformation repair and bronchoscopy.

Genitourinary tract surgery included cystostomy and inguinal hernia repair. The musculoskeletal surgeries were all arthrotomies.

Major birth defects were present in 166/319 neonates (52.0%) (Table 3). The frequencies of the major birth defects, with respective outcomes, are shown in Fig. 2.

There was a total of 166 neonates with birth defects, with a mortality rate of 24.7% (41/166). Gastrointestinal defects were the most common major birth defects, making up 138/166 cases (83.1%). Gastroschisis was the most common of these, with a 50.0% mortality rate (18/36). Intestinal atresia (all types) made up a large percentage of gastrointestinal defects (46/138; 33.3%) with a mortality rate

Table 2. Continuous variables relating to outcome (died v. survived) of neonates with surgical diagnoses (N=319) admitted to the neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2015

| Variable | Died | Survived | p-value |
|---------------------------------------|-------------------|-------------------|---------|
| Birth weight (g), mean (SD) | 1 722.52 (684.85) | 2 203.32 (810.99) | <0.001 |
| Head circumference (cm), mean (SD) | 28.67 (2.63) | 30.06 (3.67) | 0.029 |
| Gestational age (weeks), mean (SD) | 32.44 (4.35) | 35.22 (4.58) | <0.001 |
| Age at admission (days), median (IQR) | 0 (0 - 4) | 1 (0 - 6) | 0.042 |
| Age at outcome (days), median (IQR) | 17 (0 - 21.3) | 20 (0 - 31.5) | 0.037 |

Table 3. Categorical variables relating to outcome (died v. survived) of neonates with surgical diagnoses (N=319) admitted to the neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2015

| Variable | Died, n/N (%) | Survived, n/N (%) | p-value |
|-------------------------|---------------|-------------------|---------|
| Outborn | 66/114 (57.9) | 103/205 (50.2) | 0.029 |
| NEC | 70/114 (61.4) | 55/205 (26.8) | <0.001 |
| Late sepsis | 70/114 (61.4) | 82/205 (40.0) | <0.001 |
| Gram-positive organisms | 37/70 (52.9) | 59/82 (72.0) | 0.015 |
| Gram-negative organisms | 49/70 (70.0) | 39/82 (47.6) | 0.005 |
| Major birth defect | 41/114 (36.0) | 125/205 (61.0) | <0.001 |

NEC = necrotising enterocolitis.

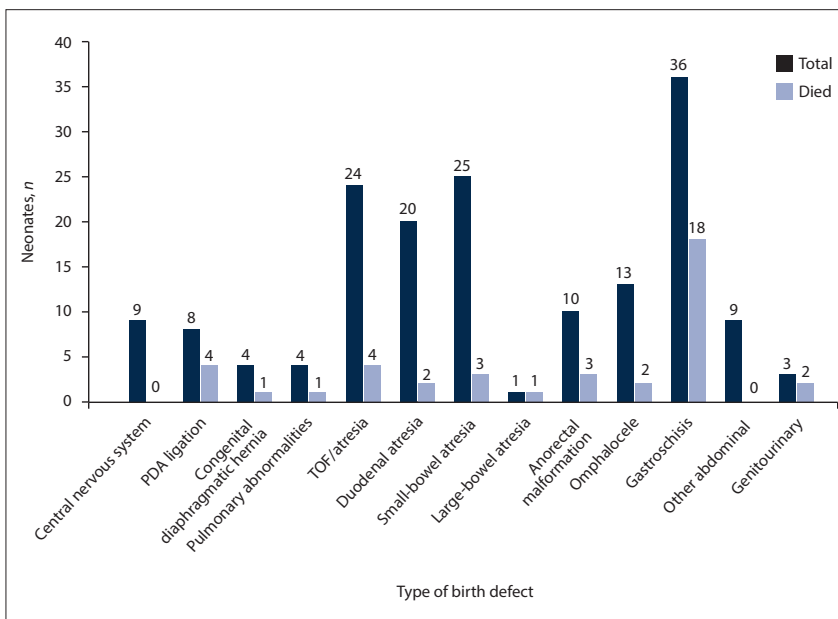


Fig. 2. Frequencies of major birth defects according to system, with outcome, of neonates with surgical diagnoses admitted to the neonatal intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 - 31 December 2015. (PDA = patent ductus arteriosus; TOF = tracheo-oesophageal fistula.)

of 13.0% (6/46). Tracheo-oesophageal and oesophageal atresia had a combined mortality rate of 16.7% (4/24).

Central nervous system abnormalities consisted of myelomeningoceles and congenital hydrocephalus. Genitourinary conditions consisted of polycystic kidneys and obstructive uropathy.

Discussion

There is limited information on neonatal surgical conditions in LMICs. The present study, conducted in a large academic referral centre in Johannesburg, showed that one-third of neonatal admissions to the NICU were surgical. Of this third of admissions to the NICU, a third of neonates died. These figures highlight the large burden of surgical diseases and the associated high mortality rate.

In this study, most neonates with surgical conditions were outborn and referred

in, which was associated with increased mortality. Firstly, referral indicates the need for improved access to antenatal screening, which could enable mothers to be counselled and advised to deliver in a hospital where paediatric surgical services are available.^[11] Secondly, an efficient referral and neonatal transport system is essential in our setting. Thirdly, earlier and wider access to specialist care would be of benefit, as well as easier access to NICU beds at this and other centres.

The most common neonatal surgical problems were abdominal conditions, accounting for almost 80% of all cases. The overall mortality rate was 34.7%, with mortality being highest in neonates with NEC. Other predictors of poor outcome were the presence of sepsis and major birth defects. The overall mortality rate in this study correlates with other studies in Africa, which report a mortality range of 16 - 45%.^[1,5]

Major birth defects were present in 52.0% of neonates. The presence of a major birth defect was associated with survival. An explanation for this finding is that >80% of birth defects were gastrointestinal abnormalities, which are amenable to surgical correction. The abnormalities were mainly intestinal atresias (29.5%), followed by gastroschisis (21.7%). Without a paediatric surgical facility, none of these neonates would have survived. Antenatal screening, genetic counselling and planned termination of pregnancy are not commonly available in LMICs, so a large number of neonates with life-threatening birth defects requiring paediatric surgery in this setting is to be expected.

Half the neonates with gastroschisis in the current study died. While this is a high mortality rate, it is comparable to a study at Inkosi Albert Luthuli Central Hospital in Durban, in which a mortality rate of 43% in all neonates with gastroschisis admitted over a 6-year period (2002 - 2007) was found.^[12] Through the rest of Africa, mortality rates are as high as 84% (80/95) in a study at Harare Children's Hospital in Zimbabwe for a 1-year period (2013) and 100% (20/20) in a study at Mulago Hospital, Uganda, over the same period.^[13,14] Mortality rates in Africa are considerably higher than those reported in HICs, where survival exceeds 90%.^[15]

Prematurity and low birth weight are predictably a risk for death. A high proportion of surgical neonates had NEC. Although severe cases of NEC are managed surgically, medical management of the condition is just as important. In addition, measures to prevent NEC should be emphasised, including avoidance of broad-spectrum antibiotic use in VLBW neonates and promotion of breastfeeding.^[16]

Bacterial rather than fungal infection was associated with poor outcome in the present study. Previous studies in our unit have shown that neonatal surgical patients are at increased risk of fungal sepsis.^[17] While Gram-positive sepsis appeared to

be associated with survival, this is confounded by the fact that sepsis was classified as culture proven and may therefore reflect many coagulase-negative staphylococcus infections that were not clinically significant. The presence of late-onset sepsis, particularly with Gram-negative bacilli, highlights the need for improved infection prevention and control measures.

As the under-5 mortality rate decreases due to a reduction in mortality from communicable diseases, including HIV-related causes, the relative importance of neonatal mortality as a cause of childhood deaths increases.^[18] Paediatric surgery, particularly neonatal surgery, and an improved referral and transport system are essential components in any healthcare intervention to reduce neonatal mortality, and hence childhood mortality.

Study limitations

This was a retrospective analysis of an existing database, so some information was missing. In addition, certain data, such as the time of onset of infection in relation to the surgery and catheter-related infections, were not routinely collected in the database and were therefore not analysed. As stated under 'Methods', the study does not account for neonates with surgical conditions not admitted to the NICU. If neonates managed in the high-care unit and outlying wards had been included, the demonstrated burden of disease could be higher. Furthermore, this was not a population-based study. It was conducted in a referral hospital with access to the appropriate level of surgical and ICU care, despite resource limitations.

Conclusions

Neonates with major surgical conditions accounted for one-third of NICU admissions in the present study. The study highlights the large burden placed on paediatric surgical services at a large quaternary referral hospital in SA. Earlier identification and easier access to an NICU with paediatric surgery coverage are essential to improve outcomes. Paediatric surgical services, with early referral and an improved neonatal transport system, must be a priority in planned healthcare interventions to reduce neonatal mortality in LMICs. Further studies are required to determine the burden of disease in LMICs. The present study provides a good starting point for further studies.

Declaration. The research for this study was done in partial fulfilment of the requirements for RTS's MMed (Paediatrics) degree at the University of the Witwatersrand.

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