Paediatric Hydrocephalus in the Province of KwaZulu-Natal, South Africa: A Study Towards Understanding the Burden of Disease and Developing an Integrated Model Aimed at Improving Outcomes

By

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Durban

As the candidate's supervisor, I have approved this thesis for submission.

Signed: [redacted] Name: **Prof Colleen Aldous** Date: **27 February 2025**

Declaration

I, **Basil Enicker** declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs, or additional information unless expressly acknowledged as being sourced from other persons.

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Signed: _____ Date **27 February 2025**

Dedication

To my beloved wife, Zanele—your unwavering love and belief in me have been the cornerstone of this journey. Without your endless support, this achievement would have remained a distant dream. Your strength and compassion have been my guiding light, and I am eternally grateful for the love that binds us.

To my precious children, Lisolethu, Nala, and Manelesi—you are the heartbeat of my life, the inspiration behind every step I take. Watching you grow has been the greatest joy and privilege of my life. I am beyond proud of the remarkable individuals you are becoming, and I am humbled and honored to be your father.

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Abbreviation List

AC	Arachnoid cyst
AIDS	Acquired immunodeficiency syndrome
AIS	Antibiotic impregnated shunt
ART	Anti-retroviral therapy
AS	Aqueduct stenosis
BBB	Blood-brain barrier
BSI	Bloodstream infections
BT	Brain tumour
CBF	Cerebral blood flow
CM	Cryptococcal meningitis
CPC	Choroid plexus coagulation
CSF	Cerebrospinal fluid
DoN	Department of Neurosurgery
DWM	Dandy-Walker Malformation
ETV	Endoscopic third ventriculostomy
EVD	External ventricular drain
IALCH	Inkosi Albert Luthuli Central Hospital
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICP	Intracranial pressure
IQR	Interquartile range
IRIS	Immune reconstitution inflammatory syndrome
IVH	Intraventricular haemorrhage

HIC	High-income country
HIV	Human immunodeficiency virus
KZN	KwaZulu-Natal
LMIC	Low and middle-income country
LOHS	Length of hospital stay
LPS	Lumboperitoneal shunt
MRA	Multiple regression analysis
MRSA	Methicillin-resistant Staphylococcus aureus
MMC	Myelomeningocoele
NCC	Neurocysticercosis
NTD	Neural tube defect
PIH	Post-infectious hydrocephalus
PHH	Post-haemorrhagic hydrocephalus
PMB	Pietermaritzburg
SA	South Africa
SAH	Subarachnoid haemorrhage
SSA	Sub Saharan Africa
TBI	Traumatic brain injury
TB	Tuberculosis
TBM	Tuberculous meningitis
VAS	Ventriculoatrial shunt
VPS	Ventriculoperitoneal shunt
VSGS	Ventriculosubgaleal shunt

Prologue

The History of Neurosurgery in KwaZulu-Natal, South Africa

The Establishment of the Medical School in the Province of KwaZulu-Natal

The idea of establishing a medical school in KwaZulu-Natal (formerly Natal) was initially conceived by Dr. JB McCord, an American medical missionary, physician and the founder McCord Zulu Hospital [1,2]. However, his vision was only realized years later after his retirement in 1940, largely due to the commitment of his colleague Dr. AB Taylor, who would become the first Dean of the Medical School [1,2].

The medical school officially opened in 1950, specifically intended to train Black, Indian and Coloured doctors, due to Apartheid policies that existed at the time [3]. Initially housed in repurposed army barracks in Wentworth, a township in Durban's southern basin the school would later see Wentworth Hospital, located in the same township, play a crucial role in the development of the neurosurgery specialty within the province of KwaZulu-Natal (KZN) [4].

In 1953 the medical school was relocated to Umbilo, where the current Nelson R. Mandela School of Medicine (NRMSM) now stands [3]. This move placed the medical school in close proximity to King Edward VIII Hospital (now named Victoria Mxenge Hospital), a teaching hospital established in 1936, which was designated exclusively for treating Black patients under the Apartheid regime [5].

It is important to acknowledge that these developments took place during one of the most challenging periods in South Africa's history. The Apartheid system imposed severe inequalities in access to resources such as health, education, the economy, housing, employment, security, and justice for the majority Black population. The impact of these policies continues to resonate to this day. As a result, the medical school became a center of political activism during this era.

Apartheid eventually ended and in 1994 South Africa (SA) held its first democratic elections. For the first time, all citizens had the right to vote, leading to the election of Mr. Nelson R. Mandela as the first democratically elected President of the Republic of South Africa. In honor of his legacy, the medical school was renamed the Nelson R Mandela School of Medicine, on the 29th of July 2000 [6].

Figure 1: The Opening Ceremony of the Medical School Building in 1955[7,8].

*Picture courtesy the University of KwaZulu-Natal archives.

Figure 2: Entrance to the Nelson R Mandela School of Medicine

***Picture courtesy of the University of KwaZulu-Natal archives**

Figure 3: Arial View of the Nelson R Mandela School of Clinical Medicine

***Picture courtesy of https://www.santheafrica.org/sites/default/files/K-RITH-Tower-Building**

Department of Neurosurgery at Wentworth Hospital: 1968 to 2002

Prior to 1957, there were no dedicated neurosurgery services in KZN and neuro-trauma cases were treated by general surgeons [9]. Neurosurgical services were accessible to only a small, select group of patients, who were sent to Johannesburg and Cape Town for procedures. This service was mainly reserved for White patients, approximately 30 cases per year at an estimated cost of ZAR 90,000.00 (USD 5,046.00) [9].

In 1957 Dr. MJ Joubert who trained at the Walton Neuroscience Centre in Liverpool and Groote Schuur Hospital in Cape Town, arrived in Durban to establish a private neurosurgery practice [10]. He also provided neurosurgical services in the public sector, operating between hospitals such as Addington and King Edward VIII, as there was no designated neurosurgery department in Durban at the time. This arrangement, however, proved to be unsustainable.

Significant progress was made with the establishment of a neurosurgery unit at Wentworth Hospital in 1968 [11]. Originally a Royal Navy Auxiliary Hospital established in 1943, Wentworth Hospital was acquired by the KZN government in 1948 and initially served as a treatment center for tuberculosis patients [11]. Over the years, several neurosurgeons joined the unit. The first CT scanner in KZN was installed in Wentworth Hospital in 1975 [11].

NEUROSURGERY AT WENTWORTH

Largest single unit in Southern Africa

UNTIL 17 years ago, when the first neurosurgeon settled in Durban, neurosurgery was available only to a small selected number of patients, who were sent to Johannesburg and Cape Town for surgery. Approximately 30 White patients were sent annually to Johannesburg and a similar number of non-White patients to Cape Town, at a cost of R90 000. The arrangement was unsatisfactory in many respects. It was not only costly, but this form of surgery was denied to many patients who were too ill to travel and where delay was not in their interest. This was not only inconvenient to the patient, but also to the relatives who wished to accompany and remain with him.

The first neurological surgeon did not find it easy to start a service in Durban, because there were innumerable obstacles. The overcrowding of the two main Durban hospitals, namely Addington and King Edward VIII hospitals, was so acute that it was not possible to allocate beds for neurosurgical cases. The new Addington Hospital had not reached the planning stage and it was common to find a neurosurgical patient in every ward of the hospital. There were *no neurosurgically trained nurses available and it was necessary for the neurosurgeon to teach the interested nurse individually how to care for patients, some of them in coma.*

The theatres were inadequately equipped and, for more complicated procedures, specialised instruments and diathermy apparatus had to be taken from theatre to theatre.

There was not a single neurosurgically trained theatre nurse in Natal. Neurosurgical operations were looked upon by most theatre nurses as far too formidable for their capabilities and experience. Such operations were usually preceded by instructions to the nurse in the identification of specialised instruments and the details of the procedure.

The post-operative care of the patient was a nightmare to the neurosurgeon. He spent many a night in a hospital bed close to his patient to "pilot" the patient through the deep waters of post-operative shock and early recovery.

A year later the second neurosurgeon arrived, but he decided to give up the struggle after two years of working under such conditions, and left Durban. A further two years elapsed before the third neurosurgeon ventured into the field.

BIRTH OF THE NEUROSURGICAL UNIT AT WENTWORTH

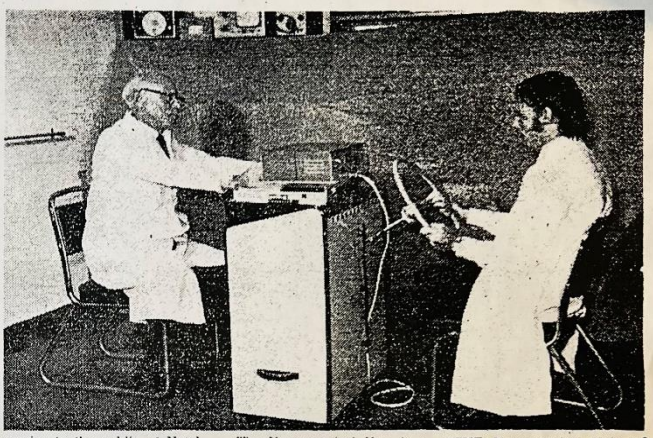
Some 12 years ago an existing ward in the old Naval Hospital of the Second World War at Wentworth was renovated as the nucleus of a neurosurgical unit of 12 beds. The first trained nurse, now Clinical Matron in the Unit, and two auxiliary nurses were appointed.

It was the loyal and able support of the hospital management at Wentworth that made it possible for the Neurosurgical Unit to take shape and function efficiently. During the first year 125 major operations and 250 neurosurgical investigations were undertaken.

The idea of a multi-racial unit was conceived during the early formative years and put into practice. It proved a tremendous success in the light of the chronic shortage of trained medical and nursing personnel, and several other centres in the country have followed suit.

The Neurosurgical Unit at Wentworth is the largest single unit in Southern Africa. There are 125 beds with nearly 100 per cent occupancy throughout the year. There is a 24-hour service to the public of Natal, irrespective of race and financial status.

The neurosurgeons on the staff are closely associated with other major Provincial hospitals in Durban and Pietermaritzburg, the main receiving centres of road accidents.

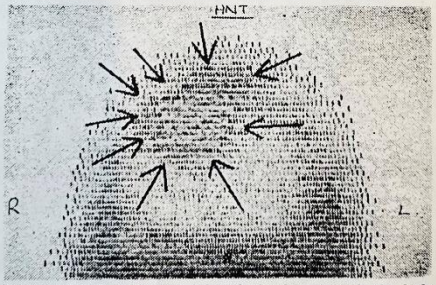


The Neurosurgical Unit is a recognised training centre for neurological surgeons, under the aegis of the Medical School of the University of Natal. It has five qualified neurosurgeons on its staff. It plays a role in teaching medical students and nurses in training in Addington, King Edward VIII and Grey's Hospitals.

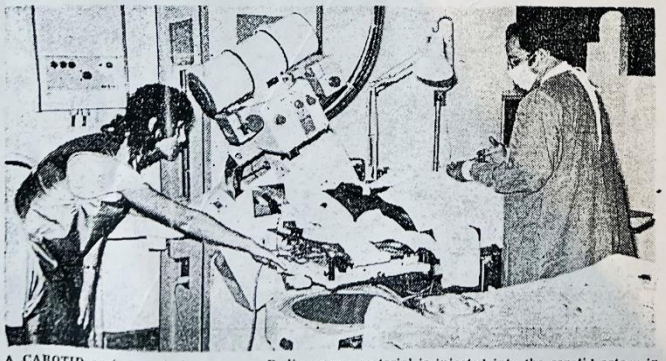
An intensive care course was launched three years ago and 26 nurses qualified, six with honours, with only one failure. This is a record for this country. The intensive care wards are designed on modern lines and the facilities afford the patient the best chance of survival.

Today, more than 1 000 neurosurgical operations and over 2 000 investigations are carried out per year. The theatres are well equipped with the most modern instruments in the field of neurological surgery.

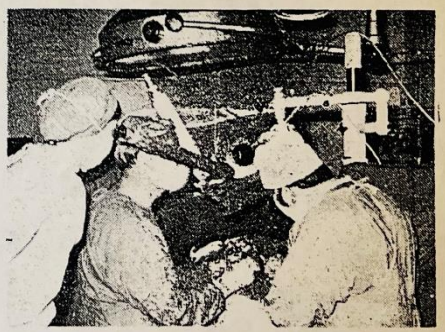
THE Neurosurgical Unit is also active in brain research. Photo shows a reaction-meter designed by a neurological surgeon and the electronic technician, who is seen operating the machine. This machine is designed to assist the District Surgeon in determining the degree of drunkenness of a patient arrested for driving under the influence of liquor or drugs. The designers also hope to put the reaction-meter at the disposal of the Licensing Officer. It is hoped that before a candidate for a driver's licence is issued with a licence, his reaction time can be measured. If the reaction time were above normal (and if this apparatus is accepted) it could eliminate the man who is a danger or limit his speed according to his reaction time.



RADIO-ACTIVE substances injected circulate through the body and the differential take-up by the brain and brain lesions of the radio-active substance leads to the identification of the lesion. Photo shows a radio-active scan of the brain with the brain tumour arrowed.



A CAROTID angiogram is in progress. Radio-opaque material is injected into the carotid artery in the neck and serial X-rays taken as the dye flows through the brain.



A SCENE in the operating theatre showing neurological surgeons operating on a patient with the aid of an operating microscope. The operation is televised for the doctors and nurses in the theatre and is also relayed to another television screen where doctors and nurses in training can follow the operation. The proceedings are also put on a video tape-recorder, which can be stored and played back at a later date.

Figure 4: Newspaper Article Reporting on the Neurosurgery Unit in Wentworth Hospital[9]

***Courtesy of the Witness Supplement**

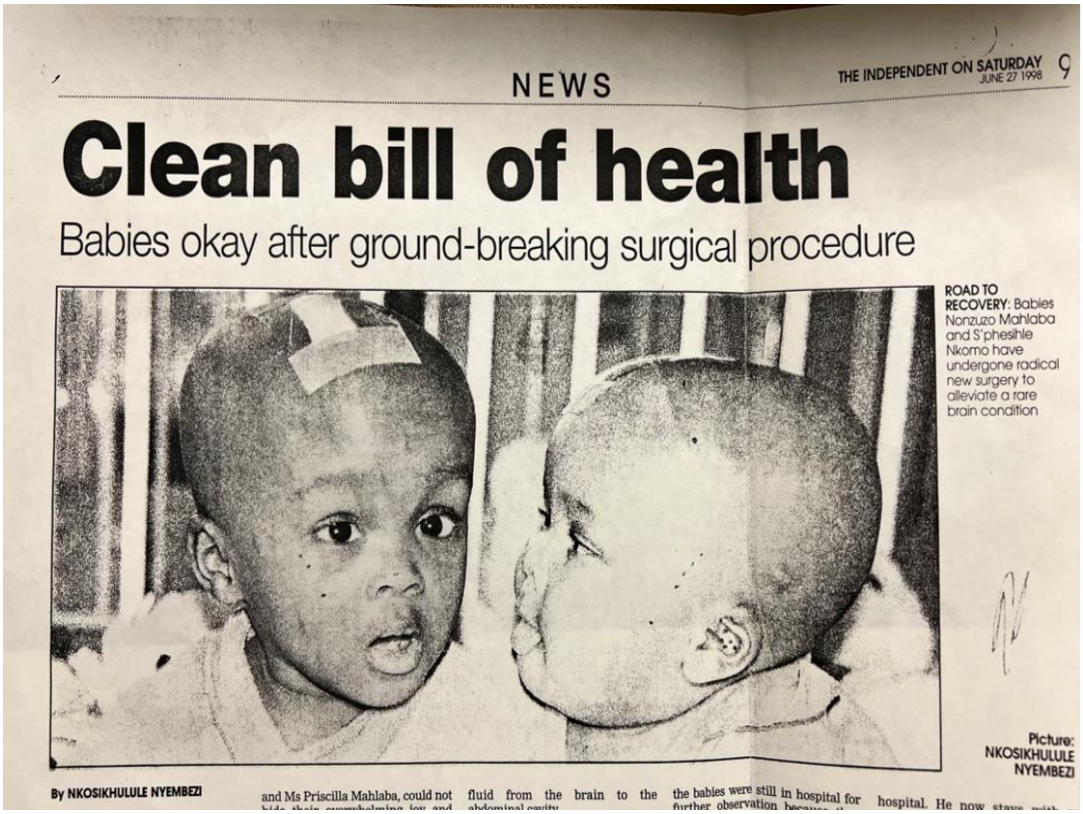
During this period Dr. MJ Joubert left in 1974 and in 1980 Prof. JR Van Dellen was appointed first Professor and Head of the Department of Neurosurgery (DoN), a position he held until 1992 when he was appointed Dean of the medical school in Durban, serving until 1998.

The DoN at Wentworth Hospital served as the sole referral center for the entire province of KZN and parts of the Eastern Cape, namely Mthatha, and grew from a 12-bed unit to 125 beds in the 1980s

Figure 5: Aerial View of Wentworth Hospital

***Courtesy of the KZN Department of Health**

By 1983, there was a need to develop a paediatric neurosurgery unit, driven by the growing demand for paediatric services. Admission statistics from 1983, indicated that children accounted for one-third of all admissions. At this time, the DoN was servicing a population of 8.5 million in KZN. Endoscopic third ventriculostomy (ETV) for the management of paediatric hydrocephalus was first performed in 1998 in the DoN in KZN [12]



NEWS

THE INDEPENDENT ON SATURDAY JUNE 27 1998 9

Clean bill of health

Babies okay after ground-breaking surgical procedure

ROAD TO RECOVERY: Babies Nonzuzo Mahlaba and S'phesihle Nkomo have undergone radical new surgery to alleviate a rare brain condition

Picture: NKOSIKHULULE NYEMBEZI

By NKOSIKHULULE NYEMBEZI

and Ms Priscilla Mahlaba, could not fluid from the brain to the the babies were still in hospital for hospital. He now stays with

Figure 6: News Article Reporting on the First Endoscopic Third Ventriculostomy for the Treatment of Hydrocephalus in KwaZulu-Natal[12].

*Courtesy of the Independent on Saturday

Department of Neurosurgery at Inkosi Albert Luthuli Central Hospital: 2002 to current

In December 2002, the DoN relocated to Inkosi Albert Luthuli Central Hospital (IALCH), a state-of-the-art quaternary and central hospital. At IALCH the DoN has 101 beds (64 adult beds, 20 paediatric beds, 6 high care beds, and 11 ICU beds. The DoN also has two theatres, one of which operates 24 hours. I, Dr Basil Enicker, am the current Head of the Department of Neurosurgery at IALCH and the University of KwaZulu-Natal.

Figure 7: Inkosi Albert Luthuli Central Hospital

***Courtesy of the KZN Department of Health**

The current staff complement of the DoN includes seven full-time specialist neurosurgeons, 10 registrars (residents), and seven medical officers. The DoN also trains supernumerary registrars from various countries across Africa.

In KZN, there are seven full-time specialist neurosurgeons in the public sector compared to 20 in the private sector. This disparity exists in a province with a population of 12 million, of which approximately 9.8% have private medical insurance [13]. The remaining population relies on the public healthcare system, highlighting the unequal distribution and access to healthcare in SA.

Neurosurgery at Greys Hospital, Pietermaritzburg: 2018 to current

Greys Hospital, a tertiary facility located in Pietermaritzburg (PMB), began offering neurosurgery services in 2018, with the aim of decentralising some services and reducing the burden on IALCH. A limited neurosurgery service in Greys Hospital was initially established to manage paediatric hydrocephalus cases residing in PMB and surrounding areas, who use this facility for healthcare services. The service has continued to grow over the years.

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Abstract

Background

Paediatric hydrocephalus is a major contributor to morbidity and mortality in low- and middle-income countries (LMICs), with sub-Saharan Africa disproportionately affected. In KwaZulu-Natal (KZN), South Africa, this burden is exacerbated by a high HIV prevalence, limited access to specialist neurosurgical care, and a predominance of central nervous system (CNS) infections. This thesis aimed to comprehensively investigate the epidemiology, aetiology, and treatment outcomes of paediatric hydrocephalus in KZN, with particular emphasis on HIV-related infections and health service disparities.

Methods

A mixed-methods approach comprised a scoping review, followed by retrospective and prospective data analysis over a 20-year period (2003–2022). Data was collected from 3,325 children treated at Inkosi Albert Luthuli Central Hospital. Data was analysed to assess epidemiological trends, treatment modalities—including ventriculoperitoneal shunts (VPS) and endoscopic third ventriculostomy (ETV)—complication rates, HIV status, and outcomes, in particular, predictors of mortality. Subgroup analyses were performed to examine the role of tuberculous meningitis (TBM) and cryptococcal meningitis in HIV-infected children, as well as the effect of geographical proximity to centralised neurosurgery services on clinical outcomes.

Results

Post-infectious hydrocephalus (PIH) was the most common aetiology (32.7%), primarily due to TBM and pyogenic meningitis. HIV-infected children had higher complication and mortality rates, with TBM-related hydrocephalus associated with a 35.5% mortality rate. VPS procedures were the predominant treatment modality (84.2%), with an overall infection rate of 9.6%. Proximity to centralised neurosurgery services significantly impacted outcomes, with children living further away from neurosurgical services experiencing higher complication rates. Overall mortality was 7.9%, with predictors including older age, low GCS, cerebral infarcts, extra meningeal tuberculosis (TB), VPS infection, low CD4 count and hyponatraemia.

Conclusions:

CNS infections remain the predominant cause of paediatric hydrocephalus in KZN, with HIV infection significantly worsening outcomes. The findings highlight the urgent need for increased access to neurosurgery services and integrated public health strategies. A framework: AGILE-WIN (Antenatal care, Genetic counselling, Infection control, Localised services, Early diagnosis, Workforce improvement, Immunisation, and Networked reporting) is proposed to reduce disparities, promote early diagnosis, and improve outcomes for children with hydrocephalus in LMICs.

Iqoqa

Isendlalelo

Ukukhiqiza amanzi amaningi ebuchosheni bezingane kuneqhaza elikhulu kusimokugula nasekushoneni kwabahola kancane nabaphakathi nendawo emazweni (e-LMIC) anemiphumela yokwehliswa kwamazwe amancane athintekayo aseSaharan Africa. KwaZulu-Natal (KZN), eNingizimu Afrikha, le nkinga ibhebhethekiswa inani eliphezulu labane-HIV, ukunqindeka kokufinyelela kongoti emkhakheni wonakekelo lokwelashwa kwemizwa, nokubaphezulu kwezifo zohlelomizwa olunqala (CNS). Lo mqingo wocwaningo uhlose ukuphenya ngokubanzi okudidiyele, isifundo ngembangela nokusabalala kwezifo, (i-epidemiology), isifundo ngembangelasifo (i-aetiology), nemiphumela yokwelashwa kokukhiqizeka kwamanzi amaningi ebuchosheni bezingane e-KZN, kunokugcizelela okuthile ezifweni ezihlobene ne-HIV nokungalingani kosizo lwezempilo.

Izindlelakwenza

Indlela yezindlelakwenza ezingxube ihlanganisa ukubuyekezwa kokuklama, kulandelwe ukuhlaziywa kwemininingo yakamuva neyangaphambilini esikhathini esingaphezu kweminyaka engama-20 (2003–2022). Imininingo yaqoqwa ezinganeni ezelashwa eziyizi-3,325 eNkosi Albert Luthuli Central Hospital. Imininingwane yahlaziywa ukuze kuhlolwe inkombamvama yokwesifundo ngembangela nokusabalala kwezifo izinhlobo zokwelapha—kubandakanya amashanti olwelwesi lomgudu wamanzi ebuchosheni, amaventriculoperitoneal shunt (VPS) kanye nohlolomgudu lukapopopo (i-endoscopic) lwesithathu lomgudu wamanzi ebuchosheni ì-endoscopic third ventriculostomy (ETV)—amazinga ezinkinga, isimo se-HIV kanye nemiphumela, kakhulukazi izinhlaselakufa. Kwenziwa ukuhlaziywa kwamaqoqo amancane ukuze kuhlolwe iqhaza lofuba lovuvukontwentwesi lobuchopho, ituberculous meningitis (TBM)novuvukontwentwesi lobuchopho lwesikhuntamhlabathi, icryptococcal meningitis ezinganeni ezihaqwe i-HIV, kanjalo nomphumela wokusondelana nokwesifundo ngamazwe ukuze kubekwe phakathi nendawo usizo lokwelashwa kwemizwa emiphumelweni yezempilo.

Imiphumela

Ukukhiqiza amanzi amaningi ebuchosheni kotheleleko lwakamuva imbangelasifo, i-aetiology (32.7%) kwakuyiyona eyayivame kakhulu, ikakhulu ngenxa yovuvukontwentwesi lwe-TBM nolwepyogenic. Izingane ezihaqwe i-HIV zaziba namazinga aphezulu ezinkinga nawokushona, one-TBM nokuhlobene nokukhiqiza amanzi amaningi ebuchosheni okuhambisana nezinga lokushona elingama-35.5%. Izinhlelo ze-VPS izinhlobo zokwelaphayizona ezinamandla ngamaphesenti angama-(84.2%), ezinga lokutheleleka sekukonke kungamaphesent ayisi-9.6%. Ukusondela kuzinsiza eziphakathi nendawo zokwelashwa kwemizwa kwabanemithelela esemqoka emiphumelweni, ngezingane ezihlala kude nezinsiza zokwelashwa kwemizwa zaba namazinga aphezulu ezinkinga. Abashonayo sebebonke baba ngamaphesenti ayisi-7.9%, nababikezelayo kubandakanya nasebekhulile, i-GCS ephansi, ukungafinyeleli kwegazi ebuchosheni, okofuba lovuvukontwentwesi okunezelekile, imeningeal tuberculosis (TB), isifo se-VPS, izinga le-CD4 count eliphansi nezinga eliphansi leswayi egazini, ihyponatraemia.

Isiphetho

Izifo ze-CNS zihlale ziyizimbangela ezinamandla zokukhiqizwa kwamanzi amaningi ebuchosheni bezingane e-KZN, ezinesifo se-HIV okwenza imiphumela ibe mibi kakhulu. Okutholwe ucwaningo kugqamisa isidingo esiphuthumayo sokukhuliswa kokufinyelela kuzinsiza zokwelashwa kwemizwa namasu ezempilo adidiyelwe. Uhlaka: i-AGILE-WIN (unakekelo lwangaphambi kokubeletha, ukwelulekwa ngokwengqondo okuphathelene nofuzo, ukulawulwa kwesifo, usizo olusendaweni, ukuhlonzwa kwesifo kusenesikhathi, ukuthuthukiswa kwabantu abazosebenza, ukugoma nokubika ngohleloxhumano) kuyaphakanyiswa ukuze kuncishiswe ukungalingani, kukhuthazwa ukuhlonzwa kwesifo kusenesikhathi nokuthuthukiswa kwemiphumela yezingane ezikhiqiza amanzi amaningi ebuchosheni kuma- LMIC.

Overview of the Thesis

Background

Paediatric hydrocephalus presents a substantial global health burden, particularly in low and middle-income countries (LMICs) like South Africa (SA). The Province of KwaZulu-Natal (KZN) has a high prevalence of HIV infection, which exacerbates the complexity of hydrocephalus management. Despite advancements in treatment, morbidity and mortality rates among children diagnosed with hydrocephalus remain a challenge. The intersection of paediatric hydrocephalus and HIV has not been adequately studied in the current literature. The lack of data on the burden of paediatric hydrocephalus in KZN prompted the need for an in-depth investigation. This thesis explores the multifaceted aspects of paediatric hydrocephalus in KZN, focusing on factors influencing outcomes and strategies to alleviate the burden of the disease.

Research Question

The research question that shaped this thesis is: What are the factors influencing the epidemiology, treatment outcomes, and mortality in paediatric hydrocephalus in KZN, SA, and how does HIV infection and proximity to centralised neurosurgery services influence these outcomes?

Aims of the Thesis

The overarching aim of the study is to investigate the epidemiology, clinical factors, and surgical outcomes of paediatric hydrocephalus in KwaZulu-Natal, with a focus on the role of HIV and CNS infections, the effectiveness of treatment modalities, and healthcare disparities, to inform policy recommendations for improved care in low- and middle-income countries.

Objectives of the Study

In order to achieve the aim of the study, the following objectives were laid out to answer the research question.

1. To describe the epidemiology of paediatric hydrocephalus in KZN, including its aetiology and demographic trends.
2. To evaluate the influence of HIV infection and central nervous system (CNS) infections, such as tuberculous meningitis (TBM) and cryptococcal meningitis (CM) on the development and outcomes of hydrocephalus in children.
3. To evaluate the outcomes of common surgical modalities, such as ventriculoperitoneal shunts (VPSs) and endoscopic third ventriculostomy (ETV), used to treat paediatric hydrocephalus in KZN.
4. To investigate the impact of proximity to centralised neurosurgery services on surgical outcomes, complication rates, and mortality.
5. To recommend policy changes that address healthcare disparities and improve outcomes for children with hydrocephalus in KZN and other LMICs.

Methods

The study used diverse research methodologies to address each research question. The methodology included a scoping review, and longitudinal retrospective and prospective data analyses to investigate various facets of paediatric hydrocephalus over 20 years. Data captured included demographic information, referral patterns, aetiology, treatment modalities, surgical outcomes, and mortality rates.

Study Setting

The study was conducted at Inkosi Albert Luthuli Central Hospital (IALCH), a quaternary and central hospital in KZN, where the Department of Neurosurgery (DoN) is located.

Structure of the Thesis

The thesis is composed of a series of related chapters, each contributing to the overall research objectives. It is further divided into two parts: Part 1, *Healthcare Disparities and Paediatric Hydrocephalus: An Epidemiological and Proximity-Based Analysis*, which includes Chapters 3 and 4; and Part 2, *HIV and the Developing Brain*, which comprises Chapters 5 and 6. Chapters 2 through 6 are presented either as published papers or in publication-ready format.

Chapter 1 sets the foundation by outlining the global epidemiology of paediatric hydrocephalus, its classification, pathophysiology, and the role of CNS infections in its development. It further discusses the research question, aims and objectives of the study.

Chapter 2 presents a scoping review of the factors associated with mortality in children diagnosed with hydrocephalus, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. Hydrocephalus is one of the leading causes of morbidity and mortality, particularly in LMICs. Understanding the factors associated with mortality is important for improving clinical outcomes and developing protocols aimed at reducing mortality. Data for the review were obtained from original peer-reviewed articles focusing on epidemiology, aetiology, treatment, and management outcomes of paediatric hydrocephalus. The results revealed that mortality is influenced by the aetiology of hydrocephalus, comorbidities, socioeconomic status, age, type of surgical intervention and postoperative complications. The review highlighted gaps in the current literature regarding the impact of HIV on mortality in children treated for hydrocephalus.

Chapter 3 presents original epidemiological research that maps the burden of paediatric hydrocephalus in KZN over a 20-year period (2003 to 2022). This study used both retrospective and prospective data, focusing on demographics, aetiology of hydrocephalus and treatment modalities and outcomes. The study analysed data from 3325 children treated for hydrocephalus during the study period.

The peak period for paediatric hydrocephalus cases was from 2008 to 2012 (35.3%), with a notable decline in cases from 2018 to 2022 (11.8%). This decline was attributed to the establishment of a satellite neurosurgery unit at Greys Hospital, located 78.1 km from IALCH, which began offering surgical treatment of paediatric hydrocephalus in 2018.

The study revealed that most children (47.9%) were referred from regional hospitals, and the majority were infants (60.2%). The overall median age at first surgery was 7 months. Black African children (96.7%) and boys (56.4%) were the predominant group. Children diagnosed with myelomeningocoele (MMC)-related hydrocephalus were the youngest to undergo cerebrospinal fluid (CSF) diversion procedures at the median age of 1 month. Post-infectious hydrocephalus (PIH) was the most common (32.7%) form in KZN, with TBM (54.1%) and pyogenic meningitis (43.8%) being significant contributors.

HIV infection was diagnosed in 84 (2.5%) children, with a median CD4 count of 202 cells/µL, and 64.3% of these children were on anti-retroviral therapy (ART). CNS infections responsible for hydrocephalus in HIV-infected children were TBM (65.5%), CM (21.4%) and pyogenic meningitis (7.1%). Idiopathic aetiology was reported in 12.1% of cases, while brain tumours (BTs) were responsible for hydrocephalus in 11.8% of cases, with 58.3% located in the infratentorial compartment.

VPSs were the most common (84.2%) CSF diversion procedure, with an overall infection rate of 9.6%, which declined during the study period. *Staphylococcus aureus* was the most common (44.6%) organism cultured from shunt infections. Most surgical procedures were performed during work hours (69.5%) and weekdays (81%). Antibiotic-impregnated shunts (AIS) were used in 47.6% of cases. Weekend VPS procedures were associated with higher complication rates. VPSs were complicated by acute abdomen in 0.8% of cases. The success rate of ETV was 89.7%.

The overall mortality rate was 7.9%, with mortality rates decreasing over the study period. Factors associated with mortality included age 1 year and older, referral from a tertiary hospital, VPS infections, acute abdomen and pneumonia.

Chapter 4 builds on Chapter 3 by narrowing the focus to investigate the impact of proximity to centralised neurosurgery services on the surgical outcomes of paediatric hydrocephalus. The study used both retrospective (2013 to 2017) and prospective (2018 to 2022) data. Children were categorised based on the distance travelled to access CSF diversion procedures and complication rates were compared. Most children were from rural areas (54.6%); although the majority were referred from a distance less than 50 km from IALCH (Durban Metropolitan area). VPS failure rates varied by distance: 4.5% (<50 km), 3.7% (50 to 149 km), 7.3% (150 to 249 km), and 8.8% (≥ 250 km). VPS complications and ETV failures in children living more than 49 km from the neurosurgery unit presented in a delayed fashion, highlighting the advantage of easier access to neurosurgery services when complications arose. These findings are important for healthcare policymaking and resource allocation, highlighting the need to decentralise paediatric hydrocephalus services in KZN.

Chapter 5 builds on the epidemiological findings from Chapters 2 and 3 by investigating PIH in the context of HIV infection. It specifically focuses on the clinical characteristics, diagnostic and treatment modalities, including factors determining outcomes of TBM hydrocephalus in HIV-infected children.

Data from 31 HIV-infected children were analysed, and 61.2% of the children were 6 years old and younger. Using the refined British Medical Research Council grading system for TBM, 45% of children were classified as grade 3. The median CD4 count on admission was 151 cells/ cells/μL interquartile range (IQR):70-732. The study found that HIV-infected children diagnosed with TBM hydrocephalus presented with severe neurological deficits before surgery. Radiological investigations revealed associated intracranial tuberculomas (45.2%), TB pneumonia (13%), and TB abdomen (6.5%).

VPS was the procedure of choice in 84% of cases, while ETV was performed in the remaining 16%. The VPS complication rate in this group was 27%. While Chapter 3 outlined broader factors associated with mortality, Chapter 5 delved into the specific impact of HIV infection and TBM hydrocephalus on mortality. TBM-related hydrocephalus in HIV-infected children carried high mortality (35.5%) and factors associated with mortality included Glasgow Coma

Scale (GCS), cerebral infarcts, low CD4 count, VPS infection and hyponatraemia. Most children (67%) were found to have severe disability on long-term follow-up.

This study emphasised the importance of prevention, early diagnosis and treatment of HIV and TBM to prevent the development of hydrocephalus. In cases where hydrocephalus is diagnosed, the study recommended early CSF diversion to improve outcomes.

Chapter 6 builds on the findings from Chapters 3 and 5 by investigating the role of CM in the development of hydrocephalus and refractory increased intracranial pressure (ICP) in HIV-infected children. This chapter details surgical CSF diversion options available for this group of children**.** Seventeen HIV-infected children were included in the study, with a median age of 10 years, which was older than the children discussed in Chapter 5. The median CD4 count was 45 cells/ μL, IQR: 17- 56, which was lower than that of HIV-infected children treated for TBM-related hydrocephalus in Chapter 5. Visual impairment was the most common neurological deficit, affecting 82% of children, and is often non-reversible. CSF diversion procedures included VPS in 82% of cases and lumboperitoneal shunts (LPS) in 18%. The shunt complication rate was 35%, and the in-hospital mortality rate was 18%. At one year follow-up, 59% of children were alive.

Chapter 7 synthesises and discusses the key findings of the thesis. The main findings were that CNS infections were responsible for the majority of paediatric hydrocephalus cases in KZN. The introduction of a satellite neurosurgery service in Greys Hospital has reduced the number of paediatric hydrocephalus cases at treated IALCH.

Additionally, children living farther from centralised neurosurgery services had higher rates of VPS failures, highlighting the need for decentralised neurosurgery services so that these children can be treated closer to their place of residence. The thesis also highlighted the intersection of hydrocephalus and HIV-related CNS infections, demonstrating that HIV-infected children had high surgical complication rates and mortality.

Recommendations

Neurosurgeons practising in high HIV prevalence regions, like KZN, should ensure that they are up to date with the current clinical guidelines for the management of HIV, as this will improve their understanding of HIV infection in the context of neurosurgical pathology.

This thesis contributes to the growing body of literature on paediatric hydrocephalus in LMICs and provides recommendations for reducing the burden of hydrocephalus and improving outcomes through a novel framework termed the **AGILE-WIN strategy,** which is an acronym for **A**ntenatal care services, **G**enetic counselling, **I**nfection control, **L**ocalized (decentralised) services, **E**arly diagnosis, **W**orkforce improvement, **I**mmunization programmes and **N**etworked reporting.

AGILE-WIN Strategy

A. Antenatal Care Services

- Strengthening maternal health services to identify at-risk pregnancies early and implement interventions to reduce complications leading to hydrocephalus in newborns e.g. perinatal infections.

B. Genetic Counselling

- Improving understanding of the genetic causes of hydrocephalus in the local setting, which will facilitate better planning and interventions.

C. Infection Control

- Achievable through strategies such as using AISs in high-risk children and enforcing stringent protocols in the operating theatre during shunt procedures,
- Promotion of healthy education and good hygiene.
- The prevention of mother-to-child transmission programme has been an important tool for reducing HIV infections in children.

D. Localized (Decentralised) services

- Efforts should be made to improve access to neurosurgical services, especially in rural areas, to ensure timely intervention and reduce disparities in outcomes.

E. Early Diagnosis

- Collaborative efforts between neurosurgeons, paediatricians, infectious disease and public health specialists should be encouraged to implement holistic, multidisciplinary approaches to clinical management, research, and policymaking aimed at addressing the burden of paediatric hydrocephalus
- Healthcare providers should maintain a high index of suspicion for hydrocephalus, particularly in high-prevalence regions, to ensure early treatment to reduce complications and mortality

F. Workforce improvement

- Train and employ more neurosurgeons to work in decentralised neurosurgery units to improve access to care.

G. Immunisation Programmes

- Since meningitis was responsible for most cases of paediatric hydrocephalus in KZN and other LMICs, immunisation programmes should be promoted to reduce the burden of CNS infections.

H. Networked Reporting

- Developing a centralised paediatric hydrocephalus database or registry for South Africa and collaborating with partners across Africa will allow for data-driven decision-making, which will result in the overall improvement of outcomes.

Keywords: Cryptococcal meningitis, Low- and middle-income countries, Paediatric hydrocephalus, Tuberculous meningitis, Ventriculoperitoneal shunt

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Chapter 1: Introduction

1. Epidemiology

Hydrocephalus is a common neurological disorder affecting children globally, imposing a substantial burden on healthcare systems, particularly in terms of costs, morbidity, and mortality. This impact is evident across both high-income countries (HICs) and low and middle-income countries (LMICs), although the epidemiology varies significantly by geographic location. A detailed systematic review by Dewan et al. revealed the highest incidence of congenital hydrocephalus in Latin America, with 316.1 cases per 100,000 births, followed by Africa at 144.9 per 100,000 births [1]. Other regions, including the Eastern Mediterranean (110/100 000), Western Pacific (83.5/100 00), European regions (83.3/100 000), South-East Asia region (76.3/100 000) and the United States/Canada (67.5/100 000), reported lower incidences, highlighting the disparity in disease prevalence across the globe [1].

In terms of new cases, Africa accounts for 31.4% of the global burden of congenital hydrocephalus, with an estimated 52,709 new cases annually, far surpassing cases in North America [1]. Furthermore, Africa also bears the highest burden of post-infectious hydrocephalus (PIH), with 66.6% of global cases occurring on the continent [1]. These findings highlight the disproportionate impact of hydrocephalus in LMICs, where the incidence of congenital hydrocephalus is significantly higher than observed in HICs.

The variability in incidence rates across countries further illustrates the complex interplay of genetic, environmental, and healthcare factors. For example, Nigeria reports an incidence of 0.34 per 1,000 births [2], while in China, the rate ranges from 6.9 to 9.2 per 10,000 births [3]. Similarly, Brazil reports an incidence of 3.16 per 1,000 newborns [4]. Data from the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) also confirms differences in prevalence according to geographic location [5]. Additionally, studies indicate that maternal age, rural residence, male sex, and multiple births are significant risk factors for congenital hydrocephalus, further emphasising the need for targeted interventions and healthcare strategies tailored to the unique demographic and socio-economic contexts of each region [6,7].

This evidence highlights the urgent need for improved prevention, early diagnosis, and effective management of hydrocephalus, particularly in LMICs, where the burden of disease is most severe.

2. Defining the Clinical Problem

Hydrocephalus is characterised by the active distension of the ventricular system, a consequence of impaired cerebrospinal fluid (CSF) flow from its production within the ventricles to its absorption into the systemic circulation [8]. This results in increased intracranial pressure (ICP) and, if left untreated, leads to severe neurological deterioration [8].

In South Africa (SA), the burden of disease is heavily influenced by infectious diseases, mainly human immunodeficiency virus (HIV) infection, respiratory infections, diarrheal disease, malaria, and tuberculosis (TB) [9]. However, the burden of neurological disorders, particularly hydrocephalus, remains under-recognized and inadequately addressed within the national health landscape. Despite its significant morbidity, mortality, and financial strain on healthcare systems, hydrocephalus lacks the necessary public awareness in SA. This oversight is especially detrimental given the lifelong sequelae that can arise from delayed or inadequate diagnosis and treatment of childhood hydrocephalus. This thesis examines the burden of paediatric hydrocephalus in the Province of KwaZulu-Natal (KZN), a region profoundly affected by both infectious diseases and healthcare disparities.

The clinical presentation of hydrocephalus varies with age and the disease's progression. Neonates and children under two years often present with macrocephaly, bulging fontanelles, distended scalp veins, Parinaud syndrome, developmental delays, vomiting, and irritability. In contrast, older children typically exhibit symptoms such as headaches, visual deterioration, papilloedema, altered consciousness, regression of developmental milestones, seizures, and spasticity.

3. Pathophysiology of Hydrocephalus

The bulk flow theory proposes that CSF is produced by the choroid plexus and flows in a unidirectional manner [10]. It moves from the lateral ventricles to the third ventricle through the foramen of Monro, then from the third ventricle to the fourth ventricle via the cerebral aqueduct. From the fourth ventricle, CSF exits through the foramina of Magendie and Luschka into the subarachnoid space [10].

The CSF then moves through the basal cisterns and Sylvian fissure before being absorbed into the superior sagittal sinus via the arachnoid granulations. This absorption relies on a pressure gradient between the subarachnoid space and the venous system [10].

While the bulk flow theory has been fundamental to understanding hydrocephalus, recent research advances have introduced newer concepts, enhancing our knowledge of its pathophysiology.

Current theories suggest that CSF dynamics are influenced by molecular transport mechanisms, including aquaporins [10-12]. These theories propose that both ventricular and subarachnoid CSF are primarily derived from interstitial fluid and that the glymphatic system plays a vital role in the clearance of CSF and the movement of interstitial fluid in the brain [10-12].

Furthermore, CSF absorption in the subarachnoid space is thought to occur through dural lymphatic vessels running parallel to the venous sinuses and through nerve foramina at the skull base, draining extracranially [10-12]. CSF moves in a pulsatile manner, driven by cerebral circulation and respiration, with its flow further modulated by physical activity [10-12]. CSF within the ventricles exhibits a steady microflow, driven by the motile cilia lining the ventricular walls [11,12]. These theories highlight the complexity of the CSF movement and its regulation.

The pathophysiology of hydrocephalus is multifaceted, with numerous mechanisms contributing to the disease's progression. Paediatric hydrocephalus requires an understanding of these complex factors to inform clinical decision-making and improve patient outcomes. Pathophysiology of hydrocephalus involves the following factors:

3.1 Cerebrospinal Fluid Overproduction

CSF production is predominantly associated with the choroid plexus; however, it also involves contributions from capillary systems within the ependyma and brain parenchyma [11,12]. Pathologies affecting the choroid plexus, such as hyperplasia or tumours, often result in hypersecretion of CSF [12]. Numerous studies in Africa and North America have focused on the coagulation of the choroid plexus (CPC) and endoscopic third ventriculostomy (ETV) in attempts to treat hydrocephalus, with variable results [13-18].

3.2 Disruption of Absorption of Cerebrospinal Fluid

Various structures, including low-pressure capillaries, lymphatic pathways, and arachnoid villi facilitate CSF absorption. These structures are frequently affected in congenital hydrocephalus, PIH, and post-haemorrhagic hydrocephalus (PHH). Hydrocephalus occurs following failure of absorption mechanisms, either due to structural malformations or secondary compression from elevated ICP [11,12,19-21].

3.3 Major and Minor Pathway Obstruction

Blockage of major CSF pathways results in obstructive or non-communicating hydrocephalus, which is caused by space-occupying lesions in the brain. A careful review of neuroimaging allows neurosurgeons to offer optimal CSF diversion procedures to relieve hydrocephalus. The procedure of choice is determined by the child's pathology and clinical condition.

Minor CSF pathways involve ependymal cells and aquaporin channels, which are involved in interstitial water movement along perivascular spaces. Disruptions of these pathways often are due to post-inflammatory hydrocephalus [10-12].

3.4 Breathing Alterations

The respiratory system plays a role in the circulation of CSF, particularly through spinal epidural venous filling. This influences the venous pump in horizontal body positions. Breathing can drive CSF flow from the spinal to the intracranial compartment [11].

3.5 Pulsatility

Pulsatility plays an important role in the circulation of CSF and is influenced by cardiac activity. There is an important interplay between cardiac activity and normal CSF dynamics, requiring careful balance [11,12].

3.6 Obstruction of the Venous System

Obstruction or compression of the major venous channels, e.g. the sagittal sinus and right heart failure, often result in venous congestion, which leads to impaired CSF absorption. Craniofacial syndromes in children contribute to venous congestion and secondary hydrocephalus [11,12,20].

4. Classification of Hydrocephalus

The modern understanding of hydrocephalus is largely credited to the pioneering work of Walter Dandy, a neurosurgeon [22]. He was the first to classify hydrocephalus into two types: communicating and obstructive (non-communicating). Through his experiments he identified the choroid plexus as the source of CSF production [22]. At the beginning of the 20th century, Walter Dandy collaborated with a paediatrician, Kenneth Blackfan to develop a dog model for studying hydrocephalus [22]. In one experiment, they placed a cotton ball in the aqueduct of Sylvius, blocking the flow of CSF and causing hydrocephalus, which Dandy classified as "obstructive" [22]

During this period, diagnostic tools for hydrocephalus were limited. Plain x-rays, ventricular and lumbar punctures were the primary methods used in human and experimental animal studies [22]. They performed ventricular punctures, injecting dyes into the ventricles and performing delayed lumbar punctures (LPs) [22]. If the dye appeared in the CSF obtained from the LPs, the hydrocephalus was classified as "communicating". If no dye was found, it was classified as "obstructive" [22].

For the treatment of obstructive hydrocephalus, Dandy performed third ventriculostomies via a subfrontal approach. However, these procedures were associated with high morbidity. In communicating hydrocephalus, Dandy proposed removing the choroid plexus in the third and fourth ventricles for the purpose of reducing CSF production [22].

Hydrocephalus is also classified into congenital or acquired forms. Congenital hydrocephalus, which is caused by genetic factors affecting in-utero CNS development, contrasts with acquired hydrocephalus, which arises from haemorrhage, infection, trauma, or space-occupying brain lesions.

In communicating hydrocephalus, the bulk flow of CSF through the ventricles is unobstructed, but absorption is impaired at the arachnoid granulations or subarachnoid space. In non-communicating hydrocephalus, a blockage within the ventricular system prevents CSF from reaching the subarachnoid space.

In specific cases, such as tuberculous meningitis (TBM)-related hydrocephalus, routine CT scans may suggest communicating hydrocephalus. However, air encephalograms can distinguish between communicating and non-communicating types, influencing treatment strategies [21]. For instance, medical therapy may be sufficient for communicating hydrocephalus, whereas non-communicating hydrocephalus typically requires permanent CSF diversion using a ventriculoperitoneal shunt (VPS) or ETV [21].

5. Overview of the Aetiology of Hydrocephalus

5.1 Congenital Hydrocephalus

Congenital hydrocephalus, recognised as a priority congenital disorder in SA, typically manifests prenatally, often without a clear primary cause [23]. It is frequently associated with structural abnormalities of the CNS present at birth. However, the exact incidence of congenital disorders, including hydrocephalus, remains underreported in SA [23,24].

Studies from SA have identified cardiovascular anomalies as the most common congenital disorders, accounting for 43.9% of cases, followed by gastrointestinal (21%), musculoskeletal (13.2%), and CNS anomalies (12.3%) [25].

Within the spectrum of CNS disorders, congenital hydrocephalus and myelomeningocoele each represented 35.7% of cases, with encephalocoeles and anencephaly contributing 7.1% respectively [25]. Specifically, in KZN, CNS congenital disorders comprise 7.7% of congenital anomalies, with the birth prevalence of congenital hydrocephalus and Chiari malformation reported at 0.13 per 1,000 live births respectively and Dandy-Walker syndrome at 0.27 per 1,000 live births [26].

The prevalence of congenital hydrocephalus varies across SA's provinces, ranging from 0.53 to 0.98 per 1,000 live births [27-31]. A detailed mortality analysis from 2005 to 2017 revealed that 10% of congenital disorder-related deaths were attributable to CNS anomalies, with 4% specifically linked to congenital hydrocephalus [31].

5.1.1 Genetic Hydrocephalus

The pathophysiology of congenital hydrocephalus is multifaceted, often involving a combination of primary genetic abnormalities and secondary injury mechanisms. Primary genetic factors can independently influence the disease outcome, while secondary mechanisms, such as ventricular expansion and altered CSF dynamics, exacerbate the condition [32].

Despite significant advances, the genetic basis of hydrocephalus remains poorly understood due to its polygenic nature and the challenges posed by phenotypic heterogeneity and co-occurring conditions [32-34].

Numerous genes have been implicated in various forms of hydrocephalus, reflecting a diverse genetic landscape that includes pathways involved in neurogenesis, ion transport, and extracellular matrix integrity [32-36].

5.1.2 Hydrocephalus Secondary to Aqueduct Stenosis

Genetic studies have identified 15 gene mutations across 11 chromosomes linked to aqueduct stenosis (AS) [32-35]. Key genes such as L1CAM, ATP1A3, and FGFR3 play important roles [32-36]. L1CAM mutations, associated with X-linked hydrocephalus, lead to significant structural brain anomalies that impede CSF flow [32-36]. Other mutations, like those in ATP1A3 and SLC12A6, affect ion transport and contribute to ventricular dilation and aqueduct stenosis [32-36].

X-linked hydrocephalus affects males and is associated with learning difficulties, spastic paraplegia, aphasia, adducted thumbs and agenesis of the corpus callosum. Other genes involved in X-linked hydrocephalus include AIFM1, which regulates apoptosis, and AP1S2, implicated in endosomal protein trafficking [32-36]. In African countries such as Zimbabwe, Namibia, and the Democratic Republic of Congo, AS was the predominant aetiology [37].

5.1.3 Dandy-Walker Malformation

The hallmark of Dandy-Walker malformation (DWM) includes cystic dilation of the fourth ventricle, enlargement of the posterior fossa, and partial or complete dysgenesis of the cerebellar vermis [36]. DWM is linked to mutations in genes such as FOXC1, FKTN, and KCTD3 [32-36]. These mutations affect various developmental processes, including brain development, protein trafficking, and ion channel regulation leading to hydrocephalus [32-36].

5.1.4 Ciliopathies

Cilia, which are essential for CSF flow and brain development, are frequently implicated in hydrocephalus [32-36]. Mutations in ciliary genes can result in defective CSF flow and accumulation, leading to ventricular dilation. Mutations in FOXJ1, a gene vital for ciliary function, are associated with motile ciliopathy and hydrocephalus. Patients with FOXJ1 mutations may also present with systemic abnormalities, such as situs inversus, pneumonia, and congenital cardiac defects [32-36].

5.1.5 PI3K-Akt-mTOR Pathway

The PI3K-Akt-mTOR signalling pathway, known for regulating cell growth and proliferation, has also been implicated in hydrocephalus. Disruptions in this pathway can lead to abnormal brain development and hydrocephalus. Mutations in PIK3CA and PTEN, both key regulators of this pathway, are linked to overgrowth syndromes, including megalencephaly and polymicrogyria, which contribute to hydrocephalus [32-36].

5.1.6 MPDZ and Ependymal Cell Integrity

The MPDZ gene encodes a protein involved in cell junctions and has been implicated in hydrocephalus through its effects on ependymal cell integrity. Mutations in MPDZ lead to increased permeability of the choroid plexus, resulting in hydrocephalus. Patients with MPDZ mutations also display a range of neurodevelopmental abnormalities, including AS and seizures [32-36].

5.1.7 WNT Signalling and CCDC88C

The CCDC88C gene, which is a negative regulator of the WNT signalling pathway, is linked to a form of congenital hydrocephalus known as HYC1. Mutations in this gene lead to ventriculomegaly, developmental delays, and craniofacial abnormalities [32-36].

5.1.8 Myelomeningocoele-Related Hydrocephalus

Myelomeningocoele (MMC) is characterised by the protrusion of the meninges and spinal cord through a defect in the vertebral arches, together with a lack of skin covering [38]. The global incidence of MMC varies between 0.2 and 2 per 1,000 live births [38]. In HICs such as Norway, Sweden, and the United States, the incidence of neural tube defects (NTDs) has significantly declined over recent decades, largely due to widespread periconceptional folic acid supplementation, prenatal ultrasound screening, and selective termination of affected pregnancies [39-42].

In Sweden, the rate of spina bifida in newborns decreased from 0.55 to 0.29 per 1,000 live births between 1973 and 2003 [42], while in the United States, the NTD rate declined from 1.3 to 0.6 per 1,000 births between 1970 and 1989 [43,44]. The incidence of NTD-related hydrocephalus was highest in Africa (53.8 per 100 000) and lowest in Europe at 17.7 per 100 000 [1].

In SA, efforts to reduce the incidence of NTDs include the mandatory fortification of certain maize and wheat products with folic acid and other essential nutrients following the promulgation of R504 regulations relating to the fortification of certain foodstuffs on the 7th of April 2003 [45]. In KZN, the prevalence of MMC was reported at 0.27 per 1,000 live births [26]. African countries such as Ethiopia and Kenya report NTD-related hydrocephalus as the predominant aetiology of hydrocephalus [46,47].

The pathophysiology of MMC-related hydrocephalus is complex and not fully understood. The prevailing theory suggests that inappropriate in-utero CSF outflow through the MMC defect leads to the underdevelopment of normal CSF drainage pathways [48]. The Management of Myelomeningocele Study (MOMS) provided important insights, demonstrating that foetuses undergoing prenatal surgery had a lower rate of CSF shunt placement (40%) compared to those who received standard postnatal repair (82%) [48]. However, the generalizability of these findings outside of highly specialised centres remains uncertain.

The SMARCC1 and TRIM71 genes involved in chromatin remodelling and neural tube development are associated with NTDs, developmental delays, and macrocephaly [32-36]. The prevalence of hydrocephalus in children diagnosed with MMC varies widely, with reported rates ranging from 57% to 86% following postnatal closure of the MMC defect [49-51]. In KZN, the prevalence rate of MMC-related hydrocephalus was 51.1% [52].

5.1.9 Hydrocephalus Associated with Encephalocoeles

Encephalocoele is a congenital anomaly characterised by the herniation of intracranial contents through a defect in the skull present at birth. The occipital region is the most frequent site for encephalocoeles, accounting for over 75% of all cases [53].

These can be further classified into infra-torcular or supra-torcular encephalocoeles based on their location relative to the torcula, the junction of the venous sinuses. This distinction is important as it influences both the clinical presentation and the surgical approach [54].

The incidence of encephalocoeles varies globally, ranging from 0.8 to 5.6 per 10,000 live births [55]. In Europe and North America, occipital or posterior cephaloceles represent 66% to 89% of cases, with the remaining cases occurring in the frontal or parietal lobes [56 -58]. However, in regions such as Thailand and other Southern Asian countries, frontal encephaloceles are more prevalent [57-58].

Hydrocephalus is a frequent complication in children with posterior encephalocoeles, with an incidence ranging from 60% to 90% [58]. This high prevalence is believed to be associated with the torsion or stenosis of the Sylvian aqueduct, which often develops post-operatively [58]. The presence of hydrocephalus significantly complicates the management of encephalocoeles, requiring a multidisciplinary approach that addresses both the structural anomaly and the resultant CSF dynamics [57,58].

5.2 Post-Infectious Hydrocephalus

5.2.1 Bacterial or pyogenic infections

Newborns are particularly susceptible to invasive diseases such as neonatal sepsis, meningitis, and pneumonia due to their immature immune systems. High-grade bacteraemia can lead to the invasion of the meninges once the pathogens cross the blood-brain barrier (BBB) [59]. This invasion triggers an immune response, with pro-inflammatory substances prompting the migration of leukocytes, particularly neutrophils, across the BBB [59].

The incidence of meningitis ranges from 0.2 to 0.5 per 1,000 live births [59]. In SA, the incidence is particularly high, at 13.7 per 1,000 live births [60], compared to 4.5 to 9.7 per 1,000 in the United States of America [61] and 6.1 per 1,000 in the United Kingdom [61].

The incidence of bacterial meningitis in SA was notably higher among infants with a subsequent, decrease in older children [62]. A study conducted in SA from 2014 to 2019 on culture-confirmed neonatal bloodstream infections (BSI) and meningitis found that gram-negative bacteria accounted for 57% of the 43,438 pathogens isolated, followed by gram-positive bacteria (36%) and fungi (7%) [60]. *Klebsiella pneumoniae* was the most common organism (25%), followed by *Acinetobacter baumannii* (13%) and *Staphylococcus aureus* (12%) [60].

The study also found differences in pathogen distribution by hospital level and attributed this to variations in antibiotic-prescribing practices and access to advanced treatments, with national central and tertiary hospitals showing higher incidences of resistant gram-negative bacteria (60%), followed by gram-positive bacteria (30%) [60].

The study also found that gram-positive bacteria (49%) were relatively more common causes of BSI and meningitis at district hospitals, with a similar proportion of gram-negative bacteria (48%) [60]. They also found significant regional variations, with the highest incidence highest in the provinces of Gauteng (13.9 per 1000 live births), Free State (13.7 per 1000 live births), and KZN (8.2 per 1000 live births), and lowest in Limpopo (2.5 per 1000 live births) and Northern Cape (3.3 per 1000 live births) [60].

Neurosurgeons working in LMICs often encounter infants with hydrocephalus, with no documented history of meningitis. In these circumstances, a prior history of fever and ventricular loculations on cranial ultrasonography, or CT/MRI brain scans and ependymal scarring on neuro-endoscopy are important clues of an infectious aetiology [63,64].

5.2.2 Tuberculous Meningitis

TBM is a severe form of tuberculosis (TB) that typically follows the inhalation of *Mycobacterium tuberculosis* (Mtb) [65]. Mtb infects the lung dendritic cells, neutrophils, and alveolar macrophages [65]. The infected dendritic cells are then carried to the lymph nodes, where they stimulate differentiation of T-helper 1 cells, which release interferon-gamma (IFN-*y*) and TNF-α, which further activates macrophages and dendritic cells to produce cytokines, leading to the formation of a granuloma. The granuloma encapsulates the infected cells, resulting in latent infection. However, in immunocompromised patients, granuloma formation may be halted, resulting in progression to active pulmonary TB [65,66].

After initial infection in the lungs, Mtb disseminates haematogenously to the brain, where it forms small TB lesions known as *Rich foci* on the subpial or subependymal surfaces [65,66]. These lesions can remain dormant for extended periods before rupturing into the ventricular system or subarachnoid space, leading to meningitis [65].

TBM is associated with significant morbidity and mortality, particularly in immunocompromised individuals such as those with HIV infection. The pathogenesis of TBM involves the formation of a thick gelatinous exudate around the brainstem, sylvian fissures, and basal cisterns, obstructing CSF flow and causing hydrocephalus.

Hydrocephalus complicates TBM in 80-90% of cases, with basal exudates leading to vasculitis resulting in infarction of the caudate nucleus, internal capsule, and brainstem, further complicating the clinical course [66-68].

Hydrocephalus associated with TBM can be classified as either communicating or non-communicating, depending on whether the obstruction to CSF flow occurs within the subarachnoid space or at the ventricular outlets. Intracranial tuberculomas present as space-occupying lesions in the brain, resulting in obstructive hydrocephalus.

The frequent involvement of basal vessels (medial striate and thalamic perforating arteries) and the resultant ischemia, elevated ICP, and cerebral oedema highlight the importance of early diagnosis and treatment to prevent irreversible neurological damage.

5.2.3 Cryptococcal Meningitis

Cryptococcal meningitis (CM), caused primarily by *Cryptococcus neoformans*, is an important cause of hydrocephalus in immunocompromised individuals, particularly those with HIV/AIDS. The infection begins with the inhalation of airborne spores, which can remain dormant in the lungs and reactivate during periods of immunosuppression [69]. Once the spores proliferate and disseminate to the CNS, they cause meningitis, meningoencephalitis, or cerebral mass lesions known as *Cryptococcomas* [69]. Defects in T-cell immunity are associated with the development of CM [69,70].

Cryptococcus species have several virulence factors, including a polysaccharide capsule and phenolic melanin deposition, which help the pathogen evade immune responses and survive within the host [69,70]. CM-related hydrocephalus occurs secondary to obstruction of CSF flow due to cryptococcal growth within the ventricular system or as a consequence of the inflammatory response, leading to elevated ICP and progressive neurological decline [70].

5.2.4 Neurocysticercosis

The highest prevalence of neurocysticercosis (NCC) in SA, is in the Eastern Cape province [71]. NCC, caused by the larval stage of the pork tapeworm *Taenia solium*, is a common parasitic infection of the CNS, particularly in regions with endemic zoonotic transmission [71]. The life cycle of the parasite in the brain progresses through four stages: vesicular, colloidal, granular, and calcified. Each stage triggers varying degrees of inflammation, recruitment of immune cells, and granuloma formation [72]. Hydrocephalus, occurring in 15% to 30% of NCC cases, is a common complication, particularly when cysts obstruct the ventricular system or CSF flow [72].

5.3 Post-Haemorrhagic Hydrocephalus

Intraventricular haemorrhage (IVH) and germinal matrix haemorrhage remain well-recognized complications of prematurity, affecting 10%–20% of preterm neonates, particularly those with very low birth weight (<1500 g) [73]. The incidence of PHH was reported at 38.5 per 100 000 births in the United States/Canada and Europe respectively [1].

PHH is characterised by the progressive dilation of the ventricular system following IVH, typically accompanied by increased ICP [74]. Advances in neonatal care have significantly improved the survival rates of preterm infants, particularly those weighing less than 1000 grams. However, this improvement has been accompanied by an increase in both IVH and PHH, despite the overall reduction in IVH incidence from 50% in the early 1980s to around 20% by 2005 in the United States [74].

The pathophysiology of PHH is multifactorial, involving the initial obstruction of the ventricular system by blood clots, which impairs CSF reabsorption. Over time, this leads to chronic arachnoiditis, with extracellular matrix deposition in the foramina of the fourth ventricle and subarachnoid space, further obstructing CSF flow. IVH and ventricular expansion cause detrimental effects on the immature periventricular white matter, exacerbated by elevated ICP, free radical generation from free iron, and inflammation [75].

Management of PHH varies across neurosurgery centres, with temporary treatment options including ventricular taps, external ventricular drain (EVD) insertion, ventriculosubgaleal shunts (VSGS), and CSF reservoirs before definitive CSF diversion procedures such as VPS insertion are performed. PHH requires a tailored approach based on individual needs of the neonate.

5.4 Brain Tumours

Hydrocephalus is a common complication in children with brain tumours (BTs). Posterior fossa tumours (PFTs) present a high risk for hydrocephalus both at diagnosis and post-operatively. The prevalence of hydrocephalus at presentation in this subgroup can be as high as 87.18% [76,77]. Post-operative hydrocephalus requiring permanent CSF diversion remains an important concern, with rates ranging from 21.53% in children with medulloblastoma to 10 to 38.71% in those with various PFTs at long-term follow-up [76-78].

5.5 Post-Traumatic Hydrocephalus

Factors such as increasing age, IVH and the thickness or distribution of the traumatic subarachnoid haemorrhage (SAH) have been significantly associated with the onset of hydrocephalus [79,80]. Decompressive craniectomy, a common intervention following traumatic brain injury (TBI), also poses a risk for the development of hydrocephalus [81].

6. Brain Injury Secondary to Hydrocephalus

Hydrocephalus, whether congenital or acquired, induces a cascade of pathological changes that can severely damage brain structures [82]. The progression of hydrocephalus triggers both acute and chronic mechanisms of injury. The ependyma, is often one of the first structures to suffer damage, manifesting as focal destruction. In the acute phase, which occurs within hours to a few days after the onset of ventriculomegaly, periventricular tissues experience compression and stretching. This mechanical stress leads to ischaemia, hypoxia, and increased CSF pulsatility, most prominent in the cerebral aqueduct [82]. There is distortion and collapse of cerebral blood vessels, stretching, thinning and upward displacement of the corpus callosum [82].

The axons and myelin within the periventricular white matter are particularly vulnerable, leading to compromised connectivity and function. The caudate nucleus is compressed, and cortical neurons may also experience injury, leading to a reduction in overall brain mass and thinning of the cortical mantle, especially in the parietal and occipital regions [82,83].

As hydrocephalus transitions into a chronic state, additional mechanisms come into play, including gliosis and neuroinflammation, periventricular oedema, demyelination, axonal degeneration, and impaired axoplasmic transport. Metabolic dysfunction and stagnant CSF flow further exacerbate the condition, leading to altered BBB transport, which can increase toxicity through reduced amyloid clearance and other harmful processes. Ultimately, these cumulative insults result in dendritic and synaptic deterioration, altered neural connectivity, and cell death [11,20,82-84].

Neuronal cell death in hydrocephalus, particularly apoptosis and necrosis of cortical neurons, tends to occur after prolonged exposure to elevated ICP. However, despite significant reductions in neuron populations, the biological impact may be minimal in some cases, given the relatively small number of apoptotic neurons compared to the total population in the cerebral cortex [85-87].

Oligodendrocytes and astrocytes in the germinal matrix, critical for brain development, are also susceptible during the early stages of hydrocephalus. Germinal matrix haemorrhage further compounds these effects by damaging glial cells, reducing cerebral white matter volume, and causing venous ischemia and infarction due to compression of the terminal vein, a key determinant of long-term neurological outcomes [85].

PHH introduces additional challenges, as cytotoxins released into the periventricular white matter, such as glutamate and iron, contribute to free radical injury of oligodendrocytes [85]. PHH also has a direct negative impact on dendritic morphology, reducing dendritic length, branch density, and spine density and disrupting normal synaptogenesis [85]. Increased ICP associated with PHH raises cerebral vascular resistance, leading to reduced cerebral blood flow (CBF) and diminished tissue perfusion [73,74,85]. Hydrocephalus can result in hyponatraemia, further exacerbating cerebral oedema and worsening ICP, particularly in TBM [88,89].

7. Cerebral Blood Flow Changes in Hydrocephalus

The impact of hydrocephalus on CBF and brain development is multifaceted, driven primarily by the increased ICP that expands the ventricles and displaces adjacent brain structures. This mechanical distortion of the brain is compounded by disruptions in CBF, alterations in metabolism, and impaired neurotransmission [82,83,90,91]. The resulting changes can significantly compromise neurological function, especially in the developing brain.

In conditions such as acute bacterial meningitis, dysregulated CBF is common. Dysregulation may initially lead to increased CBF and cerebral blood volume, thereby elevating ICP [21]. This pattern of impaired autoregulation is often seen in TBI and can similarly occur in bacterial meningitis [21]. When autoregulation fails, CBF becomes passively dependent on systemic blood pressure, increasing the risk of ischemia at lower blood pressures and exacerbating ICP at higher pressures [21,90,91].

8. Natural History of Untreated Hydrocephalus

Untreated hydrocephalus is associated with mortality rates ranging from 20% to 87% [92]. In addition to high mortality, untreated hydrocephalus is associated with progressive cognitive decline, severely impacting the quality of life for survivors [93-95]. Historical data indicate that, before the advent of shunting procedures, approximately 50% of children with untreated hydrocephalus died, and of those who survived were dependent or unable to work as adults [96]. Only a minority (20%) were able to lead relatively normal lives. Shunting procedures over the years have reduced mortality and morbidity considerably. However, even with modern treatment options, outcomes vary widely.

Most children treated for hydrocephalus now reach adulthood; however, there is still a paucity of studies investigating the impact of childhood hydrocephalus during adulthood. These patients require lifelong follow-up and may require shunt revisions in adulthood [97-99].

The quality of life is variable from independent to fully dependent. Vinchon et al. reported a series of 456 children treated for hydrocephalus and followed into adulthood and found a mortality of 6.3% after 20 years, with 47.6% having autonomous activity, while 13.6% and 23% were diagnosed with behavioural disturbances and seizures, respectively. They also reported that 41.4% attended the normal curriculum at school, and 25.4% had normal jobs [97].

9. Research Question

What are the factors influencing the epidemiology, treatment outcomes, and mortality in paediatric hydrocephalus in KZN, SA, and how does HIV infection and proximity to centralised neurosurgery services influence these outcomes?

10. Aims of the Study

To investigate the burden of paediatric hydrocephalus in KZN, focusing on the impact of HIV-related infections on the progression of hydrocephalus, treatment outcomes, and mortality.

11.Objectives of the Study

1. To describe the epidemiology of paediatric hydrocephalus in KZN, including its aetiology and demographic trends.
2. To evaluate the influence of HIV infection and CNS infections, such as TBM and CM, on the development and outcomes of hydrocephalus in children.
3. To evaluate the outcomes of common surgical modalities, such as VPSs and ETV, used to treat paediatric hydrocephalus in KZN.
4. To investigate the impact of proximity to centralised neurosurgery services on surgical outcomes, complication rates, and mortality.
5. To recommend policy changes that address healthcare disparities and improve outcomes for children with hydrocephalus in KZN and other LMICs.

12. Rationale for the Study

In SA, socioeconomic disparities and healthcare access significantly influence disease prevalence and outcomes. By 2022, the population had reached 62 million, with nearly 21 million children, representing 34% of the total population [100]. This study was conceived due to the lack of data on the burden of paediatric hydrocephalus in KZN, a province with 12 million residents [100]. The thesis aims to address knowledge gaps in the epidemiology, treatment modalities, management outcomes, and factors associated with mortality in children diagnosed with hydrocephalus in KZN, which has the second-largest paediatric population in the country [101].

With KZN also having the highest HIV prevalence in SA, the impact of HIV infection on hydrocephalus outcomes in children remains largely unexplored [100]. The findings from this research are intended to guide strategies for reducing the disease burden and improving outcomes for children, as hydrocephalus currently accounts for 29% of neurosurgery theatre cases in KZN [102].

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Chapter 2: Factors Associated with Mortality in Children Diagnosed with Hydrocephalus: A Scoping Review

This chapter presents a scoping review of the factors associated with mortality in children diagnosed with hydrocephalus, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. It discusses the important determinants of mortality in paediatric hydrocephalus, a condition that significantly contributes to the global burden of neurological disorders in children. Despite advances in surgical techniques and postoperative care, hydrocephalus remains one of the leading causes of morbidity and mortality. Understanding these mortality drivers is vital for enhancing clinical outcomes and shaping effective policy interventions. This chapter synthesizes findings from a comprehensive scoping review, providing information that will inform both clinical practice and broader public health strategies.

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Colleen Aldous: Analysis and interpretation of data, critical revision of the article for important intellectual content and final approval of the version to be submitted

Factors Associated with Mortality in Children Diagnosed with Hydrocephalus: A Scoping Review

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Abstract

Background

Paediatric hydrocephalus significantly contributes to the global disease burden, with notable morbidity and mortality rates. Childhood mortality is a crucial metric for evaluating a country's health status. While numerous reviews address the aetiology, management, and complications of surgically treated childhood hydrocephalus, this scoping review specifically aims to identify the factors associated with mortality in children treated for hydrocephalus.

Methods

This review adhered to Arksey and O'Malley's five-stage framework. Four electronic databases—PubMed, Google Scholar, EBSCOhost, and Web of Science—were searched. The inclusion criteria focused on studies involving children (birth to 18 years) treated for hydrocephalus, with mortality as the outcome. Articles published between January 1, 2001, and January 1, 2024, were included, while non-English articles were excluded.

Results

A total of 5,003 studies were identified, with 4,907 (98%) excluded during the title and abstract screening and 12 (0.2%) during full-text screening. Sixty-three articles (1.3%) were eligible for final review. Most studies involved infants, with post-infectious hydrocephalus being the predominant aetiology (69.8%). Ventriculoperitoneal shunt (VPS) insertion was the most frequent procedure (85.7%), followed by endoscopic third ventriculostomy (ETV), which accounted for 26.9%. Complication rates for VPS ranged from 1.3% to 57.1%, and ETV failure rates ranged from 2.5% to 67%. Most common causes of mortality were shunt infections and procedure-related meningitis (38.1%), shunt failure (25.4%), respiratory complications including pneumonia (17.5%), and brain tumours (15.9%).

Conclusion

Paediatric hydrocephalus remains a significant clinical challenge, with mortality influenced by the aetiology of hydrocephalus, comorbidities, socioeconomic status, age at diagnosis, type of surgical intervention, and postoperative complications.

Keywords: Brain Tumours, Endoscopic Third Ventriculostomy, Low- and Middle-Income Country, Post-Infectious Hydrocephalus, Ventriculoperitoneal Shunt

Introduction

Paediatric hydrocephalus is a significant contributor to the global burden of disease, associated with substantial morbidity and mortality [1]. The natural history of untreated hydrocephalus or severe delays in treatment includes progressive cognitive decline, macrocephaly in children with open fontanelles, and early mortality [2,3]. A previous study reported the mortality rate of untreated hydrocephalus to be 50% [4].

The primary treatment for hydrocephalus involves cerebrospinal fluid (CSF) diversion surgical procedures, which impose a significant financial burden, particularly in low- and middle-income countries (LMICs), especially those in Sub-Saharan Africa (SSA). The annual cost of treating hydrocephalus amounts to billions of US dollars [5,6].

Childhood mortality is a critical metric for assessing a country's national health status. The United Nations Sustainable Development Goals (SDGs) aim to end preventable deaths of newborns and children under five years old, targeting a reduction in neonatal mortality to at least 12 per 1,000 live births and under-five mortality to at least 25 per 1,000 live births by 2030 [7]. In 2021, the global under-five mortality rate was 38 per 1,000 live births, a significant improvement from 93 per 1,000 live births in 1990 [8]. These improvements are attributed to better education, access to quality healthcare, improved nutrition, and immunization programs. Regional under-five mortality rates per 1,000 live births in 2021 were 72 in Africa, 45 in the Eastern Mediterranean, 29 in South-East Asia, 13 in the Americas, 12 in the Western Pacific, and 8 in Europe [8]

The SDGs also aim to end epidemics of AIDS, tuberculosis (TB), and other communicable diseases, which are particularly relevant in LMICs, especially SSA and South-East Asia, where post-infectious hydrocephalus (PIH) is predominant [7,9,10].

Numerous reviews focus on the aetiology, management, and complications following the surgical treatment of paediatric hydrocephalus [1,9-11]. However, there is no comprehensive focus on the understanding of mortality in children diagnosed with hydrocephalus. To address this gap, we performed a Scoping review aimed at identifying causes or factors associated with mortality in children treated for hydrocephalus, based on internationally published research. This review aims to highlight key areas for prevention and reduction of mortality.

Methods

The scoping review was performed in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [12]. This review followed the five-stage principles of Arksey and O'Malley's framework, namely: (i) identify the research question, (ii) identify all the relevant published studies (iii) refine the study selection criteria, (iv) collect the relevant data from each published article and (iv) collate, summarize, report and interpret the data. [13]

Objectives

The review question is structured within the framework of the Population-Concept-Context (PCC) model, signifying that the primary focus of the study is on children, with the concept under investigation being childhood mortality following diagnosis of hydrocephalus. Thus, to fulfill the overall objective of this study, this review set out to answer the question: What are the factors associated with mortality in children diagnosed with hydrocephalus?

Inclusion Criteria

We selected all articles published in journals that involved children (birth to 18 years) diagnosed and treated for hydrocephalus, where the outcome was death. We included articles published from the 1st of January 2001 to the 1st of January 2024.

We included observational studies, randomized controlled trials, non-randomized trials, and cross-sectional studies reporting on the mortality rate of children diagnosed with hydrocephalus and factors associated with or predictors of mortality. Screening of titles and abstracts was done. Full-text articles were assessed by authors and those found unsuitable were excluded.

Exclusion Criteria

We excluded articles not published in English. We excluded systematic reviews or narrative reviews, dissertations, book chapters, letters, conference presentations, and case reports. We focused on studies assessing mortality as an outcome.

Search Strategy and Study Selection

The electronic databases of PubMed, Web of Science, Google Scholar, and EBSCOhost were searched. The search strategy used is presented in Table 1. The full texts of the articles were retrieved and reviewed by the two investigators independently for inclusion as per the inclusion criteria. Differences were resolved by discussion.

Table 1: Search Strategy

Search	Search terms
# 1	Mortality OR Death OR Survival status OR Dying OR Fatal
#2	Factors associated with death OR Predictors of death OR Factors associated with mortality OR Predictors of mortality
# 3	Childhood hydrocephalus OR Paediatric hydrocephalus OR Hydrocephalus in children OR Infantile hydrocephalus
#4	Shunting for hydrocephalus OR Ventriculoperitoneal shunt OR Endoscopic third ventriculostomy
#5	# 1 AND #2 AND #3 AND #4

Data Extraction

Data was extracted into a Microsoft Excel proforma sheet. The Excel sheet included columns of specific interest for data extraction which included variables such as the author details, year of publication, country, age, sex, study design, number of participants, aetiology of hydrocephalus, CSF diversion procedure, complications, mortality rate, and causes or factors associated with mortality identified from the articles.

Results

Study Selection

A PRISMA flow diagram for study selection is presented in Figure 1. We identified 5,003 studies via the database search and excluded 4907 (98%) at title and abstract screening and 12 (0.2%) at full-text screening. Sixty-three articles (1.3%) were eligible for inclusion.

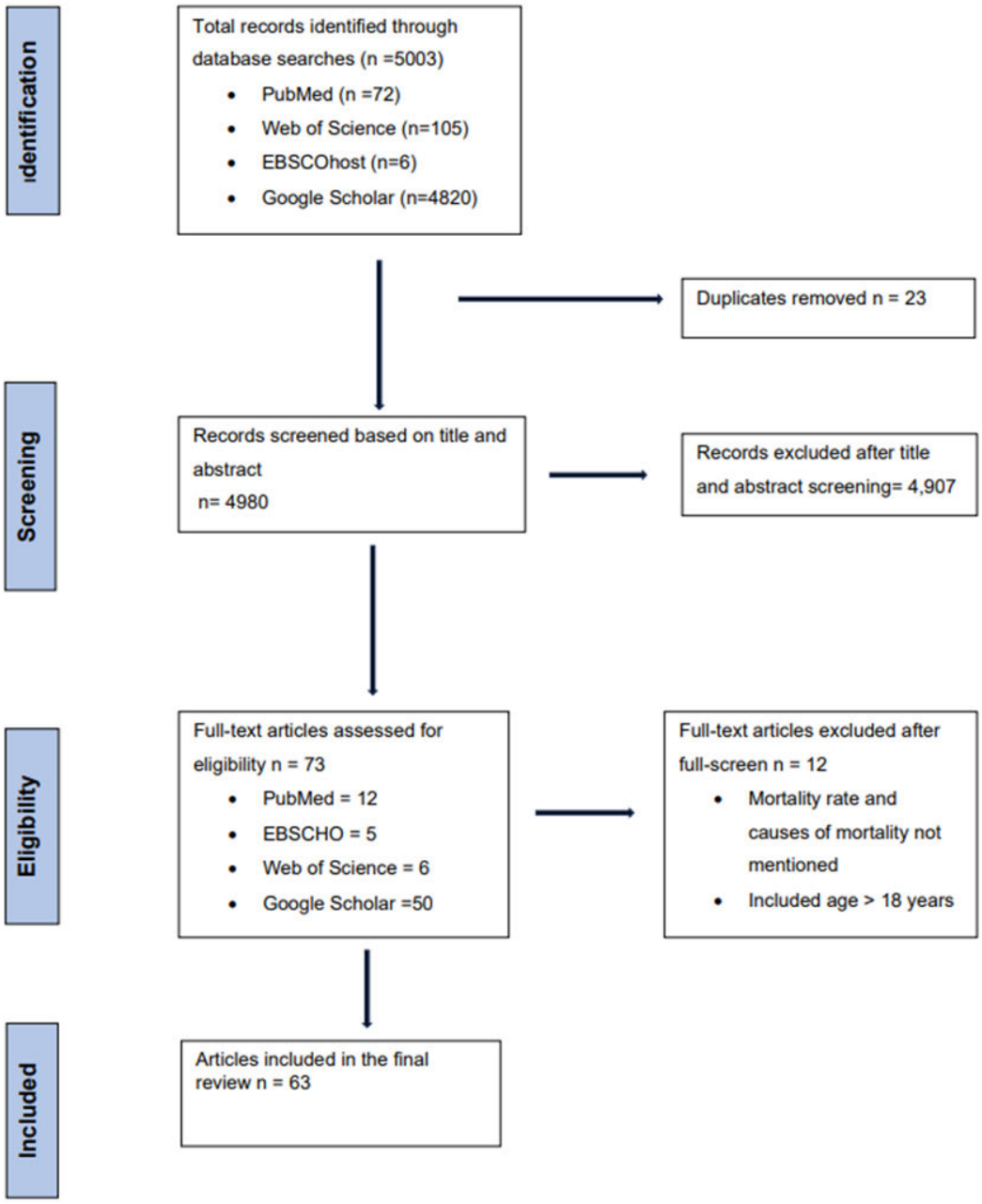

Figure 1: A PRISMA Flow Diagram for Study Selection

Synthesis of Result Characteristics of Studies Included

The characteristics of the studies included in the scoping review are presented in Table 2. The list of countries where these studies were performed is presented in Figure 2. The study designs were retrospective (n=43; 68.3%), while 20 (31.7%) were prospective. The studies were performed in a total of 33 countries, of which 11 (33.3%) were from high-income countries (HIC), while 22 (66.7%) were from LMICs.

Table 2: Summary of the Studies Evaluating Causes and Factors Associated with Mortality in Children Diagnosed with Hydrocephalus

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
1. Joseph et al [14]	2017	Haiti	5 months (median)	1.02:1	Retrospective	75	PIH (21.3%), IVH (5.3%) & TBI (2.7%)	VPS (40%) ETV (24%) ETV&CPC (20%) No treatment (16%)	Infection (8%), Shunt dysfunction (5.3%), Shunt migration (1.3%)	6.7%	Respiratory distress (n=4), seizures (n=3) febrile diarrhea(n=1), unshuntable hydrocephalus (n=1), extreme malnutrition (n=1)
2. Cabacungan et al [15]	2023	USA	≤28 days, n=123. >28 days, n=365	1.2:1	Retrospective	488	IVH (100%)	≤28 days: temporary procedures (57%) and VPS (18.7%), spinal tap (28.5%). >28 days: temporary procedures (47.6%), VPS (77%), spinal tap (29.6)	≤28 days: shunt malfunction (9.8%), thrombocytopenia (44.7%), meningitis (11.4%) >28 days: shunt malfunction (14.3%), thrombocytopenia (43%), meningitis (15.9%)	≤ 28 days= 12.2% >2 8 days= 4.4%	Odds of death were 0.27 higher in children with PHH intervention at >28 days 0.27 (0.09–0.77) p = 0.05. Ref ≤ 28 days.
3. Stevic et al [16]	2018	Serbia	≤28 days	1.7:1	Retrospective	74	IVH (100%)	VPS (59.5%), Ommaya (40.5%)	Multiple revisions (9.46%)	6.7%	ASA-PC score 4 (P=0.000), pneumothorax (P=0.003), DAP (P=0.000), BPD (P=0.003)
4. Khan et al [17]	2017	Pakistan	6.2 months (median)	1.2:1	Retrospective	90	Congenital (100%)	VPS (90%)	Shunt blockage (53.6%), Septic complication (57.1%), Seizures (21.4%)	31%	Septic complications (50%), including meningitis and metabolic disease (p=0.012) and delayed milestones (p=0.003.) Shunt blockage (42.8%) and uncontrolled seizures (n=8). Unknown (n=2)
5. El-Ghandour et al [18]	2011	Egypt	6.5 yrs. (ETV) and 7.2 yrs. (VPS) median	1.3:1	Retrospective	53	Posterior fossa tumours (100%)	VPS (n=21) ETV (n=32)	VPS complication (38%) ETV complication (9.3%)	ETV (0%) VPS (4.7%)	Shunt infection/ ventriculitis
6. Rashid et al [19]	2012	Pakistan	≤15 yrs.	2.1:1	Retrospective	338	CH (20.4%), PIH (38.1%), BT (8.3%), SD (7.7%), IVH (7.7%), AC (2.4%)	VPS (65.9%), EVD (18.4%,	Shunt infection (11.24%), blocked shunt (16%)	11.2%	IVH (23.1%), BT (21.4%), SD (11.5%).

Author	Year	Country	Age	M: F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
7. Munch et al [20]	2020	Denmark	3.3 months (median)	1.9:1	Retrospective	374	Isolated (27%); syndromic (24%); PIVH (22%), PIH/TBI (6%), MMC (11%), Congenital (24%), CNS tumours (5%), Chiari (1%), DWM (4%)	VPS (100%)	3 month and 1 year cumulative risk for SR were 36% and 50% respectively	12%	10-year cumulative risk mortality: Tumour-related 53% (95%CI:22-72), syndromic HC 16% (95%CI:7-23) , MMC 15%(95%CI:1-12) LGWA and DWM 15% (95%CI:0-32).
8. Pan et al [21]	2018	India	20.7 months (median)	1.3:1	Retrospective	137	CH (n=62), TBM (n=35), SD (n=29), IVH (n=11)	VPS (100%)	Shunt complication (35.7%), Infection (16.21%)	5.1%	Shunt complications
9. McClugage et al [22]	2020	USA	1 month (median)	1:1	Retrospective	130	IVH (100%)	VSGS (100%)	Not mentioned	2-year mortality was 16%	Oscillating ventilation (p = 0.001)
10. Wubie et al [23]	2023	Ethiopia	≤15 yrs.	1.4:1	Retrospective	337	SD (30.9%), PIH (11.9%), DWM (10.6%), BT (7.4%), AS (6.8%), encephalocoele (4.7%), Idiopathic (4.5%), IVH (3.9%), CM (3.8%), AC (1.4%) ,	VPS (100%)	Not mentioned	29.4%	Communicative hydrocephalus (AHR: 1.99, 95% CI: 1.18–3.36). Post-TBI (AHR: 7.43, 95% CI: 3.21–16.88). Emergency surgery (AHR: 1.86, 95% CI: 1.17–3.13). Revised shunt procedure (AHR: 8.01, 95% CI: 6.12–13.43). Sunset eye (ARH: 2.01; 95% CI: 1.17–3.47) Rapidly increased head size (ARH: 2.05, 95% CI: 1.14–3.37). Prolonged antibiotics treatment > 7 days (AHR: 2.46, 95% CI: 1.82–7.37) Gram-negative infections (AHR: 1.95, 95% CI: 1.60–12.64).
11. Reynolds et al [24]	2020	Zambia	5.5 months (median)	1.1:1	Retrospective	378	PIH(65%), non-PIH (35%)	VPS (75%), ETV/CPC (14%), VPS revision (12%)	Overall complications (20%), infection (8%)	7%	Failure to thrive (p = 0.012). Complications p < 0.001).
12. Reid et al [25]	2019	Malawi	4.5 months (median)	1.2:1	Prospective	100	PIH (10.8%)	VPS (88%)	SR (5.7%), OD (1.3%), meningitis (3.8%), burst abdomen (1%), umbilical hernia (1%), febrile illness (3%), VPS exposure (7.4%)	In hospital =5.5%. 3 months =32.1%. 6 months =62.3%.	Younger maternal age

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
13. Mbabazi-Kabachelor et al [26]	2019	Uganda	8.4 & 7.4 months (median)	1.8:1	Prospective	248	PIH (77%), NPIH (17%), MMC (6%)	AIS (50%). Non-AIS (50%).	Overall infection (14%) AIS (4.8%) Non-AIS (6.5%)	Overall mortality (5.6%) AIS (4.0%) Non-AIS (7.3%)	Shunt infection (n=2) Seizures (n=3) Childhood infection (n=2) Malnutrition (n=5)
14. Agrawal et al [27]	2004	India	11.4 yrs. (mean)	2:1	Retrospective	37	TBM (100%)	VPS (100%)	Complications (30%) Infection (14%)	5.4%	Multiple infarcts
15. Rohlwink et al [28]	2016	South Africa	3.3 yrs. (mean)	1.6:1	Prospective	44	TBM (100%)	VPS/EVD (30.8%)	Not mentioned	16%	Multiple (P = 0.03), bilateral (P = 0.006) and large infarcts (P < 0.0001). Number of vascular territories involved in infarction were positively associated with death (P < 0.001).
16. Beuriat et al [29]	2017	France	3.2 yrs. (mean)	1.2:1	Retrospective	975	Inflammation (20.9%), malformation (24.5%), AS (32.3%), BT (32.3%)	VPS (71.3%) ETV (28.7%)	Overall OSV shunt survival was 70% at 1 year, 58% at 10 years, and 49% at 20 years. Commonest cause for mechanical shunt failure was obstruction (50.7%) & Shunt infection (6.7%) ETV overall survival,76.9% at 1 year and 70% at 10 and 20 years.	16.5%	Mortality due to tumour progression was 12.5%. The mortality rate due to the hydrocephalus itself was 1%.
17. Perdaens et al [30]	2018	Belgium	13 months (median)	1.4:1	Retrospective	142	IVH (16%), BT (16%), SB (15%), AS (8%), PIH (8%), PH (8%) DWM (6%), AC (5%), Unknown (6%)	VPS =99 ETV=40	70% VPS complication Infection =19% ETV failure =50% ETV infection =5%	16%	Predominantly (52%) in the BT group. Two deaths directly related to treatment i.e. post-operative haemorrhage and acute VPS malfunction

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
18. Faghih Jouibari et al [31]	2011	Iran	3 months (median)	1.2:1	Retrospective	9	AS (n=5), MMC (n=3), IVH (n=1)	VPS (100%)	Subdural effusion (n=6), skull deformity (n=3) shunt malfunction (n=2), shunt infection (n=4)	33.3%	Shunt infection (n=3), organisms cultured in each infection were pseudomonas, E. coli &Klebsiella
19. Ferraris et al [32]	2021	Philippines, Russia & Japan	2.42 yrs (mean)	1:1.2	Prospective	159	PHH (23.9%),BT (22%), CH (21.4%), PIH (19.5%), MMC (8.8%)	VPS (62.3%), ETV (13.8%), VPS revision (15.1%), EVD (3.8%), Ommaya (0.6%)	Revision rate of 15.1%	Three (1.9%) children died in the Philippine cohort but none in the Russian and Japanese cohorts	EVD insertion was associated with mortality (OR 14.45, 95% CI 1.28–162.97, p = 0.031)
20. Warf et al [33]	2011	Uganda	9.5 months (median)	Not mentioned	Prospective	149	PIH (100%)	ETV &CPC (n=109) VPS (n=40)	5-year survival 72.8% in ETV and 67.6% in VPS with no difference in survival (log-rank p = 0.43, Breslow p = 0.46).	Mortality; ETV =1.2% & VPS= 4.4 %	Operative mortality (death from any cause within 30 days of the procedure) was 1.2% (1 death in 81 procedures) for ETV. Deaths related to a shunt complication were malfunction, and ventriculitis (gram-negative infection).
21. Gonzalez et al [34]	2018	Argentina	62 months (mean)	2.3:1	Retrospective	49	BT(40%), CH (20%), Malformations (12%), MMC (10%), PIH (8%), IVH (4%), TBI (2%), stroke (2%)	VPS (100%)	Not mentioned	9%	Positive blood cultures (p= 0.04), fever (p= 0.04), & septic shock (p= 0.0006).
22. Singh et al [35]	2021	India	≤ 12 years	1.3:1	Retrospective	117	PIH (35%), BT (32.5%), AS (12.8%), DWM (4.3%), TBI (2.6%), PHH (2.6%), SB (0.9%)	VPS (90.3%), ETV (7%), Ommaya (1.7%)	Shunt obstruction (11.6%), infection (5.8%), migration (1.9%), extrusion (4.8%), disconnection (1%) over drainage (1.9%), SH (1%)	10.5%	Disease-specific mortality was 10.5% and shunt-related mortality was 1.7%. Mortality was significantly (P = 0.0139) higher in patients with neoplastic aetiology.
23. Kulkarni et al [36]	2014	Canada and US	< 2 years	Not mentioned	Retrospective	36	IVH (25%), AS (22%), MMC (11%), CH (6%), TBI (6%), PIH (6%)	ETV & CPC (100%)	50% ETV &CPC failure in 30 days	5.5%	ETV & CPC failure and abdominal compartment syndrome (n=1) and seizures (n=1)
24. Green et al [37]	2006	England	Not mentioned	1.3:1	Retrospective	253	BT(29.6%), IVH (19.4%), AS (9.9%), CH(9.5%), PIH (5.5%), MMC (4.7%), AC (2%)	VPS and ETV	Not mentioned	15.5%	77% of mortalities had BTs

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
25. Rohwlink et al [38]	2016	South Africa	3.3 years (mean)	1.8:1	Prospective	44	TBM (100%)	VPS (56.8%)	Not mentioned	16%	British MRC (p<0.001); more deaths occurred in severe categories IIb and III; (p=0.06). Bilateral (p<0.001), large infarcts (p<0.001), multiple vascular territories infarcts (p<0.001), females (p=0.05).
26. Acakpo-Satchivi et al [39]	2008	USA	Not mentioned	Not mentioned	Retrospective	39	Not mentioned	VPS	Not mentioned	All 39 children had died	10.3% were due to shunt malfunction
27. Jin et al [40]	2016	USA	Not mentioned	1.4:1	Retrospective	13,736	IVH and PHH	VPS	Shunt infection (2.5%), mechanical complication (3%), Shunt removal (6%)	10.6%	Black patients had a 47% increased risk of inpatient death compared with white patients (RR 1.47; P < 0.01). Medicaid patients had a 20% increased rate of mortality compared with those with private insurance (RR 1.20; P = 0.04). Female gender (p=0.04), weight <750 g (p<0.01), gestational age <27 weeks (p<0.01), and grade 4 IVH (p<0.01) had increased inpatient mortality. Teaching hospitals had lower mortality compared with nonteaching hospitals (p<0.01)
28. Warf et al [41]	2005	Uganda	5 months (median)	n/a	Prospective	550	PIH (58%), non-PIH (28%, PHH (1%), MMC (13%)	ETV (n=284), ETV/CPC (n=266)	< 1% infection	1.3%	Related to surgery
29. Alenezi et al [42]	2018	Saudi Arabia	≤ 28 days	1.5:1	Prospective	23	PIH (34.8%), Hereditary (65.2%)	VPS (56.5%), medical (43.4%)	VPS blockage (13%), VPS infection (17.4%)	47.8%	Died during operation (8.7%). Died due to complications (34.7%). Did not receive treatment (4.3%)

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
30. McAlpine et al [43]	2022	USA and Canada	≤ 18 years	1.3:1	Retrospective	154	Unknown (36%), AS (28%), MMC (17%), DWM (12%), CM (6.9%), IVH (61%), BT (16%), AC (7.3%), PIH (6.2%), TBI (3.1%)	VPS (88%), VAS(2.6%), Ommaya (2.6%), VPLS (1.3%)	Not mentioned	5.8%	Shunt infections in all 9 children
31. Schiff et al [44]	2021	Uganda	3.1 months (median)	1.5:1	Prospective	100	PIH (100%)	ETV/ CPC (51%), VPS (49%)	35.3% treatment failures for ETV/CPC and 30.6% for VPS	15%	ETV/CPC failure (n=1) Infection (n=1) GE =(n=4) Malnutrition (n=4) Febrile illness (n=3) Pneumonia (n=1) Measles (n=1)
32. Persson et al [45]	2005	Sweden	≤ 1 year	1.3:1	Retrospective	208	Infantile HC (n=124) MMC (n=84)	VPS (91%) Ventriculostomy (9%)	Revision rate: 69% (once), 44% (twice), 18% ≥ 3	5%	CNS malformation (n=5) Perinatal cerebral haemorrhage (n=1) MMC (n=5)
33. Aranha et al [46]	2018	India	< 18 years	1.5:1	Prospective	52	TBM (100%)	ETV (n=26) VPS (n=26)	CSF leak post ETV (n=1) ETV failure (34.6%) VPS failure (38.4%) Lower-end malfunction (n=6), infection (n=3), ventricular end malfunction (n=1)	Overall mortality 7.7% i.e. ETV group (7.7%) VPS group (7.7%)	Ventriculitis (n=2) Status epilepticus &hyponatremia (n=1) Vasculitis with multiple infarcts (n=1)
34. Gathura et al [47]	2010	Kenya	8.5 mo. (median)	1.2:1	Retrospective	574	SB (43.4%), PIH (27.7%)	VPS (100%)	Complication rate (20%) i.e mechanical (11%), infection (7%), mixed (2%)	8.5%	Causes of death were shunt complication (n=5), pneumonia (n=5), malaria (n=1) & unknown (=26). Death was associated with, younger children (p =0.001), SB (p = 0.015) & spasticity (p = 0.026).
35. Clark et al [48]	2016	England	7.6 years (mean)	1.5:1	Retrospective	38	PHH (39%), unknown (24%), MMC (13%), BT (8%), DWM (5%), PIH (5%), BIH (3%), CS (3%)	VA (100%)	Shunt malfunction (59%), Infection (11%)	18% with only 8% directly related to VPS	Septic embolus (n=1), malignant BT with metastasis (n=1), cardiac arrest (n=2), renal failure (n=1), DU (n=2)

Author	Year	Country	Age	M: F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
36. Christian et al [49]	2016	USA	Preterm infants	1.8:1	Retrospective	91	Preterm IVH (100%)	VPS/VAS (45%), VR (55%)	Infections (10.9%) Loculated HCP (12%)	10%	Congenital cardiac defect [n=1] Small bowel perforation (not related to shunt) [n=2] Birth weight less than 1500g (n=9)
37. Leidinger et al [50]	2018	Tanzania	203 days (median)	1:1	Prospective	63	PIH (40%), unknown (22%), NTD (20%), malformation (10%), BT (5%), AS (3%)	VPS (85%) ETV (15%)	Shunt malfunction (10.6%), infection (14.9%), none for ETV	19%	Mortality higher in PIH vs non-PIH (27.7% vs. 20%; p= 0.522). Mortality associated with surgical complications in 3 children. Mortality higher in Pemba vs other residential areas.
38. Wellons et al [51]	2017	USA & Canada	Premature infants	1:1.1	Prospective	102	IVH (100%)	VSGS (35.3%) VR (64.7%)	VSGS infection (14%) vs VR infection (17%) (p=0.71), VSGS CSF leak (6%) vs VR (5%) p=1.0	Total mortality (12.7%)	Mortality VSGS (17) and VR (11%) (p=0.54)
39. Kankane et al [52]	2016	India	3.5 years (mean)	1.2:1	Prospective	50	TBM (100%)	VPS (100%)	VPS complication (10%) Infection (4%),	10%	Palur grade 4 TBM
40. Zhou et al [53]	2023	China	Infants	2:1	Retrospective	113	PHH (48%), PIH (25%), combined (15%), IEOM (9.7%), BTs (2.7%)	Ommaya (41.6%), EVD (21.2%), VSGS (5.3%), VPS (3.5%), ICVS (1.8%)	Not mentioned	21.2%	Late surgical intervention (p=0.002), Papile IVH grade 3&4 (p=0.036), severe ventricular dilatation (p<0.001), IEOM, combination of PHH and PIH (p=0.02)
41. Aukrust et al [54]	2022	Tanzania	98.5 days (median)	1.2:1	Prospective	38	Congenital abnormalities (28.6%), DWM (23.1%), ACM (6.7%), Meningitis (3.6%)	VPS (n=23) ETV (n=7) Unknown (n=3) No surgery (n=5)	Not mentioned	13.2%	Hydranencephaly, not operated (n=1) Unknown aetiology, not operated (n=1) Died following VPS(n=3)
42. Mohamed et al [55]	2021	England	Infants	1.4:1	Retrospective	323	PHH (31.9%), NTD (12.4%), Genetic (13.9%), CH (19,2%), others (22.6%)	VPS (100%)	Revision rate (33.8%), caused by obstruction (61.3%), infection (14.4%), migration (12.5%), CSF leak (7.7%) & OD (1.9%)	9.3%	Genetic hydrocephalus had a higher probability of death p =0.04) One death was shunt-related (shunt infection)

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality rate	Factors associated with mortality
43. Han et al [56]	2018	USA	Preterm infants	1.2:1	Retrospective	7437 of which 627 (8.4%) were diagnosed with HCP	Preterm IVH (100%)	327 (52.2%) required VPS	Shunt revisions (51.5%) Infection (18.1%)	Grade 4 IVH (36.1%) Grade 3 IVH (21.3%) Grade 2 IVH (7.8%), Grade 1 IVH (3.1%)	Male sex (HR 1.3 [95% CI 1.1–1.5]), Asian race (HR 1.5 [1.1–2.2]), lower EGA (HR 9.9 [6.3–15.5] for < 25 weeks), higher IVH grade (HR 6.1 [4.9–7.6] for grade IV), gastrostomy (HR 4.0 [2.0–7.7]), tracheostomy (HR 3.5 [1.7–7.1])Shunt infection (HR 3.2 [1.0–9.9], p=0.04, were independently associated with increased mortality risk
44. Gmeimer et al [57]	2017	Austria	34 days (median)	1.2:1	Retrospective	137	IVH (31.4%), MMC (25.5%), PIH (11.7%), CH (10.2%), AC (8.8%), AS (8%) & others (4.4%)	VPS (33.6%), VAS (38.7%), EVD (27%), VR (0.7%)	Shunt infection (40.9%)	Overall mortality 38.7% 1) Related to VPS (43.4%) (2)Not related to VPS (43.4%) (3) Not determined (13.2%)	(1) Related to VPS: Shunt infection (n=18), shunt malfunction(n=5) (2) Not related to VPS: pneumonia (n = 10), cardiac dysfunction (n = 5), or pyonephrosis (n = 1) (3) Direct cause (n=23) (4) Unknown (n =7)
45. Tuli et al [58]	2003	USA	6 days (median)	Not mentioned	Retrospective	189	MMC (100%)	VPS (100%)	Shunt failure (64%) Shunt infection (24%)	8%	Shunt malfunction/ infection (n=4) Chiari malformation complication (n=9) Unrelated to HCP/Chairi (n=2)
46. Yusuf et al [59]	2017	Nigeria	3 months (median)	1.3:1	Retrospective	58	ACM (24%), AS (14%), unknown (32%), IVH (17%), PIH (12%)	VPS (91%), ETV (5%), VSGS (4%)	Shunt infection (12%), obstruction (12%), OD (5.2%) disconnection (3.4%) migration (1.7%)	3.4%	Respiratory arrest in child with CRM (n=1) Preterm IVH (n=1)
47. Dakurah et al [60]	2016	Ghana	5.35 yrs. (mean)	Not mentioned	Retrospective	109	AS (24.2%), PIH (16.9%), DWM (13.7%), ACM (13.7%), BT (34.6%)	VPS (100%)	Shunt complications (33.9%) which included infections (54.2%), blockages (13.5%) and disconnections (13.5%)	4.59%	Primary disease progression and shunt sepsis

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
48. Tully et al [61]	2022	USA	9 yrs. (mean)	1.2:1	Retrospective	1705	CH (25.9%), PHH (24.9%), MMC (20.2%), CF (5.9%), PIH (4.8%), TBI (4.5%)	VPS (78.8%), ETV/CPC (3.2%), Cyst fenestration (0.5%), TD (2.7%)	Not mentioned	5.2% (n=88)	Medical comorbidities (n=65), Elevated ICP (n=21) i.e. ICH due to primary disease (n=7). Deaths directly due to HCP (n=14), which were shunt complications. MRA showed no difference in mortality due to sex. Risk of death was higher among non-White and Hispanic children (not statistically significant).
49. De la Cerda-Vargas et al [62]	2024	Mexico	116 months (mean)	1:1.5	Prospective	10	Coccidiodal meningitis	VPS & EVD	Not mentioned	20%	Asymmetric hydrocephalus ($p = 0.335$), cerebral vasculitis ($p = 0.176$), IFV ($p < 0.001$), bacterial superinfection, ($p = 0.017$), lower mRS scores at discharge ($p = 0.017$) and follow-up ($p = 0.004$).
50. Ghritlaharey et al [63]	2023	India	≤ 12 years	2.3:1	Retrospective	30	CH (56.7%), MMC (20%) TBM (23.3%)	VPS (100%)	All were complications	6.6%	Died after VPS revision due to poor pre-operative condition
51. Biluts et al [64]	2016	Ethiopia	11.22 months (mean)	1.2:1	Retrospective	122	MMC (34.4%), AS (33.6%), PIH (12.3%), DWM (8.2%), BT (6.6%), Undetermined (3.3%)	ETV(n=122) ETV&CPC (n=21)	Infection (6%), bleeding (4.9%)	2.4%	Cardiac arrest (n=2), intracranial bleeding (n=1)
52. Heinsbergen et al [65]	2002	Netherlands	5 yrs (median)	1.3:1	Retrospective	119	SB (35%), IVH (29%), Unknown (13%), PIH (10%), CH (8%), BT (6%)	VPS (100%)	21% shunt revision	8%	Brain tumours (n=4) Drain related (n=2) Not related to hydrocephalus (n=3)
53. Idowu et al [66]	2009	Nigeria	8 months (median) for VPS & 7 months (median) for ETV	1.3:1	Retrospective	65	AS (n=27) DWM (n=15)	VPS (n=36) ETV (n= 29)	ETV: CSF leak (n=2), wound infection (n=1), ETV failure (n=1) VPS: shunt obstruction (n=1), ventriculitis(n=2), subdural hygroma (n=1)	3.1%	Ventriculitis (n=2)
54. Santos et al [67]	2017	Tanzania	Infants	1.3:1	Prospective	125	Unknown (56%), PIH (22.4%), MMC (16%)	VPS (100%)	Infection (13.6%), mechanical (9%), wound complications (6.4%)	9%	Respiratory failure (n=2), sepsis (n=5), VPS malfunction (n=1), aspiration pneumonia (n=2). Unrelated: malaria (n=3) Unknown (n=3)

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
55. Pedrosa et al [68]	2017	Brazil	88 days (median)	1.5:1	Retrospective	34	Hydranencephaly	CPC (88.1%), ETV&CPC (11.9%)	Treatment failure in 29.4% CSF leak (n=2), Sodium disorders (n=2), skin burns (n=2), thermal fluctuations (n=2), diabetes insipidus (n=1), cardiac arrest (n=1), wound infection (n=1)	28.57%	Nine children (21.43%) died after discharge. Three children (7.14%) died during hospitalization after surgery. Respiratory failure (n=2) Septic shock (n=1)
56. Warf et al [69]	2008	Uganda	< 1 year	Not mentioned	Prospective	93	MMC (100%)	ETV/CPC (100%)	Treatment failure in 24%	1.1%	Procedure-related
57. Tuli et al [70]	2004	USA	1.6 years (alive) & 1.1 years (dead) (mean)	1.1:1	Retrospective	907	MMC (n=191), IVH (n=114), BT (n=190), PIH (n=40), encephalocoele (n=32), DWM (n=21), AS (n=56), CF (n=19), AC (n=57), TBI (n=21), CH (n=91), hydranencephaly (n=3), VOGM (n=2)	VPS (79%)	Shunt failure (55.5%) Shunt infection (18.5%)	13.6%	Predictors of death revealed a statistically significant effect of infection with a hazard ratio of 1.66 (p = 0.04). Highest mortality in BTs (32.6%)
58. Smith et al [71]	2004	USA	Not mentioned	Not mentioned	Retrospective	5955	Not mentioned	Not mentioned	Not mentioned	Mortality rates were 0.8% at LQVC (< 28 admissions/year) and 0.3% at HQVC (> 121 admissions/year). In terms of surgeon volume, mortality was 0.8% for LQVP (< nine admissions/year) and 0.1% for HQVP (> 65 admissions/year).	Hospital volume of care was a significant predictor of death (OR 10-fold increase in caseload 0.38; 95% (CI 0.18–0.81). Surgeon volume of care was significant on multivariate model (OR for a 10-fold increase in caseload 0.3; 95% CI 0.13–0.69).

Author	Year	Country	Age	M:F ratio	Study design	Sample	Aetiology	Surgical procedure	Complication rate	Mortality	Factors associated with mortality
59. Paulsen et al [72]	2017	Norway	3 yrs (mean)	1.2:1, 1.9:1 and 1.5:1	Retrospective, comparing 3 distinct periods	400	BTs (31%), IVH (12%), NTD (8%), AS (3%), PIH (2%), IIH (4%), Unknown (17%), others (29%)	VPS (n=98), CPS (n=2), LPS (n=2), S-DPS (n=2), ETV (n=31)	ETV failure (67%), shunt infection (9%)	12%	Malignant CNS tumour (n=15) Anencephaly (n=1)
60. Kulkarni et al [73]	2017	Uganda	3.1 mo (median)	1.6:1	Prospective	100	PIH (100%)	ETV/CPC (n=51) VPS (n=49)	ETV failure (35%), VPS failure (24%). VPS infection (8%)	6%	ETV/CPC failure (n=1) VPS-related ventriculitis (n=1) Unrelated (n=9)i.e. GE (n=4), malnutrition (n=3), pneumonia (n=1), measles (n=1).
61. Warf et al [74]	2005	Uganda	Mostly infants	Not mentioned	Prospective	195	PIH (100%)	VPS (100%)	Shunt infection (10%), wound complication (6.3%), proximal obstruction (2.5%), distal obstruction (1.3%), valve malfunction (3.4%)	15.9%	Shunt complications
62. Chimaliro et al [75]	2023	Malawi	5 mo (median)	1.2:1	Retrospective	153	MMC (18%), encephalocele (1%), PIH (7%), CH (17%), PHH (3%), BT (3%), Malformation (1%), AC (0.01%), unknown (50%)	VPSI (26.8%), ETV/CPC (73.2%)	Shunt infection (21.4%)	15.2%	Shunt failures and infections ETV failure
63. Verma et al [76]	2021	India	4.66 months (mean)	5.7:1	Prospective	40	CH (100%)	ETV	ETV bulge (20%), meningitis (15%), CSF leak (10%), subdural hygroma (7.5%), IVH =2.5%, seizures =2.5%	17..5%	Prematurity (n=2), LBW (n=2), prenatal complications (n=2), ICU stay (n=3, failure to thrive (n=3), poor Denver score (n=2), OP >20 (n=3), poor respiratory effort (n=2), ventilator support (n=3) haemorrhagic rashes /oedema (n=2)

AC= arachnoid cyst; AIS = antibiotic impregnated shunt; ASA-PC=American Society of Anaesthesiologists Physical status score; ACM= Arnold Chiari malformation; BT = brain tumours; CF= craniofacial ;CH= congenital hydrocephalus; CI = confidence interval, CM = chiari malformation; CPC= choroid plexus coagulation; CRM= Chiari II Malformation; DAP= ductus arteriosus persistens; DU= data unavailable, BPD=bronchopulmonary dysplasia, CPS = cystoperitoneal shunt, EGA= estimated gestational age; EVD = External ventricular drain, HCP= hydrocephalus; HQVC= highest -quartile volume centers; HQVP= highest -quartile volume providers, ICU = intensive care unit, IFV = isolated fourth ventricle; ICH = intracerebral haematoma; ICVS = intracranial cysto-ventricular shunt (ICVS); IEOM= Inherited errors of metabolism; IIH= idiopathic intracranial hypertension, IVH= intraventricular haemorrhage; ETV = endoscopic third ventriculostomy; LBW= low birth weight, LGWA= low gestational weight for age,;LQVC = lowest quartile volume centre, LQVP= lowest quartile volume providers; MO= months, mRS = modified Rankin Score, MRA= multivariate regression analysis; NA = not available; NPIH= non-post infectious hydrocephalus; NTD= neural tube defects; OD= over drainage; OP = opening pressure, OR= Odds ratio; PHH= post haemorrhagic hydrocephalus; PIH= post infectious hydrocephalus, PIVH= perinatal intraventricular haemorrhage; PH:= post haemorrhage; SD= spinal dysraphism; S-DPS = subdural peritoneal shunt, SH= subdural haematoma; SR= shunt revision; TBI = traumatic brain injury; TBM = tuberculous meningitis, TD =temporary drains; VAS= ventriculoatrial shunt; VOGM= vein of Galen malformation , VPLS= ventriculopleural shunt, VSGS= ventricular subgaleal shunts; VPS = ventriculoperitoneal shunt; VR= ventricular reservoir, Yrs=years

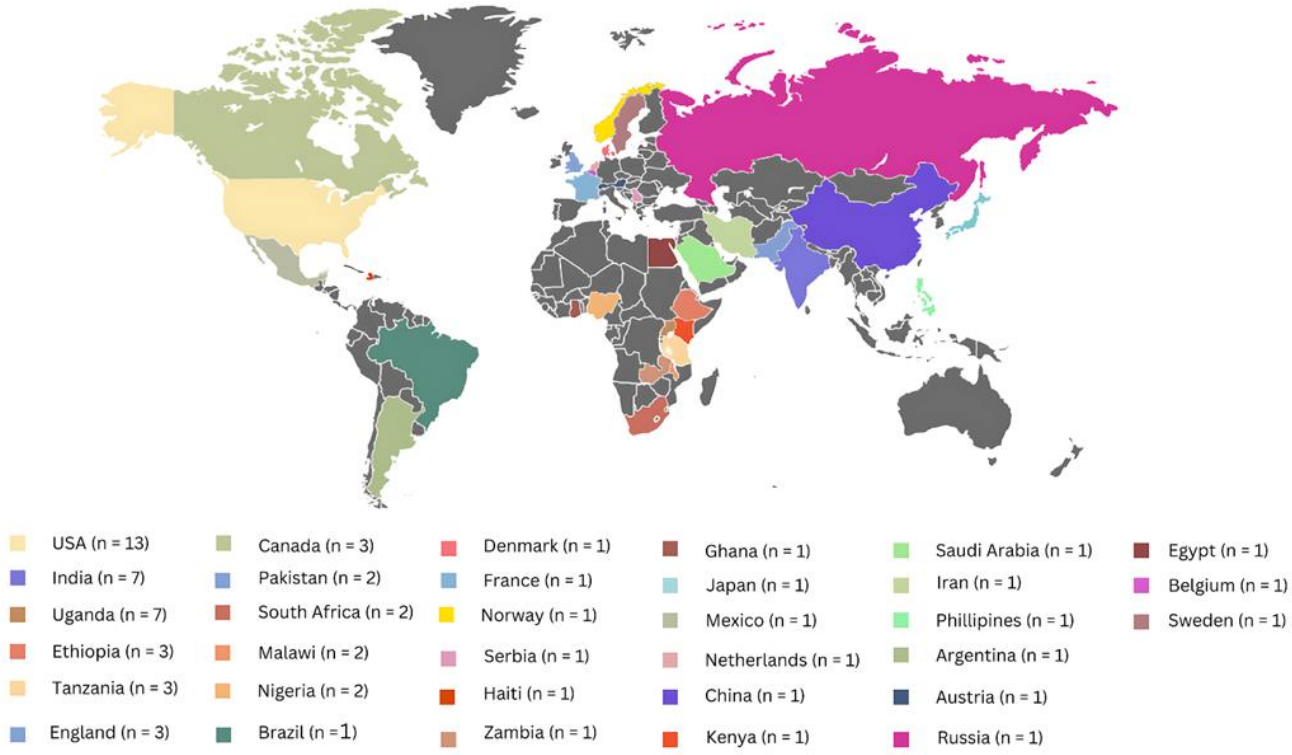

Figure 2. Map Showing Countries where Data was Collected

Age and Demographic Categories

In 23 (36.5%) articles the median age was less than 1 year, while in 17 (26.9%) the median age was 1 year and above. A further 12 (19%) studies reported children to be infants, without referring to a specific age. Boys were the majority in 51(80.9%) studies, while girls were the majority in three (4.8%). In nine (14.3%) studies, gender was not mentioned.

Aetiology

In the articles reviewed the frequency of aetiology of hydrocephalus was reported as follows, PIH [n=44; 69.8%], congenital hydrocephalus [n=33; 52.4%], spinal dysraphism/myelomeningocoele (MMC) [n=34; 53.9%], post-haemorrhagic hydrocephalus (PHH)/Intraventricular haemorrhage (IVH) [n =32; 50.8%], brain tumours (BT) [n = 20; 31.7%], Aqueduct stenosis (AS) [n=16; 25.4%], Idiopathic /unknown [n=12, 19%], Dandy-Walker Malformation (DWM) [n=11; 17.5%], traumatic brain injury (TBI) [n=8; 12.7%], arachnoid cyst (AC) [n=7; 11.1%], encephalocoele [n=3, 4,8%], vascular pathologies [n=2, 3.2%]. Non-PIH aetiology was reported in two (3.2%) articles.

CSF Diversion Procedures

CSF diversion procedures reported in the reviewed articles included, ventriculoperitoneal shunts (VPSs) [n= 54; 85.7%], endoscopic third ventriculostomy (ETV) [n=17; 26.9%], ETV and choroid plexus coagulation (CPC) [n=12; 19%], CSF reservoirs [n=8; 12.7%], external ventricular drain (EVD) [n=7; 11.1%], ventriculosubgaleal shunt (VSGS) [n=4; 6.3%], ventriculoatrial shunt (VAS) [n=4; 6.3%], lumboperitoneal shunt (LPS) [n=1; 1.6%], ventriculopleural shunt (VPLS) [n=1; 1.6%], and intracranial cysto-ventricular shunt (ICVS) (n=1; 1.6%). In two articles (3.2%), some children did not undergo surgical treatment.

Surgical Complications

VPS complications ranged from 1.3% to 57.1%, while ETV failure rates ranged from 2.5% to 67%. Shunt infections were reported in 35 (55.6%) studies. Other complications reported were ETV failure [n=14;22.2%], CSF leak [n=6; 9.5%], ETV infective complications [n=5; 7.9%], over drainage [n=4, 6.3%], subdural hygroma (n=4, 6.3%), shunt migration [n=4, 6.3%], shunt disconnection [n=3, 4.8%], IVH post-ETV [n=2; 3.2%], shunt extrusion [n=2; 3.2%], abdominal complications [n=2; 3.2%], skull deformity [n=1; 1.6%] and located hydrocephalus [n=1; 1.6%].

Mortality

The mortality rate in the articles reviewed ranged from 0.1 to 49%. The causes of death are summarized in Table 3.

Table 3: Summary of Causes of Death Reported in Selected Articles

Cause of Death	N	%
1. Shunt infection and procedure-related meningitis	24	38.1%
2. Shunt malfunction /failure	16	25.4%
3. Respiratory complications including pneumonia	11	17.5%
4. Brain tumours	10	15.9%
5. Medical co-morbidities	10	15.9%
6. Hydrocephalus secondary to congenital malformation	9	14.3%
7. Severe grade of IVH related to prematurity	7	11.1%
8. Surgical procedure-related complications	6	9.5%
9. TBM-related hydrocephalus (i.e. infarcts and poor grade)	6	9.5%
10. Seizures	5	7.9%
11. Severe hydrocephalus	5	7.9%
12. Failure to thrive and delayed milestones	5	7.9%
13. Low birth weight	4	6.3
14. Malnutrition	4	6.3
15. ETV failure	4	6.3%
16. Non-CNS congenital abnormalities	4	6.3%
17. Unknown	4	6.3%
18. GE	3	4.8%
19. Sex	3	4.8%
20. Race	2	3.2%
21. Level of care of hospital	2	3.2%
22. Measles	2	3.2%
23. Malaria	2	3.2%
24. ICU admission	2	3.2%
25. Post-infectious hydrocephalus	2	3.2%
26. Post-traumatic hydrocephalus	1	1.6%
27. Emergency surgery	1	1.6%
28. Septic shock	1	1.6%
29. Abdominal complication	1	1.6%
30. Delayed surgery	1	1,6%
31. Metabolic diseases	1	1.6%
32. Hyponatraemia	1	1.6%
33. Younger maternal age	1	1.6%
34. Residential area	1	1.6%

CNS, Central nervous system; ETV, Endoscopic third ventriculostomy; GE Gastroenteritis; ICU, Intensive care unit; IVH, Intraventricular haemorrhage; TBM ,Tuberculous meningitis

Discussion

This is the first scoping review to report on factors associated with mortality in children diagnosed and treated for hydrocephalus. While mortality is an undesirable outcome, it remains a possible consequence of hydrocephalus. Information gathered from the existing literature is important in guiding the approach to surgical decision-making, prognosis, counselling, and reasonable expectations of goals of care for children diagnosed with hydrocephalus.

Geographic and Genetic Factors

Most (66.7%) studies included in the review were from LMICs, where the highest burden of paediatric hydrocephalus is reported, particularly in Africa, Latin America, and Southeast Asia. Many of these regions lack sufficient neurosurgery workforce and supporting infrastructure, which is critical in reducing mortality [77]. The prevalence of congenital hydrocephalus is reported to be 145 per 100,000 births in Africa, 316 per 100,000 births in Latin America, and lowest in the United States and Canada at 68 per 100,000 births [11].

In Sweden, the prevalence was reported at 0.82 per 1,000 live births, with a notable decline over the years due to improved medical interventions [45]. In contrast, the prevalence in Saudi Arabia was 0.38%, with a high rate of consanguinity (60.9%) contributing to the incidence [42]. Genetic factors play a crucial role, as evidenced by the higher prevalence of hereditary causes (65.2%) compared to infections (34.8%) in Saudi Arabia [42]. In a study from England, genetic hydrocephalus accounted for 13.9% of the aetiology and was associated with a higher probability of death [55]. Given the high incidence of hereditary hydrocephalus in certain regions, genetic counselling and preventive measures are essential to help reduce the incidence of congenital hydrocephalus.

Aetiology of hydrocephalus

Understanding the diverse aetiology of hydrocephalus and the role of underlying pathologies are crucial in reducing mortality. PIH was the predominant aetiology in SSA and Southeast Asia [9,10,78]. Studies conducted in Uganda and Zambia found that 77% and 65% of the cases, respectively, were PIH, primarily resulting from central nervous system (CNS) infections, contrasting with only 6% in the US and Canadian studies [24,26,36,43]. AS and neural tube defects (NTD) were also predominant aetiologies in certain regions in SSA [64,79]. An Ethiopian study on the surgical outcomes of NTDs, found hydrocephalus to be a risk factor for mortality [80]. BTs also contribute significantly to mortality in children with hydrocephalus [19, 20, 29, 30, 37, 48, 65,72]. Beuriat et al. reported a mortality rate of 16.5% among 975 children treated for hydrocephalus, with the highest mortality observed in those with BTs [29], while Singh et al. also reported higher mortality in children with neoplastic aetiology [35].

North American studies reported hydrocephalus secondary to IVH of prematurity as the predominant aetiology [15,22,43,49,51,56]. Gilard et al found that higher grades of IVH, increased head circumference of more than two standard deviations, and low gestational age were important risk factors for developing PHH requiring shunting [81]. They further found that high-grade IVH (3 to 4) and low gestational age (less than 30 weeks) were significant predictors of mortality [81].

Wubie et al in their case series of children treated for hydrocephalus reported post-traumatic hydrocephalus (PTH) to be a predictor of mortality [23]. Rumalla et al reported a higher mortality rate for TBI patients presenting without PTH (5.4%) when compared to those diagnosed with PTH (1.1%) [82]. They found that VPS insertion was associated with a decreased likelihood of in-hospital mortality [82].

TBM, the most severe form of meningitis, is associated with high mortality and morbidity and was responsible for hydrocephalus in 7.9% of the articles reviewed [83]. There are various grading systems for TBM-related hydrocephalus, with the Refined Modified British Medical Research Council (BMRC) and Vellore grading systems being the most used [84,85]. Poor outcomes which include mortality and severe morbidity are often reported in patients with poor TBM grades. Despite optimization of treatment of increased intracranial pressure (ICP) and hydrocephalus, mortality occurs because of chronic ischaemia resulting in infarcts affecting areas such as the thalamus, basal ganglia, and brainstem [27, 28, 38, 46, 52, 86]

A South African study reporting on biomarkers of cerebral injury and inflammation in children with TBM hydrocephalus found that neuromarkers such as S100B, neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP) were associated with increased mortality [83]. These biomarkers are important tools that will enable physicians to better prognosticate children with TBM-related hydrocephalus and counsel parents regarding outcomes.

Hydranencephaly is characterized by the absence or near-total absence of cerebral hemispheres. It is thought to result from the destruction of the developing brain in-utero due to bilateral vascular occlusion, though genetic factors, exposure to drugs, and intrauterine infections may contribute to the development of hydranencephaly [68]. Infants diagnosed with hydranencephaly have a shortened life span, with 2-year mortality estimated at 84% [68]. Mortality is caused by complications, such as aspiration pneumonia, malnutrition, and infections. Morbidity is further compounded by scalp erosion by shunts and from difficulty in caring for infants with grossly enlarged heads.

A dilemma often arises as to whether to offer treatment to children diagnosed with hydranencephaly, particularly in developing countries where resources are scarce, and whether these resources should be prioritized for children with better prognoses. In a Kenyan study that included 52 children diagnosed with hydranencephaly, 11 underwent VPS insertion, 17 CPC, 14 open choroid plexectomy, and 10 were palliated. The mortality rate (82%) at 1 year was identical in both the VPS and CPC groups, and was 70% in the palliative care group, but substantially lower (43%) in the open choroid plexectomy group [87]. All deaths occurred at home; their causes were unknown [87]. Pedrosa et al, in a series of children diagnosed with hydranencephaly, reported a mortality rate of 28.57% [68]. Nine children (21.43%) died after discharge, but these deaths were not related to the surgical procedure. Three children (7.14%) died during hospitalization after surgery and two of these children died from respiratory failure and refractory shock, while the third died from septic shock [68].

Demographic and Socioeconomic Factors

Across the reviewed studies, paediatric hydrocephalus affects boys more the girls. However, there was variability in the role of sex on mortality. Jin et al. found that female sex was associated with mortality [40], while Han et al. reported male sex [56]. Tully et al. found no differences in mortality due to sex [61]. The age of presentation varied (neonates to adolescents), with a significant number of cases occurring in the first year of life. Younger age at diagnosis, particularly in neonates and infants, was associated with higher mortality [15,40, 47,49,56,76]. This was attributed to the greater vulnerability of this age group to complications such as infections. Gmeimer et al. also found that children who died were younger at first operation than surviving patients [57].

Socioeconomic status and access to healthcare are important determinants of outcomes in childhood hydrocephalus [17, 31,32]. A Zambian study also highlighted a high incidence of PIH, with complications and mortality significantly influenced by the socioeconomic and healthcare access challenges specific to LMICs [24]. Limited access to timely and appropriate medical care can lead to delayed diagnosis and treatment, increasing the risk of complications and mortality. This emphasizes the need for policies and interventions that improve access to healthcare for underserved populations. Providing guidelines to the patients, family, and caregivers on detecting shunt failure along with increased surveillance scans could contribute to earlier detection and prevention of mortality related to shunt failure. Younger mothers may also be less established socioeconomically, with access to fewer resources and this has contributed to mortality in Malawi [25]. In Saudi Arabia, 47.8% of mothers and 39.1% of fathers of affected children had higher education [42]. This contrasts with findings from a study in Brazil, where lower socioeconomic status and limited access to healthcare were linked to higher mortality rates [88,89].

Studies have reported on racial disparities influencing the outcomes of children with hydrocephalus. Jin et al, in a study of children with PHH, reported Black patients had a 47% increased risk of inpatient death compared to white patients [40]. Han et al, also in a study of PHH, reported that Asian children had an increased risk of mortality [56]. Tully et al found non-White and Hispanic children to have a high risk of death [61].

Addressing these disparities requires a multifaceted approach, including policy changes to ensure equitable access to healthcare, community education programs to raise awareness, and targeted interventions to support underserved populations.

Presence of Comorbidities

The presence of comorbidities significantly increases the risk of mortality, highlighting the need for holistic care that addresses not only hydrocephalus but also associated conditions [14,16,17,26,44,47,48,49,56,57,61,67,73,76]. Malnutrition emerged as a contributor to mortality in studies from Haiti, Uganda, and India [14, 26, 44, 73]. Malnutrition is commonly diagnosed in children with TBM-related hydrocephalus [90]. Children with hydrocephalus often have imbalanced energy intake and gastrointestinal problems, making them susceptible to nutritional challenges leading to wasting. Malnutrition renders them susceptible to an increased risk of shunt infection, failure to thrive, dysfunctional metabolic profile, poor wound healing, and impaired immunity, which delays the recovery process and increases healthcare costs. In a study from India, patients undergoing shunt surgery had a high prevalence (53%) of malnutrition [91]. Postoperative complications and mortality were significantly common in malnourished patients compared to those with normal nutritional status [91]. Serum albumin levels were identified as an important predictor of postoperative mortality [91].

In a study from Uganda, the prevalence of wasting among children with hydrocephalus was 23.2% [92]. The factors associated with wasting among children with hydrocephalus included difficulty in chewing and swallowing, poor appetite, difficulty in breathing, and choking on food [92]. Children diagnosed with hydrocephalus should assessed for feeding difficulties and when found these should be addressed urgently.

Surgical Interventions and Outcomes

Studies conducted in Ethiopia and Norway observed that children who underwent timely CSF diversion had better functional outcomes and lower mortality rates [23,93].

Infections

VPS placement remains the predominant procedure used for the treatment of hydrocephalus in children, however, it is associated with a high risk of complications, including infections and mechanical failures. Other surgical interventions include ETV and temporary CSF diversion procedures such as ventricular reservoirs and EVDs.

The complication rates of VPS range from 0.3% to 39% [94]. Infections were a predominant cause of mortality in multiple studies [17, 18, 23, 26, 31-34, 43,46,55-58,60,73,75].

The predominance of *coagulase-negative Staphylococcus*, followed by *Staphylococcus aureus* as causative organisms suggests that infection control protocols should focus on preventing surgical site contamination and managing biofilm-associated infections. Gram-negative organisms are also responsible for infections and mortality [23,31].

Gmeiner et al. identified a higher risk of mortality in children with the first surgical procedure being an EVD (65%) compared to those with the first surgical procedure being a VPS or VAS, likely due to the high risk of infection in children with EVD [57]. They found that almost 89.1 % of the children were shunted before the age of 6 months, with 80.4 % of first shunt infections occurring during the first postoperative year [57].

Positive blood cultures and septic shock at the time of infection were significant predictors of mortality [34,68]. Advancements in radiological imaging, such as high-resolution MRIs, CT scans, and ultrasound, along with improved shunt technology, namely antibiotic-impregnated shunts, and neuro-endoscopic procedures, have substantially reduced surgical morbidity and mortality over the years.

Surgical Procedures

The relatively lower complication rates and shorter hospital stays associated with ETV have made it an attractive alternative, especially where long-term follow-up and shunt revisions are challenging. The complication rates of ETV vary from 5% to 15%, with lower failure rates after the initial high-risk period [95]. The comparison between VPS and ETV indicates a nuanced balance between the risks and benefits of each procedure. While VPS is widely used, its high complication rates, particularly infections, necessitate rigorous postoperative management and follow-up. Though ETV presents a viable alternative with potentially fewer complications, its success is contingent on patient selection and the underlying aetiology of hydrocephalus.

A study comparing ETV and VPS in children by Pan et al. found that the ETV performed in children aged less than 1 year had lower ETV success rates than those with shunts [96]. Similar findings were not found in children aged 1 year and above [96].

Kulkarni et al. in their study found that the risk of ETV failure was initially higher than that for VPS, but after about 3 months, the risk became progressively lower for ETV [98], meaning that after the early high-risk period of ETV failure, children could experience a long-term treatment survival advantage when compared with a shunt [97].

The International Infant Hydrocephalus Study (IIHS) reported success rates for ETV versus VPS at 3, 6, and 12 months as follows: 68% vs. 95%, 66% vs. 88%, and 66% vs. 83%. The 6-month ETV success rate of 66% was slightly higher than predicted by the ETV Success Score (57%) [98]. These results also suggested that VPS had a superior success rate compared to ETV, although the success rate for both was relatively high [98]. The results of the reviewed article showed that children undergoing VPS had a higher early postoperative mortality compared to those undergoing ETV.

ETV with CPC has also emerged as a favourable alternative, especially in resource-limited settings where shunt failure can be associated with increased mortality. In SSA, the ETV-CPC was more successful (66%) than ETV alone (47%) in infants younger than 1 year of age [41]. The study also found that ETV-CPC may be the best option for treating hydrocephalus in infants with non-post infectious hydrocephalus (NPIH) and MMC [41]. The ETV-CPC combined procedure was superior in infants with MMC (76% vs 35%) and those with NPIH (70% vs 38% success) [41]. The overall surgical mortality rate was 1.3%, and the infection rate was less than 1% [41]. However, in North America, Stone and Warf et al achieved a success rate of 57 % at 1 year [99]. The Hydrocephalus Clinical Research Network (HCRN) conducted a prospective study of ETV and CPC in infants. ETV and CPC appeared to have a higher failure rate than shunt alone, although ETV and CPC results were similar to ETV alone [100]. The difference in the success rate for ETV-CPC in children in North America and those Uganda may be attributed to differences in: (i) patient selection criteria, (ii) definitions of success, (iii) study population characteristics, (iii) surgical techniques, (iv) prevalence of comorbidities, (v) criteria for repeat ETV-CPC among neurosurgical units and surgeons [101]

Seizures

Children with VPS have a higher incidence of seizures than the general population, varying from 6% to 59% [102,103]. The aetiology of seizures is multifactorial and includes underlying pathology, treatment, shunt infections, multiple revisions, and structural brain damage. Seizures contribute to poor health-related quality of life in children with hydrocephalus and, if not managed appropriately result in mortality [14, 17, 26, 36,76, 102,103].

Hyponatraemia

Hyponatraemia has long been recognized as a serious potential metabolic consequence of TBM, occurring in 35–65% of children with the disease [104]. Cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone secretion are considered the most likely causes of hyponatremia in these patients. Hyponatraemia exacerbates cerebral oedema, contributing

to increased ICP, increasing susceptibility to seizures and increased mortality, particularly in children with TBM-related hydrocephalus [105]. Appropriate management of hyponatraemia is vital to reduce mortality.

Improvement of Mortality

Gmeiner et al. reported an improvement in mortality over the years. More children with the first operation in the period 1982–1987 compared to the period 1988–1992 died i.e. 36 deaths (mortality of 51.4%) versus 17 deaths (mortality of 25.4%) [57]. Green et al, in a study comparing two 5-year periods (1992–1995 and 1997–2002), reported 40.0% mortality, with 42.2% of the children being well and without deficits, while in the later period, the mortality rate was 29.0%, with 25.8% of the children having no neurological deficits [37].

Implication of the Findings

The findings of this scoping review reveal important insights into the factors associated with mortality in paediatric hydrocephalus. The high mortality rates in regions with limited healthcare infrastructure emphasize the need for improved healthcare delivery and access. Investment in diagnostic and therapeutic techniques, increased medical personnel, and effective family education are important for the reduction of mortality.

There should be an emphasis on strengthening surveillance and prevention strategies, particularly in PIH. Studies have consistently shown that delayed diagnosis and treatment lead to poorer neurodevelopmental outcomes and higher mortality rates. Therefore, implementing routine prenatal screening and postnatal monitoring can significantly reduce the burden of hydrocephalus. None of the studies in the review addressed the impact of HIV infection on mortality, particularly in children presenting with opportunistic CNS infections related to HIV. This highlights a gap in the literature.

Limitations

This review has several limitations. The heterogeneity of the included studies, variations in study design, differences in healthcare settings, diagnostic criteria, treatment modalities over different decades, and the number of children lost to follow-up limit the generalizability of the findings. Additionally, the retrospective nature of many studies and the use of only English language articles introduces the potential for bias and confounding factors that may not have been fully accounted for. Further research, including well-designed prospective studies and randomized controlled trials, are needed to validate these findings and provide more findings on factors associated with mortality in paediatric hydrocephalus.

Conclusions

Childhood hydrocephalus remains a significant clinical challenge, associated with mortality, particularly in LMICs. Key factors influencing mortality include the aetiology of hydrocephalus, comorbidities, socioeconomic status, age at diagnosis, type of surgical intervention, and postoperative complications. Addressing the disparities in healthcare access and quality between is essential for improving outcomes. Optimizing the selection of children for surgical interventions and improving infection control measures are important strategies to improve outcomes.

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Part 1: Healthcare Disparities and Paediatric Hydrocephalus – An Epidemiological and Proximity-Based Analysis

Part 1 of this doctoral thesis presents an analysis of the burden of paediatric hydrocephalus and the impact of proximity to neurosurgery services on treatment outcomes in KwaZulu-Natal (KZN), South Africa. The two chapters that form this part of the thesis provide an examination of the epidemiology, referral patterns, and surgical outcomes over two decades and address a critical public health issue: access to centralized neurosurgical care for paediatric hydrocephalus patients.

In Chapter 3, the focus is on the epidemiological landscape of paediatric hydrocephalus in KZN, covering four distinct five-year periods. The analysis highlights the trends in referral patterns, demographic characteristics, aetiology, and treatment outcomes for paediatric hydrocephalus over the 20-year period. The data show a peak in the incidence of hydrocephalus cases between 2008 and 2012 and indicate that the majority of cases are referred from rural areas and regional hospitals, with males and infants being the most affected groups. A significant proportion of the cases were due to post-infectious hydrocephalus, with tuberculous meningitis and pyogenic meningitis as the predominant aetiologies. The chapter emphasizes the role of ventriculoperitoneal shunts as the primary treatment modality and discusses the complications associated with this intervention, particularly infections and mechanical failures.

The analysis in Chapter 3 establishes a foundation for understanding the burden of paediatric hydrocephalus and the challenges faced in managing this condition. The findings highlight the disparities in access to neurosurgical services, with rural areas bearing a higher burden of disease. It also highlights the important role that referral patterns and the level of healthcare facilities play in determining the outcomes of hydrocephalus management.

Building on the insights gained from the epidemiological analysis, Chapter 4 provides a focused investigation into the impact of proximity to centralized neurosurgery services on the surgical outcomes of paediatric hydrocephalus patients. This chapter compares the outcomes of children treated for hydrocephalus based on their proximity to Inkosi Albert Luthuli Central Hospital (IALCH), the main neurosurgery centre in KZN.

The study assesses the influence of travel distances on factors such as the timing of surgical intervention, complication rates, length of hospital stay, and mortality. The data show that children living farther from IALCH experience higher rates of VPS failure.

Chapter 4's findings suggest that proximity to centralized neurosurgery services may not uniformly influence outcomes, as various factors such as socioeconomic conditions, access to transportation, and healthcare infrastructure also play a role. It calls for a re-evaluation of resource allocation and healthcare strategies to ensure equitable access to neurosurgery services, especially for children living in remote and underserved areas in KZN.

Together, these chapters provide a holistic view of the challenges and outcomes associated with paediatric hydrocephalus in KZN, offering insights for improving healthcare interventions and outcomes. The epidemiological trends set the stage for a more detailed exploration of healthcare access and service delivery issues in Chapter 4, making Part 1 a contribution to the understanding of paediatric hydrocephalus management in low- and middle-income settings.

Chapter 3: The Landscape of Paediatric Hydrocephalus in the Province of KwaZulu-Natal. A Comparative Analysis of the Referral Pattern, Aetiology and Management Outcomes Over Four Distinct Five-year Periods.

This chapter of the thesis presents a study spanning two decades, beginning at the time of the relocation of neurosurgery services to Inkosi Albert Luthuli Central Hospital in Durban. As the first comprehensive analysis of its kind in this region, the study compares the burden of paediatric hydrocephalus across four distinct five-year periods

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The Landscape of Paediatric Hydrocephalus in the Province of KwaZulu-Natal. A Comparative Analysis of the Referral Pattern, Aetiology and Management Outcomes Over Four Distinct Five-Year Periods.

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Abstract

Background

Paediatric hydrocephalus causes significant health burden globally, particularly in low and middle-income countries. There's a dearth of data from specific regions such as KwaZulu-Natal, South Africa. This study aimed to investigate the landscape of paediatric hydrocephalus, comparing four distinct five-year periods.

Methods

Data were collected retrospectively (2003 to 2007, 2008 to 2012, and 2013 to 2017) and prospectively (2018 to 2022). Children (≤18 years) treated for hydrocephalus were included. Data on demographics, referral patterns, aetiology, treatment modalities, and outcomes were collected and analyzed.

Results

A total of 3325 children were treated. The peak period was 2008 to 2012 (35.3%). Majority (51.4%) were from rural areas (p=0.013) and 47.9% were referred from regional hospitals, p=<0.001. Males (56.4%) and infants (60.2%) were predominant groups (p<0.001). Post-infectious aetiology (32.7%) was predominant (p<0.001), particularly tuberculous meningitis (54.1%). Ventriculoperitoneal shunts (VPSs) were the mainstay treatment (84.2%), with notable complication rates (20.4%), including infections (9.6%). HIV co-infection was diagnosed in 2.5% of cases. Weekend procedures were associated with VPS complications (HR1.3, CI:1.03-1.66, p=0.03). The mortality rate was 7.9%, and age ≥1 year (HR, 2.43 CI: 1.87-3.17, p<0.001), tertiary hospital referral (HR 1.48, CI: 1.06-2.04, p=0.019), VPS infection (HR, 3.63 CI: 2.66-4.95, p<0.001), acute abdomen (HR 2.17, CI: 1.11-4.25, p=0.024) and pneumonia (HR 7.32, OR 4.84 -11.06, p<0.001) were associated with mortality.

Conclusion

This study provides comprehensive insights into pediatric hydrocephalus in KZN. Monitoring temporal trends and predictors of outcomes will aid guide future interventions aimed at mitigating the burden of pediatric hydrocephalus in the region.

Keywords: Endoscopic third ventriculostomy, KwaZulu-Natal, Paediatric hydrocephalus, Tuberculous meningitis; ventriculoperitoneal shunt.

Introduction

Paediatric hydrocephalus causes a significant health burden globally, particularly in low and middle-income countries (LMICs) [1]. The aetiology is influenced by geographic variations, particularly between high-income countries (HICs) and LMICs [2].

Reports suggest a higher incidence of paediatric hydrocephalus in LMICs, estimated at 123 cases per 100,00 compared to HICs, estimated at 79 cases per 100,000 [3]. This difference can be explained by socio-economic inequities, including the high burden of communicable diseases and limited access to health care services in LMICs.

Epidemiological studies report 180,000 new cases of paediatric hydrocephalus in Sub-Saharan Africa annually, with the incidence reported at 145 cases per 100,000 births, compared to 68 cases per 100,00 births in North America and 316 cases per 100,000 births in Latin America [3].

The continent of Africa has a young population, with children 15 years and younger comprising 40% of the population when compared to the worldwide average of 25% [4]. The current population of South Africa (SA) is estimated at 62 million, with 34% being children under the age of 18 years [5]. The province of KwaZulu-Natal (KZN), the second most populous province in SA has a population of 12 million, with the second largest population of children at 4.3 million [6].

Hydrocephalus entails a dual insult on the brain, caused by initial causative pathology and further exacerbated by increased intracranial pressure (ICP) associated with delays in treatment. In SA, child health has been set as a priority, in keeping with Sustainable Development Goals, which include the reduction of childhood mortality [7].

Paediatric hydrocephalus represents one of the highest surgical burdens in the neurosurgery department at KZN [8]. However, there remains a dearth of data on the referral patterns, aetiology, treatment modalities, and outcomes of paediatric hydrocephalus in KZN. To address this gap, we conducted a comprehensive study, comparing four distinct five-year periods to elucidate the landscape of paediatric hydrocephalus in KZN.

Materials and Methods

Study design and setting

Data was collected retrospectively and prospectively over four, five-year periods. The five-year periods spanned from 2003 to 2007, 2008 to 2012, 2013 to 2017 (all retrospective), and the last period from 2018 to 2022 (prospective).

The study was conducted at the Department of Neurosurgery (DoN), at Inkosi Albert Luthuli Central Hospital (IALCH), which is a quaternary hospital located in KZN, SA. The DoN was previously located in Wentworth Hospital, KZN from 1968 to 2002 and moved to IALCH, a new hospital in December 2002. The DoN provides both adult and paediatric neurosurgery services for the entirety of KZN.

In 2018 a small satellite neurosurgery unit commenced operations at Grey's Hospital, a tertiary hospital located in Pietermaritzburg (PBM) the capital city of KZN, catering to 3 million people in PMB and surrounding areas [5]. This unit is approximately 78.1 km away from IALCH and functions in conjunction with the DoN. The study enrolled children (birth to 18 years), newly diagnosed and treated for hydrocephalus. Children not treated at IALCH were excluded.

All the clinical and radiological records are stored electronically in the hospital-integrated information management systems (Soarian®, Siemens Healthcare, Germany and MEDITECH®, South Africa) used at IALCH. Data collected included age at surgical procedure, sex, race, residential area (rural versus urban), level of care of referring hospital (tertiary, regional or district), aetiology, HIV co-infection, cerebrospinal fluid (CSF) diversion

procedure, timing of procedure (weekdays versus weekends and work-hours versus after-hours) and whether antibiotic-impregnated shunts (AISs) or non-AIS were used.

Further data collected included CSF diversion procedure complications, length of hospital stay (LOHS), follow-up, and in-hospital mortality. Hydrocephalus was categorized into three groups; (i) post-infectious hydrocephalus (PIH); when the aetiology was due to infection; (ii) non-post infectious hydrocephalus (non-PIH); when the aetiology was due to pathology other than infection (i.e. brain tumours (BTs), congenital, myelomeningocoele (MMC), aqueduct stenosis (AS), Dandy-Walker Malformation (DWM), arachnoid cyst, encephalocoele, spontaneous subarachnoid haemorrhage (SAH)/ intraventricular haemorrhage (IVH) and trauma) and (iii) idiopathic hydrocephalus; when the cause was unknown. Weekday was Monday to Friday and weekend was Saturday and Sunday. Work-hours were from eight o'clock in the morning to four o'clock in the afternoon, while after-hours were between four o'clock in the afternoon and eight o'clock in the morning. The VPS complications were categorized into VPS failure (mechanical failure) and infection. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics of the children. Normality of numeric data was assessed; normally distributed variables were presented using the mean and standard deviation, while non-normally distributed variables were reported using the median and interquartile range (IQR). Chi-square tests were used to determine the association between categorical factors.

T-tests or Mann-Whitney tests were utilized to compare differences in numeric measurements between two groups. On the other hand, Kruskal-Wallis test was applicable for the skewed distributions between at least three groups. Kaplan-Meier survival analysis was utilized to assess time to death and CSF diversion procedure complications. The regression analysis on time to event was also visually displayed on forest plot. Other visual displays employed multiple bar charts. The significance level was set at 0.05.

Results

During the four study periods, 3325 newly diagnosed paediatric hydrocephalus cases were treated. Comparisons of the residential area, hospital referral pattern, and demographic characteristics are presented in Table 1. The peak period for referral and treatment of hydrocephalus was observed between 2008 to 2012 (35.3%). The overall median age was 7 months (IQR =3-36). The median age (months) for boys was 8 (IQR =3-36 months) and for girls was 7 (IQR =3-30 months, (p=0.177). Age categories for boys and girls treated for hydrocephalus are presented in Table 2. Infants were the largest subgroup (60.2%). Comparison of median age according to the residential area and level of hospital care are presented in Tables 3 and 4.

Table 1: Comparison of Residential Area, Level of Care of Referring Hospitals, and Demographic Characteristics of Paediatric Hydrocephalus Cases in KwaZulu-Natal During the Study Periods

Period	2003-2007 (N=870)	2008-2012 (N=1174)	2013-2017 (N=887)	2018-2022 (N=394)	p-value	Overall (N=3325)
Residential area					**0.013**	
Urban	428 (49.2%)	606 (51.6%)	412 (46.4%)	170 (43.1%)		1616 (48.6%)
Rural	442 (50.8%)	568 (48.4%)	475 (53.6%)	224 (56.9%)		1709 (51.4%)
Hospital levels					**<0.001**	
District	258 (29.7%)	264 (22.5%)	210 (23.7%)	83 (21.1%)		815 (24.5%)
Regional	354 (40.7%)	549 (46.8%)	456 (51.4%)	235 (59.6%)		1594 (47.9%)
Tertiary	258 (29.7%)	361 (30.7%)	221 (24.9%)	76 (19.3%)		916 (27.5%)
Age					**<0.001**	
<1yr	524 (60.2%)	658 (56.0%)	564 (63.6%)	255 (64.7%)	.	2001 (60.2%)
1-<6yrs	224 (25.7%)	331 (28.2%)	180 (20.3%)	77 (19.5%)		812 (24.4%)
6-<12yrs	84 (9.7%)	140 (11.9%)	98 (11.0%)	40 (10.2%)		362 (10.9%)
12+yrs	38 (4.4%)	45 (3.8%)	45 (5.1%)	22 (5.6%)		150 (4.5%)
Race					0.365	
Black	841 (96.7%)	1136 (96.8%)	854 (96.3%)	383 (97.2%)		3214 (96.7%)
Indian	20 (2.3%)	25 (2.1%)	19 (2.1%)	6 (1.5%)		70 (2.1%)
White	8 (0.9%)	10 (0.9%)	8 (0.9%)	3 (0.8%)		29 (0.9%)
Coloured	1 (0.1%)	3 (0.3%)	6 (0.7%)	1 (0.3%)		11 (0.3%)
Other	0 (0%)	0 (0%)	0 (0.0%)	1 (0.3%)		1 (0%)
Sex					0.911	
Male	494 (56.8%)	668 (56.9%)	496 (55.9%)	217 (55.1%)		1875 (56.4%)
Female	376 (43.2%)	506 (43.1%)	391 (44.1%)	177 (44.9%)		1450 (43.6%
LOHS (median, IQR)	6(4-10)	5 (3-10)	7 (5-15)	8 (5-26)	<0.001	
Follow-up, months (median, IQR)	24(2-60)	24.5 (2-60)	12 (4-36)	11 (2-24)	<0.001	

***IQR, Interquartile range; LOHS, Length of hospital stay**

Table 2: Age Categories of Boys and Girls Treated for Hydrocephalus

Sex	Boys (N=1875)	Girls (N=1450)	p-value	Overall (N=3325)
Age groups (years)			0.165	
<1yr	1119 (59.7%)	882 (60.8%)		2001 (60.2%)
1-<6yrs	445 (23.7%)	367 (25.3%)		812 (24.4%)
6-<12yrs	218 (11.6%)	144 (9.9%)		362 (10.9%)
12+yrs	93 (5.0%)	57 (3.9%)		150 (4.5%)

Table 3: Median Age According to Urban versus Rural Residential Area

Residential area	Urban (N=1616)	Rural (N=1709)	p-value	Overall (N=3325)
Age in months				
Median(Q1-Q3)	8 (3 - 36)	7 (3 - 29)	0.087	7 (3 -36)

Table 4: Comparison of the Median Age According to Level of Care of the Referring Hospital

Hospital level	District (N=815)	Regional (N=1594)	Tertiary (N=916)	p-value	Overall (N=3325)
Age (months)					
Median(Q1-Q3)	6 (3 - 17)	7 (3 - 36)	9 (4 -51)	<0.001	7 (3 - 36)

Paediatric hydrocephalus categories are presented in Figure 1. Infections were the most frequent cause of hydrocephalus [n=1088; 32.7%] (Figure 2), with tuberculous meningitis (TBM) emerging as the most prevalent (54.1%) infectious aetiology (Table 5). However, during the last two five-year periods pyogenic meningitis cases were predominant at 56.2% and 54.8% respectively.

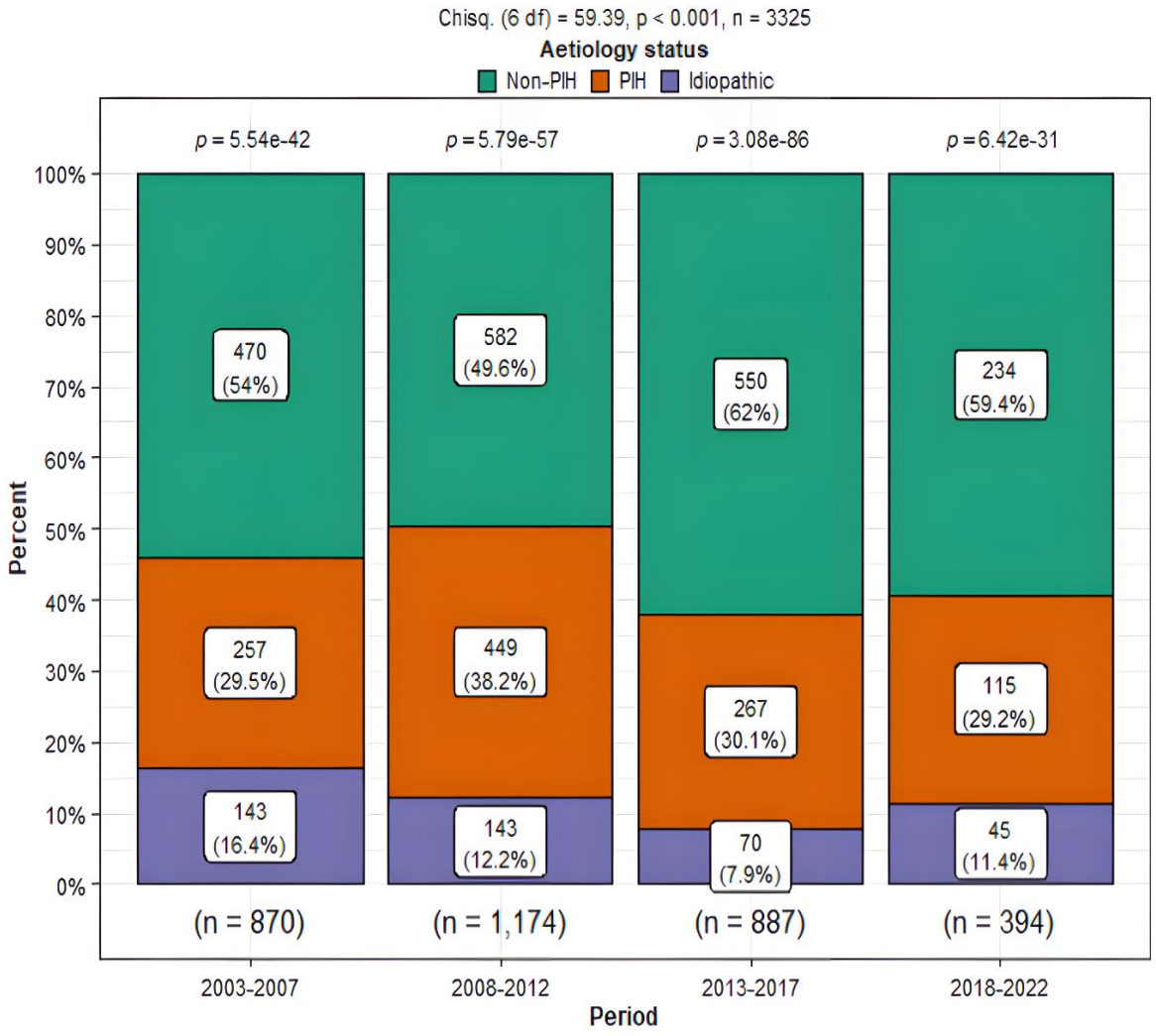


Figure 1: Comparison of Paediatric Hydrocephalus Aetiology Categories in KwaZulu-Natal Over Four Time Periods. The Categories were Post-infectious Hydrocephalus, Non-PIH, and Idiopathic Hydrocephalus (P < 0.001). PIH, Post-infectious hydrocephalus.

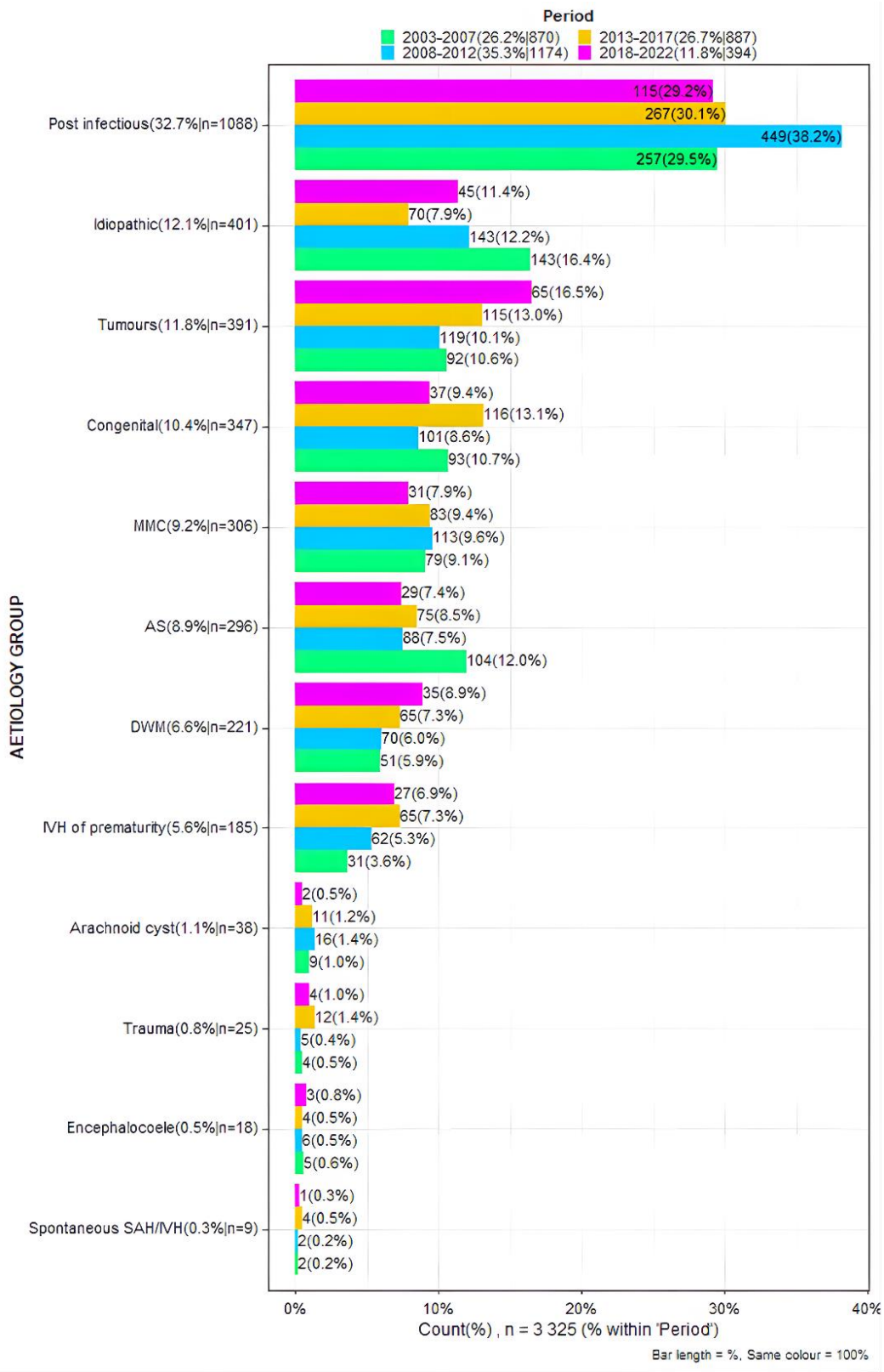


Figure 2: Bar Graph Showing Frequencies of Aetiologies of Paediatric Hydrocephalus During the Four Time Periods (P < 0.001). MMC, Myelomeningocele; AS, Aqueduct stenosis; DWM, Dandy-Walker malformation; IVH, Intraventricular haemorrhage; SAH, Subarachnoid haemorrhage

Table 5: The Aetiology of Post-infectious Hydrocephalus in Children Treated During the Study Periods

Period	2003-2007 (N=257)	2008-2012 (N=449)	2013-2017 (N=267)	2018-2022 (N=115)	p-value	Overall (N=1088)
Aetiology					<0.001	
TBM	144 (56.0%)	285 (63.5%)	108 (40.4%)	52 (45.2%)		589 (54.1%)
Pyogenic meningitis	111 (43.2%)	153 (34.1%)	150 (56.2%)	63 (54.8%)		477 (43.8%)
Cryptococcal meningitis	2 (0.8%)	9 (2.0%)	7 (2.6%)	0 (0.0%)		18 (1.7%)
Neurocysticercosis	0 (0.0%)	2 (0.4%)	2 (0.7%)	0 (0.0%)		4 (0.4%)

***TBM, Tuberculous meningitis**

BTs [n=391; 11.8%] were predominantly infra-tentorial [n=228; 58.3%] and the rest supra-tentorial [n=163; 41.7%]. BTs were; brainstem glioma [n=83; 21.2%], supra-tentorial glioma [n=71; 18.2%], medulloblastoma [n=67; 17.1%], pineal tumours [n=49; 12.5%], pilocytic astrocytoma [n=48; 12.3%], ependymoma [n=25; 6.4%], craniopharyngioma [n=23; 5.9%], choroid plexus tumours [n=12; 3.1%], meningioma [n=9; 2.3%] and others [n=4; 1%]. The median age at which CSF diversion procedures were performed per aetiology is shown in Figure 3.

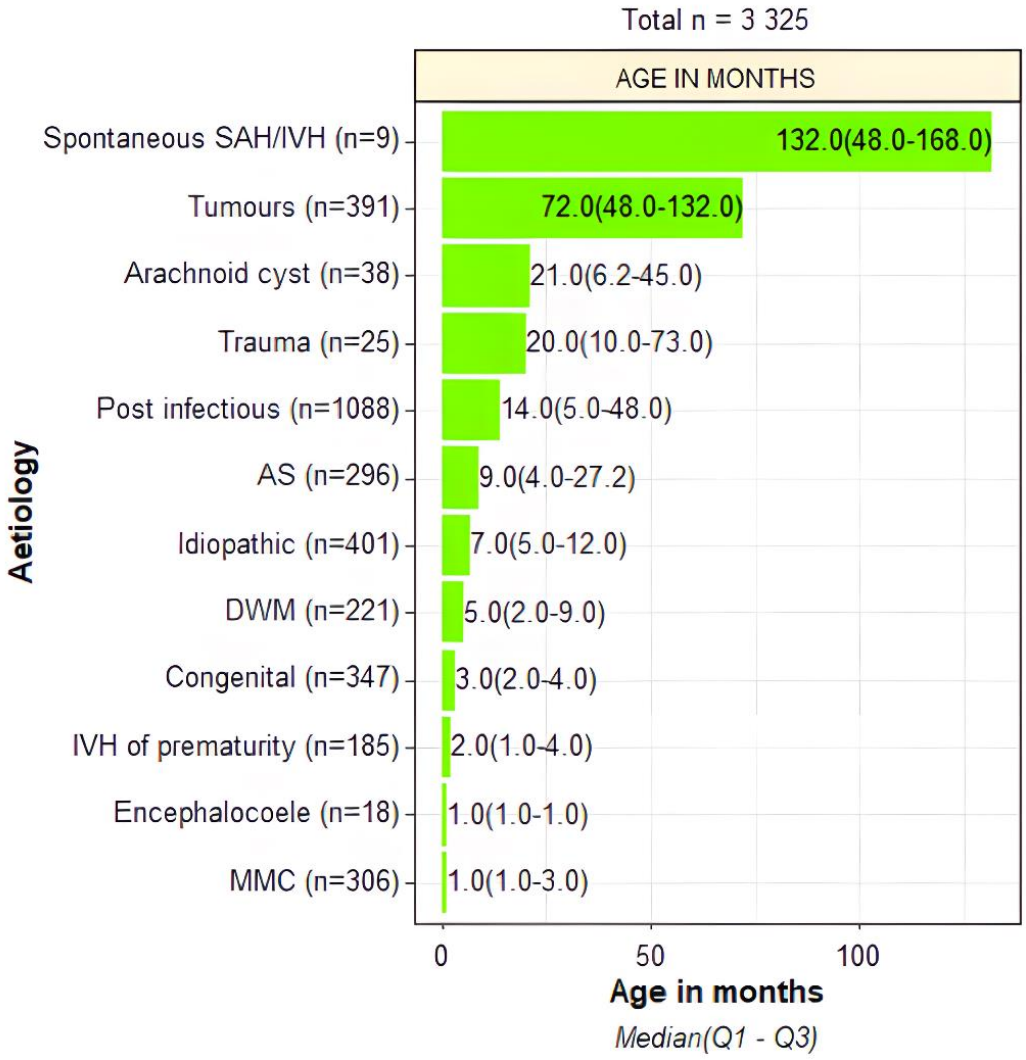


Figure 3: Median Age at Cerebrospinal Fluid Diversion Procedures per Aetiology of Hydrocephalus. SAH, Subarachnoid haemorrhage; IVH, Intraventricular haemorrhage; AS, Aqueduct stenosis; DWM, Dandy-Walker malformation; MMC, Myelomeningocoele.

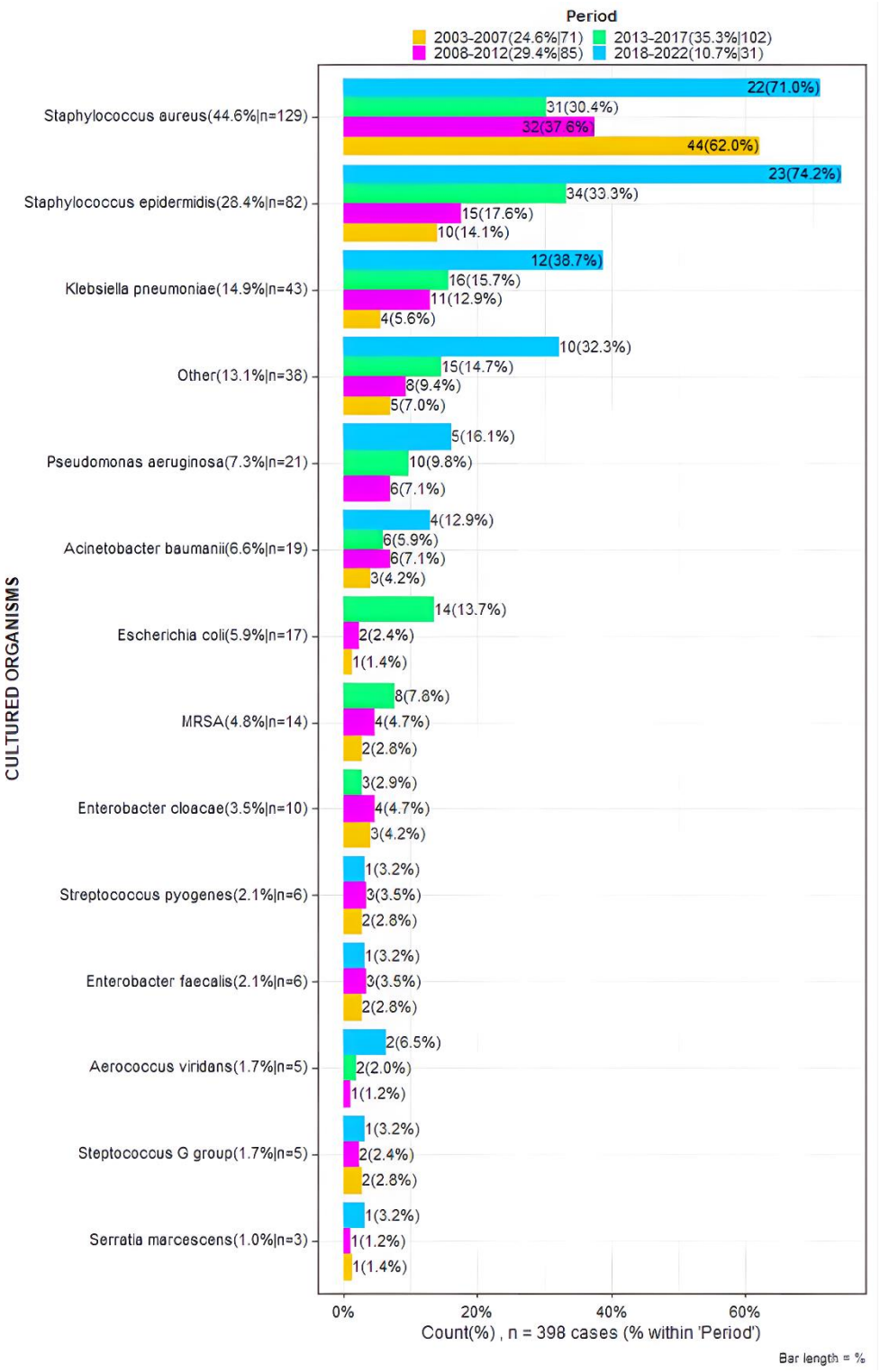
Multiloculated hydrocephalus was diagnosed in 139 (4.2%) children. Eighty-four (2.5%) children were diagnosed with HIV co-infection, with 54 (64.3%) receiving anti-retroviral therapy (ART). The median CD4 count was 202 cells /µL, (IQR= 54.5-505.8). The aetiology of hydrocephalus in children diagnosed with HIV co-infection included: TBM [n=55; 65.5%], cryptococcal meningitis (CM) [n=18; 21.4%], pyogenic meningitis [n=6; 7.1%], BTs [n=2; 2.4%], IVH of prematurity [n=1; 1.2%], AS [n=1; 1.2%] and spontaneous SAH [n=1;1.7%].

Primary permanent CSF diversion procedures performed were ventriculoperitoneal shunt (VPS) insertion [n=2798; 84.2%] and endoscopic third ventriculostomy (ETV) [n=527; 15.8 %]. VPS was the predominant procedure in all the study periods. AISs were utilized in 1333 (47.6%) cases, while non-AISs were used in the rest [n=1465; 52.4%]. Majority of surgical procedures were performed during work-hours [n=2310; 69.5%] and the rest [n=1015; 30.5%] were performed after-hours. Majority of surgical procedures were performed during weekdays [n=2692; 81%], while the rest [n=633; 19%] were performed on weekends. The VPS complication rates during the study periods are presented in Table 6, showing a significant decline over the periods.

Table 6: Comparison of Ventriculoperitoneal Shunt Complication Rates During the Study Periods

Period	2003-2007 (N=770)	2008-2012 (N=1013)	2013-2017 (N=683)	2018-2022 (N=332)	p-value	Overall (N=2798)
VPS complication					<0.001	
No	611 (79.4%)	790 (78.0%)	533 (78.0%)	293 (88.3%)		2227 (79.6%)
Yes	159 (20.6%)	223 (22.0%)	150 (22.0%)	39 (11.7%)		571 (20.4%)
Mechanical failure					<0.001	
No	677 (87.9%)	869 (85.8%)	625 (91.5%)	322 (97.0%)		2493 (89.1%)
Yes	93 (12.1%)	144 (14.2%)	58 (8.5%)	10 (3.0%)		305 (10.9%)
VPS infection					0.002	
No	704 (91.4%)	930 (91.8%)	591 (86.5%)	303 (91.3%)		2528 (90.4%)
Yes	66 (8.6%)	83 (8.2%)	92 (13.5%)	29 (8.7%)		270 (9.6%)

There were 398 organisms cultured from the CSF of all shunt infections, with the commonest organisms being *Staphylococcus aureus* [n=129; 44.6%.] and *Staphylococcus epidermis* [n=82; 28.4%]. The rest are presented in Figure 4.



***MRSA= Methicillin resistant staphylococcus aureus**

Figure 4: Bar Graph Showing Frequencies of Organisms Cultured from the Cerebrospinal Fluid of Children with Ventriculoperitoneal Shunt Infections. MRSA, Methicillin-resistant Staphylococcus aureus.

Intra-abdominal complications (Figure 5) occurred in 39 (1.4%) cases, including acute abdomen (peritonitis) [n=23; 0.8%], abdominal pseudocyst [n=16; 0.6%], and rectal protrusion of the shunt [n=8; 0.3%]. Pneumonia was diagnosed in 45 (1.4%) children. VPSs were inserted in 80/84 (95.2%) HIV-infected children and VPS complications were reported in 27 (33.8%) cases, which included infections (n=13; 16.3%) and mechanical failures (n=14; 17.5%).

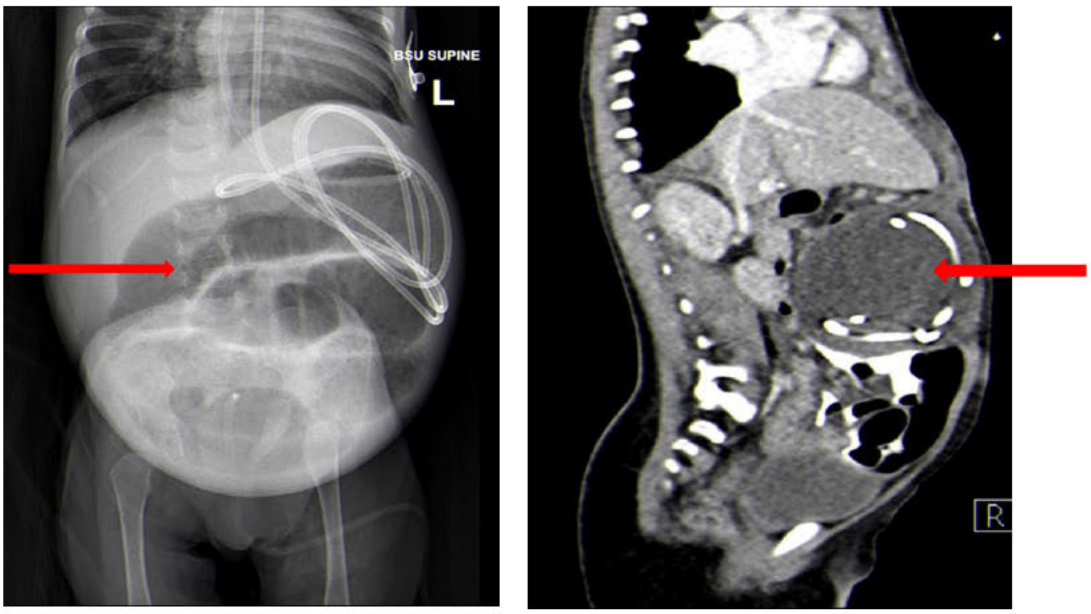


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Figure 5: An abdominal X-ray (A) Shows Distension and Dilated Loops of Bowel in a Child with a Ventriculoperitoneal Shunt, Diagnosed with an Acute Abdomen. A CT scan of the Abdomen (B) Reveals a Shunt Within a Pseudocyst.

Univariate and multiple regression analysis of factors associated with VPS complication rates are presented in Tables 7 and 8 respectively. Weekend procedures were associated with an increased risk of VPS complication (HR1.3, CI:1.03-1.66, p=0.03), while idiopathic hydrocephalus was less likely to be associated with complications (HR 0.78, CI: 0.60-1.02, p =0.07). Multiple regression anaylsis of factors associated with VPS infection are presented in Table 9. Time to VPS infection and mechanical failure according to age group and aetiology category, is presented in Kaplan- Meier graphs in Figures 6 and 7. A comparison of time to VPS complication according to infectious aetiology is presented in Figure 8, showing no statistical difference between hydrocephalus caused by TBM, CM and pyogenic meningitis.

Table 7: Univariate Analysis of Factors Associated with Ventriculoperitoneal Shunt Complications

VPS complication	No (N=2227)	Yes (N=571)	p-value	Overall (N=2798)
Age group			<0.001	
<1yr	1376 (61.8%)	416 (72.9%)		1792 (64.0%)
1+yr	851 (38.2%)	155 (27.1%)		1006 (36.0%)
Sex			0.985	
Male	1251 (56.2%)	321 (56.2%)		1572 (56.2%)
Female	976 (43.8%)	250 (43.8%)		1226 (43.8%)
Timing of procedure			0.001	
Work-hours	1527 (68.6%)	432 (75.7%)		1959 (70.0%)
After-hours	700 (31.4%)	139 (24.3%)		839 (30.0%)
Day of procedure			0.001	
Weekday	1765 (79.3%)	493 (86.3%)		2258 (80.7%)
Weekend	462 (20.7%)	78 (13.7%)		540 (19.3%)
Aetiology category			0.296	
Non-PIH	1127 (50.6%)	278 (48.7%)		1405 (50.2%)
PIH	799 (35.9%)	224 (39.2%)		1023 (36.6%)
Idiopathic	301 (13.5%)	69 (12.1%)		370 (13.2%)
Type of shunt			0.134	
Non-AIS	1182 (53.1%)	283 (49.6%)		1465 (52.4%)
AIS	1045 (46.9%)	288 (50.4%)		1333 (47.6%)
Multiloculated			<0.001	
No	2161 (97.0%)	502 (87.9%)		2663 (95.2%)
Yes	66 (3.0%)	69 (12.1%)		135 (4.8%)
Residential area			0.329	
Urban	1104 (49.6%)	270 (47.3%)		1374 (49.1%)
Rural	1123 (50.4%)	301 (52.7%)		1424 (50.9%)
Hospital levels			0.072	
District	549 (24.7%)	167 (29.2%)		716 (25.6%)
Regional	1073 (48.2%)	253 (44.3%)		1326 (47.4%)
Tertiary	605 (27.2%)	151 (26.4%)		756 (27.0%)

***AIS, Antibiotic impregnated shunt**

Table 8: Multiple Regression Analysis of Factors Associated with Ventriculoperitoneal Shunt Complications

Variable	HR CI, p-value) Unadjusted	HR (CI, p-value) Adjusted	HR (CI, p-value) BackStep
Age ≥ 1 year	1.08 (0.89-1.30, p=0.435)	1.02 (0.83-1.25, p=0.885)	-
Female sex	1.05 (0.89-1.24, p=0.576)	1.11 (0.93-1.31, p=0.246)	-
After-hours procedure	1.05 (0.87-1.27, p=0.611)	1.05 (0.85-1.30, p=0.655)	-
Weekend procedure	1.28 (1.01-1.63, p=0.042)	1.30 (1.02-1.66, p=0.034)	1.30 (1.03-1.66, p=0.030)
PIH aetiology	1.06 (0.88-1.26, p=0.549)	1.09 (0.90-1.31, p=0.386)	1.06 (0.89-1.26, p=0.541)
Idiopathic aetiology	0.77 (0.59-1.01, p=0.056)	0.76 (0.58-1.00, p=0.049)	0.78 (0.60-1.02, p=0.070)
AIS	0.90 (0.76-1.06, p=0.192)	0.90 (0.76-1.07, p=0.234)	-
Multiloculated hydrocephalus	0.88 (0.68-1.13, p=0.317)	0.89 (0.68-1.15, p=0.354)	-
Rural residential area	0.77 (0.65-0.91, p=0.002)	0.77 (0.64-0.91, p=0.002)	0.77 (0.65-0.91, p=0.002)
Regional hospital	1.03 (0.84-1.25, p=0.784)	1.02 (0.83-1.25, p=0.836)	-
Tertiary hospital	1.01 (0.81-1.26, p=0.949)	0.90 (0.72-1.14, p=0.386)	-

***AIS, Antibiotic-impregnated shunts**

Table 9: Multiple Regression Analysis of Factors Associated with Ventriculoperitoneal Shunt Infection

Variable	HR (CI, p-value) Unadjusted	HR (CI, p-value) Adjusted	HR (CI, p-value) BackStep
Age ≥ 1 year	1.13 (0.86-1.47, p=0.378)	1.09 (0.81-1.47, p=0.577)	-
Female sex	1.26 (0.99-1.60, p=0.056)	1.35 (1.06-1.72, p=0.016)	1.33 (1.05-1.70, p=0.020)
After-hour procedure	1.01 (0.76-1.33, p=0.969)	0.99 (0.73-1.36, p=0.969)	-
Weekend procedure	1.28 (0.91-1.81, p=0.149)	1.35 (0.95-1.91, p=0.091)	1.35 (0.96-1.91, p=0.082)
PIH aetiology	1.06 (0.83-1.37, p=0.628)	1.09 (0.83-1.43, p=0.523)	1.06 (0.83-1.37, p=0.638)
Idiopathic aetiology	0.64 (0.42-0.98, p=0.039)	0.62 (0.40-0.95, p=0.028)	0.62 (0.41-0.95, p=0.028)
AIS	0.86 (0.68-1.10, p=0.232)	0.87 (0.68-1.11, p=0.251)	-
Multiloculated hydrocephalus	0.98 (0.69-1.39, p=0.898)	0.99 (0.69-1.42, p=0.957)	-
Rural area	0.62 (0.49-0.80, p<0.001)	0.63 (0.49-0.81, p<0.001)	0.63 (0.49-0.80, p<0.001)
Regional hospital	1.17 (0.87-1.56, p=0.294)	1.14 (0.85-1.54, p=0.381)	-
Tertiary hospital	1.08 (0.77-1.49, p=0.662)	0.92 (0.65-1.29, p=0.625)	-

***AIS, Antibiotic-impregnated shunts**

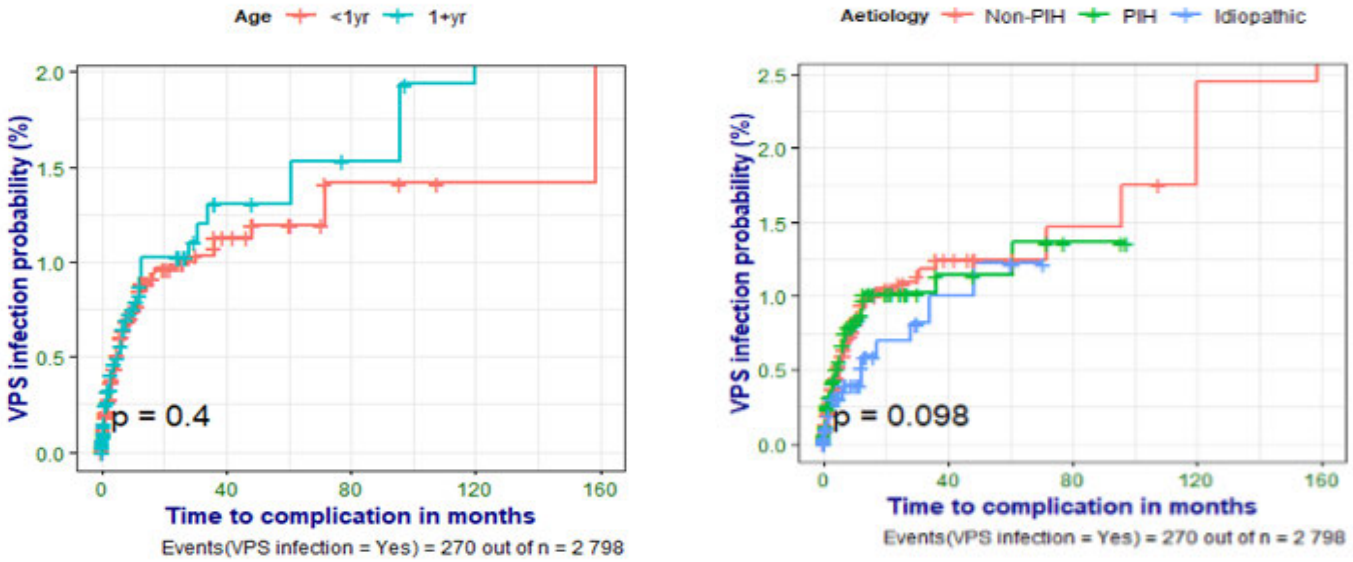

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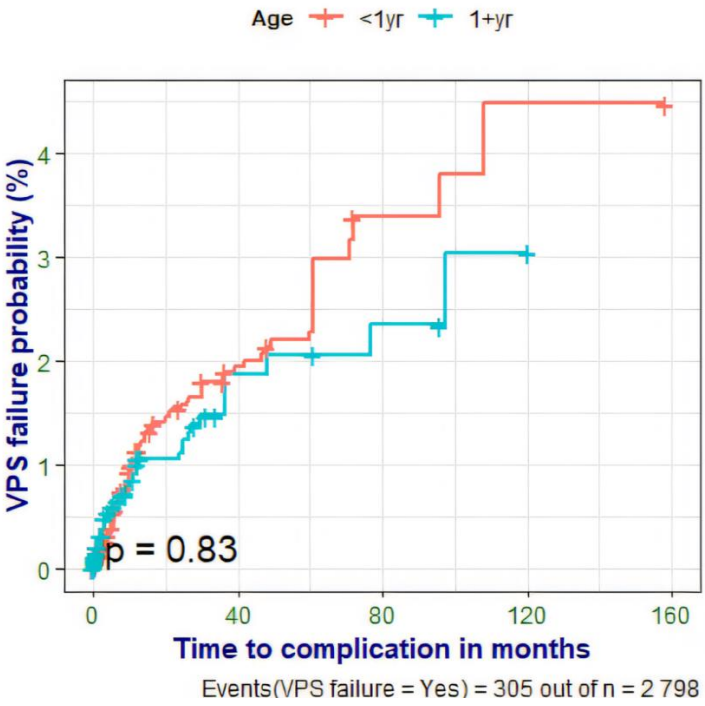
Figure 6: Kaplan-Meier Graphs Depicting the Time to Ventriculoperitoneal Shunt Infection According to Age Group (A) and Aetiology Category (B). VPS, Ventriculoperitoneal shunt; PIH, Post-infectious hydrocephalus.



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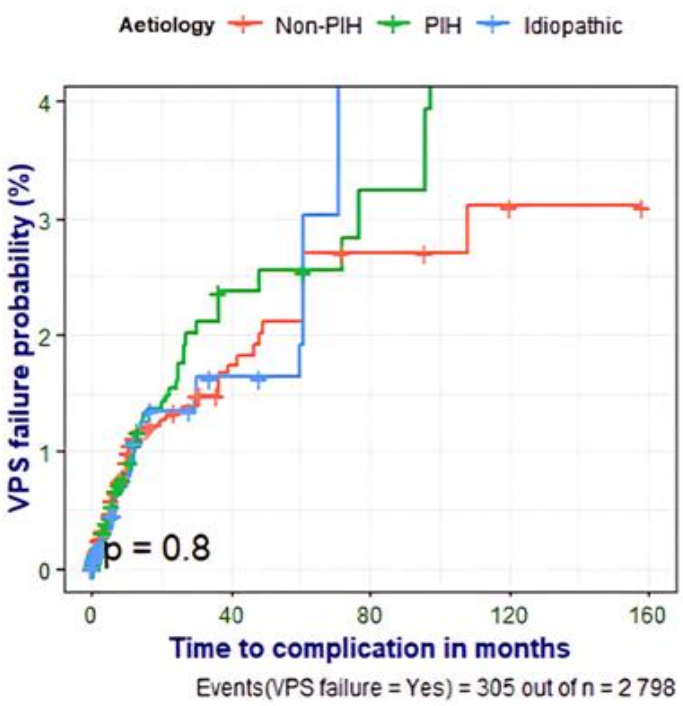

B

Figure 7: Kaplan-Meier Graph Depicting the Time to Ventriculoperitoneal Shunt Mechanical Failure According to Age and Aetiology Category. VPS, Ventriculoperitoneal shunt; PIH, Post-infectious hydrocephalus

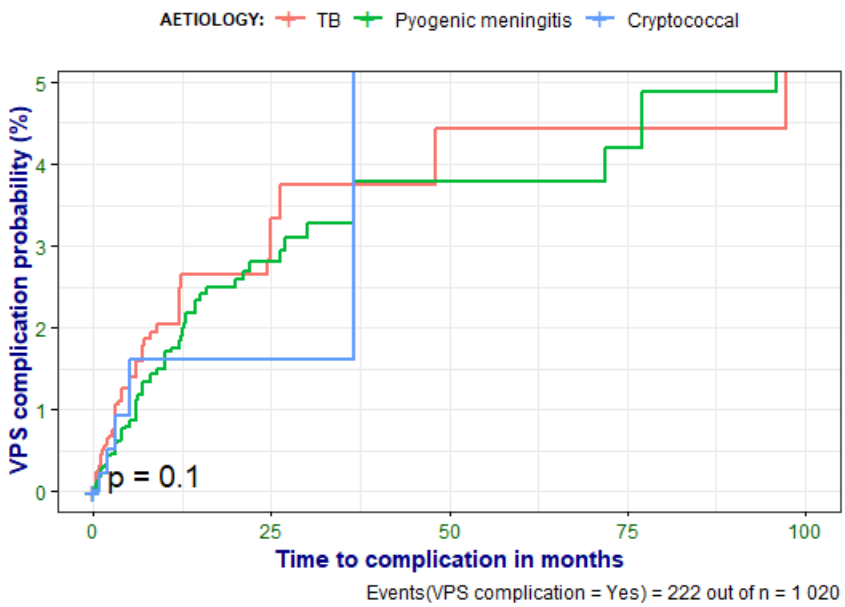

Figure 8: **Kaplan-Meier graph Depicting the Time to Ventriculoperitoneal Shunt complications according to Post-Infectious Hydrocephalus Aetiology, Showing no Statistical Difference in the Time to Complication Between the Aetiologies. TB, Tuberculosis; VPS, Ventriculoperitoneal shunt.**

A total of 573 ETV procedures were performed, with ETV failure diagnosed in 59 (10.3%) cases. Table 10 presents univariate analysis of factors associated with ETV failure. Multiple regression analysis did not reveal any significant factors associated with ETV failure (Table 11). ETV failure rate per period and time to ETV failure according to age group, and aetiology category (Kaplan-Meier graphs) are presented in Table 12 and Figure 9 respectively. Time to VPS complications and ETV failure according to residential areas are presented in Kaplan-Meier graphs in Figure 10.

Table 10: Univariate Analysis of Factors Associated with Endoscopic Third Ventriculostomy Failure

ETV failure	No (N=514)	Yes (N=59)	p-value	Overall (N=573)
Age group			0.046	
<1yr	201 (39.1%)	31 (52.5%)		232 (40.5%)
1+yr	313 (60.9%)	28 (47.5%)		341 (59.5%)
Sex			0.166	
Male	301 (58.6%)	29 (49.2%)		330 (57.6%)
Female	213 (41.4%)	30 (50.8%)		243 (42.4%)
Timing of procedure			0.627	
Work-hours	341 (66.3%)	41 (69.5%)		382 (66.7%)
After-hours	173 (33.7%)	18 (30.5%)		191 (33.3%)
Day of procedure			0.368	
Weekday	420 (81.7%)	51 (86.4%)		471 (82.2%)
Weekend	94 (18.3%)	8 (13.6%)		102 (17.8%)
Aetiology category			0.422	
Non-PIH	408 (79.4%)	51 (86.4%)		459 (80.1%)
PIH	74 (14.4%)	6 (10.2%)		80 (14.0%)
Idiopathic	32 (6.2%)	2 (3.4%)		34 (5.9%)
Residential area			0.876	
Urban	232 (45.1%)	26 (44.1%)		258 (45.0%)
Rural	282 (54.9%)	33 (55.9%)		315 (55.0%)
Hospital levels			0.133	
District	102 (19.8%)	12 (20.3%)		114 (19.9%)
Regional	254 (49.4%)	36 (61.0%)		290 (50.6%)
Tertiary	158 (30.7%)	11 (18.6%)		169 (29.5%)

Table 11: Multiple Regression Analysis of Factors Associated with Endoscopic Third Ventriculostomy Failure

Variable	HR (CI, p-value) Unadjusted	HR (CI, p-value) Adjusted	HR (CI, p-value) BackStep
Age ≥ 1 year	0.97 (0.58-1.62, p=0.901)	0.92 (0.52-1.62, p=0.767)	-
Female sex	1.04 (0.62-1.75, p=0.871)	1.09 (0.64-1.87, p=0.758)	-
After-hours procedure	1.13 (0.64-2.00, p=0.675)	1.40 (0.72-2.73, p=0.320)	-
Weekend procedure	0.92 (0.44-1.95, p=0.830)	1.16 (0.49-2.71, p=0.739)	-
PIH aetiology	0.48 (0.21-1.13, p=0.093)	0.45 (0.18-1.13, p=0.088)	0.51 (0.21-1.22, p=0.131)
Idiopathic aetiology	0.65 (0.16-2.69, p=0.554)	0.29 (0.05-1.55, p=0.147)	0.36 (0.08-1.57, p=0.173)
Rural residential area	0.63 (0.38-1.06, p=0.082)	0.56 (0.31-1.01, p=0.054)	0.61 (0.35-1.06, p=0.079)
Regional hospital	2.22 (1.05-4.67, p=0.036)	2.11 (0.95-4.68, p=0.067)	2.21 (1.03-4.74, p=0.042)
Tertiary hospital	1.38 (0.58-3.28, p=0.465)	1.30 (0.50-3.36, p=0.592)	1.34 (0.54-3.35, p=0.528)

Table 12: Comparison of Endoscopic Third Ventriculostomy Failure Rates per Period

Period	2003-2007 (N=121)	2008-2012 (N=177)	2013-2017 (N=212)	2018-2022 (N=63)	p-value	Overall (N=573)
ETV failure					0.021	
No	115 (95.0%)	161 (91.0%)	180 (84.9%)	58 (92.1%)		514 (89.7%)
Yes	6 (5.0%)	16 (9.0%)	32 (15.1%)	5 (7.9%)		59 (10.3%)

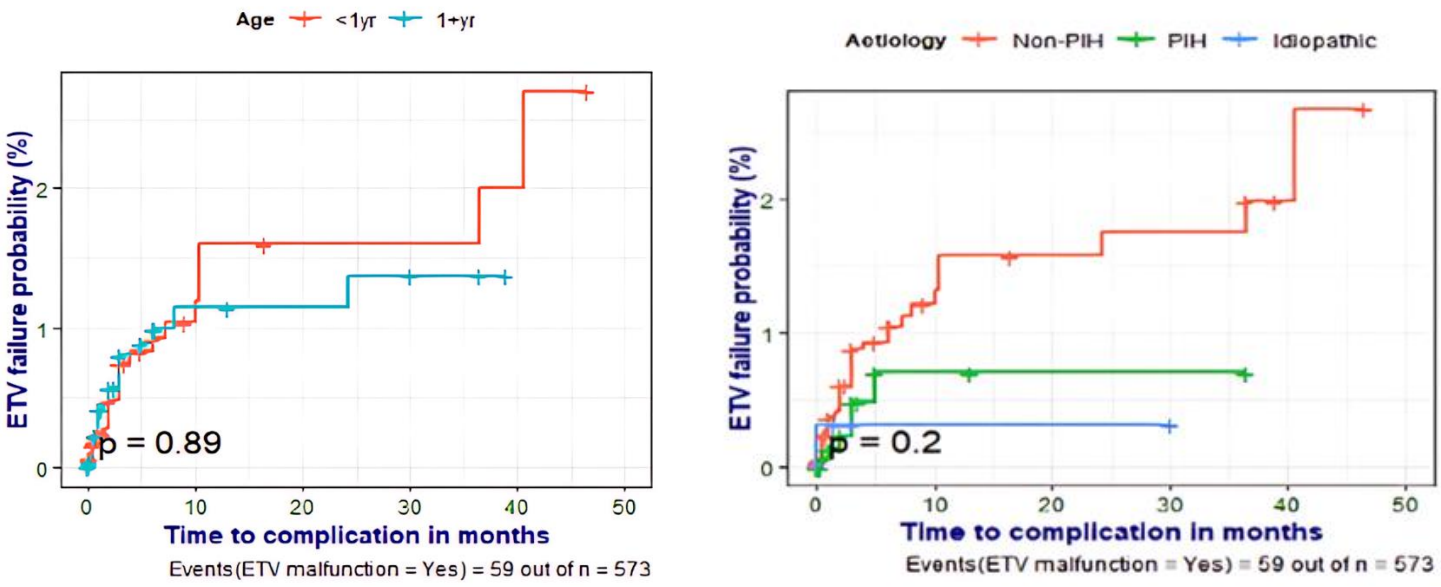

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Figure 9: Kaplan-Meier Graph Depicting Time to Endoscopic Third Ventriculostomy Failure According to Age Group (A) and Aetiology category (B). ETV, Endoscopic third ventriculostomy; PIH, Post-infectious hydrocephalus.

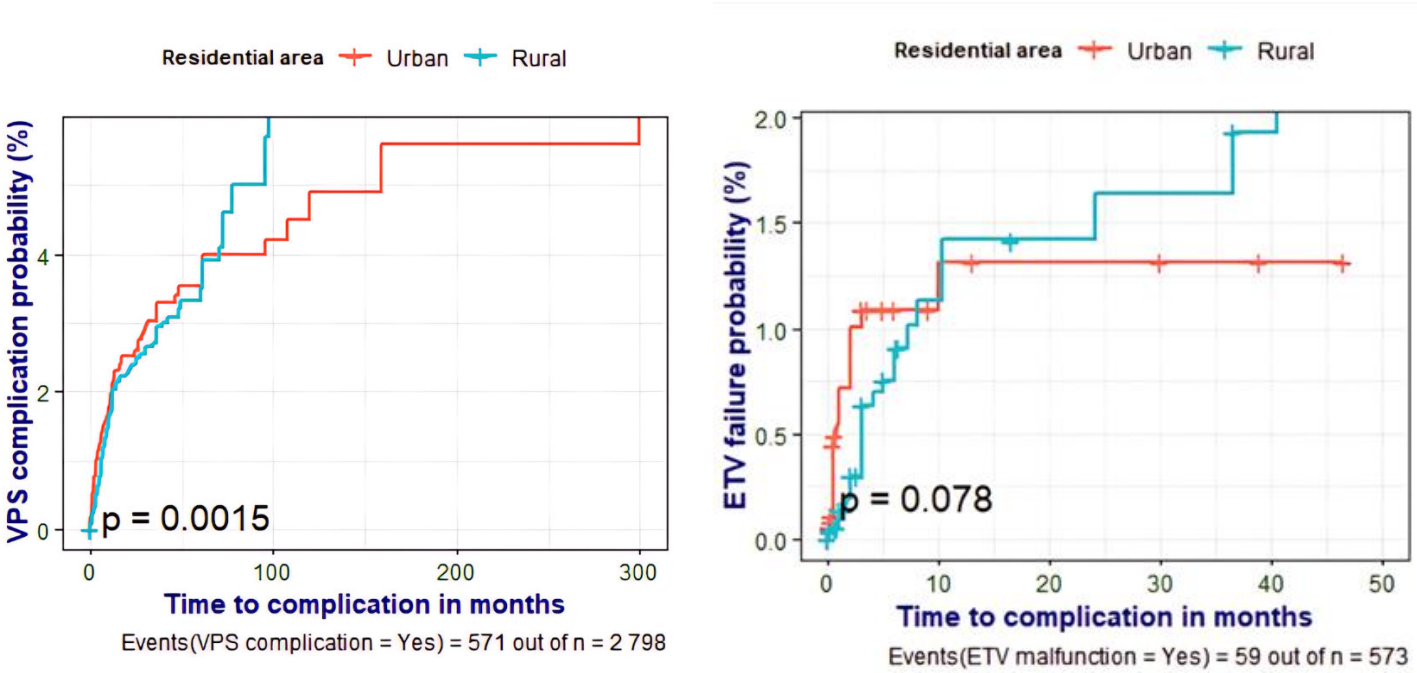

Figure 10: Kaplan-Meier Graph Depicting the Time to Ventriculoperitoneal Shunt Complications and Endoscopic Third Ventriculostomy Failure According to Urban and Rural Residential Areas. VPS, Ventriculoperitoneal shunt; ETV, Endoscopic third ventriculostomy.

A total of 264 (7.9%) children died during the 20 years and the comparison of mortality rate per period is shown in Figure 11, showing a significant decline over the years (p <0.001). Table 13 presents univariate analysis of factors associated with mortality. Post-infectious hydrocephalus accounted for 47.3% of mortalities; secondary to TBM (57.6%), pyogenic meningitis (37.6%), CM (4%), and neurocysticercosis (0.8%), (p =0.072).

Multiple regression analysis of factors associated with mortality is presented in Figure 12. Age ≥1 year (HR, 2.43 CI: 1.87-3.17, p<0.001), tertiary hospital referral (HR 1.48, CI: 1.06-2.04, p=0.019), VPS infection (HR, 3.63 CI: 2.66-4.95, p<0.001), VPS mechanical failure (HR 2.47, 1.77-3.46, p<0.001), acute abdomen (HR 2.17, CI: 1.11-4.25, p=0.024) and pneumonia (HR 7.32, OR 4.84 -11.06, p<0.001) were associated with increased mortality. Mortality was less likely in children diagnosed with idiopathic hydrocephalus (HR, 0.40 (0.21-0.74, p=0.003).

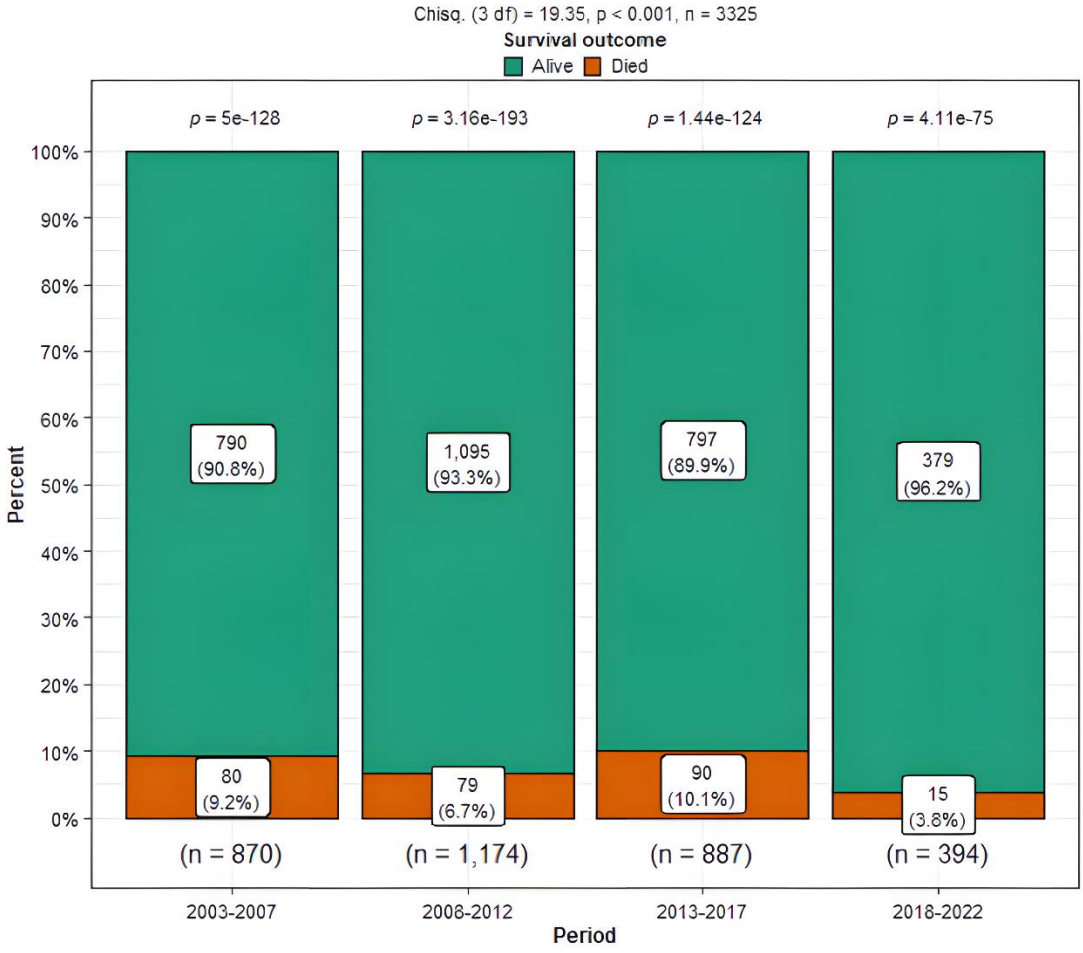

Figure 11: Mortality Rate Per Five-Year Period.

Table 13: Univariate Analysis of Factors Associated with Mortality

Survival outcome	Alive (N=3061)	Died (N=264)	p-value	Overall (N=3325)
Age group			<0.001	
<1yr	1889 (61.7%)	112 (42.4%)		2001 (60.2%)
1+yr	1172 (38.3%)	152 (57.6%)		1324 (39.8%)
Sex			0.293	
Male	1718 (56.1%)	157 (59.5%)		1875 (56.4%)
Female	1343 (43.9%)	107 (40.5%)		1450 (43.6%)
Residential area			0.016	
Urban	1469 (48.0%)	147 (55.7%)		1616 (48.6%)
Rural	1592 (52.0%)	117 (44.3%)		1709 (51.4%)
Hospital levels			0.001	
District	755 (24.7%)	60 (22.7%)		815 (24.5%)
Regional	1493 (48.8%)	101 (38.3%)		1594 (47.9%)
Tertiary	813 (26.6%)	103 (39.0%)		916 (27.5%)
Aetiology category			<0.001	
Non-PIH	1708 (55.8%)	128 (48.5%)		1836 (55.2%)
PIH	963 (31.5%)	125 (47.3%)		1088 (32.7%)
Idiopathic	390 (12.7%)	11 (4.2%)		401 (12.1%)
Timing of procedure			0.007	
Work-hours	2146 (70.1%)	164 (62.1%)		2310 (69.5%)
After-hours	915 (29.9%)	100 (37.9%)		1015 (30.5%)
Day of procedure			0.837	
Weekday	2477 (80.9%)	215 (81.4%)		2692 (81.0%)
Weekend	584 (19.1%)	49 (18.6%)		633 (19.0%)
VPS complication			<0.001	
No	2582 (84.4%)	146 (55.3%)		2728 (82.0%)
Yes	479 (15.6%)	118 (44.7%)		597 (18.0%)
ETV failure			0.687	
No	3004 (98.1%)	260 (98.5%)		3264 (98.2%)
Yes	57 (1.9%)	4 (1.5%)		61 (1.8%)
Abdominal pseudocyst			0.001	
No	3050 (99.6%)	259 (98.1%)		3309 (99.5%)
Yes	11 (0.4%)	5 (1.9%)		16 (0.5%)
Acute abdomen			<0.001	
No	3049 (99.6%)	253 (95.8%)		3302 (99.3%)
Yes	12 (0.4%)	11 (4.2%)		23 (0.7%)
Pneumonia			<0.001	
No	3049 (99.6%)	231 (87.5%)		3280 (98.6%)
Yes	12 (0.4%)	33 (12.5%)		45 (1.4%)

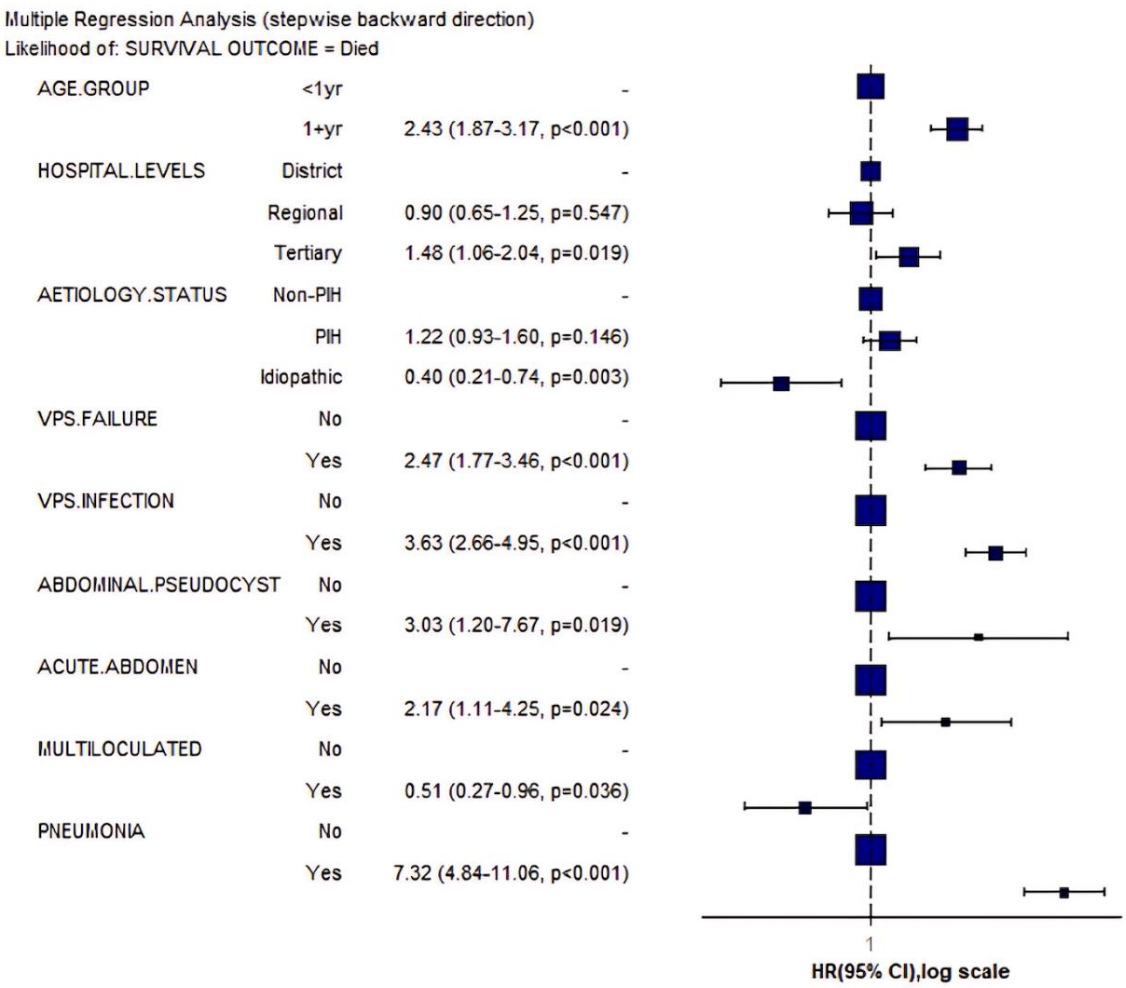

Figure 12: Forest Plot Depicting Multiple Regression Analysis of Factors Associated with Mortality. PIH, Post-infectious hydrocephalus; VPS, Ventriculoperitoneal shunt.

Kaplan-Meier graph in Figure 13 presents the time from the first operation to mortality according to age and aetiology category. The analyses reveal early time to death in children, ≥ 1 year of age (p<0.001), including those diagnosed with PIH (p <0.0001).

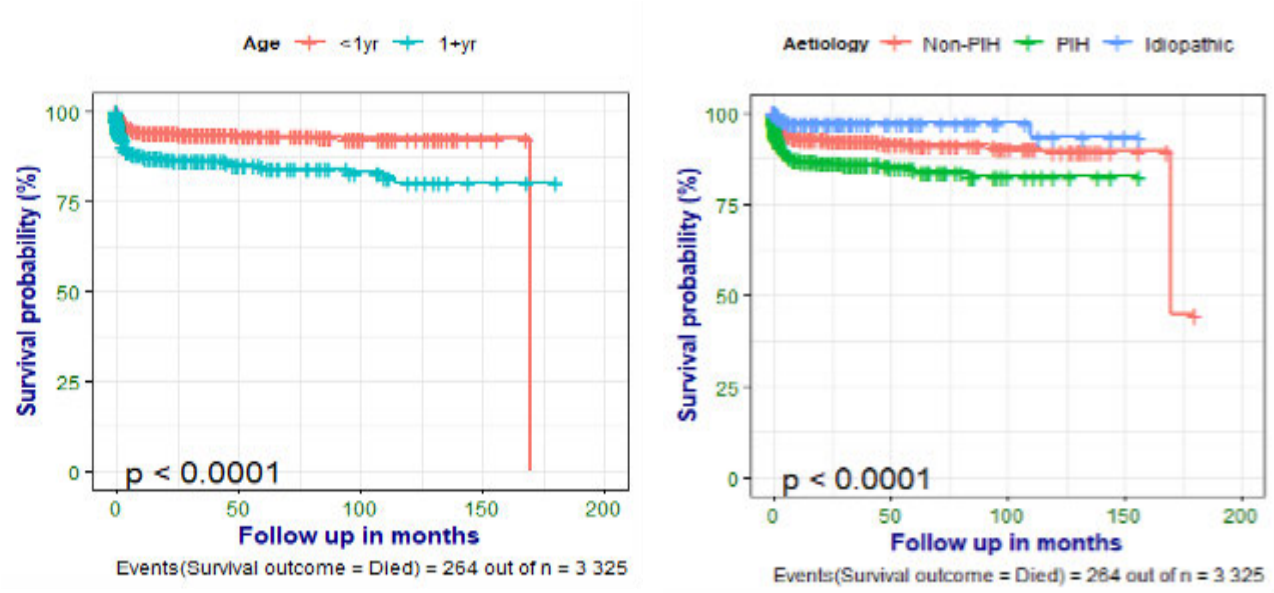

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Figure 13: Kaplan-Meier Graphs Depicting the Time from the First Operation to Death According to Age Group (A) and Aetiology Category (B). PIH, Post-infectious hydrocephalus.

Discussion

Our study revealed that a significant number of children hailed from rural areas, aligning with reports indicating that 54% of KZN's populace reside in rural regions [9]. SA's healthcare system is organized into 5 levels, which include from lowest to highest: clinics, district, regional, tertiary, and central hospitals [10]. A significant number of children were referred from regional hospitals, which provide second-level healthcare which includes medical specialists and radiology services such as CT scans. Given that hydrocephalus necessitates thorough evaluation before referral, these findings underscore the importance of adequate infrastructure and expertise at various levels of healthcare provision.

Our study revealed a significant decrease in the number of paediatric hydrocephalus cases in the last period. We attribute this to the establishment of a satellite neurosurgery unit in PMB. In addition, the COVID-19 pandemic contributed to the overall decrease in 2020, as reported by other studies [11,12].

There exists variability of the age at surgical intervention among different aetiologies with children diagnosed with neural tube defects undergoing treatment at significantly younger ages, compared to other groups. In a study from the Philippines, children diagnosed with infantile or post-haemorrhagic hydrocephalus were more likely to undergo treatment earlier than those with congenital hydrocephalus, while those with MMC and PIH were less likely to receive early surgery [13]. Most children in our study were infants and males, consistent with trends reported in other paediatric hydrocephalus series [13-19]. The racial distribution of children mirrors the overall demographics of SA [5].

Infections emerged as a significant contributing aetiology (32.7%). Systematic reviews reported aetiology in Africa to be PIH (28%), non-PIH (21%), and unclear (20%) [20]. However, studies from Kenya and Lesotho reported spina bifida (43.4%) and congenital (49.3%) as predominant aetiologies respectively [14,21]. A study that included children from Zimbabwe, Namibia, and the Democratic Republic of Congo reported aqueduct stenosis (84.9%) as a frequent aetiology [15].

The aetiology of hydrocephalus in Asia is also diverse with systematic reviews reporting non-PIH (29%), PIH (10.7%), and spinal dysraphism (7.6%) [22]. PIH was predominant in South-East Asia (35%) and non-PIH (38.3%) in East Asia [22,23], while in European series, the commonest aetiology was IVH [19, 24].

Notably, TBM emerged as the predominant aetiology (54.1%) of PIH, reflecting the high prevalence of TBM in SA [25], however, pyogenic meningitis was predominant during the last two periods. The decline of TBM-related hydrocephalus could be explained by efforts to improve the prevention and treatment of childhood communicable diseases in SA [26]

Children younger than 15 years of age constitute approximately 11% of the global burden of TB, with the largest burden in South East Asia (35.8%), Africa (29%), and the Western Pacific Region (20.5%) [27]. Wolzak et al in a local study of 557 cases of paediatric meningitis reported the commonest causative organisms to be TBM (22%), *Streptococcus pneumoniae* (4%), *Klesbsiella pneumonia* (3%) and *Haemophilus influenza* (< 1%) [28]. Since 1973 in SA, the Bacille Calmette-Guerin (BCG) vaccine has been administered in newborn children in efforts to protect against severe forms of TB such as TBM [29].

Only 2.5% of children were diagnosed with HIV co-infection and this is attributed to the prevention of mother-to-child transmission (PMTCT) program, implemented in 2006 [30]. Notably, all children diagnosed with cryptococcal meningitis (CM) related hydrocephalus were HIV infected. The decline of CM-related hydrocephalus in the last period is attributed to the success of the PMTCT and ART programs.

BTs constituted the third largest aetiology, predominantly located in the infra-tentorial compartment. Supra-tentorial compartment was the commonest location in a Ugandan study (62%) and mainly pilocytic astrocytoma (23.2%) [31]. Optimal treatment choice for pre-resection hydrocephalus remains debated, ranging from medical therapy (steroids) to external ventricular drain (EVD), VPS, and ETV. Treatment strategy depends on the condition of the child, including the resources of the institution. Concerns regarding pre-resection VPS include upward herniation and seeding of malignant cells to the abdomen.

In our unit, we prefer to divert CSF either with EVD, VPS, or ETV before resection of the tumour, depending on the clinical condition and radiological findings, due to concerns regarding hydrocephalus-related complications while awaiting definite surgery.

VPS remains crucial in hydrocephalus management, albeit associated with complications. We previously reported VPS complication rates of 27% and 35% in HIV-infected children diagnosed with TBM and CM-related hydrocephalus respectively [32, 33]. Weekend procedures were significantly associated with VPS complications, likely due to surgical procedures being performed by junior surgeons on weekends. Despite advancements in shunt technology infection rates remain variable (1% to 30%) with reports of lower infection rates in HIC when compared to LMICs [34-37]. For this reason, it has been the preference of our unit to use AIS, whenever possible, including other described protocols aimed at reducing VPS infection [34,35]. This has contributed to the significant decline in VPS complications over the study periods. However, in resource-limited settings, the costs of AISs, restrict their routine use. In our study AISs were utilized in 47.6% of cases, primarily for children at high risk for infection, particularly those with PIH.

Previously the neurosurgery unit in KZN reported on the use of AIS and reported an overall infection rate of 12%, with fewer infections (6%) in the AIS compared to non-AIS (16.7%) [38]. In a Ugandan study, 248 children were randomized into AIS (124) and non-AIS (124), The use of AIS did not result in a lower incidence of shunt infection or other complications with 4% infection in AIS versus 4.8% in non-AIS, including similar re-operations and 5.6 % deaths in AIS versus 7.3% in non-AIS [39]. However, Malluci et al, in a single-blind, randomized controlled trial, have provided evidence for support of AIS in reducing shunt-related infection [40].

Multiloculated hydrocephalus was associated with VPS complications on univariate analysis, however, on multiple regression analysis, this was not significant. Chronic inflammation of the ependyma and intraventricular debris often results in a high incidence of shunt failure. We aim for a single VPS after using the endoscope to connect loculations. Most of these children have poor neurological outcomes.

Staphylococcus aureus was identified as the commonest pathogen responsible for VPS infection. Coagulase-negative staphylococci (39%) and Staphylococcus *aureus* (30%) have been identified as the commonest organisms in most series [37]. Gathura et al reported gram negatives to be the commonest organisms [14].

Only a small proportion of children in our series were diagnosed with abdominal pseudocyst (0.6%) and acute abdomen (0.8%) following the VPS procedure. The incidence of abdominal complications is variable with abdominal pseudocysts occurring in less than 1% of cases [41]. Acute abdomen is rare but was associated with mortality in our study [42]. Surgical management of abdominal complications is tailored according to clinical conditions and intra-abdominal findings. Possible causes of bowel perforation include iatrogenic injury, erosion by VPS catheter, and shunt infections. The overall mortality rate of bowel perforation is nearly 15% [42]. The shunt should be removed and EVD inserted in the acute stages. Permanent CSF diversion options in our unit include ETV or ventriculoatrial shunts.

ETV was used less than VPS, which is not surprising due to the predominant PIH and infants in our study. On univariate analysis, ETV failure was noted in higher frequency in children < 1 year of age. In Uganda ETV and choroid plexus cauterization have been reported to be as effective as standard VPS, with the advantage of being cost-effective, with less post-operative care and infection [43,44,45]. In a systemic review of children with posterior fossa tumours and hydrocephalus, Dewan et al found no significant survival difference between ETV and VPS, however, post-operative complications were higher (31%) in VPS compared to ETV (17%) [46].

Mortality rates range from 5.5% to 32.1% within the first year [47, 48,49]. The mortality rate in our study was 7.9%. It is often difficult to determine the exact role hydrocephalus plays in mortality, especially in children with malignant CNS tumours. Brainstem gliomas, which are associated with poor outcomes were the predominant tumour associated with hydrocephalus in our series.

Factors associated with mortality in our study were age ≥ 1 year, children referred from tertiary hospitals, VPS complications, and acute abdomen. The reason referrals from tertiary hospitals were associated with increased mortality is that they tend to admit sicker children when compared to lower-level care hospitals.

Over the years the mortality rate has declined due to a decrease in PIH, particularly, TBM hydrocephalus which is associated with infarcts, altered levels of consciousness, and electrolyte imbalances, all contributors to mortality [32]. Additionally, there has also been an increase in paediatric critical care units in KZN, contributing to improved outcomes. Ferraris et al in their series reported EVD insertion to be associated with death, as these children tended to be in critical condition [13].

The study limitations include the retrospective aspect of the study which might result in inherent biases. The findings of the study may not be generalizable to other regions, especially those with different healthcare systems.

Conclusion

This study provides comprehensive insights into pediatric hydrocephalus in KZN, highlighting epidemiology trends, treatment, and associated outcomes. It underscores the need for ongoing surveillance, an increase in neurosurgical services, and tailored management strategies aimed at improving outcomes. Monitoring temporal trends and predictors of outcomes will aid in guiding future initiatives aimed at mitigating the burden of pediatric hydrocephalus in the region.

Declaration of Conflict of Interest

None

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Chapter 4: A Comparative Analysis of the Impact of Proximity to Centralised Neurosurgery Services on Surgical Outcomes of Paediatric Hydrocephalus in KwaZulu-Natal

The previous chapter established the epidemiological landscape, highlighting demographic trends, referral patterns, and treatment outcomes over two decades. This set the foundation for Chapter 4, which narrows the focus to assess how the proximity to centralised neurosurgery services influences surgical outcomes. By linking regional data with proximity analysis, these chapters together offer a holistic view of the challenges and outcomes in treating paediatric hydrocephalus in KZN, informing potential healthcare interventions and policy improvements.

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Colleen Aldous: Analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

A Comparative Analysis of the Impact of Proximity to Centralised Neurosurgery Services on Surgical Outcomes of Paediatric Hydrocephalus in KwaZulu-Natal

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Abstract

Background

Centralised neurosurgery services in KwaZulu-Natal (KZN) have resulted in long travel distances for the treatment of paediatric hydrocephalus. The impact on surgical outcomes is unknown. The purpose of this study was to assess the impact of proximity to centralised neurosurgery services on surgical outcomes of paediatric hydrocephalus in KZN.

Methods

We collected retrospective (2013 to 2017) and prospective (2018 to 2022) data from a single institution. We included children (≤18 years) treated for hydrocephalus. Data collected included age at surgical treatment, sex, race, residential area (urban versus rural), aetiology of hydrocephalus, surgical treatment, timing of procedure, length of hospital stay (LOHS), treatment failure and mortality rate. Distances from the neurosurgery unit were classified into four categories: (i) < 50 km, (ii) 150 to 149 km, (iii) 150 to 249 km and (iv) ≥ 250 km.

Results

A total of 1281 children were included in the study. Most children (54.6%) were from rural areas. Majority of children (34.2%) lived < 50 km from the neurosurgery unit. Median age was 7 months for distances < 250 km and 6 months for ≥ 250 km (p=0.288). Post-infectious hydrocephalus was the predominant (29.8%) diagnosis (p=0.090). Ventriculoperitoneal (VPS) failure rates per distance were 4.5% (<50 km), 3.7% (50-149 km), 7.3% (150 -249 km) and 8.8% (≥ 250 km), (p=0.035). Endoscopic third ventriculostomy (ETV) failure rates per distance were 16.7% (< 50 km), 16.1 % (50-149 km), 10% (150-249 km) and 4.8% (≥ 250 km), (p=0.203). VPS complications and ETV failures presented in a delayed fashion in travel distances > 49 km (p <0.0001). Median LOHS was 8 days for <250 km and 7 days for ≥ 250 km (p=0.636). Median follow-up was 12 months across all distances (p=0.796).

Conclusions

The study provides insight into the impact of proximity to centralised neurosurgery services on paediatric hydrocephalus outcomes in KZN. VPS failures were higher in children living farther from the neurosurgery unit. Travel distances significantly impacted on time to presentation to the neurosurgery unit for treatment of surgical complications. The study findings support the need for decentralised neurosurgery services in KZN.

Keywords: Low- and Middle-Income Country; Paediatric Hydrocephalus, Pyogenic Meningitis, Tuberculous Meningitis, Ventriculoperitoneal Shunt

Introduction

The global burden of childhood hydrocephalus is widely acknowledged [1 - 5], with increasing recognition of existing inequalities in access to neurosurgery services globally, particularly in Sub-Saharan Africa (SSA), due to the limited availability of neurosurgeons relative to population size [6-8]. This has prompted various initiatives aimed at enhancing access to these services, particularly in low-middle-income countries (LMIC) [9-12].

Barriers to access include inadequate resources, levels of urbanization, and distance to centralised specialized services. Reports suggest that the burden on the surgical services in LIMCs will increase in the future and untreated surgical conditions will impact human and economic resources negatively [6]. In high-income countries (HICs) the incidence of congenital hydrocephalus is reported at 79 per 100 0000 births, contrasting with 123 per 100 000 births in LMICs and 145 per 100 000 births in Africa [2].

South Africa (SA) has made substantial efforts to improve healthcare access, particularly for women and children, aligning with the millennium developmental goals aimed at reducing childhood mortality [13 –15]. Childhood mortality serves as a crucial metric for assessing the national health status of any country. SA's current infant mortality rate stands at 23 per 1000 live births, a notable improvement from 27 per 1000 live births recorded in 2021 [15,16].

KwaZulu-Natal (KZN), the country's second populous province, encompasses 94,361 km^2, constituting 7.8% of SA's landmass (Figure 1), with a population of 12 million, representing 19% of the nation's total population [15]. Bordering Mozambique, Eswatini, and Lesotho, KZN contributes 16% to SA's gross domestic product (GDP) [17].

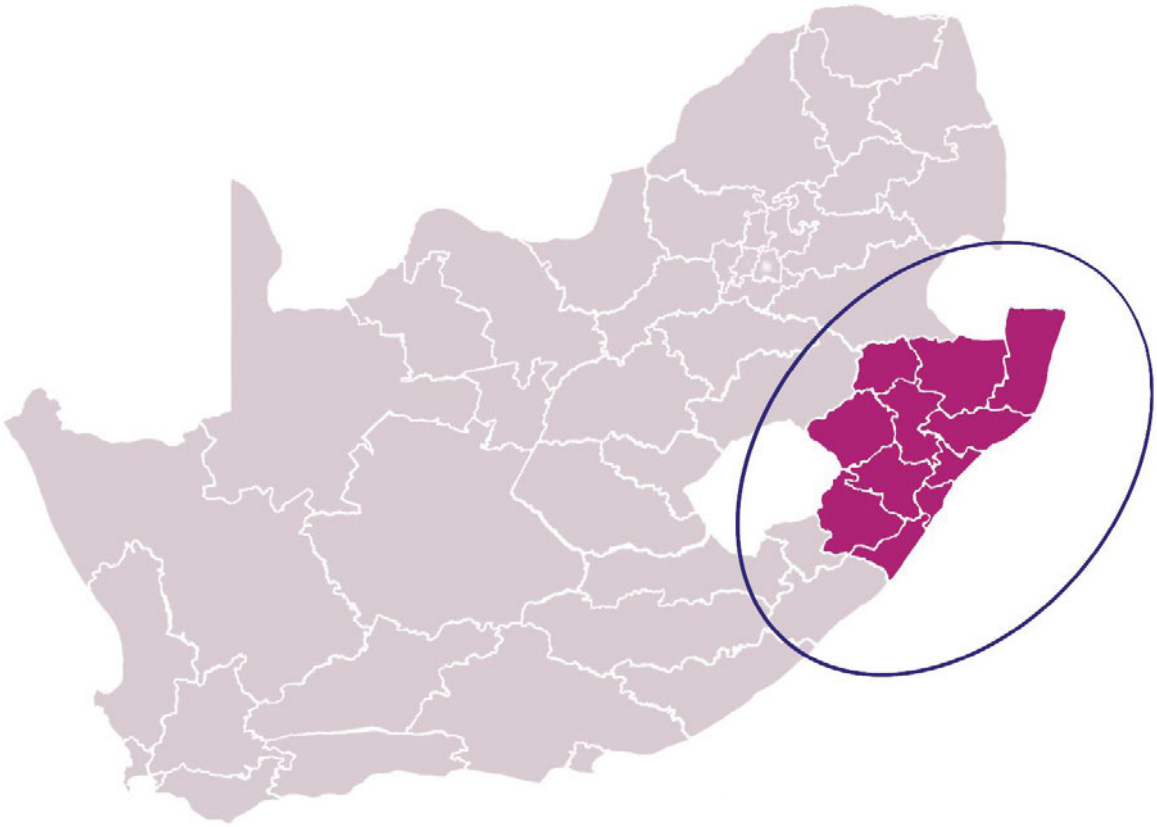


Figure 1: Map Showing the Location of the Province of KwaZulu-Natal Within South Africa

Despite this, the majority (54%) of KZN's population resides in rural areas, with only approximately 10 % covered by private medical insurance [17]. SA's National Health Insurance Bill aims to address healthcare access disparities by providing quality, affordable healthcare services to all South Africans irrespective of socio-economic status [18]

Reports from paediatric surgery cases series suggest poor post-surgical outcomes in children residing in rural areas who must travel greater distances to care [19,20]. Given the Inkosi Albert Luthuli Central Hospital (IALCH) neurosurgery service's large catchment, there is a lack of data on the impact of distance travelled to access these services in KZN on surgical outcomes.

The purpose of this study was to assess the impact of proximity to centralised neurosurgery services on surgical complications and mortality in children treated for hydrocephalus. This information is crucial for resource allocation, service expansion, and policy formulation aimed at prioritizing the management of paediatric hydrocephalus in KZN.

Methods

Study Design and Setting

We collected retrospective and prospective data at a single institution, IALCH, situated in the metropolitan municipality of eThekwini in KZN. The retrospective period was from the 1st of January 2013 to the 31st of December 2017 and the prospective period was from the 1st of January 2018 to the 31st of December 2022. The study included all newly diagnosed children with hydrocephalus aged from birth to 18 years, excluding those who had received treatment elsewhere. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Referral system

KZN comprises 11 distinct districts including eThekwini, which is the economic hub of the province [21]. The rest are UMgungundlovu, UGu, Amajuba, uMkhanyakude, King Cetshwayo, iLembe, Harry Gwala, UThukela, Zululand and UMzinyathi which are further categorized into three healthcare areas, classified as Area 1 to 3 [17].

As a central hospital, IALCH provides the fifth or highest level of specialized care and receives referrals for neurosurgery services from three provincial tertiary hospitals, 12 regional hospitals, and 39 district hospitals (Figure 2).

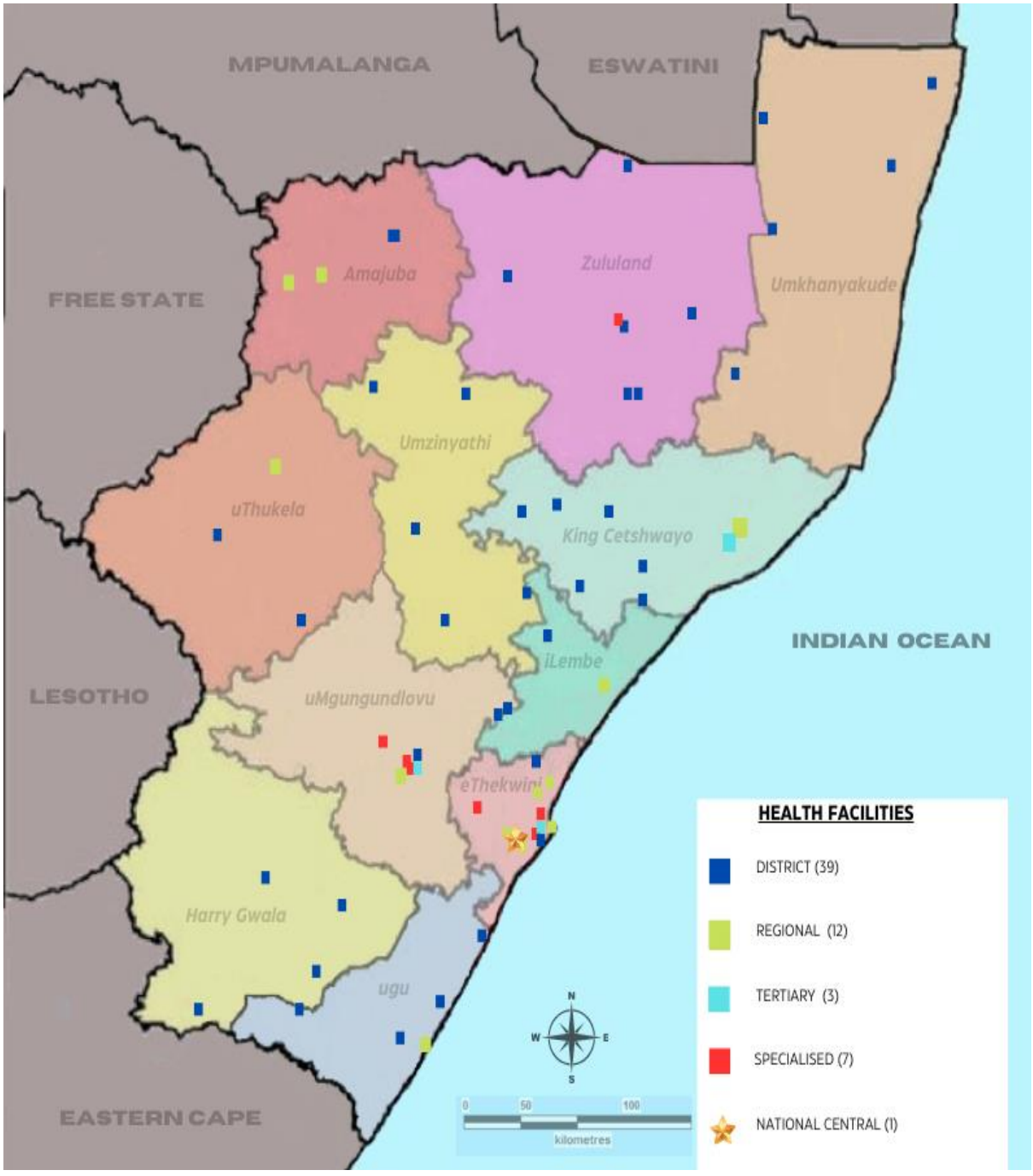


Figure 2: Map Showing 11 Healthcare Districts and Hospitals Within these Districts in KwaZulu-Natal

Referrals were conducted telephonically after consultation with the neurosurgeon on duty, facilitated by a teleradiology system enabling remote viewing of neuroradiology investigations performed at referring healthcare facilities [22].

Data Collection

Data collected was entered into a structured pro forma sheet and radiology data were collected from a picture archiving and communication system (PACS). Variables collected included age at surgical treatment, sex, race, residential area (urban versus rural), referral pattern (health district and level of care of referring facility), aetiology of hydrocephalus, surgical treatment, the timing of procedure; in terms of weekdays versus weekends and work hours versus after-hours, length of hospital stay (LOHS), treatment failure, mortality and follow-up period. The aetiology of hydrocephalus was categorized: (a) post-infectious hydrocephalus (PIH), (b) idiopathic when the cause was not known and (c) non-PIH when the aetiology was neither due to infection nor idiopathic. Weekday was defined as Monday to Friday and weekend as Saturday and Sunday. Work hours were defined as from eight o'clock in the morning (08h00 am) to four o'clock in the afternoon (16h00 pm), while after hours were defined as between 16h00 pm and 08h00 am, the following day.

Distance Measurement

The Global Positioning Systems (GPS) coordinates and physical addresses of all the hospitals in KZN were retrieved from the Department of Health. These were entered into Google Maps™ and used to determine the distance from the referring healthcare facility to IALCH**.** The distance was measured in kilometres (km). Distances were classified according to four categories; (i) < 50 km, (ii) 50 to 149 km, (iii) 150 to 249 km and (iv) ≥ 250 km.

Primary Outcomes Measures

Using these four distance categories we compared the age at surgical intervention, aetiology of hydrocephalus, surgical management and complications, LOHS, follow-up period and mortality.

Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics of the children. Normality of numeric data was assessed; normally distributed variables were presented using the mean and standard deviation, while non-normally distributed variables were reported using the median and interquartile range (IQR). Chi-square and Fisher's tests were used to determine the association between categorical factors.

T-tests or Mann-Whitney tests were utilized to compare differences in numeric measurements between two groups. On the other hand, the Kruskal-Wallis test was applicable for the skewed distributions between at least three groups. Kaplan-Meier survival analysis was utilized to assess time to death and presentation of CSF diversion procedure complications to the neurosurgery unit. Other visual displays employed multiple bar charts. The significance level was set at 0.05.

Results

A total of 1281 children diagnosed with hydrocephalus received treatment during the study period. The majority (49.6%) of children resided in the Area 1 Health District (Table 1).

Table 1: Proportion of Children According to Healthcare District in KwaZulu-Natal

Health District	Overall (N=1281)
Area 1 (n=635; 49.6%)	
eThekwini	430 (33.6%)
Ugu	113 (8.8%)
iLembe	92 (7.2%)
Area 2 (n=351; 27.4%)	
uMgungundlovu	193 (15.1%)
uThukela	78 (6.1%)
Amajuba	60 (4.7%)
Harry Gwala	19 (1.5%)
uMzinyathi	1 (0.1%)
Area 3 (n=295; 23%)	
King Cetshwayo	184 (14.0%)
Zululand	66 (5.2%)
uMkhanyakude	45 (3.5%)

The hospital referral pattern is presented in Figure 3. Most children (54.6%) were from rural areas (Figure 4).

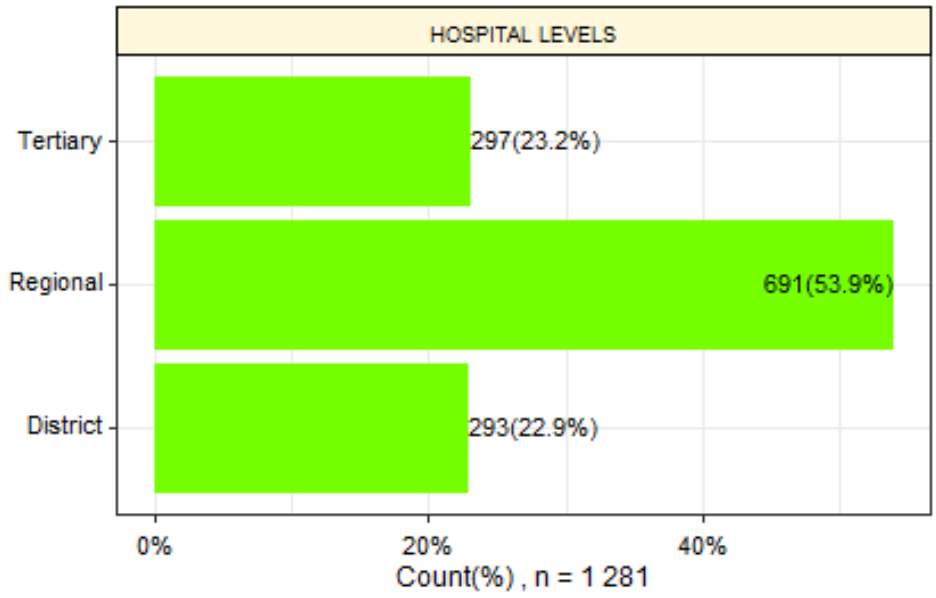


Figure 3: Bar Graph Showing the Level of Care of Hospitals Referring Children Diagnosed with Hydrocephalus

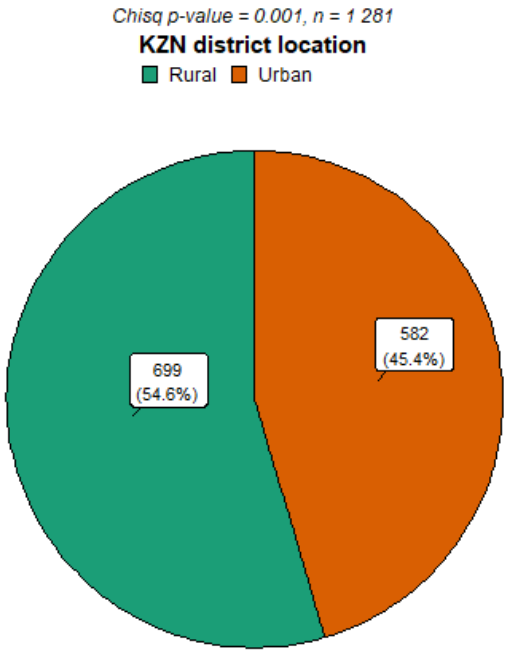


Figure 4: Pie Chart of Residential Location (Urban versus Rural) of the Children Diagnosed with Hydrocephalus.

The distribution of the distances travelled to the neurosurgery unit was: < 50 km (n=440; 34.3%), 50 -149 km (n=408; 31.9%), 150 - 249 km (n=262; 20.5%) and ≥ 250 km (n=171; 13.3%). The comparison of the median age according to distance travelled to the neurosurgery unit is presented in Figure 5. The median age and IQR (months) per distance were as follows: (i) < 50 km =7 (IQR 2 – 30), (ii) 50 – 149 km = (IQR 3 7– 41), (iii) 150 – 249 km = 7 (IQR 3 – 35) and (iv) ≥ 250 km = 6 (IQR 3 – 14).

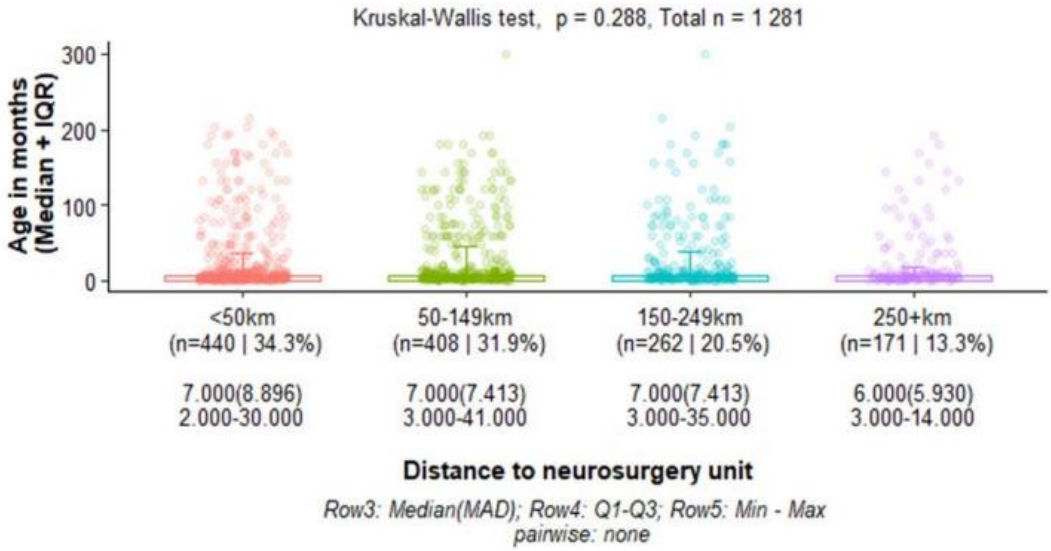


Figure 5: The Median Age (Months) According to the Distance to the Neurosurgery Unit

The demographic profile and aetiology per distance are outlined in Table 2.

Table 2: Comparison of the Demographic Profile and Aetiology According to Distance to Neurosurgery Unit

Distance to neurosurgery unit	<50km (N=440)	50-149km (N=408)	150-249km (N=262)	250+km (N=171)	p-value	Overall (N=1281)
Age					0.691	
<1yr	280 (63.6%)	256 (62.7%)	163 (62.2%)	120 (70.2%)		819 (63.9%)
1-<6yrs	91 (20.7%)	81 (19.9%)	53 (20.2%)	32 (18.7%)		257 (20.1%)
6-<12yrs	43 (9.8%)	51 (12.5%)	31 (11.8%)	13 (7.6%)		138 (10.8%)
12+yrs	26 (5.9%)	20 (4.9%)	15 (5.7%)	6 (3.5%)		67 (5.2%)
Ethnicity					<0.001	
Black	413 (93.9%)	396 (97.1%)	261 (99.6%)	167 (97.7%)		1237 (96.6%)
Other	27 (6.1%)	12 (2.9%)	1 (0.4%)	4 (2.3%)		44 (3.4%)
Sex					0.280	
Boys	254 (57.7%)	211 (51.7%)	149 (56.9%)	99 (57.9%)		713 (55.7%)
Girls	186 (42.3%)	197 (48.3%)	113 (43.1%)	72 (42.1%)		568 (44.3%)
Aetiology					0.090	
PIH	140 (31.8%)	126 (30.9%)	74 (28.2%)	42 (24.6%)		382 (29.8%)
BTs	58 (13.2%)	62 (15.2%)	35 (13.4%)	25 (14.6%)		180 (14.1%)
Congenital	46 (10.5%)	54 (13.2%)	26 (9.9%)	27 (15.8%)		153 (11.9%)
Idiopathic	30 (6.8%)	39 (9.6%)	30 (11.5%)	16 (9.4%)		115 (9.0%)
MMC	37 (8.4%)	37 (9.1%)	22 (8.4%)	18 (10.5%)		114 (8.9%)
AS	35 (8.0%)	33 (8.1%)	18 (6.9%)	18 (10.5%)		104 (8.1%)
DWM	28 (6.4%)	30 (7.4%)	29 (11.1%)	13 (7.6%)		100 (7.8%)
IVH of prematurity	47 (10.7%)	19 (4.7%)	19 (7.3%)	7 (4.1%)		92 (7.2%)
Arachnoid cyst	6 (1.4%)	4 (1.0%)	1 (0.4%)	2 (1.2%)		13 (1.0%)
Encephalocoele	3 (0.7%)	0 (0.0%)	3 (1.1%)	1 (0.6%)		7 (0.5%)
TBI	7 (1.6%)	2 (0.5%)	5 (1.9%)	2 (1.2%)		16 (1.2%)
Spontaneous SAH/IVH	3 (0.7%)	2 (0.5%)	0 (0.0%)	0 (0.0%)		5 (0.4%)

***AS, aqueduct stenosis; BTs, brain tumours; DWM, Dandy walker malformation; IVH, intraventricular haemorrhage; MMC, myelomeningocoele; PIH, post infectious hydrocephalus; SAH, subarachnoid haemorrhage; TBI, traumatic brain injury**

PIH was the commonest overall aetiology (29.8%). Pyogenic meningitis was the most common (55.8 %) cause of PIH, across all distances (Table 3).

Table 3: Comparison of Infectious Aetiology According to Distance to the Neurosurgery Unit

Distance to neurosurgery unit	<50km (N=140)	50-149km (N=126)	150-249km (N=74)	250+km (N=42)	p-value	Overall (N=382)
Aetiology					0.276	
Pyogenic meningitis	71 (50.7%)	69 (54.8%)	42 (56.8%)	31 (73.8%)		213 (55.8%)
TB	65 (46.4%)	54 (42.9%)	30 (40.5%)	11 (26.2%)		160 (41.9%)
Cryptococcal	3 (2.1%)	2 (1.6%)	2 (2.7%)	0 (0.0%)		7 (1.8%)
Neurocysticercosis	1 (0.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)		2 (0.5%)

***TB, tuberculosis**

VPS placement was the most frequent CSF diversion procedure (79.2%), whilst the ETV procedure was performed in 21.5% of cases. Most surgical procedures were performed during work hours (68.2%) and weekdays (83.8%), irrespective of distance (Table 4). Comparison of the LOHS and follow-up period per distance is presented in Table 4.

Table: 4: Comparison of the Surgical Treatment, Length of Hospital Stay and Follow-up.

Distance to neurosurgery unit	<50km (N=440)	50-149km (N=408)	150-249km (N=262)	250+km (N=171)	p-value	Overall (N=1281)
VPS					0.760	
No	91 (20.7%)	85 (20.8%)	50 (19.1%)	40 (23.4%)		266 (20.8%)
Yes	349 (79.3%)	323 (79.2%)	212 (80.9%)	131 (76.6%)		1015 (79.2%)
ETV					0.595	
No	344 (78.2%)	321 (78.7%)	212 (80.9%)	129 (75.4%)		1006 (78.5%)
Yes	96 (21.8%)	87 (21.3%)	50 (19.1%)	42 (24.6%)		275 (21.5%)
Type of shunt					0.399	
Non-AIS	256 (58.2%)	258 (63.2%)	153 (58.4%)	99 (57.9%)		766 (59.8%)
AIS	184 (41.8%)	150 (36.8%)	109 (41.6%)	72 (42.1%)		515 (40.2%)
Time of operation 24h					0.684	
Work-hours	304 (69.1%)	273 (66.9%)	175 (66.8%)	122 (71.3%)		874 (68.2%)
After-hours	136 (30.9%)	135 (33.1%)	87 (33.2%)	49 (28.7%)		407 (31.8%)
Weekday of operation					0.304	
Weekday	374 (85.0%)	339 (83.1%)	212 (80.9%)	149 (87.1%)		1074 (83.8%)
Weekend	66 (15.0%)	69 (16.9%)	50 (19.1%)	22 (12.9%)		207 (16.2%)
LOHS						
Median(Q1-Q3)	8.00(5.00-17.0)	8.00(5.00-20.0)	8.00(5.00-21.0)	7.00(5.00-19.5)	0.636	8.00(5.00-19.0)
Follow-up in months						
Median(Q1-Q3)	12.0(4.00-34.0)	12.0(3.00-36.0)	12.0(4.00-29.0)	12.0(3.00-34.0)	0.796	12.0(4.00-34.0)

***AIS, antibiotic impregnated shunt; ETV, endoscopic third ventriculostomy; LOHS, length of hospital stay; VPS, ventriculoperitoneal shunt**

The overall VPS complication rate was 14.9%, with 5.4% due to mechanical failure and 9.5% due to infection (Table 5).

Table 5: Comparison of the Ventriculoperitoneal Shunt Complications per Distance to the Neurosurgery Unit

Distance to neurosurgery unit	<50km (N=440)	50-149km (N=408)	150-249km (N=262)	250+km (N=171)	p-value	Overall (N=1281)
VPS complication					0.618	
No	369 (83.9%)	354 (86.8%)	220 (84.0%)	147 (86.0%)		1090 (85.1%)
Yes	71 (16.1%)	54 (13.2%)	42 (16.0%)	24 (14.0%)		191 (14.9%)
VPS failure					0.035	
No	420 (95.5%)	393 (96.3%)	243 (92.7%)	156 (91.2%)		1212 (94.6%)
Yes	20 (4.5%)	15 (3.7%)	19 (7.3%)	15 (8.8%)		69 (5.4%)
VPS infection					0.056	
No	387 (88.0%)	369 (90.4%)	241 (92.0%)	162 (94.7%)		1159 (90.5%)
Yes	53 (12.0%)	39 (9.6%)	21 (8.0%)	9 (5.3%)		122 (9.5%)

***VPS, ventriculoperitoneal shunt**

Time to presentation of VPS complications to the neurosurgery unit according to distance is presented in the Kaplan Meier graphs in Figures 6 and 7. Children from areas located more than 49 km from the neurosurgery unit presented in delayed fashion for admission to the neurosurgery unit.

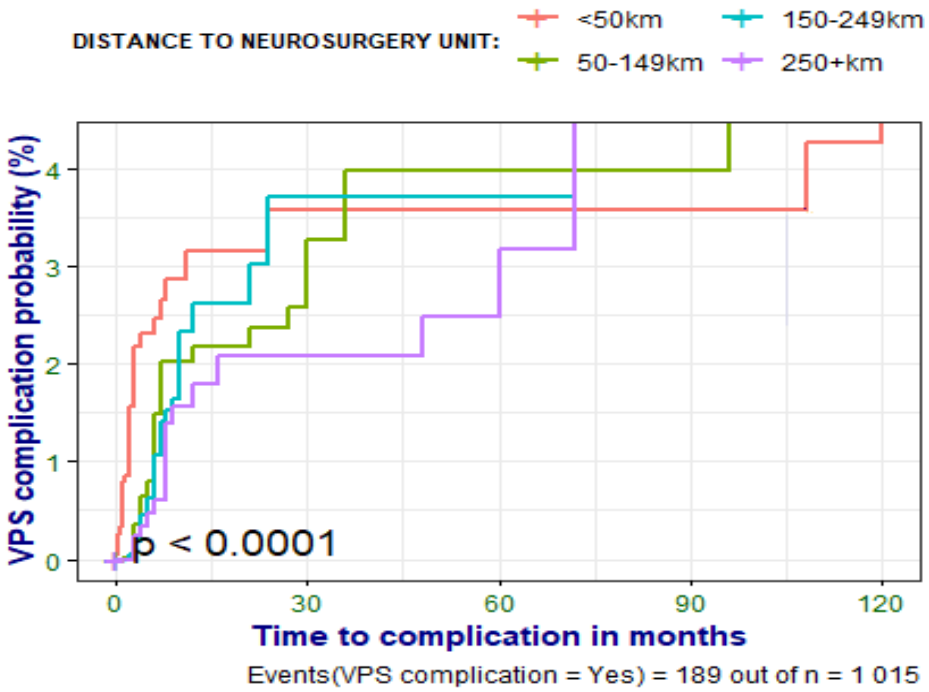
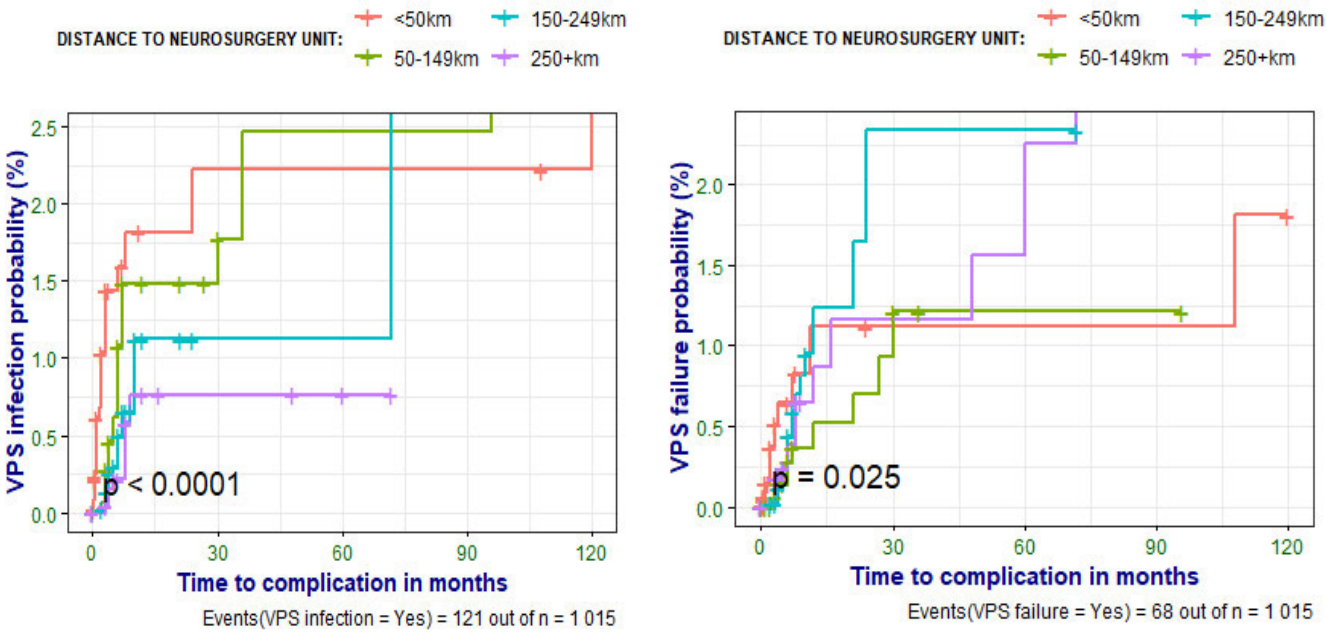


Figure 6: Kaplan Meier Graph Depicting Time to Presentation of Ventriculoperitoneal Shunt Complications to the Neurosurgery Unit.



A **B**

Figure 7: Kaplan Meier Graph Depicting Time to Presentation of Ventriculoperitoneal Shunt Infection (A) and Mechanical Failure (B) to the Neurosurgery Unit

The organisms cultured per distance are presented in Figure 8, with *Streptococcus epidermidis* and *Staphylococcus aureus,* equally being the most cultured organisms (42.3%).

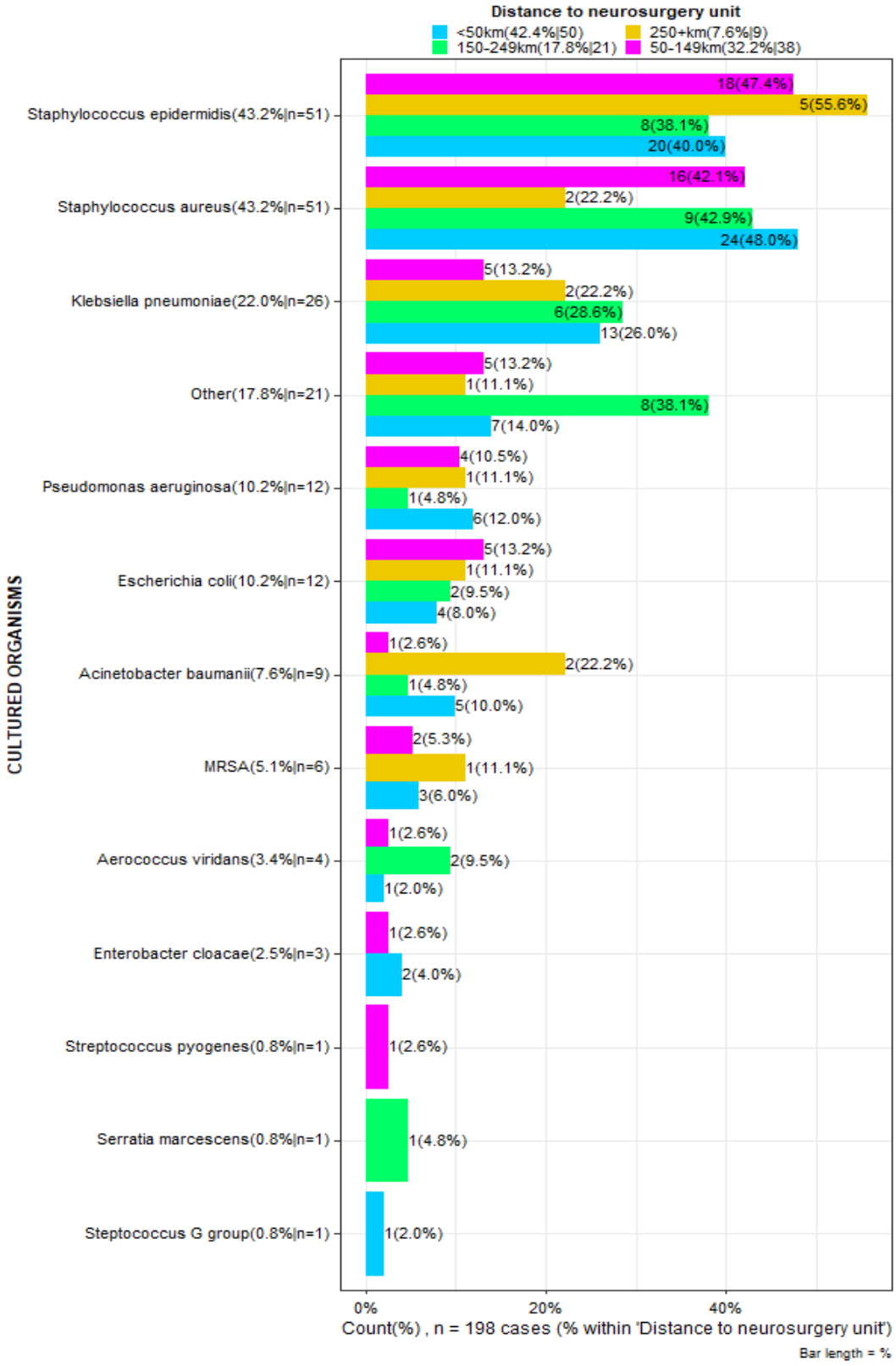


Figure 8: List of Organisms Cultured Following Ventriculoperitoneal Shunt Infections per Distance to the Neurosurgery Unit. The graph illustrates the distribution of organisms cultured, with percentages reflecting the frequency of each organism relative to the total number of cultures, rather than the total number of patients.

Table 6 outlines the ETV failure rates per distance. The time to presentation of ETV failure to the neurosurgery unit per distance is presented in Kaplan Meier graph in Figure 9. Children from areas located more than 49 km from neurosurgery unit, presented in a delayed fashion to the neurosurgery unit for admission.

Table 6: Comparison of the Endoscopic Third Ventriculostomy Failure Rates According to the Distance to Neurosurgery Unit

Distance to neurosurgery unit	<50km (N=96)	50-149km (N=87)	150-249km (N=50)	250+km (N=42)	p-value	Overall (N=275)
ETV failure					0.203	
No	80 (83.3%)	73 (83.9%)	45 (90.0%)	40 (95.2%)		238 (86.5%)
Yes	16 (16.7%)	14 (16.1%)	5 (10.0%)	2 (4.8%)		37 (13.5%)

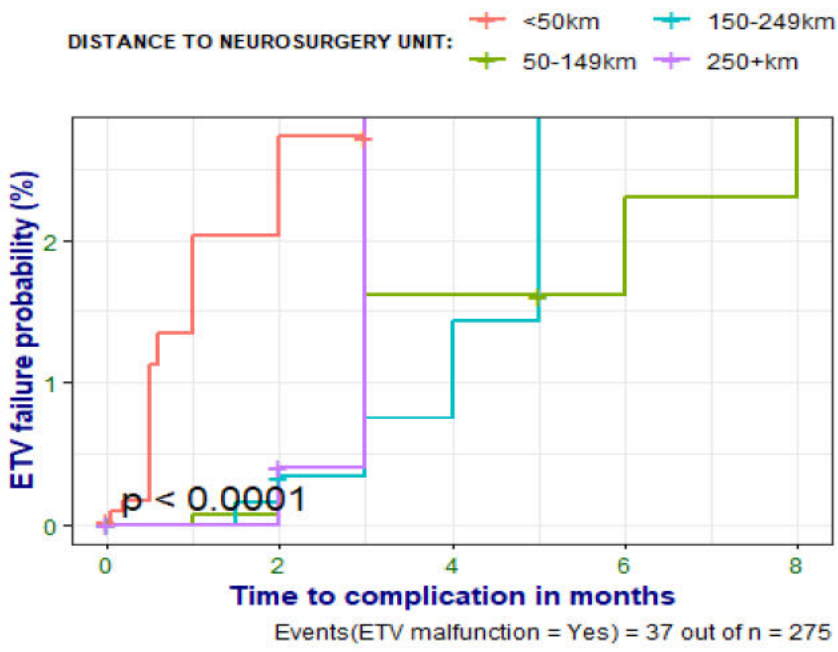


Figure 9: Kaplan Meier Graph Depicting Time to Presentation of Endoscopic Third Ventriculostomy Failure to the Neurosurgery Unit.

The mortality rate was 8 %, with a decreasing rate farther away from the neurosurgery unit (Figure 10). Time of death according to distance is presented in the Kaplan Meier graph in Figure 11, showing a trend towards early mortality in children from areas located less than 50 km from the neurosurgery unit, however, this was not statistically significant.

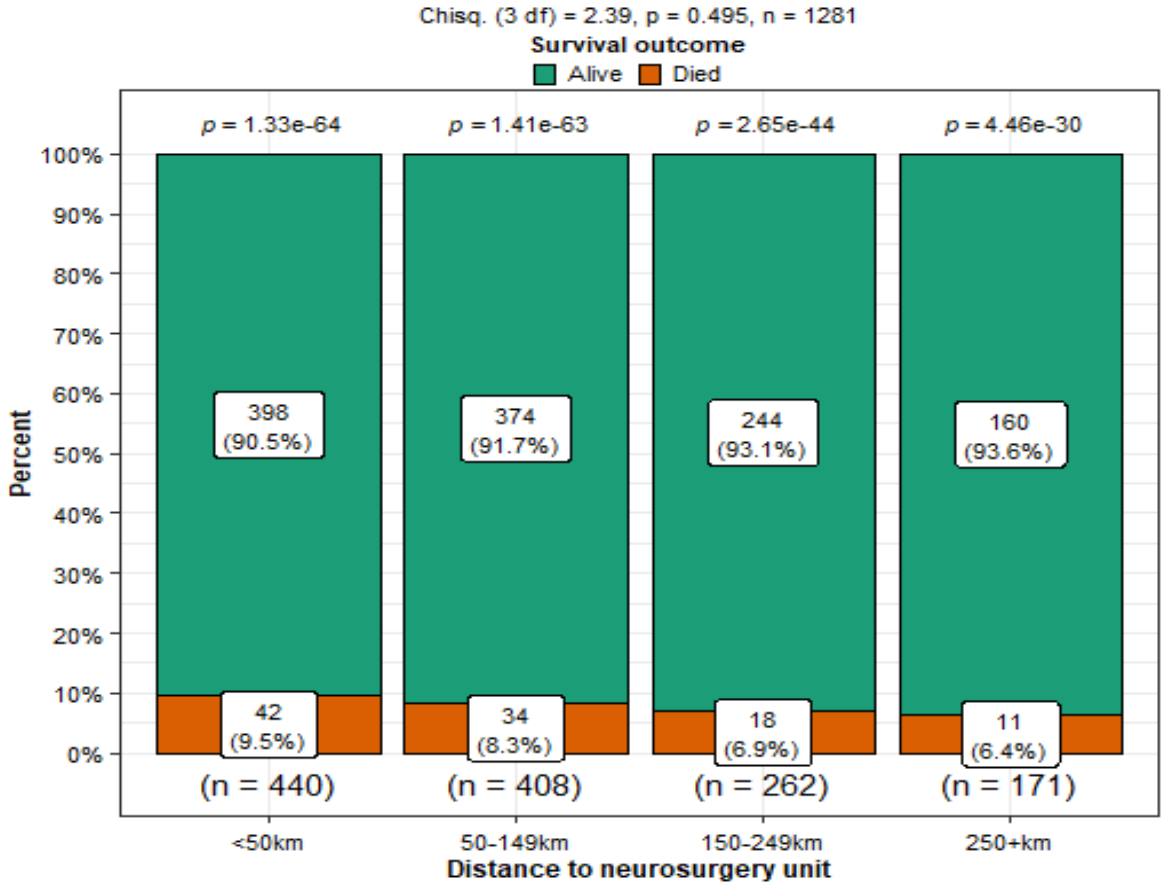


Figure 10: Mortality Rate Per Distance

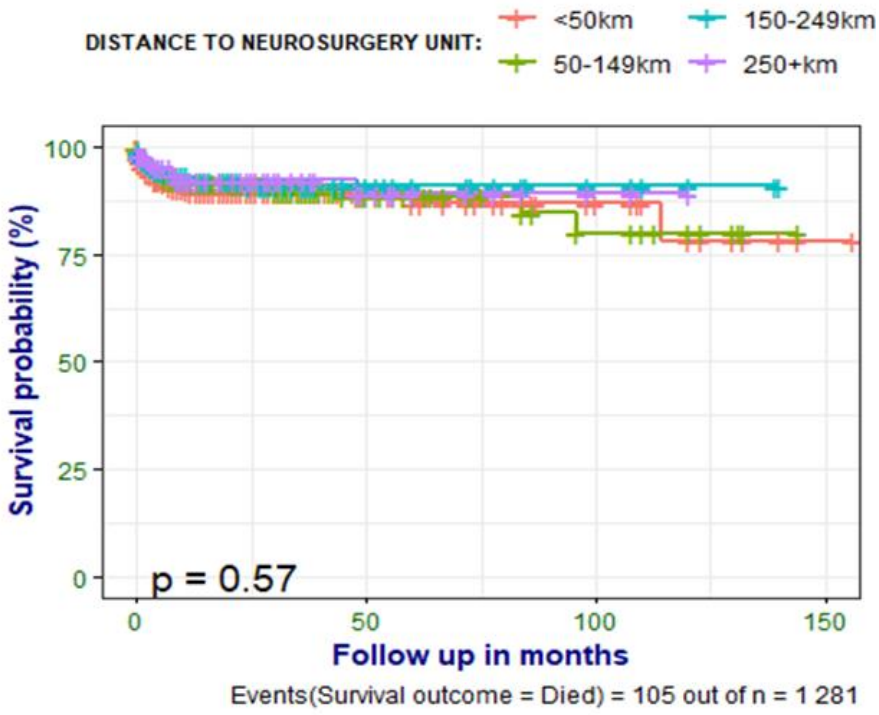


Figure 11: Kaplan Meier Graph Depicting Time to Mortality per Distance

Discussion

Neurosurgical services have been centralised in KZN since the inception of the neurosurgery unit in 1968 [23]. The advantages of centralized services are better efficiency and optimization of healthcare resources and infrastructure, in that expert clinicians are located under one roof. Centralized care pathways allow for multidisciplinary engagements, ensuring good surgical outcomes and facilitating high-impact research. However, this model may inadvertently create disparities in access, particularly for children residing in peripheral or underserved areas.

Most paediatric hydrocephalus cases (33.6%) treated were from eThekwini district, where centralized neurosurgery services are located, aligning with the district's significant population density (4.2 million), which makes up 34.7% KZN's population [24]. Nevertheless, rural areas still accounted for a substantial portion of cases.

Demographic profile reflected regional trends, with Black African children comprising the majority (96.6%) [24]. Studies from other regions, such as the United States examined the impact of racial and socioeconomic status on outcomes following paediatric CSF shunting procedures, finding that African American children had higher mortalities compared to other racial groups [25]. However, Walker et al in their study found no differences between racial groups when assessing shunt survival [26]

Infants predominated across all distances, a common trend in paediatric hydrocephalus series [27-33]. PIH remained the most frequent type across the distances, with pyogenic meningitis contributing 55.8% of PIH, highlighting the significant burden of preventable infectious diseases in LMIC. Notability there was a high proportion of TBM-related hydrocephalus cases (46.4%) in areas located less than 50 km from the neurosurgery unit, which is not surprising as eThekwini district has a high prevalence of TB in KZN [34,35].

VPS insertion remained the most common procedure for CSF diversion across distances. CSF diversion procedures are essential surgical skills, for neurosurgeons practicing in LMIC where the burden of paediatric hydrocephalus is the highest [2,4], however, meticulous care is essential to mitigate shunt-related complications, which strain healthcare resources, particularly in resource-limited settings [36,37]. Only 21.5% of children underwent ETV, which reflects our strict selection criteria for ETV, aimed at enhancing success rates.

Interestingly majority of surgical procedures were performed during regular work hours and on weekdays, irrespective of distance, suggesting an opportunity to improve surgical access during off-peak hours and on weekends.

Our study revealed high VPS failure rates among children from areas located more than 49 km from the neurosurgery unit. This supports the need for decentralised neurosurgery services in KZN, to treat these complications closer to where the children reside. Living farther from the neurosurgery unit is associated with challenges of ease of access, particularly when there are complications, which explains why all the VPS and ETV complications presented earlier to the neurosurgery unit for treatment in children living in areas located less than 50 km from the neurosurgery unit, when compared to those living 50 km and above.

Existing literature demonstrates variable outcomes regarding the impact of distance on surgical outcomes in children. While some studies associated longer travel distances with poor outcomes such as adverse events and mortality, others find no significant differences, suggesting potential confounding factors such as socioeconomic status and comorbidities [20,38,39].

Cockrell et al in a surgical series found that children living more than two hours from the health care facility had a 59% higher risk of death and 97% higher risk of serious complications compared to children living closer to the services [20]. This study suggested that proximity to surgical services positively influences surgical outcomes in children. Etzioni et al also concluded that patients treated closer to services had better outcomes when compared to those who travel long distances [40], a finding confirmed by Karra et al noting that even small distances from health facilities are associated with significant mortality [38]

Contrastingly Georges et al found no differences in post-operative outcomes in urban and rural children, despite long distances travelled by rural infants [41], while Wiebe et al also reported that distance played no role in follow-up attendance and post-operative complication in children [42]. This might suggest that factors other than proximity, such as economic status, co-morbidities, and pre-operative clinical status may play a role in outcomes. Ahmed et al in a study on geographic proximity to specialized paediatric neurosurgery services in the United States reported a correlation between socioeconomic disparities and distance to services [43]

Furthermore, a systematic review by Buss et al analysed the findings of multiple studies investigating the associations between rurality or distance travelled to outcomes of surgical care among children. They found that most studies suggested that distance travelled has an impact on the surgical outcomes in children [44]

We found no statistically significant difference in mortality when comparing distances from the neurosurgery unit. However, there was a trend toward higher mortality rates and earlier deaths in children living closer to the neurosurgery unit. This may be explained by easier access to care for those residing nearby, leading to more frequent admissions and documentation of deaths at IALCH when complications arise. In contrast, children living farther away may be admitted to hospitals closer to home due to transportation challenges, and deaths occurring in these hospitals may not be captured in the IALCH records, potentially affecting the reported mortality rates.

This study lays the groundwork for policy development aimed at decentralizing neurosurgery in KZN. Strategies such as telemedicine and outreach programs can mitigate access, particularly for distance populations. The COVID-19 pandemic has accelerated this initiative, which offers cost-effective solutions, reducing burdens on patients and healthcare systems [45]. In KZN some children and parents travel through two hospitals, sleeping overnight in the second hospital before making the trip to the neurosurgery unit due to the long distance. Long travel distances, lack of transportation and financial constraints may contribute to delays in seeking care, which can lead to negative surgical outcomes. While the establishment of satellite neurosurgery units, such as Greys Hospital in Area 2, has eased the burden on IALCH, further expansion is warranted.

Limitations

The study only focuses on children treated in a single centre and region and thus results may not be generalizable to other populations groups and regions. Additionally, incomplete data on patients who died outside the central hospital may skew mortality statistics.

Conclusions

This study offers important insights into the impact of proximity to centralised neurosurgery services on paediatric hydrocephalus outcomes in KZN. VPS failures were higher in children living farther from the neurosurgery unit. Travel distances significantly impacted on time to presentation to the neurosurgery unit for treatment of surgical complications. These findings are important for healthcare policymaking and resource allocation, ensuring that services are more accessible to children living in rural areas. The study findings support the need for decentralised neurosurgery services in KZN

Declaration of conflict of interest

None

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Part 2: HIV and the Developing Brain

Part 2 is built on Part 1 and comprises two Chapters. It specifically focuses on post-infectious hydrocephalus in the context of HIV co-infection. It describes the impact of tuberculous meningitis (TBM) and cryptococcal meningitis (CM), which are prevalent in HIV-positive paediatric populations. These opportunistic infections complicate the diagnosis, treatment, and long-term outcomes of hydrocephalus.

Introduction

The HIV/AIDS pandemic has profoundly impacted children globally, with the highest burden in Sub-Saharan Africa [1]. First reported in children in 1983, the infection continues to affect millions of young lives [2]. By 2023, the global population of people living with HIV had risen to 39.9 million, with 52% residing in Eastern and Southern Africa [3]. Although new infections have decreased globally from 2.8 million in 2000 to 1.3 million in 2023, children remain disproportionately affected [3]. In South Africa (SA) alone, between 120,000 and 290,000 children under 14 years of age live with HIV, contributing to a substantial disease burden [4].

However, data from 2023 suggest that new infections in children under 14 years of age have declined globally to 120,000, with 42% of these new infections reported in Eastern and Southern Africa [3].

Human Immunodeficiency Virus (HIV)

HIV is an RNA virus from the lentivirus family, with two primary types affecting humans: HIV-1 and HIV-2 [5,6]. HIV-1 is responsible for the global pandemic and has several subtypes, the most prevalent in SA being subtypes A and C [6]. HIV-2, predominantly found in West Africa, follows a less aggressive clinical course [7].

HIV infection results in profound immunosuppression, leaving children particularly vulnerable to opportunistic infections, degenerative conditions, and malignancies due to the developing central nervous system (CNS) [8 -10].

The CNS opportunistic infections include bacterial meningitis, tuberculosis, and cryptococcal meningitis, which can be complicated by hydrocephalus. Common bacterial pathogens include Streptococcus pneumoniae, Haemophilus influenzae type B, and Neisseria meningitidis [8-10]. Furthermore, HIV-infected children are susceptible to viral meningoencephalitis caused by Cytomegalovirus, Herpes Simplex virus, Enterovirus, and Varicella-Zoster virus [8 -10].

Co-morbidities, such as pneumonia and severe malnutrition, further compound mortality risks in these children [11]. The HIV/AIDS pandemic has been a significant driver of child mortality in SA, particularly during the 1990s and early 2000s [12].

Modes of Transmission

HIV infection in children primarily occurs via vertical transmission during pregnancy, delivery, or breastfeeding. The risk of mother-to-child transmission has significantly decreased with the use of antiretroviral therapy (ART) in pregnant women and children. This has also led to marked improvements in child survival [13-15]. Factors contributing to vertical transmission include low maternal CD4 counts (< 200 cells/uL), viral load > 1000 copies/mL, and opportunistic infections during pregnancy [13-15].

Horizontal transmission can occur in older children through sexual activity, abuse, or sharing contaminated needles [13-15]. Without treatment, HIV causes progressive immunosuppression, primarily by depleting CD4+ lymphocytes. [13-15].

Pathogenesis of HIV-related Central Nervous System injury

Various pathways have been proposed, including direct viral entry and cell-mediated transmission. The "Trojan horse" hypothesis suggests that the virus enters the CNS through infected CD4 T lymphocytes or monocytes, which cross the compromised blood-brain barrier (BBB). [16,17]. HIV may also disrupt the BBB, compromising its integrity and facilitating viral entry [16-18].

Once in the CNS, these immune cells release pro-inflammatory molecules, such as cytokines (monocyte chemoattractant protein-1 and interferon-inducible protein-10) and matrix metalloproteinases, further weakening the BBB. HIV proteins, particularly Tat cross the BBB or are released by infected CNS cells, further contributing to neuronal dysfunction [16 -1].

The infected CNS cells also support localized HIV replication, leading to the emergence of compartmentalized HIV variants distinct from those in the peripheral system [16-18].

Together, these processes underline the complex interplay between HIV infection and neuroinflammation in driving CNS damage [14-16]. In some cases, receiving ART, HIV can continue to replicate in the CNS, a phenomenon known as "CSF escape" [16 -18]

Many HIV-infected children, once not expected to survive childhood, are now reaching adolescence and young adulthood. The next chapters examine the intricate association between HIV-related opportunistic CNS infections and hydrocephalus in children.

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Chapter 5: Factors Associated with In-Hospital Mortality in HIV-Infected Children Treated for Tuberculous Meningitis Hydrocephalus

This chapter focuses on the outcomes in managing children diagnosed with tuberculous meningitis-related hydrocephalus and HIV infection in KwaZulu-Natal. Key factors determining these outcomes are discussed

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RESEARCH

Factors associated with in-hospital mortality in HIV-infected children treated for tuberculous meningitis hydrocephalus

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Abstract

Purpose The study aimed to investigate factors associated with in-hospital mortality in children diagnosed with tuberculous meningitis (TBM) hydrocephalus and HIV co-infection undergoing cerebrospinal fluid diversion procedures and their complications.

Methods Data were collected retrospectively and prospectively between 2007 and 2022. Data collected included demographics, clinical characteristics, antiretroviral therapy (ART) status, biochemistry results, CD4 count, radiology findings, CSF diversion procedures (and complications), length of hospital stay (LOHS), and in-hospital mortality.

Results Thirty-one children were included, with a mean age of 6.7 ± 5.3 years and 67.7% males. Median admission Glasgow Coma Scale (GCS) was 11 (IQR 9–15). Hypertonia (64.5%) and seizures (51.6%) were frequently observed clinical characteristics. Sixty-one percent of children were on ART. Cerebral infarcts and extra-meningeal TB were diagnosed in 64.5% and 19.3% of cases, respectively. The median CD4 count was 151 (IQR 70–732) cells/μL. Surgical procedures included ventriculoperitoneal shunt (VPS) in 26 cases and endoscopic third ventriculostomy (ETV) in five children. VPS complication rate was 27%. No complications were reported for ETV. Median LOHS was 7 days (IQR 4–21). Eleven children (35.5%) died during admission. Factors associated with mortality included GCS ($p=0.032$), infarcts ($p=0.004$), extra-meningeal TB ($p=0.003$), VPS infection ($p=0.018$), low CD4 count ($p=0.009$), and hyponatremia ($p=0.002$). No statistically significant factors were associated with VPS complications.

Conclusion TBM hydrocephalus in HIV-infected children carries a high mortality. Clinicians in high-prevalence settings should have a high suspicion index and institute early treatment.

Keywords Endoscopic third ventriculostomy · Infarcts · Tuberculoma · Ventriculoperitoneal shunt

Introduction

Tuberculous meningitis (TBM) is a frequently diagnosed central nervous system (CNS) infection in individuals living with HIV [1, 2]. HIV infection in children is particularly concerning, with high morbidity and mortality rates. In 2021 alone, it was estimated that approximately 110,000 children and adolescents died from AIDS-related pathologies, predominantly among those aged 10 years and younger [3]. The underlying immunosuppression in HIV-infected children predisposes them to increased mortality from CNS infections [2, 4].

The resurgence of TBM has been closely associated with the HIV/AIDS pandemic [4–6], with hydrocephalus detected in more than 80% of children with TBM [7–9]. The burden of disease related to TBM and HIV co-infection has been significant in South Africa [10]. However, the precise incidence of TBM-related hydrocephalus in HIV-infected children remains unknown. TBM leads to hydrocephalus through two main pathways. Firstly, cerebrospinal fluid (CSF) obstruction occurs due to accumulation of thick tuberculous exudate in the basal cisterns. Secondly, tuberculomas cause obstruction of the third ventricle, aqueduct, and fourth ventricle outlet foramina [5].

Management of TBM and HIV in children is challenging due to the necessity of treating both conditions

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simultaneously, which can result in adverse drug interactions and tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS), leading to increased morbidity and mortality [11]. In HIV infection, TBM can present with atypical CSF results, including normal CSF, further complicating diagnosis and potentially causing delays [12]. Delayed initiation of medical treatment can lead to long-term neuro-disabilities caused by various insults to the CNS, hydrocephalus, and increased intracranial pressure (ICP) [13]. Left untreated, hydrocephalus can lead to visual deterioration, coma, and even death.

Ventriculoperitoneal shunt (VPS) and endoscopic third ventriculostomy (ETV) are crucial surgical interventions for managing TBM hydrocephalus. However, the risk of complications associated with VPS is presumed high in HIV-infected patients due to their compromised immune status [14]. While previous studies have reported outcomes in the management of TBM hydrocephalus in HIV-infected patients, these studies have predominantly focused on adults [15–17]. Currently, no data exist regarding the outcomes of CSF diversion procedures, specifically VPS or ETV, in managing TBM-related hydrocephalus in HIV-infected children.

Therefore, this study aimed to investigate the factors associated with in-hospital mortality in HIV-infected children undergoing VPS and ETV procedures for treating TBM-related hydrocephalus. Additionally, we aimed to explore the factors related to complications arising from these CSF diversion procedures.

Methods

The study used retrospective data from January 2007 to January 2017 and prospectively collected data from February 2018 to February 2022 at the Department of Neurosurgery (DoN), Inkosi Albert Luthuli Central Hospital, Durban, South Africa. The study population included HIV-infected children (birth to 17 years) diagnosed with TBM-related hydrocephalus who were referred for permanent CSF diversion. HIV-non-infected children or those with hydrocephalus caused by cryptococcal or acute bacterial meningitis were excluded.

Data collected encompassed various parameters, including age, sex, clinical characteristics, admission Glasgow Coma Scale (GCS), initiation of antiretroviral therapy (ART), admission laboratory investigations (full blood count, urea, and electrolytes), CD4 count, HIV viral load, CSF results, radiology findings, CSF diversion procedure, complications of the procedure, length of hospital stay (LOHS), in-hospital mortality, time to mortality, and Glasgow Outcome Scale (GOS) at discharge and 12 months follow-up. The GOS scores were classified as mild to moderate disability (GOS 4–5) and severe disability to mortality (GOS 1–3).

The HIV status of the children was confirmed using data from the national health laboratory services. TBM was diagnosed according to consensus criteria, categorized as definite, probable, or possible [18]. Following the diagnosis of TBM hydrocephalus, medical treatment was instituted by the pediatric infectious disease unit (PIDU), including therapeutic lumbar punctures (LPs), provided there were no clinical and radiological contraindications to LP. Indications for referral to the DoN for CSF diversion included severe hydrocephalus, obstructive hydrocephalus caused by tuberculomas, alteration in level of consciousness, deteriorating vision, and worsening neurological deficits.

A four drug anti-tuberculosis (TB) regimen was administered, which included isoniazid (20 mg/kg), rifampicin (20 mg/kg), pyrazinamide (40 mg/kg), and ethionamide (20 mg/kg) for 2 months (intensive phase), followed by 10 months of continuation phase treatment with isoniazid and rifampicin. The duration of treatment could be longer depending on response to therapy. Corticosteroids were used to minimize inflammation. Adjustment of ART to minimize potential drug interactions and toxicities was managed by the PIDU. Children not on ART were assessed for initiation, preferably within 4 to 8 weeks of starting anti-TB therapy [19, 20].

Detailed clinical examination and radiology imaging (chest X-ray, CT/MRI brain scan, and abdominal ultrasound when indicated) were conducted. The severity of TBM was assessed using the refined British Medical Research Council (BMRC) grading system [21]. The diagnosis of hydrocephalus was established based on CT or MRI brain scans, which revealed dilated ventricles, with or without loss of sulcal markings, temporal horns > 2 mm, trans-ependymal seepage, and associated clinical symptoms.

While differentiating between communicating and non-communicating (obstructive) hydrocephalus using CT/MRI brain scans alone is challenging, a proportionally dilated fourth ventricle on neuroimaging suggests the possibility of communicating hydrocephalus, unless an obvious tuberculoma is causing obstructive hydrocephalus. Although some centers use air encephalogram to distinguish between communicating and non-communicating hydrocephalus in the presence of a proportionally dilated fourth ventricle, this was not part of our protocol [22].

CSF diversion procedures, such as VPS insertion or ETV, were performed following standard guidelines [22, 23]. ETV was the preferred method in children with associated tuberculoma in the posterior fossa causing obstructive hydrocephalus. Following the procedure, all children were admitted to the high care ward for a minimum of 48 h of monitoring and transferred to general ward in stable

condition. Follow-up assessments were conducted at the outpatient department after discharge.

Descriptive statistics were employed to summarize the demographic and clinical characteristics of the children. The numeric data's normality was assessed; normally distributed variables were presented using the mean and standard deviation, while non-normally distributed variables were reported using the median and interquartile range (IQR). Chi-square tests were used to identify categorical factors associated with mortality, such as sex, clinical characteristics, initiation of ART, and radiological features (infarcts, tuberculoma, basal enhancement). *T*-tests or Mann–Whitney tests were utilized to compare numeric risk factors, including age, admission GCS, CD4 count, viral load, CSF, hematology, and biochemical results, between those who died and those who survived. Kaplan–Meier survival analysis was employed to evaluate time to death. The significance level was set at 0.05. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal on the 8th of February 2018 (reference number BE607/17).

Results

A total of 31 HIV-infected children were included in the study, with 11 (35.5%) children dying during the admission period. The demographic profiles are summarized in Table 1. The mean age was 6.7 ± 5.3 years, and majority of children were males (21; 67.7%). The median admission GCS was 11 (IQR 9–15). TBM diagnosis was definite in four (13%) children and probable in the remaining (27; 87%) ($p = 0.601$). The refined BMRC grades and clinical characteristics are presented in Table 1. The majority of children (19; 61%) were on ART.

The radiological findings, CSF diversion procedures, and their complications are shown in Table 2. Basal enhancement (90.3%) and infarcts (64.5%) were the most common neuroradiological findings (Fig. 1a and b, respectively). Fourteen (45.2%) children were diagnosed with tuberculomas on CT/MRI brain scans, with one child experiencing an increase in tuberculoma size (paradoxical TB-IRIS) while on anti-TB therapy, steroids and ART (Fig. 2a–c). The child had a prolonged admission period of 92 days, responded

Table 1 Demographic profiles and clinical characteristics of HIV-infected children diagnosed with TBM hydrocephalus, comparing children alive at discharge and those who died during hospitalization

Variable	Total ($n = 31$)	Alive ($n = 20$; 64.5%)	Dead ($n = 11$; 35.5%)	p value
Age, mean (SD)	6.7 ± 5.3	7.2 ± 5.5	6 ± 5	0.521
• 0–6	19 (61.2%)	12 (60%)	7 (64%)	
• 7–12	6 (19.4%)	3 (15%)	3 (27%)	0.568
• 13–17	6 (19.4%)	5 (25%)	1 (9%)	
Sex				
• **Male**	21 (67.7%)	12 (60%)	9 (81.8%)	0.262
• **Female**	10 (32.3%)	8 (40%)	2 (18.2%)	
Admission GCS (median, IQR)	11 (9–15)	11.5 (10–15)	9 (6.5–11.5)	0.032
Refined BMRC grade				
• Grade 1	2 (6.5%)	2 (10%)	0 (0%)	
• Grade 2a	8 (26%)	7 (35%)	1 (9%)	0.113
• Grade 2b	7 (22.5%)	5 (25%)	2 (18%)	
• Grade 3	14 (45%)	6 (30%)	8 (73%)	
Clinical characteristics				
• Hypertonia	20 (64.5%)	12 (60%)	8 (72.7%)	0.698
• Seizures	16 (51.6%)	9 (45%)	7 (63.6%)	0.458
• Headaches	15 (48.4%)	9 (45%)	6 (54.5%)	0.716
• Cranial nerve deficits	7 (22.6%)	5 (25%)	2 (18.2%)	1.000
• Hemiparesis	8 (25.8%)	5 (25%)	3 (27.3%)	1.000
• Vomiting	7 (22.6%)	3 (15%)	4 (36.4%)	0.210
• Poor appetite	5 (16.1%)	4 (20%)	1 (9.1%)	0.631
• Meningism	10 (32.3%)	4 (20%)	6 (54.5%)	0.106
ART				
• Yes	19 (61%)	13 (65%)	6 (54.5%)	0.705
• No	12 (39%)	7(35%)	5 (45.5%)	

ART anti-retroviral therapy, *BMRC* British Medical Research Council, *GCS* Glasgow Coma Scale, *IQR* interquartile range, *SD* standard deviation, *TB* tuberculosis

Table 2 Radiological findings and surgical management of HIV-infected children diagnosed with TBM hydrocephalus, comparing children alive at discharge and those who died during hospitalization

Variable	Total ($n=31$)	Alive ($n=20$; 64.5%)	Dead ($n=11$; 35.5%)	p value
CT brain findings				
• Basal enhancement	28 (90.3%)	17 (85%)	11 (100%)	0.290
• Infarcts	20 (64.5%)	9 (45%)	11 (100%)	0.004
• Tuberculoma	14 (45.2%)	10 (50%)	4 (36.4%)	0.707
Extra meningeal TB	6 (19.3%)	0	6 (54.5%)	0.003
• TB pneumonia	4 (13%)	0	4 (36.4%)	0.010
• TB abdomen	2 (6.5%)	0	2 (18.2%)	0.118
VPS procedure	26 (84%)	16 (80%)	10 (91%)	0.631
• **Shunt type**				
o **AIS**	21 (81%)	15 (94%)	6 (60%)	0.055
o **Non-AIS**	5 (19%)	1 (6%)	4 (40%)	
VPS complication (in those who had shunt $n=26$)	7 (27%)	2 (12.5%)	5 (50%)	0.069
• Time to shunt complication, days (median, IQR)	48 (25–84)	205 (54–357)	43 (25–48)	0.190
VPS infection (in those who had shunt $n=26$)	6 (23%)	1 (6.3%)	5 (50%)	0.018
ETV	5 (16%)	4 (20%)	1 (9%)	0.631
Length of hospital stay (days), median, IQR	7 (4–21)	6 (4–8)	22 (4–50)	0.095

AIS antibiotic impregnated shunt, *CT* computerized tomography, *ETV* endoscopic third ventriculostomy, *IQR* interquartile range, *TB* tuberculosis, *VPS* ventriculoperitoneal shunt

to treatment, however, had residual severe neurocognitive deficits. Among the 14 children with tuberculomas, nine (64%) were on ART, while five (36%) were not ($p=0.756$). Extra-meningeal TB was diagnosed in six (19.3%) children, and TB pneumonia was diagnosed in four children (Fig. 3a). Two children developed TB abdomen, complicated by ascites (Fig. 3b). All children with extra-meningeal disease died ($p=0.003$).

The median CD4 count was 151 (IQR 70–732) cells/μL, and the median viral load was 7449 (370–81,441) copies/mL. The median hemoglobin was 10.3 g/dL (9.1–12.2), and mean serum sodium was 133 ± 7. The mortality group had a mean sodium level of 128 ± 6.7 mmol/L, significantly lower than the group that survived ($p=0.002$). The remaining laboratory findings are presented in Table 3.

VPS procedures were performed in 26 (84%) children, while five (16%) underwent ETV. Seven (27%) VPS complicated, while there were no complications related to ETV. Six VPS complications were associated with infection, with five infections occurring in the mortality group ($p=0.018$). Among the VPS infections in the mortality group, three were culture negative, while the other two cultured *Staphylococcus aureus* and *Proteus mirabilis* (both in the same child) and *Viridans streptococcus*. The analysis of factors associ-

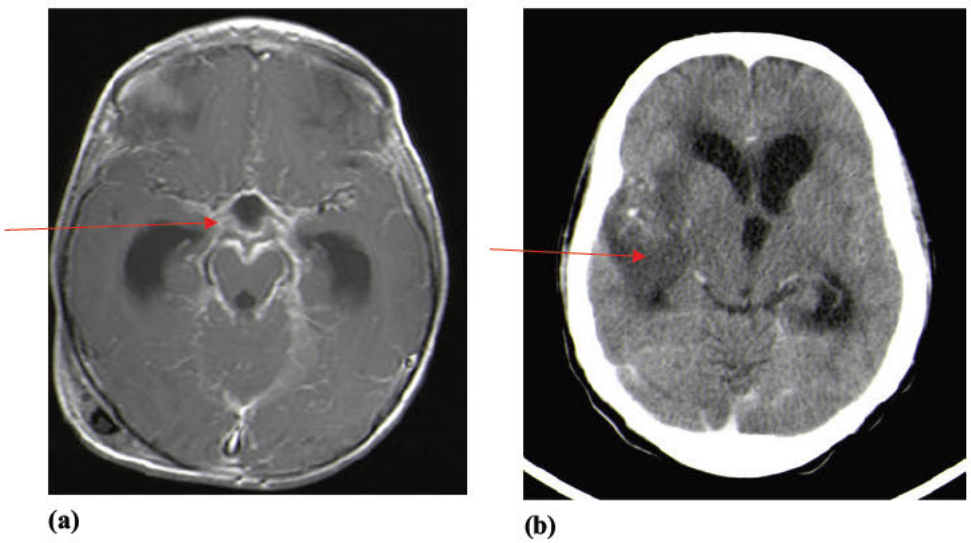

Fig. 1 **a** T1-weighted post contrast MRI brain scan showing basal enhancement and **b** post contrast CT brain scan showing right middle cerebral artery territory infarct

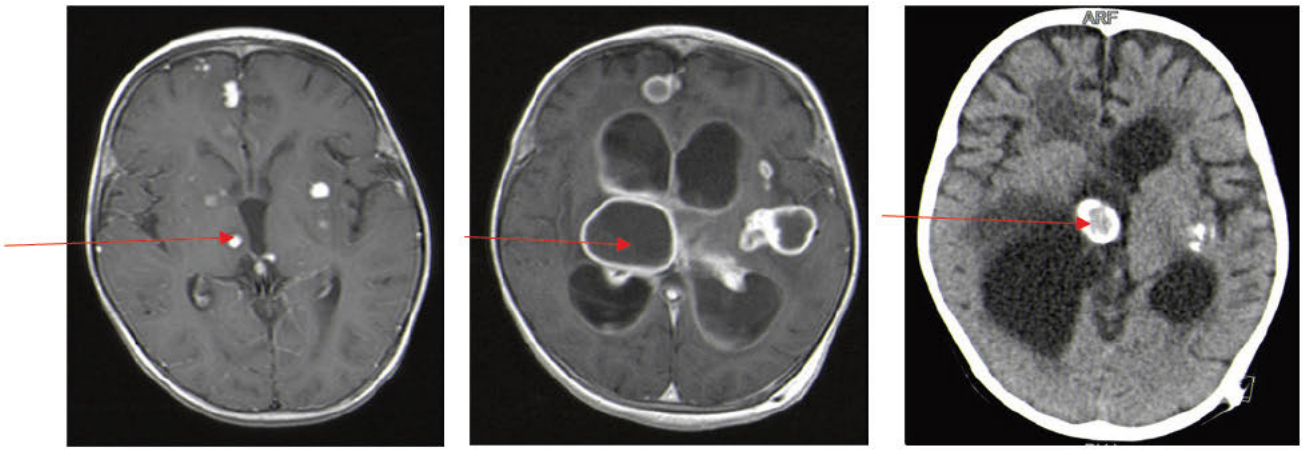

Fig. 2 **a** T1-weighted post contrast MRI brain scan showing multiple tuberculomas in a 4-year-old child on anti-TB therapy and ART. The tuberculomas increased in size (paradoxical TB-IRIS) while the child was on anti-TB therapy and ART (**b**). A non-contrast CT brain (**c**) performed at 12 months follow-up showed calcification of tuberculomas

ated with VPS complications is shown in Tables 4 and 5. Figure 4 presents the overall time to in-hospital mortality using a Kaplan–Meier plot.

Regarding children alive at discharge, six (30%) had mild to moderate disability, while 14 (70%) had severe disability. The median follow-up period was 15.5 months (IQR 3–91.3). Twelve (60%) of the 20 children alive at discharge were followed up for at least 12 months, with four (33%) experiencing mild to moderate disability and eight (67%) having severe disability. The median CD4 count at the last follow-up was 736.5 cells/μL (IQR 615–1265.3) for the eight children followed up for 12 months or more.

Univariate analysis of baseline characteristics (Tables 1 and 2) showed lower admission GCS, infarcts, extra-meningeal TB, VPS infection, lower CD4 count, and hyponatremia as factors trending towards association with mortality. Univariate analysis of baseline characteristics did not identify statistically significant factors associated with VP shunt complications (Tables 4 and 5), although there was a trend observed in children diagnosed with TB abdomen.

Discussion

This is the first pediatric series giving the results of HIV-infected children treated for TBM hydrocephalus in the literature, such as rates of in-hospital mortality and VPS complications.

Our study reported an in-hospital mortality rate of 35.5%, which is lower than the reported rates in cohorts of shunted adult series [15, 16]. Sharma et al. reported a mor-

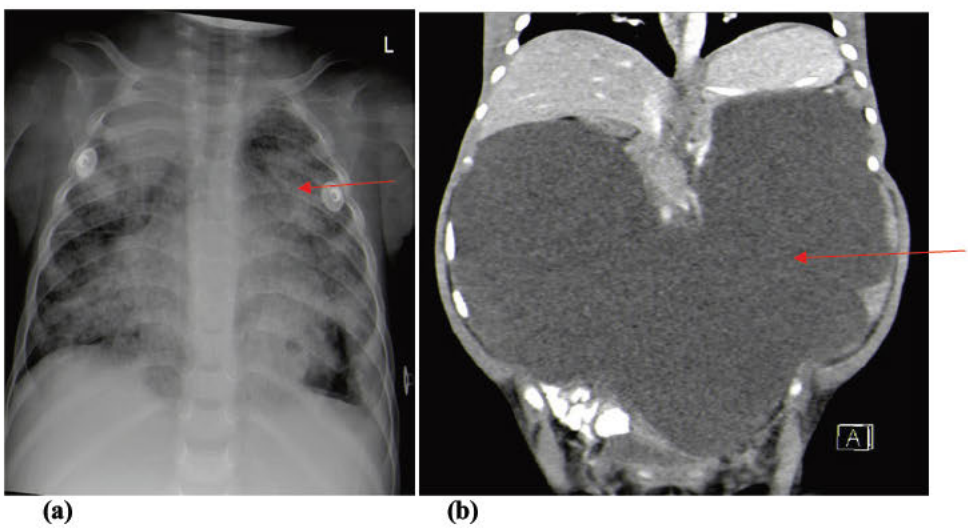

Fig. 3 Chest X-ray of child with TB pneumonia (**a**) and abdominal CT showing ascites in a child diagnosed with TB abdomen (**b**)

Table 3 Association between laboratory results at admission for surgery and mortality

Variable	Total ($n=31$)	Alive ($n=20$, 64.5%)	Dead ($n=11$, 35.5%)	p value
Admission CD4 count cell/mL (median, IQR)	151 (70–732)	535 (124–756)	100 (22–202)	0.009
Viral load, copies/mL, (median, IQR)	7449 (370–81441)	3349 (236–77,721)	11,751 (890–81823)	0.310
Hemoglobin (g/dl)	10.3 (9.1–12.2)	10.3 (8.8–12.4)	10.2 (9.1–12)	1.000
White cell count ($\times 10^9$/L), IQR	7.9 (6.2–10.2)	7.7 (5.9–10.1)	9.0 (6.2–10.2)	0.403
Platelets, count ($\times 10^9$/L), IQR	422 (332–539)	423 (323–515)	413 (326–601)	0.555
Polymorphs (cells X 10^6/L), IQR	24 (8–44)	26 (9–46)	23 (4–38)	0.919
Lymphocytes (cells X 10^6/L), median, IQR	48 (22–70)	54 (34–72)	32 (18–70)	0.289
Protein g/L, median IQR	1.33 (1.07–2.08)	1.2 (0.8–2.1)	1.7 (1.2–2.5)	0.133
Chloride (mmol/L), IQR	112 (106–120)	113 (110–124)	110 (100–118)	0.197
CSF glucose (mmol/L), median, IQR	1.7 (1.3–2.0)	1.4 (1.2–2.0)	1.8 (1.4–2.0)	0.317
Sodium (mmol/L) mean ± SD	133 ± 7	136 ± 5	128 ± 7	0.002
Potassium (mmol/L), mean ± SD	4.2 ± 0.7	4.3 ± 0.7	4.1 ± 0.6	0.629
Urea (mmol/L), mean ± SD	4.5 ± 4.7	5.3 ± 5.6	3.0 ± 1.6	0.207
Creatinine (mmol/L), mean ± SD	32 ± 22	36 ± 25	26 ± 13	0.240

IQR interquartile range, *SD* standard deviation

Table 4 Analysis of key factors and their association with VPS complications

Variable	Total ($n=26$)	No VPS complication ($n=19$; 73%)	VPS complication ($n=7$; 27%)	p value
Age, mean (SD)	5.9 (5.1)	6.7 (5.5)	3.7 (2.9)	0.196
• 0–6	19 (73.1%)	13 (68.4%)	6 (85.7%)	
• 7–12	3 (11.5%)	2 (10.5%)	1 (14.3%)	0.517
• 13–17	4 (15.4%)	4 (21.1%)	0 (0%)	
Sex				
• **Male**	17 (65.4%)	12 (63.2%)	5 (71.4%)	1.000
• **Female**	9 (34.6%)	7 (36.8%)	2 (28.6%)	
Admission GCS (median, IQR)	11 (8–13)	10 (7–13)	11 (8–15)	0.572
Refined BMRC grade				
• Grade 2a	6 (23.1%)	4 (21.1%)	2 (28.6%)	1.000
• Grade 2b	7 (26.9%)	5 (26.3%)	2 (28.6%)	
• Grade 3	13 (50%)	10 (52.6%)	3 (42.9%)	
TB diagnosis				
• Definite	2 (7.7%)	1 (5.3%)	1 (14.3%)	
• Probable	24 (92.3%)	18 (94.7%)	6 (85.7%)	1.000
Radiological findings				
• Basal enhancement	26 (100%)	19 (100%)	7 (100%)	-
• Infarcts	19 (73.1%)	12 (63.2%)	7 (100%)	0.134
• Tuberculoma	9 (34.6%)	5 (26.3%)	4 (57.1%)	0.188
Extra-meningeal TB	5 (19.2%)	2 (10.5%)	3 (42.9%)	0.101
• TB pneumonia	4(15.4%)	2 (10.5%)	2 (28.6%)	0.546
• TB abdomen	2 (7.7%)	0 (0%)	2 (28.6%)	0.065
VPS type				
• **AIS**	5 (19.2%)	2 (10.5%)	3 (42.9%)	0.101
• **Non-AIS**	21 (80.8%)	17 (89.5%)	4 (57.1%)	
ART				
• Yes	17 (65.4%)	11 (57.9%)	6 (85.7%)	0.357
• No	9 (34.6%)	8 (42.1%)	1 (14.3%)	

AIS antibiotic impregnated shunt, *CT* computerized tomography, *ETV* endoscopic third ventriculostomy, *IQR* interquartile range, *TB* tuberculosis, *VPS* ventriculoperitoneal shunt

Table 5 Association between laboratory results at admission for surgery and shunt complications

Variable	Total ($n=26$)	No VPS complication ($n=19$; 73%)	VPS complication ($n=7$; 27%)	p value
Admission CD4 count cell/mL (median, IQR)	177 (100–701)	202 (70–732)	151 (100–399)	0.611
Viral load, copies/mL, (median, IQR)	12,050 (370–81,823)	11,401 (241–74,000)	81,441 (890–574,712)	0.185
Hemoglobin (g/dl)	10.3 (8.6–12)	10.3 (8.5–12.5)	10 (8.6–11.8)	0.534
White cell count ($\times 10^9$/L), IQR	7.6 (6–10.2)	7.89 (6.2–10.2)	6 (4.0–10.76)	0.279
Platelets, count ($\times 10^9$/L), IQR	418 (332–521)	413 (318–460)	539 (363–601)	0.120
Polymorphs (cells X 10^6/L), IQR	28 (10–48)	31 (16–48)	22 (4–64)	0.497
Lymphocytes (cells X 10^6/L), median, IQR	54 (22–77)	62 (32–88)	36 (22–52)	0.169
Protein g/L, median IQR	1.41 (1.1–2.09)	1.4 (1.07–2.08)	1.54 (1.1–3.14)	0.534
Chloride (mmol/L), IQR	110 (106–118)	110 (106–117)	113 (100–128)	0.306
CSF Glucose (mmol/L), median, IQR	1.8 (1.3–2.0)	1.5 (1.3–2.0)	2.0 (1.7–2.1)	0.120
Sodium (mmol/L) mean ± SD	132 (7)	133 (7)	131 (7)	0.681
Potassium (mmol/L), mean ± SD	4.2 (0.7)	4.2 (0.7)	4.2 (0.6)	0.815
Urea (mmol/L), mean ± SD	4.5 (5.1)	5.1 (5.8)	2.9 (1.2)	0.336
Creatinine (mmol/L), mean ± SD	31 (22)	32 (25)	26 (6)	0.503

IQR interquartile range, *SD* standard deviation

tality rate of 66.7%, with 57% of deaths occurring within the first month; however, ART status was not documented [16]. Nadvi et al. reported a similar mortality rate of 66.7%, and none of the patients was on ART [15]. Access to ART, including improved TB and HIV treatment strategies over the years in South Africa, would explain the lower mortality in our series when compared to Nadvi et al.

Harrichandparsad et al. reported a mortality rate of 26.7% in patients with TBM-related hydrocephalus on ART, compared to historical controls who were not on ART, with a mortality rate of 66.7% [17]. In our study, only 61% of children were on ART, and 45.5% of the mortalities were not on ART; however, this difference was not statistically significant. In South Africa, ART was only initiated in individuals with a CD4 count below 200 cells/μL, but since 2016, all HIV-infected individuals are eligible for ART regardless of CD4 count [24, 25]. In our study, low CD4 counts were associated with in-hospital mortality but not with VPS complications, possibly due to the small sample size of VPS complications. Other authors reported no correlation between CD4 count and poor outcomes in shunted HIV-infected adult patients [16, 17].

Seizures were diagnosed in 51.6% of children, occurring in 63.6% of those who died; however, this was not statisti-

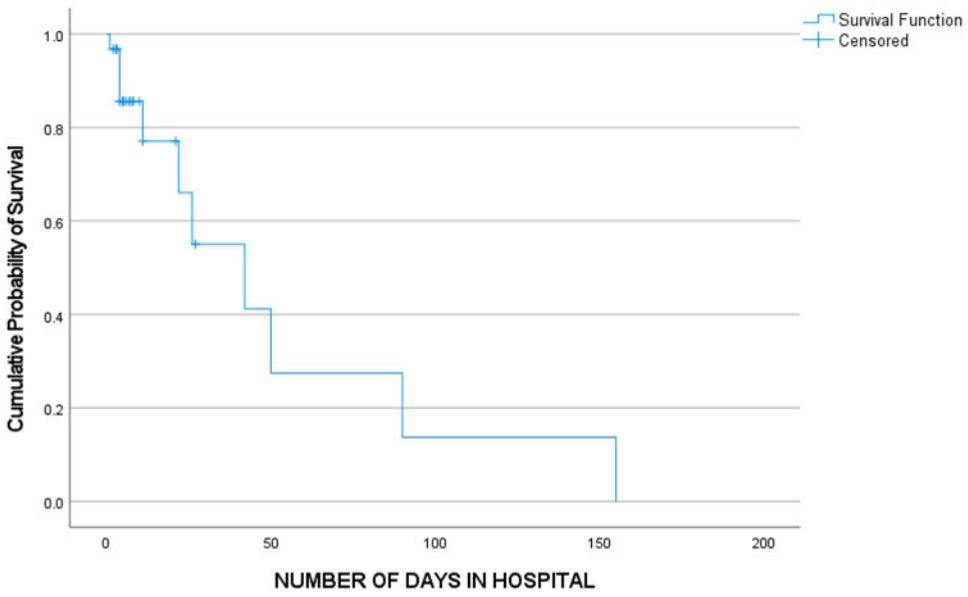

Fig. 4 Kaplan–Meier plot of time to in-hospital mortality ($n=31$). The overall median time to in-hospital mortality was 42 days

cally significant. Seizures increase cerebral metabolic rate, inducing oxygen insufficiency which prevents aerobic glycolysis and oxidative phosphorylation. The end results are worsening ischemia and cellular death [22].

In our study, hyponatremia was found to be associated with in-hospital mortality. Hyponatremia can be due to syndrome of inappropriate antidiuretic hormone (SIADH) secretion or cerebral salt-wasting syndrome [26]. Hyponatremia exacerbates cerebral edema, increasing susceptibility to seizures and poor outcomes. It is crucial to differentiate between SIADH and cerebral salt-wasting syndrome in order to ensure appropriate fluid and intravascular volume management.

Hemoglobin (Hb) levels were not found to be predictors of mortality in our study. Karande et al. reported lower Hb levels (less than 8 g/dl) in eight HIV-infected children, with a mortality rate of 12.5% [27], while another study found no differences in Hb levels between HIV-infected and non-infected children [28]. Hb plays a pivotal role in oxygen delivery to the brain, especially in the context of TBM hydrocephalus, due to susceptibility of the brain to ischemia from increased ICP and vasculitis.

Marais et al. reported BMRC grades 2 and 3 to be significant predictors of mortality in both HIV-infected and non-infected patients; however, our study did not confirm statistical significance in this regard [29]. Definite TB was diagnosed in 13% of children in our study. The culture of *Mycobacterium tuberculosis* (Mtb) from the CSF is considered the gold standard; however, the rate of positive culture varies in the literature. For instance, Bang et al. reported definite TB in 6% of children, while the remaining cases were categorized as probable (66%) and possible (28%) [30]. Grobbelaar et al. reported Mtb culture positivity rates of 17% and 56.4%, respectively [31, 32]. A Durban study on HIV-infected adults with TBM reported definite TB in 15.5% of patients [33].

Enhancing the diagnostic yield requires increased CSF submission volumes, laboratory infrastructure, expertise, and molecular tests such as GeneXpert MTB/RIF®, offering rapid results, improved sensitivity and specificity. The low rate of microbiological confirmation of Mtb in our study reflects the challenges confronting researchers in LMICs with the highest burden of HIV and TBM.

Cerebral infarcts, reported in 64.5% of children in our study, were associated with mortality. Infarcts are caused by vasculitis and intimal proliferation of cerebral arteries, commonly affecting areas such as the caudate nucleus, internal capsule, and thalamus [22]. This explains the documented hypertonia and hemiparesis in our series. Rohwlink et al. reported a 66% rate of infarcts and a mortality rate of 16% in a series of 44 children with tuberculous hydrocephalus [34]. The delayed resolution of cerebral exudate leads to ongoing inflammatory responses, even after initiating anti-TB medication, resulting in delayed infarcts [35]. Clemente Morgado et al., in a study of adult patients with TBM hydrocephalus, reported infarcts in 45.5% of patients, with 100% mortality in the HIV-infected group [36]. TB exudates can also infiltrate cranial nerves, resulting in deficits, as reported in 22.6% of children in our study [37].

Intracranial tuberculomas are frequently diagnosed pathology in HIV-infected children. Nevertheless, tuberculomas were not associated with mortality in our study. Notably, one child was diagnosed with neurological paradoxical TB-IRIS, characterized by progressive enlargement of tuberculomas, while on anti-TB therapy and ART. This occurred despite the child being on steroids, a phenomenon reported by other authors as well [11]. TB-IRIS manifests when initiation of ARTs occurs within a period ranging from 2 weeks to 3 months after commencement of anti-TB therapy [38]. It is postulated that ARTs result in restoration of the immune response to Mtb. Consequently, this immune resurgence, marked by an increase in CD4 T cell count, triggers excessive production of pro-inflammatory cytokines. Paradoxical TB-IRIS is differentiated from unmasking TB-IRIS, which refers to TB that only becomes clinically evident after initiation of ART [38, 39].

Risk factors for TB-IRIS include low CD4 count, high viral load, disseminated TB, increased CSF neutrophil count, and positive Mtb culture in the CSF [39]. The spectrum of neurological TB-IRIS can include worsening TBM, intracranial TB abscess, spinal epidural abscess, and TB radiculomyelitis [38, 39].

Corticosteroids are recommended therapy. It is advisable to continue ART during TB-IRIS episodes, as discontinuation may result in drug resistance. However, instances where there is depressed level of consciousness or severe disease nonresponsive to corticosteroids, discontinuation of ART should be considered [38, 39]. Marias et al. reported a 13% mortality in a series of 16 HIV-infected adults with TB-IRIS, while van Toorn et al. reported a single fatality within a series of four HIV-infected children diagnosed with TB-IRIS [40].

Indications for resection of tuberculomas include progressive enlargement, inducing mass effect and visual deterioration despite adequate medical treatment, particularly in posterior fossa [41]

Proactive management and prevention of HIV in children assume a critical role in reducing CNS infections and their complications. Successful prevention of mother-to-child transmission (PMTCT) programs in South Africa has precipitated a decline in the number of children born with HIV [42].

Effective management of communicating TBM hydrocephalus primarily involves anti-TB therapy, acetazolamide, corticosteroids, and frequent LPs. However, successful outcomes require strict adherence to treatment protocols, close monitoring, and follow-up [22]. Debates still persist regarding the optimal duration of anti-TB therapy for TBM-diagnosed patients [43].

Surgical treatment options vary from temporary measures such as external ventricular drain (EVD) placement to alleviate ICP, to permanent procedures, namely VPS or ETV [22]. Agrawal et al. recommended VPS for children with Palur grade II to III and EVD for grade IV, with progression to VPS if there is clinical improvement [44]. None of the children in our study underwent a trial of EVD placement. All children underwent early permanent CSF diversion, thus allowing focus on the medical management of TBM and its complications. Majority of children (84%) in our study were treated with VPS, and the shunt complication rate was 27%, which falls within the reported range of 10 to 40% [13, 44–47].

Mortality rates are notably elevated in HIV-infected individuals diagnosed with TB meningitis and concurrent secondary bacterial meningitis [2]. This observation elucidates the association between mortality and VPS infections in the current study.

ETV was performed in five children who had associated tuberculomas in the posterior fossa causing obstructive hydrocephalus. Some experts hold the view that ETV should be offered even in patients with communicating hydrocephalus; however, our approach remains selective [22]. ETV can convert non-communicating to communicating hydrocephalus thereby circumventing VPS-related complications. Figaji et al. reported an ETV success rate of 41% [48], while other studies reported success rates ranging from 59 to 65.4% [13, 49]. Performing ETV in the acute phase can be challenging due to the distortion of the anatomy of the third ventricle, thickened floor, and basal exudates. Some authors have suggested performing ETV during the chronic phase of TBM to enhance the prospects of success [50]. At the 12-month follow-up, 67% of children in our study were assessed as having a poor outcome, while adult series reported poor outcomes in 64.7% and 76.2% of cases, respectively [15, 16].

Limitations of the study

Our study has certain limitations that should be acknowledged. First, the sample size was relatively small, which may have limited the statistical power to detect significant associations and generalize the findings to larger populations. Additionally, the lack of a comparison group of HIV-non-infected children prevented us from directly comparing outcomes between the two groups. Future studies with larger sample sizes and the inclusion of a control group are warranted to elucidate further the impact of HIV infection on the outcomes of children with TBM hydrocephalus.

The data were obtained from a single institution, which may introduce institutional biases and limit the generalizability of the findings to other settings. Multi-center studies involving different geographic locations and diverse populations would provide a more comprehensive understanding of the outcomes in this patient population. Despite these limitations, our study provides important insights into the outcomes of HIV-infected children undergoing treatment for TBM-related hydrocephalus.

Conclusion

Our study highlights the high mortality associated with TBM-related hydrocephalus in HIV-infected children and complexities of managing this high-risk population. While the risk factors for mortality were elucidated, no statistically significant factors were found to be associated with VPS complications. Our findings underscore the urgent need for improved strategies for managing TBM-related hydrocephalus in HIV-infected children.

Author contribution **BE:** conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be submitted. **CA:** analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be submitted.

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Data availability The datasets collected and analyzed during the current study are available from the corresponding author on request.

Declarations

Conflict of interest The authors declare no competing interests.

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Chapter 6: Cerebrospinal Fluid Shunting in Children with Hydrocephalus and Increased Intracranial Pressure Secondary to Human Immunodeficiency Virus-related Cryptococcal Meningitis

This chapter further highlights the outcomes in the management of hydrocephalus caused by cryptococcal meningitis in HIV-infected children.

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Colleen Aldous: Analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be submitted.

Cerebrospinal Fluid Shunting in Children with Hydrocephalus and Increased Intracranial Pressure Secondary to Human Immunodeficiency Virus–Related Cryptococcal Meningitis

***Basil Enicker*[1,2] *and Colleen Aldous*[2]**

■ BACKGROUND: **Hydrocephalus and increased intracranial pressure secondary to human immunodeficiency virus–related cryptococcal meningitis are rare in children. The role and outcomes of cerebrospinal fluid (CSF) shunting in children are not well reported. We report our experience with CSF shunting in the management of this condition in children over a 14-year period.**

■ METHODS: **This was a retrospective review of data collected from a single neurosurgery unit. Data collected included demographics, clinical characteristics, Glasgow Coma Scale score, lumbar puncture opening pressure, antiretroviral therapy, laboratory results, neuroimaging findings, shunting procedures, complications, and mortality.**

■ RESULTS: **Seventeen children underwent CSF shunting. Median age was 10 years (range, 6–13), most being male (76%). All children were on antiretroviral therapy. Median Glasgow Coma Scale score was 15 (interquartile range [IQR], 14–15). Clinical characteristics included headaches (100%), visual impairment (82%), and seizures (47%). Lumbar puncture opening pressure was >30 cm H_2O in 88% of children. Median CD4 count was 45 cells/μL (IQR, 17–56). Computed tomography brain scans showed hydrocephalus in 14 children (82%). Surgical procedures included ventriculoperitoneal shunts (82%) and lumboperitoneal shunts (18%). Shunt complications included infection (18%) and obstruction (18%). *Staphylococcus aureus* was cultured in all infections. Median follow-up was 45 months (IQR, 7.5–74). Three children (18%) died during the admission period. Ten children (59%) were alive at 1 year follow-up.**

■ CONCLUSIONS: **This study is the largest series reporting on CSF shunting of hydrocephalus and increased intracranial pressure in children with human immunodeficiency virus–related cryptococcal meningitis. Treatment with ventriculoperitoneal shunt and lumboperitoneal shunt regardless of the CD4 count is an important option in suitable children to reduce mortality.**

INTRODUCTION

Cryptococcal meningitis (CM) caused by *Cryptococcus neoformans*, an encapsulated yeast, is a major opportunistic infection in patients infected with the human immunodeficiency virus (HIV) in low- and middle-income countries (LMICs).[1] Cryptococcal antigenemia is reported to be a predictor

Key words
- Children
- Cryptococcal meningitis
- HIV
- Hydrocephalus
- Increased intracranial pressure
- Lumboperitoneal shunt
- Ventriculoperitoneal shunt

Abbreviations and Acronyms
AIS: Antibiotic-impregnated shunt
ART: Antiretroviral therapy
CM: Cryptococcal meningitis
CSF: Cerebrospinal fluid
CT: Computed tomography
DoN: Department of Neurosurgery
GCS: Glasgow Coma Scale
HIV: Human immunodeficiency virus
IALCH: Inkosi Albert Luthuli Central Hospital
ICP: Intracranial pressure
KZN: KwaZulu-Natal
LMIC: Low- and middle-income country
LPOP: Lumbar puncture opening pressure
LPS: Lumboperitoneal shunt
MRI: Magnetic resonance imaging
SA: South Africa
VPS: Ventriculoperitoneal shunt

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of CM in HIV-positive patients with CD4 cell counts <100 cells/μL.[2,3]

CM is considered an AIDS-defining disease, with more than 75% of cases reported in sub-Saharan Africa, where it is associated with 35%–65% mortality.[1] CM is uncommon in children, with reported incidence ranging between 0.85% and 2.9%, even in sub-Saharan Africa, where up to 60% of people diagnosed with HIV live.[1]

In 2017, there were approximately 7.2 million people living with HIV in South Africa (SA), of whom 280,000 were children (0–14 years) and approximately 60% had access to antiretroviral therapy (ART).[4,5] The province of KwaZulu-Natal (KZN) in SA, which is the second most populous province, with a population of approximately 11.5 million, of whom 3.6 million are children (aged 0–14 years), has been the worst affected, with HIV prevalence reported at 27%.[5,6]

The clinical presentation of CM in HIV-positive children includes headaches, visual deterioration, seizures, cranial neuropathies, and altered level of consciousness.[7] Hydrocephalus and increased intracranial pressure (ICP) are rare complications of CM in HIV-positive children, with no known incidence. Aggressive management of hydrocephalus and increased ICP is vital in reducing morbidity and mortality associated with CM.

The World Health Organization published updated guidelines for the diagnosis and management of cryptococcal disease in HIV-infected adults, adolescents, and children.[8] The Southern African HIV Clinicians Society further published updated guidelines regarding prevention, diagnosis, and management of cryptococcal disease among HIV-infected persons particularly in LMICs, where there are limited resources.[9]

Most studies have reported on cerebrospinal fluid (CSF) shunting using either ventriculoperitoneal shunts (VPSs) or lumboperitoneal shunts (LPSs) in the HIV-positive adult population diagnosed with hydrocephalus and increased ICP secondary to CM.[10-14]

The role and outcomes of treating hydrocephalus and increased ICP with VPSs and LPSs in children with HIV-related CM is not well reported, with no available guidelines. When shunting HIV-positive children, there is always a concern that the surgical procedure may be associated with high morbidity and mortality, especially in patients with low CD4 counts.

We report on our institutional experience with the use of VPSs and LPSs in the management of hydrocephalus and increased ICP in children with HIV-related CM over a 14-year period.

METHODS

This was a retrospective observational study conducted at the Department of Neurosurgery (DoN), Inkosi Albert Luthuli Central Hospital (IALCH). IALCH is a tertiary academic hospital located in Durban, KZN, and houses the only neurosurgery unit servicing the entire population in this province, receiving referrals from a large catchment area. Approximately 9.8% of the population in KZN have private medical insurance, leaving the rest of the population to rely on the public health care system.[15]

The inclusion criteria were all HIV-positive children (from birth to 14 years of age), diagnosed with hydrocephalus or increased ICP secondary to CM, referred to the DoN between January 2003 and December 2016 for permanent CSF diversion using either a VPS or an LPS. The diagnosis of CM had been made on the basis of a positive CSF India ink staining result, positive CSF culture, and positive CSF cryptococcal capsular antigen as determined by the latex agglutination method.

The diagnosis of hydrocephalus was made on the admission computed tomography (CT) brain scan, which showed dilated ventricles, with or without loss of sulcal markings, temporal horns >2 mm, transependymal seepage, and associated clinical symptoms.

Increased ICP was diagnosed when lumbar puncture opening pressures (LPOPs) were >25 cm H_2O and when CT brain scan did not show radiologic evidence of hydrocephalus (i.e., normal-size ventricles).

The medical management of CM is performed by the pediatric infectious disease departments located across regional, district, and tertiary hospitals in KZN. These hospitals refer to IALCH for neurosurgery services. All children diagnosed with CM receive an induction phase of 2 weeks of amphotericin B deoxycholate (1.0 mg/kg/day) and fluconazole (12 mg/kg/day), followed by a consolidation phase of fluconazole (6–12 mg/kg/day) for 8 weeks and maintenance phase of fluconazole (6 mg/kg/day).[8,9] When these children were diagnosed with hydrocephalus or persistent increased ICP for more than 10–12 days, despite repeated daily therapeutic LPSs, associated with decreased level of consciousness, deteriorating vision, or progressing neurologic deficits and failure to tolerate LPSs, they were referred to the DoN. There, they were assessed for permanent CSF shunting, if there was no evidence of systemic sepsis. Fixed medium-pressure shunt valves were used in the DoN.

Exclusion criteria were children who were HIV negative and those who did not have CSF confirmation of CM. The data were collected from the hospital integrated information management system (Soarian [Siemens Healthcare GmbH, Erlangen, Germany] and Meditech [Medical Information Technology, Incorporated (MEDITECH), Boston, MA]), which keeps all electronic and radiologic records of patients managed at IALCH and also from the National Health Laboratory Services. The radiologic reports and images were reviewed from the radiology picture archiving and communications system.

The data collected were demographic profile, clinical characteristics, Glasgow Coma Scale (GCS) score on admission and discharge, LPOP, and whether the children were on ART. The laboratory investigation results included CD4 count, viral load, hemoglobin, white cell count, platelets, urea, creatinine, and intraoperative CSF levels.

Data collected from CT and/or magnetic resonance imaging (MRI) brain scans included evidence of hydrocephalus and central nervous system abnormalities caused by CM. We also collected data regarding the type of shunt used, follow-up period, surgical complications, morbidity, and mortality.

Ethical Considerations

The study was granted full ethical approval by the biomedical research ethics committee of the University of KwaZulu-Natal Natal (reference BE 607/17).

RESULTS

A total of 138 HIV-positive patients were referred to the DoN during the study period for permanent CSF diversion after a diagnosis of hydrocephalus and increased ICP secondary to CM. Seventeen of these patients (12%) were children.

The clinical characteristics of the 17 children are summarized in Table 1. The median age was 10 years (range, 6–13) and most were male (n = 13; 76%). All the children were receiving ART. The median GCS score was 15 (interquartile range, 14–15).

The most commonly recorded clinical characteristics were headaches (n = 17; 100%), visual impairment (n = 14; 82%), seizures (n = 8; 47%), paraparesis (n = 5; 29%), meningism (n = 3; 18%), sixth cranial nerve palsy (n = 3; 18%), photophobia (n = 3, 18%), meningism (n = 2; 12%), facial weakness (n = 2; 12%), nausea and vomiting (n =2; 12%), hearing impairment (n = 1; 6%), hallucinations (n = 1; 6%), and photophobia (n = 1; 6%).

The LPOPs were between 25 and 30 cm H_2O in 2 children (12%), whereas in the remainder (n = 15; 88%), they were >30 cm H_2O. The CT brain scan showed features of hydrocephalus in 14 children (82%) (Figure 1), whereas in the remainder (n = 3; 18%), the ventricles were normal size. An MRI brain scan (Figure 2) was performed in 2 children and showed gelatinous pseudocysts (12%). The admission viral load results were available for 8 children (47%) and are shown in Table 1. The results of laboratory investigations are shown in Table 2.

Fourteen children (82%) had VPSs, whereas LPSs were inserted in 3 (18%). In children who underwent VPS insertion, 12 (86%) received antibiotic-impregnated shunts (AIS), whereas the remainder (n = 2; 14%) received non-AIS shunts. All LPSs were non–antibiotic impregnated. The headaches resolved in all the children after shunting.

Shunt complications occurred in 6 children (35%), which included shunt infection in 3 (18%) children and mechanical obstruction in the remainder (which were VPSs). The shunt infections were recorded in 2 children who received AIS VPSs and 1 child who received LPS. The organism cultured in all 3 cases was *Staphylococcus aureus*.

The mean follow-up period was 45 months (interquartile range, 7.5–74). Three children (18%) died during the admission period at IALCH. Two died within 6 months of shunt procedures. The details are given in Table 1. Ten children (59%) were alive at 1 year follow-up.

DISCUSSION

Our study is the largest case series to report on permanent CSF shunting in children with hydrocephalus and increased ICP secondary to HIV-related CM. A total of 17 children were referred for shunting over a 14-year period in a single neurosurgery unit located in a province with the highest prevalence of HIV in SA.[5,6]

The small number of HIV-positive children who underwent neurosurgical management in relation to the study period could be explained by the steady decline in the number of new HIV infections as a result of the PMTCT (Prevention of Mother to Child Transmission) program in SA, which reduced the HIV transmission rate to <1% over the years.[16]

The availability of ART in SA has also ensured the reduction of HIV viral load and repletion of CD4 T cells, resulting in an improved functional immune system, ensuring that most children with HIV are not vulnerable to opportunistic infections, such as CM.[17,18]

The incidence of HIV-positive children requiring permanent CSF diversion using either VPSs or LPSs is unknown both locally and internationally. Rowhling et al.[19] in a series of 43 children with tuberculous meningitis and hydrocephalus reported only 2 children (5%) who were HIV positive. Previous experience reported in our unit has been on the outcome of VPS insertion in HIV-positive patients with tuberculous meningitis and hydrocephalus, based on case series of 30 patients, including only 5 children.[20]

The median age in our study was 10 years, which is similar to that reported by other investigators.[21]

All children in the current study were on ART and this high rate of ART therapy in children has been reported by other investigators.[21]

Headaches (100%) and visual impairment (82%) were the most common clinical presentation in children with hydrocephalus and increased ICP in our study. Headaches are often the earliest sign of increased ICP and respond quickly to normalization of ICP after diversion of CSF. If left untreated, hydrocephalus and increased ICP result in visual deterioration through impaired cerebral circulation to the optic apparatus. In the case of CM, visual deterioration can also be a result of direct fungal infiltration of the optic pathways and preoptic meninges, causing adhesive arachnoiditis and compression of the optic nerve.[22]

Seizures were reported in 47% of children in our study, Pastick et al.[23] reported seizures in 28% of patients with HIV-associated CM. The risk factors for seizures were hydrocephalus, increased ICP, and high CSF fungal burden.[23] These investigators noted that seizures were associated with increased mortality at 10 weeks. The 3 cases of patients with in-hospital death in our study presented with seizures, with 1 child dying after status epilepticus.

One child presented with hearing impairment, presenting with LPOP >30 cm H_2O. Graybill et al.[24] proposed that hearing loss occurred frequently in patients with pressures >35 cm H_2O. Hearing loss can also be caused by the invasion of the internal auditory canal by cryptococcal organisms and degeneration of the vestibular cochlear nerve.[25]

The median CD4 count was 45 cell/μL in the current study; other investigators have also reported low CD4 count in HIV-positive patients with cryptococcosis.[26,27] Most children (88%) in the current study presented with LPS opening pressures >30 cm H_2O. It has been postulated that hydrocephalus and increased ICP is caused by the obstruction of CSF outflow by blockage across the arachnoid villi and second by accumulation of the fungal polysaccharide in the arachnoid villi and subarachnoid spaces, thus obstructing CSF reabsorption.[28,29]

Hydrocephalus was diagnosed on CT in 82% of children in the current study. Khan and Hiesgen,[30] in a study of CM in HIV-positive patients, reported findings of normal CT brain scans (13.3%), hydrocephalus (16.7%), gelatinous pseudocysts (23.3%), and dilated Virchow-Robin spaces (26.7%), and Baddley et al.[13] reported hydrocephalus in 14.3% of patients undergoing neuroimaging. Hydrocephalus secondary to CM varies widely in the literature and has been reported in 9%–63% of patients.[10,31]

Table 1. The Clinical Profile of the 17 Children Who Underwent Cerebrospinal Fluid Shunting for Hydrocephalus and Increased Intracranial Pressure Secondary to Human Immunodeficiency Virus–Related Cryptococcal Meningitis

Case Number	Age (years)/ Gender	Clinical Presentation	GCS	CD4 Count (Cells/ μL)	Viral Load (Copies/mL)	Antiretroviral Therapy	Lumbar Puncture Opening Pressure (cm H_2O)	Computed Tomography/MRI Brain Findings	Shunt Type	Shunt Complication and Number of Days to Complication	Follow-up Period (months)	Outcome at Last Visit
1	10/M	Headaches, visual impairment, paraparesis	15	17	17200	Yes	38	Features of hydrocephalus	VPS (non-AIS)	None	8	GCS score 15/15; headaches improved
2	9/M	Headaches, seizures, visual impairment, meningism	14	51	N/A	Yes	35	Normal size ventricles	LPS	None	None; died during admission period	In-hospital death 20 days after admission in intensive care unit because of respiratory complications
3	10/M	Headaches, visual impairment, meningism, hearing impairment	15	588	72	Yes	38	Features of hydrocephalus	VPS (AIS)	Mechanical obstruction diagnosed twice; first episode 92 days after procedure; second episode 31 days after procedure; CSF culture was negative on both episodes	59	GCS score 15/15; headaches improved; no improvement of visual impairment
4	12/F	Headaches, nausea, vomiting, photophobia, diplopia, facial weakness and sixth cranial nerve palsy	15	64	N/A	Yes	35	Normal-size ventricles; MRI brain showed bilateral basal ganglia gelatinous pseudocysts	LPS	None	31	GCS score 15/15; headaches improved
5	6/M	Headaches, paraparesis, visual impairment, seizures	14	48	574	Yes	32	Features of hydrocephalus	VPS (AIS)	Shunt infection diagnosed 64 days after shunt procedure; *Staphylococcus aureus* cultured from CSF	19	In-hospital death 592 days after first shunt procedure; developed toxic epidermal necrolysis, affecting approximately 80% body surface area; developed pneumonia and sepsis
6	10/M	Headaches, sixth nerve palsy, visual impairment, skin rash, seizures	14	56	N/A	Yes	36	Features of hydrocephalus. MRI brain: multiple gelatinous pseudocysts involving frontal, parietal and occipital areas	VPS (AIS)	Mechanical obstruction diagnosed twice; first episode 28 days after first procedure; second episode 23 days after second procedure; CSF culture negative on both episodes	3	In-hospital death; died 92 days after first admission after status epilepticus
7	8/F	Headaches, seizures, visual impairment	14	45	N/A	Yes	45	Features of hydrocephalus	VPS (AIS)	None	86	GCS score 15/15; headaches improved
8	13/M	Headaches, vomiting, photophobia, seizures, visual impairment	14	49	<20	Yes	35	Features of hydrocephalus	VPS (AIS)	None	86	GCS score 15/15; learning difficulties reported

GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; M, male; VPS, ventriculoperitoneal shunt; AIS, antibiotic-impregnated shunt; N/A, not available; LPS, lumboperitoneal shunt; CSF, cerebrospinal fluid; F, female.

Continues

Table 1. Continued

Case Number	Age (years)/ Gender	Clinical Presentation	GCS	CD4 Count (Cells/ µL)	Viral Load (Copies/mL)	Antiretroviral Therapy	Lumbar Puncture Opening Pressure (cm H_2O)	Computed Tomography/MRI Brain Findings	Shunt Type	Shunt Complication and Number of Days to Complication	Follow-up Period (months)	Outcome at Last Visit
9	12/F	Headaches, seizures, visual impairment, facial weakness	15	103	7203	Yes	40	Features of hydrocephalus	VPS (AIS)	None	66	GCS score 15/15; persistent visual impairment; headaches improved
10	9/M	Headaches, nausea and vomiting	15	16	Undetectable	Yes	30	Features of hydrocephalus	VPS (AIS)	Shunt infection diagnosed 153 days after procedure; *Staphylococcus aureus* cultured from CSF	9	GCS score 15/15; headaches improved
11	10/M	Headaches, nausea, vomiting, meningism	15	35	36	Yes	35	Features of hydrocephalus	VPS (AIS)	None	80	GCS score 15/15: headaches improved; learning difficulties reported
12	10/M	Headaches, visual impairment, paraparesis	15	17	8400	Yes	38	Features of hydrocephalus	VPS (AIS)	None	72	GCS score 15/15; headaches improved
13	10/M	Headaches, visual impairment	15	45	N/A	Yes	29	Features of hydrocephalus	VPS (AIS)	None	1	GCS score 15/15, headaches improved; learning difficulties reported
14	8/M	Headaches, visual impairment, paraparesis, hearing impairment	9	45	N/A	Yes	40	Features of hydrocephalus	VPS (AIS)	Mechanical obstruction diagnosed twice; first episode at 998 days after first procedure; second episode at 1124 days after second procedure; CSF culture negative in both episodes	128	GCS score 15/15, headaches improved; paraparesis improved
15	7/M	Headaches, visual impairment, seizures, paraparesis	15	70	N/A	Yes	35	Features of hydrocephalus	VPS (AIS)	None	70	GCS score 15/15, learning difficulties reported; paraparesis and headaches improved
16	13/F	Headache, visual impairment, photophobia, sixth nerve palsy	15	11	N/A	Yes	35	Normal-size ventricles	LPS	Shunt infection and associated septic wound diagnosed 30 days after shunt procedure; *Staphylococcus aureus* cultured	6	GCS score 15/15, headaches improved
17	12/M	Headaches, seizures, hallucinations, visual impairment, skin rash	15	7	N/A	Yes	38	Features of hydrocephalus	VPS (non-AIS)	None	3	GCS score 15/15, headaches improved

GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; M, male; VPS, ventriculoperitoneal shunt; AIS, antibiotic-impregnated shunt; N/A, not available; LPS, lumboperitoneal shunt; CSF, cerebrospinal fluid; F, female.

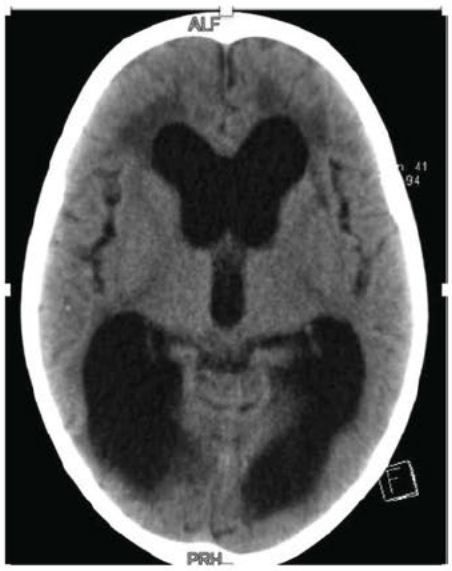

Figure 1. Noncontrast computed tomography brain scan of an 8-year-old child diagnosed with hydrocephalus secondary to human immunodeficiency virus related cryptococcal meningitis.

Table 2. Laboratory Results of the 17 Human Immunodeficiency Virus–Positive Children with Cryptococcal Meningitis

Parameter	Median	Interquartile Range
CD4 count (cells/μL)	45	17–56
Creatinine (mmol/L)	42	29–50
CSF glucose (mmol/L)	3.3	2.3–3.7
CSF lymphocytes (/μL)	2	0–6
CSF neutrophils (/μL)	0	0
CSF protein (g/L)	0.27	0.14–0.83
Hemoglobin (g/dL)	10.5	8.4–11.3
Platelets ($\times 10^9$/L)	357	317–532
Urea (mmol/L)	4.6	3.7–5.6
White cell count ($\times 10^9$/L)	5.58	8.4–11.3

CSF, cerebrospinal fluid.

Despite increased LPOPs, some patients do not show dilated ventricles on neuroimaging, as shown in 18% of children in the current study. The mechanism for this finding is not clear, but some investigators[32] have postulated that cryptococcal capsular polysaccharides coating the surfaces of the brain, as well as within the ependymal tissue, lead to failure of the ventricles to dilate after increase in the volume of CSF.

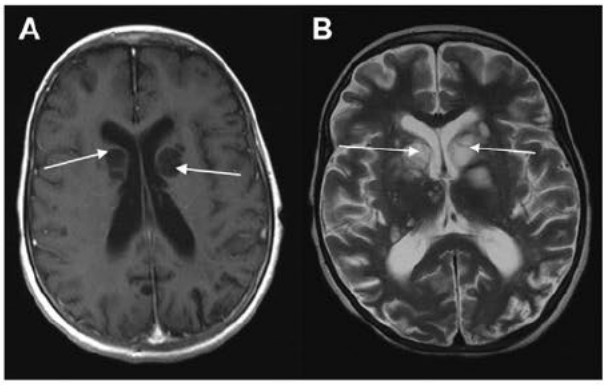

Figure 2. Magnetic resonance imaging brain scans of a 12-year-old child diagnosed with human immunodeficiency virus related cryptococcal meningitis. The T1-weighted postcontrast magnetic resonance imaging (**A**) shows nonenhancing intra-axial hypointense lesions (*arrows*), which are gelatinous pseudocysts, whereas on T2-weighted image (**B**), the gelatinous pseudocysts are hyperintense (*arrows*), located in the periventricular areas and basal ganglia.

The Infectious Diseases Society of America 2010 guidelines[31] for the management of cryptococcal disease recommended early ventricular CSF diversion for noncommunicating hydrocephalus in CM.

In patients with increased ICP, permanent CSF diversion with either VPS or LPS should be performed only when patients have received appropriate antifungal therapy and have failed management of increased ICP with therapeutic LPSs. VPSs can be placed during the active infection period, without the need to wait for complete sterilization of CSF, when clinically necessary, if patients are receiving appropriate medical therapy.

Concerns had been increased previously regarding the use of LPSs in children, because of potential cerebellar tonsillar herniation, overdrainage, failure to assess shunt failure (including tapping the shunt), increased rate of shunt infections, and revisions.[10,33,34] Singh and Vajpeyi,[35] in a study comparing LPSs versus VPSs in postmeningitis communicating hydrocephalus in children, reported LPS infection rate of 5.4% and blockage rate of 10.8% compared with a VPS infection rate of 16.9% and blockage rate of 9.4%. The availability of neuronavigation has also ensured that even patients with small or normal-size ventricles can undergo VPS placement safely.

In this study, shunt complications were reported in 6 children, in 3 of whom the cause was infection. Reports suggest that mechanical shunt obstruction could be caused by high titers of cryptococcal capsular polysaccharide in HIV-positive patients[24]; however, this was not specifically assessed in the current study.

Tang[28] in a series of 14 patients reported no shunt-related morbidity or mortality, whereas Liliang et al.,[36] in a series of 27 patients. reported shunt complication in 4 patients (15%), and no infections were reported. However, in both studies, patients were HIV negative.

Woodworth et al.[12] reported no shunt complications in 2 HIV-positive patients who underwent VPS procedure. Cherian et al.[10] in a series of 13 HIV-positive patients with CM who underwent shunting reported a 15.3% shunt revision rate caused by over-drainage and shunt malfunction. No infections were reported.

Staphylococcus aureus was cultured in 3 children diagnosed with shunt sepsis. Coagulase-negative *Staphylococci* make up 14%–60% of shunt infections, and *Staphylococcus aureus* is responsible in 18% of cases.[37,38] The shunt complication rate in children is reported at about 5%–9%[39] and occurs mostly within 3 months of surgery. However, in LMICs, shunt infection rates can range from 8.6% to 50%.[40]

Because of concerns regarding high shunt infection rate in LMICs, a local study reported on the efficacy of AIS in reducing shunt infection.[41] Hence, most children (86%) in the current study received AIS. Govender et al.[41] reported an overall 12% shunt infection rate, with fewer shunt infections occurring in AIS versus the standard group (non-AIS). The study also reported gram-negative (*Acinetobacter* species) shunt infection in an HIV-positive infant.[41] Antibiotic or silver versus standard ventriculoperitoneal shunts (BASICS): a multicentre, single-blinded, randomized trial and economic evaluation, has provided evidence for support of AIS in reducing shunt-related infection.[42]

Learning difficulties were reported in 24% of children at follow-up, which was not surprising because CM is associated with cognitive impairment in about 70% of patients.[43,44]

The mortality from CM remains highest in LMICs and contributing factors are unavailability and high cost of first-line antifungal drugs, drug-related adverse events, complications of hydrocephalus, increased ICP, and immune reconstitution inflammatory syndrome.[45] Cherian et al.[10] reported that 54% patients who were discharged remained alive with follow-up >1 year.

Limitations

The low sample number in the current study limits our ability to make statistically significant inferences. Data for admission viral loads were not available for all the children. The retrospective nature of the study design, and the fact that it is a single-center study, make it subject to potential bias.

CONCLUSIONS

To our knowledge, this study represents the largest series reporting CSF shunting of HIV-positive children with hydrocephalus and increased ICP secondary to CM. The shunt infection rate in the current study was within the rates reported in LIMCs, despite most children presenting with low CD4 counts. The disease and its complications cause devastating mortality and disability as a result of insults on the child's growing brain. ART and PMTCT have played an important role in reducing the prevalence of this disease and limiting complications. Aggressive treatment of hydrocephalus and increased ICP, regardless of the CD4 count, is an important factor for neurosurgeons to consider to reduce mortality.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Basil Enicker: Conceptualization, Methodology, acquisition of data, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, final approval of the version to be submitted. **Colleen Aldous:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing, final approval of the version to be submitted.

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Chapter 7: Synthesis and Discussion

7.1 Introduction

Paediatric hydrocephalus remains a significant health challenge in KwaZulu-Natal (KZN), exacerbated by the high prevalence of HIV and tuberculosis (TB) in the province [1]. In KZN, the burden of hydrocephalus, including its interaction with HIV is worsened by socioeconomic disparities and limited access to medical and neurosurgical services.

The chapters of this thesis form a cohesive body of work that addresses the original research question of understanding the burden and outcomes of paediatric hydrocephalus in KZN, examining its epidemiology, treatment outcomes, and the interaction with HIV, TB and cryptococcal meningitis (CM). The thesis also investigated the impact of proximity to centralized neurosurgery services on treatment outcomes. In the thesis, we documented numerous factors associated with poor clinical outcomes in children diagnosed and treated for hydrocephalus.

7.2 Synthesis of Key Findings and Contributions to Knowledge

This PhD brings together multiple studies investigating paediatric hydrocephalus, with a particular focus on low- and middle-income countries (LMICs) and the influence of infections such as HIV, TB, CM, neurocysticercosis and pyogenic infection on clinical presentation and outcomes. The research begins with a scoping review that highlights the global trends and gaps in current literature, particularly the lack of data on the impact of HIV co-infection on mortality. It identifies post-infectious hydrocephalus (PIH) as the most common aetiology associated with mortality in children diagnosed with hydrocephalus, with contributing factors including comorbidities, malnutrition, and complications from surgical interventions.

The epidemiological study conducted over 20 years at a single neurosurgery unit provides one of the largest datasets on paediatric hydrocephalus. The study reveals that central nervous system (CNS) infections, notably TB, are significant contributors to the disease burden in KZN. A decline in hydrocephalus cases in later years is attributed to the establishment of a satellite neurosurgery unit located 78.1 km from Inkosi Albert Luthuli Central Hospital (IALCH). Factors associated with mortality included children aged one year and older at surgery, complex cases from tertiary hospitals, and comorbidities such as pneumonia and shunt complications.

A comparative analysis of treatment outcomes based on proximity to the centralized neurosurgery unit highlights the disparity in outcomes. Children living farther from the neurosurgery unit at IALCH experienced higher rates of ventriculoperitoneal shunt (VPS) failures, emphasizing the need for decentralizing paediatric neurosurgery services in KZN to ensure timely diagnosis and treatment, closer to where the greatest need is located. This is particularly important since children constitute approximately 36% of the 12 million population of KZN.

The study further explores the complex interaction between HIV-related infections and hydrocephalus. Tuberculous meningitis (TBM) and CM complicate treatment in HIV infected children due to delayed presentation and advanced CNS damage, even with cerebrospinal fluid (CSF) diversion. Children with advanced HIV due to low CD4 counts face additional risks, including surgical and anaesthetic complications. Co-morbid conditions such as immune reconstitution inflammatory syndrome (IRIS) and toxic epidermal necrolysis (TEN) further complicate outcomes due to drug interactions.

We conclude by highlighting the high morbidity and mortality associated with TBM and CM hydrocephalus in HIV-infected children. The findings point to the importance of early diagnosis, preventative measures, and timely treatment to mitigate the progression of the disease and improve the outcomes of affected children.

7.3 Strengths of the Study

The study has several strengths that contribute the field of neurosurgery and global health. These include:

7.3.1 Detailed Scope of the Study

The study covers multiple facets of paediatric hydrocephalus, including epidemiology, the impact of CNS infections, impact of proximity to centralised neurosurgery services and the intersection with HIV. This detailed approach provides a holistic understanding of the disease and its contributors.

7.3.2 Longitudinal Data

The research is based on 20 years of data from a single neurosurgery unit, making it one of the largest and most extensive studies on paediatric hydrocephalus in a LMIC setting. This long-term perspective enables a detailed analysis of the trends over time. By focusing on paediatric hydrocephalus in KZN, the study fills an important gap in global health research, as this region and SA in general faces a quadruple burden of disease—HIV/AIDS, TB, violence, and maternal and child mortality—which has been described as a collision of epidemics [2,3].

7.3.3 Advocating for Expansion of Neurosurgery Services

The research demonstrates the important role that proximity to centralized neurosurgery services plays on surgical outcomes of children with hydrocephalus. It highlights health system disparities within KZN and found that children living farther from the neurosurgery unit at IALCH experience higher VPS complication rates and present later to the neurosurgery unit for treatment of complications than living in the Metropolitan area, where IALCH is located. This finding provides evidence for the need to decentralise neurosurgery services in KZN, which could lead to improved access and outcomes for children in rural areas.

7.3.4 HIV Infection and Paediatric Hydrocephalus

The study outlines in detail the relationship between HIV and hydrocephalus secondary to TBM and CM in paediatric population, where such interactions are less studied, particularly KZN with documented HIV prevalence of 27%, which is higher than the national average of 20.6% [4]. HIV exacerbates hydrocephalus primarily by increasing the risk of opportunistic CNS infections, due to immunosuppression. This interaction has important implications for diagnosis, as HIV-related CNS infections often present with normal or atypical CSF and radiological findings, leading to delays in diagnosis. These delays have dire consequences in KZN, particularly in rural areas due to limited laboratory infrastructure. Delays in diagnosis result in postponement of initiation of treatment further worsening clinical outcomes.

By linking HIV infection to poorer hydrocephalus outcomes in children, the study reinforces the necessity of integrating HIV management with neurosurgical care and multidisciplinary management which includes neurosurgeons, paediatricians, infectious disease specialists, dieticians, social workers, psychologists and rehabilitation specialists due to associated neurological deficits.

7.3.5 Multifactorial Analysis of Mortality Risk and Actionable Findings:

The identification of specific factors associated with mortality, such as VPS complications, pneumonia, metabolic disturbances such as hyponaetraemia, altered level of consciousness, disseminated TB and low CD4 counts, offers potential areas for intervention. The results are actionable, and suggest opportunities for improving outcomes through nuanced targeted interventions, such as prevention, early diagnosis, holistic management focusing not only on the brain, but other body systems and improved post-operative care.

7.3.6 Real-World Relevance

The study is based on real-world clinical challenges faced in resource-limited settings, making its findings highly applicable similar environments, where the burden of paediatric hydrocephalus, infections, congenital disorders, trauma are significant.

7.4 Limitations of the Study

The study has several limitations that should be considered when interpreting the findings:

7.4.1 Single-Centre Data

Although the study spans 20 years, it is based on data from a single neurosurgery unit. This limits the generalisability of the findings to other regions e.g. high-income countries (HIC) and particularly those with different healthcare systems, disease prevalence, resources, and patient populations. SA has nine provinces and there are interprovincial variations in health infrastructure, which might also make the results not generalisable to the rest of SA.

7.4.2 Lack of Control Group

The study does not include a control group for comparison with HIV-infected group of children, which is an important limitation.

7.4.3 Retrospective Design

Some parts of the study are based on retrospective data analysis, which is subject to potential biases such as missing data, inconsistencies in medical records.

7.4.4 Lack of documentation of external mortality

The lack of documentation of deaths occurring outside of the Inkosi Albert Luthuli Central Hospital neurosurgery unit, represents a limitation of this study.

7.5 Future Research

Future research could build upon the current study's findings and address some of the identified gaps. The following are suggestions for future research:

7.5.1 Prospective study to identify long-term cognitive and quality of life outcomes between HIV-infected and uninfected children with hydrocephalus

7.5.2 Investigating biomarkers of CNS injury in from the CSF HIV-infected children

7.5.3 Measuring ART drug concentrations in the CSF of HIV-infected children

7.5.4 Future studies to compare outcomes of children with hydrocephalus treated at IALCH versus those treated at Greys Hospital, including other decentralised sites in future e.g. VPS complications, mortality and access to care.

7.5.5 Multicentre studies across South Africa to document variations in regional trends and outcomes. This will be extended to other sites located in LMICs.

7.5.6 Further research should focus quality of life in children with hydrocephalus in KZN.

7.5.7 Future studies on the cost of managing paediatric hydrocephalus in KZN. This will include costs related to travelling costs, days in hospital, time in theatre, medication, surgical implants, investigations and treatment of complications

7.5.8 Future studies should focus on identifying the genetic factors responsible for congenital hydrocephalus in KZN. Understanding genetic causes is essential in addressing the burden of disease and creating effective interventions.

7.6 Recommendations

The thesis introduces a novel framework called **AGILE-WIN strategy** to reduce burden of paediatric hydrocephalus in KZN, and particularly in LMICs. **AGILE-WIN strategy** is an acronym which stands for **A**ntenatal care services, **G**enetic counselling, **I**nfection control, **L**ocalized (decentralised) services, **E**arly diagnosis, **W**orkforce improvement, **I**mmunization programmes and **N**etworked reporting. This model as suggests a flexible, pro-active and action-oriented approach to managing hydrocephalus in LMICs and offers a pathway for reducing mortality and long-term disability

A. Antenatal Care Services

- This calls for strengthening of maternal health services to identify at-risk pregnancies early.

- The promotion and access to antenatal care, skilled birth attendance and post-natal care are important for health education and treatment of maternal infections, including non-communicable diseases that can result in CNS complications of the neonate.
- In SA, antenatal clinic first-visit coverage improved from 74.9% between 2015 and 2016 to 83.2% between 2019 and 2020 [5].
- Deliveries of children in healthcare facilities increased from 83,4% in 1998 to 96,7% in 2016 [6], resulting in a drop in home deliveries from 14% in 1998 to 4% in 2016 [3]
- The prevention of mother-to-child transmission programme has been effective in reducing HIV infection in newborns [7,8], and antenatal care visit provide opportunities for voluntary counselling and testing for HIV, in order initiate therapy early when the expecting mothers test positive.
- Antenatal care clinics also provide an opportunity for encouragement of folic acid intake which is important for the reduction of the incidence of neural tube defects, which contribute to the aetiology of hydrocephalus.

A. Genetic Counselling

- Collaboration between genetic counsellors, neurosurgeons, and paediatricians can lead to a more holistic approach to managing paediatric hydrocephalus cases in KZN.
- Understanding genetic risks and inheritance patterns will enable the development of individualized care plans tailored to each patient's genetic profile.
- When genetic abnormalities are identified, interventions can be optimized through preventive care strategies and targeted management, addressing the genetic factors contributing to the disease burden in the KZN.

B. Infection Control

The following strategies should be implemented

- **Enforcement of Infection Control Protocols**: Adherence to strict infection control measures during and after shunt surgery can significantly reduce shunt-related infections.

- **Antibiotic-impregnated shunts (AIS)**: These are effective in reducing infection rates, validated by both local and international studies [9,10]. Despite their success, the high cost of AIS remains a barrier to widespread use in LMICs, however, we recommended investing in these alternatives, as the costs of treating shunt infections are also substantial due to prolonged admission, antibiotic usage and repeated surgical procedures.
- **Endoscopic Third Ventriculostomy and Choroid Plexus Coagulation**: Given its lower complication rate and higher success in specific infant populations, particularly in Sub-Saharan Africa, endoscopic third ventriculostomy (ETV) and choroid plexus coagulation (CPC) should be considered as the first-line surgical option where feasible [11-13].
- **Continued Professional Development**: Regular training for neurosurgeons on infection control best practices is essential to prevent post-surgical infections. This must be intentional as healthcare service delivery often takes priority over research and professional development in regions with a high burden of disease.

C. Localised (decentralized) services

- Neurosurgery services in SA remain largely centralized in urban metropolitan areas, a pattern common in many LMICs, thus limiting access for patients, particularly children from rural regions.
- This thesis advocates for investment in healthcare infrastructure and the decentralization of neurosurgery services by establishing neurosurgery units across all tertiary hospitals in KZN.
- In KZN, over half of the paediatric hydrocephalus cases originate from rural areas, highlighting the need for decentralized as children from rural areas travel long distances for life-saving procedures.
- KZN is divided into three healthcare regions, each with its own tertiary hospital. Inkosi IALCH serves as the central hospital in KZN, while Victoria Mxenge (formerly King Edward VIII), Greys and Ngwelezane Hospitals are tertiary hospitals that serve Areas 1, 2, and 3, respectively. In 2018, a satellite neurosurgery unit was established at Greys Hospital, prioritizing paediatric hydrocephalus cases in Area 2.

- This led to a significant reduction in paediatric hydrocephalus cases at IALCH from 2018 onwards, a trend that began before the COVID-19 pandemic.
- We advocate for this model to be replicated in Area 3.

D. Early Diagnosis

- Raising community awareness about hydrocephalus is important to reduce the stigma associated with having a child with hydrocephalus, particularly when associated with an enlarged head.
- This contributes to delays in seeking medical attention, resulting in poor neurological outcomes and increasing complications.
- Outreach services to medical practitioners working in centres without neurosurgery services will help improve early diagnosis and referral of paediatric hydrocephalus cases.
- Regular follow-ups are important as they result in early detection of shunt complications. Expanding telemedicine services will also facilitate remote consultations with specialists, making expert care more accessible.
- The use of biomarkers for early prognostication, in cases such as TBM, can assist with risk stratification and create tailored treatment plans, ultimately improving patient outcomes [14].

E. Workforce Improvement

- Investing in the training of neurosurgeons and other healthcare professionals is crucial for improving healthcare access and outcomes, by staffing decentralized neurosurgery units.
- Currently, in KZN 30 % of neurosurgeons work in the public healthcare system, serving 90.2% of the 12 million population who lack private medical insurance. Meanwhile, 70% of neurosurgeons serve only 9.8% with private medical insurance.
- This imbalance is reflective of the broader healthcare landscape in SA. Similar challenges are seen across Africa [15-17].

F. Immunization Programmes

- While neurosurgery is a highly specialized field, it also intersects with public health concerns, particularly in the prevention of PIH.
- PIH can largely be prevented through education and public health initiatives.
- Strengthening TB and HIV screening and treatment programs in paediatric populations is important for preventing the progression of these infections into hydrocephalus.
- One key preventive measure is ensuring widespread vaccination to combat infections which can be complicated by hydrocephalus.
- In SA, the BCG vaccine has been universally administered to all newborns since 1973 to reduce the severity of TB [18].
- BCG vaccine is a cost-effective intervention against severe childhood TB, particularly TBM, and should be used in high-incidence countries as a supplementary strategy alongside the anti-TB drugs [19].
- Similarly, vaccines targeting bacterial forms of meningitis have been introduced over time. The meningococcal conjugate vaccine, which protects against *Neisseria meningitidis*, has been available in SA since 2014 [20].
- The pneumococcal conjugate vaccine (PCV), initially introduced in SA in 2008 and updated to PCV13 in 2011, offers protection against *Streptococcus pneumoniae* [21,22].
- The *Haemophilus influenzae* type b (Hib) vaccine, first introduced in SA in 1995 as part of the Expanded Programme on Immunization (EPI), is administered from six weeks [23].

G. Networked Reporting

This strategy involves the development of a centralized database or registry for paediatric hydrocephalus in SA and collaborating with other researchers in LMICs. The benefits include

- **Data-Driven Decision Making:** This would provide real-time data that can identify regional disease patterns, risk factors and complications. Compiling data across multiple centres will provide information regarding the unique challenges of hydrocephalus in SA, including other LMICs, where CNS infections play a significant

role in disease progression. The registry would provide policymakers with reliable data on the prevalence and burden of hydrocephalus, enabling more informed decisions regarding resource allocation, healthcare infrastructure, and funding.

- **Enhanced Research Capabilities**: Pooling data across multiple centres allows for stronger research designs, larger sample sizes, and the ability to conduct multicentre trials. A centralized database and registry would facilitate large-scale research projects, collaborations, and longitudinal studies, which are currently lacking in many African settings and SA in particular. This will foster collaboration between African neurosurgeons, researchers, and international partners, accelerating the progress in paediatric neurosurgery research.

- **Improved Patient Care**: Information regarding complications, risk factors, and outcomes will lead to better clinical protocols and reduce the burden of shunt-related complications. Tracking the success rates, complications, and long-term patient outcomes of these CSF diversion procedures would help clinicians identify best practices and areas for improvement in surgical care. This will support evidence-based practice by generating regional guidelines aimed at improving outcomes of paediatric hydrocephalus in SA, also applicable to other LMICs.

7.7 Conclusion

Paediatric hydrocephalus is both preventable and treatable, but only with timely and effective care. This thesis highlights the impact of proximity to centralized neurosurgery services and HIV status on neurosurgical outcomes in regions with high burdens of HIV, TBM, CM and pyogenic meningitis. Socioeconomic factors, co-morbidities, and access to healthcare play important roles in outcomes. Hydrocephalus should be recognized not only as a surgical issue but as a public health priority. Implementing strategies such as the AGILE-WIN model and improving access to care in KZN can reduce the devastating effects of hydrocephalus, improve outcomes, and free up resources for broader healthcare investments.

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Appendices

Appendix 1

University of KwaZulu-Natal

College of Health Sciences

School of Clinical Medicine

Paediatric hydrocephalus in the Province of KwaZulu-Natal, South Africa: A study towards understanding the burden of disease and developing an integrated model aimed at improving outcomes

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A. EXECUTIVE SUMMARY

The study aims to describe the clinical characteristics, aetiology, management and outcomes of hydrocephalus in the paediatric population of KwaZulu−Natal (KZN), South Africa (SA). The study will also help in better understanding the prevalence of paediatric hydrocephalus in KZN and report on the evolving spectrum of this condition in KZN over a 20-year period; since the commencement of neurosurgery services at the state-of-the-art Inkosi Albert Luthuli Central Hospital (IALCH).

The study hopes to answer the following questions:

a. What is the burden of paediatric hydrocephalus in a single neurosurgery centre that caters for the entire Province of KZN?
b. Is there a disparity in outcome between urban and rural children with hydrocephalus managed in KZN, SA?
c. What is the financial impact of treating hydrocephalus in KZN?
d. How can a model be developed to improve outcomes of children with hydrocephalus, in KZN?
e. What is the impact of HIV/AIDS, malnutrition and immunization programs on this disease entity?

The outcomes of the study will be used to implement a standardized set of protocols focused on children with hydrocephalus that will help in developing a prognostic predictive model suitable for our environment.

Hydrocephalus is one of the common surgically treated neurological problems affecting infants, children, and adolescents in a neurosurgical practice. The incidence of paediatric hydrocephalus varies depending on the geographical location; with some reports estimating a frequency of 1 in every 500 children.

The aetiology is multifactorial: genetic causes include X-linked aqueductal stenosis, myelomeningocoele (MMC) and Chiari malformation; while acquired causes include intra-ventricular haemorrhage, trauma, tumours, and infections. The burden of disease is substantial as hydrocephalus can have an effect on development, as well as an impact on overall quality of life. The need for frequent surgical interventions in the course of a child's life due to frequent cerebrospinal (CSF) shunting device malfunctions and complications significantly affect quality of life for the child and family at large. The need for improvements in medical interventions and development of integrated predictive model, holistic multidisciplinary involvement is an urgent priority in KZN, SA.

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A. ABBREVIATIONS AND ACRONYMS

AIDS	**Acquired immunodeficiency syndrome**
ANC	**Antenatal care**
CSF	**Cerebrospinal fluid**
CT	**Computerized tomography**
ETV	**Endoscopic third ventriculostomy**
EVD	**External ventricular drain**
IALCH	**Inkosi Albert Luthuli Central Hospital**
HIV	**Human immunodeficiency virus**
ICP	**Intracranial pressure**
IVH	**Intra-ventricular haemorrhage**
KZN	**KwaZulu-Natal**
MRI	**Magnetic resonance imaging**
NSOPD	**Neurosurgery out-patient department**
OFC	**Occipito-frontal circumference**
PHHC	**Post-haemorrhagic hydrocephalus**
TB	**Tuberculosis**
VP	**Ventriculo-peritoneal**

1. BACKGROUND AND LITERATURE REVIEW

1.1 Defining the Clinical Problem

Hydrocephalus is defined as active distention of the ventricular system of the brain resulting from inadequate passage of cerebrospinal fluid (CSF) from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation resulting in dilatation of the ventricles and raised intracranial pressure (ICP) [1-3].

Hydrocephalus as a disease entity has been neglected in the South African health landscape, with no major awareness campaigns directed towards the public and medical professionals regarding understanding the disease and its impact on society at large.

South Africa (SA) faces an immense burden of disease, mainly from infectious diseases, with human immunodeficiency virus (HIV) and tuberculosis (TB) dominating the health landscape. Trauma-related conditions also pose a significant challenge to an already overstretched health care system. The burden of neurological conditions, in particular hydrocephalus, is under reported in the South African health landscape, with no major awareness campaigns directed towards the public and medical professionals regarding understanding this disease entity and its impact.

We are of the opinion that there is no better time for the spotlight to be directed towards neurosurgical conditions in SA, more specifically paediatric hydrocephalus in KwaZulu-Natal (KZN). Hydrocephalus often results in significant morbidity and considerable financial burden to the health care system as management and complications are life long [4].

Children are the greatest gift bestowed to parents. It is utterly devastating for parents when they are informed that their child has a neurological disorder, as this leaves a perpetual sense of uncertainty about the future.

Often medical practitioners, in particular Neurosurgeons, may often feel helpless when it comes to shaping the outcome of this condition.

South African diseases are intimately related to social problems and unequal access to health care resources. As a developing country, SA is overburdened with poverty and this poses a significant challenge when treating paediatric hydrocephalus. Malnutrition in children has been well documented in the SA literature and has been complicated by the HIV/AIDS pandemic [5-7]. As neurosurgeons, we are not untouched by this phenomenon, especially in children with hydrocephalus.

Our study will serve to document the prevalence of hydrocephalus in the paediatric population of KZN, as we are at an advantage to report on this condition since the only public neurosurgical service for the entire population of KZN (approximately 11.1 million people), is located at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, where the study will be based [8].

The Department of Neurosurgery was relocated to Inkosi Albert Luthuli Central Hospital from Wentworth Hospital from 1st of January 2003 and we aim to document clinical characteristics and changing patterns of paediatric hydrocephalus over a 20-year period. The will be the most expansive documentation and analysis of paediatric hydrocephalus in SA.

The purpose of our study is to develop a novel multivariate prediction model which will help reduce complications associated with paediatric hydrocephalus, as this has yet to be introduced at the paediatric neurosurgical services in KZN, SA. The benefits derived from this model will be development of individualized assessment and prediction of the risks and benefits of surgery.

This model will allow neurosurgeons in SA, particularly in KZN to offer surgical management to those children who are most likely to benefit, and reduce complications. Moreover, such a model will empower a neurosurgeon to have a more beneficial personalized discussion with parents. We aim to offer a more valued approach to the management of this condition by preventing costly shunt complications and improving outcomes.

2. THE LITERATURE REVIEW

2.1 Historical perspective

Hydrocephalus as a disease entity has been described since the 5th Century B.C. by Hippocrates (466−377 B.C.) [9-11]. Galen (130−200 AD) also reported on this condition [9,10]. Vesalius (1514−1564) was the first to describe the anatomy of a ventricle [11]. Franciscus Sylvius (1614−1672) gave a detailed account of the cerebral aqueduct and Thomas Willis (1621−1675) was the first to suggest that the CSF was formed by the choroid plexus and absorbed by the venous system [9-11].

Morgagni (1682−1771) described the pathophysiology of hydrocephalus, while Monro (1733−1817) described the ventricular foramen. Albrecht von Haller (1708−1777) described the foramen of Luschka in 1747. Francois Magendie (1783−1855) described the foramen of Magendie, and proposed a "reverse theory" which suggested that the CSF flowed into the ventricles via the foramen of Magendie [9-11]. The first cannulation of the ventricles was performed by Le Cat in 1744 and in 1881 Wernicke was the first to advocate sterile cannulation of the ventricle [11]. Quincke in 1891 suggested a lumbar puncture as an alternative choice in the management of hydrocephalus. In the late 1800's efforts were made to surgically manage hydrocephalus and one of the pioneers in these efforts was Mikulicz in 1893, who was the first person to insert a ventriculo-subarachnoid-subgaleal shunt [9].

The concept of draining the CSF into the peritoneum was pioneered by Ferguson in 1898, in which he drained the CSF from the spinal subarachnoid space. However, drainage of the CSF from ventricle to the peritoneum was first performed by Kausch in 1905 [11].

Walter Dandy further contributed to our understanding of hydrocephalus in 1913 by using animal models and suggested the removal of the choroid plexus as the definitive treatment of hydrocephalus in 1918 [12]. As from 1952 ventriculoperitoneal (VP) shunting had been established as the definitive treatment for hydrocephalus.

VP shunts have undergone modification, sophistication and improvement over the past decades and remain without a doubt one of the greatest inventions in the field of neurosurgery as many lives have been saved and their quality of life improved.

2.2 Pathophysiology

The pathophysiology of congenital and neonatal hydrocephalus is not well understood and prognosis for children with this disorder is variable. A major obstacle towards our understanding of this disorder and the cellular responses that accompany it, is the multifactorial nature of hydrocephalus [13].

CSF is mainly produced by the choroid plexus and ependyma. It flows from the lateral ventricle to the third ventricle through the foramen of Monro. From there onwards it further flows to the fourth ventricle through the aqueduct of Sylvius draining into the subarachnoid space in the basal cisterns via the foraminae of Magendie and Lushka.
It is then absorbed by the arachnoid villi inside the dural venous sinuses [14].

The pathophysiology of congenital hydrocephalus almost always includes two separate mechanisms: primary genetic abnormalities that may affect outcome individually, and secondary injury mechanisms that occur mainly as a result of expanding ventricles and/or altered CSF physiology [15].

In children, this condition is especially damaging because the expanding ventricles, accompanied by increasing CSF pressure, cause the flexible skull to enlarge; this in turn both compresses and stretches adjacent brain tissue [13].

2.3 Aetiology: multifactorial impact of hydrocephalus

The incidence of hydrocephalus has a wide geographic variation and is reported to range from 0.2 to 5 cases per 1000 live births. Hydrocephalus has been traditionally classified into communicating and non−communicating. Communicating hydrocephalus occurs as a result of obstruction in the subarachnoid space, whilst non−communicating hydrocephalus occurs from obstruction within the ventricles or at the junction between the ventricular and subarachnoid space [14, 16,17].

Aetiology of paediatric hydrocephalus is multifactorial, and can be classified into primary or secondary. The primary causes are mainly congenital e.g. aqueduct stenosis, Dandy-Walker malformation, hydrocephalus associated with myelomeningocele (MMC) and encephalocele [13].

Genetic factors have been noted to influence the pathomechanism and outcome of hydrocephalus [13-17]. Secondary causes are mainly as a result of infections (acute and chronic), intra−ventricular haemorrhage (IVH), traumatic brain injury (TBI) and neoplasms.

Peacock et al in their case series of 440 children treated in Cape Town from 1979 to 1982 reported the aetiology to be post−meningitic (48%), congenital (32%), undetermined (25%) and secondary to tumours (11%) [18]. Warf et al reported the aetiology to be post−meningitic in the majority of children (60%) presenting with hydrocephalus in Uganda [19, 20], while Gathura et al reported the aetiology to be secondary to spina bifida in the majority of children (43%) in Kenya [21].

2.4 Overview of brain damage in hydrocephalus

Acute mechanisms which are initiated hours to a few days after the onset of ventriculomegaly include compression and stretching of periventricular tissue, ischemia, hypoxia, and increased CSF pulsatility, most notably in the cerebral aqueduct [13].

Additional mechanisms are recruited as ventriculomegaly becomes chronic and/or progresses to more severe forms: i.e. gliosis and neuroinflammation, periventricular oedema, demyelination, axonal degeneration, slow axoplasmic transport, metabolic impairments, stagnant CSF flow, altered blood brain barrier transport that can lead to toxicity as with reduced amyloid clearance, dendritic and synaptic deterioration resulting in altered connectivity, and cell death [13, 22,23].

The role of neuronal cell death in the overall pathophysiology of hydrocephalus is interesting because apoptosis and necrosis of cortical neurons seem to occur only after prolonged hydrocephalus, and while statistically significant reductions have been reported it may be that these changes are not biologically significant, since the total number of apoptotic neurons in the cerebral cortex is so low compared to all neurons in that region that the overall effect is probably negligible [24,25].

Oligodendrocytes and astrocytes found in the germinal matrix are important for brain development, and appear to be vulnerable during early stages of hydrocephalus. They undergo significant apoptosis in the periventricular white matter. Thus, myelin formation in the developing hydrocephalic brain can be impeded by multiple simultaneous events: stretch, compression, interstitial oedema, hypoxia, and oligodendrocyte death [13,24,25].

Germinal matrix haemorrhage causes damage to glial cells, which result in decreased volume of the cerebral white matter, cerebral venous ischaemia and infarction from compression of the terminal vein, which lies along the ventricle. Infarction is the most important determinant of long-term neurological function.

Release of cytotoxins into the periventricular white matter following post haemorrhagic hydrocephalus (PHHC) contributes to brain injury. These include blood products such as glutamate and iron, which cause free radical injury of the oligodendrocytes [23-25]

PHHC has direct negative effect on dendritic length, branch density, spine density and normal synaptogenesis. PHHC causes a rise in the ICP, which increases the cerebral vascular resistance, thus causing a decrease in the cerebral blood flow which in turn results in decreased tissue perfusion [22- 25].

2.5 Clinical presentation

The clinical presentation depends on the age of the child and the rate of progression of hydrocephalus. Neonates and children younger than two years of age, present with macrocephaly, bulging fontanelle, distended scalp veins, parinaud syndrome, delayed milestones, vomiting and irritability. Older children present with headaches, visual deterioration, papilloedema, altered level of consciousness, regression of milestones and spasticity.

2.6 Diagnosis

Hydrocephalus can be diagnosed in−utero with the aid of an ultrasound. This investigative tool can also be used in the neonatal period when the sutures are open to assess the size of the ventricles, parenchymal haematomas and IVH. Computerized tomography (CT) scan of the brain is performed routinely to diagnose hydrocephalus and its aetiology. The concern with the use of a CT brain scan is the exposure of young children to radiation. Magnetic Resonance Imaging (MRI) scan of the brain provides detailed assessment of the cerebral cortex, ventricular distortion, tumours, vascular anomalies and CSF flow when dynamic studies are performed.

2.7 Management

Management of hydrocephalus is surgical and the options include shunting procedures namely ventriculoperitoneal (VP) shunt, ventriculo−pleural shunt, ventriculo−atrial (VA) shunt and ventriculosubgaleal shunts. Over the last decades endoscopic third ventriculostomy (ETV) has emerged as a treatment option in children with hydrocephalus caused by an obstruction to the ventricular system distal to the mammillary bodies of the third ventricle [26, 27]. The obstruction is by−passed by creating a stoma in the floor of the third ventricle, allowing CSF to flow freely into the subarachnoid space. It has the advantage of freeing patients from VP shunts and their related complications. ETV success rate ranges from 70−90% [28, 29]

2.8 Complications

Complications of VP shunt insertion are due to shunt malfunction, infection, over drainage and surgical misadventure. The incidence of shunt related infection is reported range from 0.3 to 39% [30-32]. Majority of shunt infections occur within 3 to 6 months post−insertion and 40% of shunt failures occurs after first year of insertion. The commonest organisms (70%) responsible for shunt infection are *Staphylococcus epidermis* and *Staphylococcus aureus* [30]. Mechanical obstruction of a VP shunt is caused by connective tissue, choroid plexus, chronic inflammatory debris or kinking of the shunt tube. Shunt malfunction presents with re−emergence of symptoms and signs of acute hydrocephalus.

Complications of ETV are reported to range from 0 to 20% and include CSF leak, infection, epilepsy, IVH, post−operative haematoma. Other complications are related to injury to the basilar artery, fornix and cranial nerves. ETV related mortality is reported to be less than 1 % [28,29, 33].

Mortality rate of hydrocephalus is reported to range from 5 to 10 % [34,35]. The morbidity is variable and depends on factors such as the age at diagnosis, aetiology of hydrocephalus, associated congenital malformations, timing to surgery and treatment outcomes. Majority of children (40%) with hydrocephalus are cognitively impaired ranging from mild to severe retardation. Treatment delays are associated with a poor outcome [34,35].

2.9 Follow-up

Children with hydrocephalus who have had CSF diversion procedures require regular follow−up initially at 3−month intervals, which can be extended to annual basis if no complications are detected. CT / MRI brain scans are valuable tools during follow−up period as they help assess the position of the shunt catheter, exclude shunt malfunction and assess the size of the ventricles and cortex.

2.10 Psychosocial aspects

The psychosocial aspect of children with hydrocephalus is often neglected in our environment and how this affects long-term outcome. Hydrocephalus has pervasive multi-systemic impact on the physical, neurocognitive, psychological, and social functioning of affected children. The clinical symptoms of hydrocephalus place considerable physical, psychological, and social demands on the individuals and families involved.

Hydrocephalus and its related stressors are likely have a significant and cumulative impact on individual and family functioning. The cognitive and neurological features of hydrocephalus include executive functioning deficits, attention problems, learning difficulties, effects of hydrocephalus on physical development and the multiple surgical procedures experienced by most individuals in this population (e.g., shunt revisions).

The characteristic social skills deficits, and individuals' difficulties in mastering developmental milestones (e.g. autonomy development) are also significant stressors.

Although there is considerable variability in the degree to which parents of children with hydrocephalus respond to the diagnosis. Most are at high risk of developing adjustment problems, including internalizing and social problems.

3. THE RESEARCH QUESTIONS

a. What is the burden of paediatric hydrocephalus in a single neurosurgery centre that caters for the entire Province of KZN?
b. Is there a disparity in outcome between urban and rural children with hydrocephalus managed in KZN, SA?
c. What is the impact of centralized neurosurgery services on surgical outcomes?
d. What are the factors associated with mortality in children with hydrocephalus ?
e. What is the financial cost of treating hydrocephalus in KZN?
f. How do we develop and use model to improve outcomes of children with hydrocephalus, in KZN?
g. What is the impact of HIV/AIDS, malnutrition and immunization programs on this disease entity?

4. AIMS

a. To document the burden of paediatric hydrocephalus in KZN over a 20-year period.
b. To identify factors that contribute to the development of hydrocephalus in children of KZN.
c. To determine the impact of HIV infection on the outcomes of paediatric hydrocephalus
d. To determine the profile of opportunistic infections of the brain in HIV positive children
e. To determine outcomes of HIV-positive children with cryptococcal meningitis
f. To quantify the disparity in outcome between urban and rural children with hydrocephalus in KZN, SA.
g. To identify the impact of centralized neurosurgery services on surgical outcomes
h. To develop a model based on variables that will identify children at risk of poor outcomes and use the model to improve outcomes
i. To develop a financial costing model for treatment of paediatric hydrocephalus comparing ETV and VP shunt.
j. To document the neuropsychological effects of hydrocephalus in school-going children.
k. To document factors associated with mortality

5. OBJECTIVES

a. To retrospectively review all the admission at the Department of Neurosurgery, IALCH from 1st of January 2003 to 31st of December 2017.
b. To prospectively review all admission of paediatric hydrocephalus at the Department of Neurosurgery from 1st of January 2022 to 31st of December 2022
c. To document the prevalence of infantile paediatric hydrocephalus at IALCH, KZN
d. To assess whether there has been a change in the spectrum of paediatric hydrocephalus over the last 20-year period, by comparing the first and second halves of this period.
e. To document the effect of immunization policy on hydrocephalus

f. To document the impact of HIV /AIDS on the paediatric population diagnosed with CSF disorders, in particular hydrocephalus.
g. To prospectively identify clinical, biochemical and intraoperative parameters in consecutive children treated diagnosed with hydrocephalus.
h. To prospectively compare cost of treating paediatric hydrocephalus between two modalities, namely VP shunt and ETV from 1st of January 2018 to 31st of December 2018
i. To document the neuropsychological effects of hydrocephalus in school going children, with assistance from a Neuropsychologist.

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7. METHODS

7.1 Study design

The study will be a quantitative, observational, analytical, cross-sectional study. There will be two arms to the study. The first component will be a retrospective arm and the second component will be a prospective arm.

7.1.1 Retrospective arm of the study

Retrospective review and analysis of medical records of all the children (age 0 to 18 years) with a diagnosis of hydrocephalus treated between 1st January 2003 to 31st December 2017 at the Department of Neurosurgery at IALCH. The variables outlined in the data collection sheet (Annexure A) will be collected.

7.1.2 Prospective arm of the study

The prospective arm will commence from the 1st of January 2018 to 31st of December 2022. The variables which will be collected are outlined in Annexure B. Follow-up period will be a minimum of one year or till time of death. Any child who defaults follow up within one-year period will be censored from the study, unless the cause is death.

7.2 Setting

The study will be performed at a single centre, which is the Department of Neurosurgery located at IALCH, Durban, SA. This unit provides the only paediatric neurosurgery service for the entire population of KZN. It will be an ideal setting from which to report on the prevalence, management, impact and outcomes paediatric hydrocephalus in KZN.

7.3 Participant selection and sampling strategy

Depending on the study design, different age groups will be considered. For the retrospective arm we will include all children (birth to 18 years) with a diagnosis of hydrocephalus managed at IALCH.

For the prospective arm, we will recruit children from birth to 18 years, as this is the international definition of a child. From this age group we are also going to select children of school going age (6 to 18 years of age) to assess for neuropsychological effects of hydrocephalus.

7.4 Inclusion criteria

All children (from 0 to 18 years of age) with a diagnosis of hydrocephalus confirmed by CT/MRI brain scans will be recruited into the retrospective study.

All children (from 0 to 18 years of age) who are able consent and assent, with diagnosis of hydrocephalus will be recruited into the prospective study. These will be children treated by various CSF diversion procedures at the Department of Neurosurgery, IALCH.

7. 5 Exclusion criteria

Children with no radiological and clinical features of hydrocephalus, and who are above the age of 18 years will be excluded from the study. Lack of information in the medical charts will be another exclusion criteria.

7.6 Data collection and statistical analysis

Data for the retrospective arm of the study will be collected from medical files of children diagnosed with hydrocephalus, which are kept in electronic file management program

called MediTech ®, which is utilized at IALCH. Data will be entered into a proforma (Annexure A). The proformas will be entered into a Microsoft Excel® spreadsheet and statistical analysis will be performed on this data.

Data for the prospective arm of the study will be collected from consecutive children with diagnosis of hydrocephalus treated from 1st of January 2018 to 31st of December 2022. A logistic regression analysis will be used to develop a clinical predictive model related to management complications and outcomes of hydrocephalus, using specific clinical, biochemical and intraoperative data as predictors. These can be reviewed in Annexure B.

Descriptive statistics such as frequencies, proportions, mean, standard deviation and percentages will be used to summarize the data. The median and interquartile range will be used to summarize non−normally distributed continuous data. Student t test will be used to compare parametric data. Non–parametric data will be assessed using the Mann−Whitney and Pearson chi−square tests. Multiple logistic regression analysis will be used to investigate prediction of poor outcomes. The odds ratio and 95 % confidence interval will be used to examine for association of the variables. The level of statistical significance will be set at $p<0.05$.

7.7 Sample size, statistical power and variable selection

For the retrospective arm of the study the projected sample size is approximately one thousand five hundred cases (1500). For the prospective study the projected sample size is approximated to be 500 cases. Statistical analysis will be performed with the assistance of the biostatistician. The data will be captured and analysed using the Statistical Package for Social Sciences (SPSS version 22).

8. ETHICAL CONSIDERATIONS

8.1 Community participation

There will be no community participation as this will be a hospital-based study.

8.2 Social value

It will improve our understanding of paediatric hydrocephalus in KZN and highlight the plight of children and parents who have to deal with this condition. The study will highlight importance of proper antenatal care (ANC) screening and counselling. It will also highlight the importance of early diagnosis, early referral and early treatment in order to improve outcomes. It will highlight the need of palliative care in situations when there is futility of treatment, will help foster multidisciplinary co-operation especially between paediatricians, physiotherapists, occupational therapists, social workers, dieticians and clinical psychologists.

8.3 Scientific validity

The study will be scientifically valid, as it will be performed by experts in the field. International standards and norms will be adhered to. The study will be performed in conjunction with a Biostatistician.

8.4 Fair selection of participants

Fair selection and proper informed consent and assent will be undertaken. We are fully aware that due to the neurological complications associated with hydrocephalus, some children will not be able to assent.

8.5 Risk/benefit balance

There are no risks to participants in the retrospective arm of the study. There are also no anticipated risks to participants in the prospective arm of the study, as there are no additional interventions. There are possibly minimal over minor risks. There are immense benefits anticipated, as the study will highlight the impact of hydrocephalus on the paediatric population of KZN and offer solutions aimed at improving outcomes. It will add to the body of knowledge and improve holistic management of paediatric hydrocephalus in KZN.

8.6 Independent ethics review

Ethical approval will be requested from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal, Department of Neurosurgery at IALCH, hospital management team (IALCH) and the Provincial KZN Department of Health.

8.7 Informed consent

Children between ages of seven to seventeen years will be given the opportunity to assent to the study. We are cognizant of the fact that many of these children will have neurocognitive deficits and will not be in position to assent. Informed consent will be obtained from parents or legal guardian

The best interests of the child will always be of paramount consideration and in line with the Constitution in Section 28(2). We will adhere to the following criteria as prescribed by Section 7 of the Children's Act No. 38 of 2005, in determining a child's best interests:

a. Age, maturity and stage of development
b. Background
c. The child's intellectual, emotional, social and cultural development
d. Any disability a child may have
e. Any chronic illness from which a child may suffer

8.8 On-going respect for participants

This will be maintained at all times. The data will anonymous and kept in a password protected computer. Only the study investigators will have access to the data.

9. METHODOLOGICAL CHALLENGES AND STUDY LIMITATIONS

The retrospective nature of the first arm of the study will be its first limitation. There are different surgeons (from junior to senior) performing procedures on these children, which might affect outcomes.

The prospective arm of the study will not be a randomized, double blinded study and thus subject to surgeon bias. The study will only analyse data of children with hydrocephalus who are managed in the public health care sector and will exclude patients treated in private health care centres in the province. However, the Department of Neurosurgery at IALCH is the only institution providing a paediatric neurosurgery service for the province of KZN and thus at an advantage of offering insight into the prevalence of this condition in the province. Loss to follow−up is another limitation, as parents might not have money to bring children for follow−up, due to high prevalence of poverty in the province.

10. FEASIBILITY

This will be a feasible study to perform in the Department of Neurosurgery, at IALCH and will be within the scope and financial means of IALCH and the Provincial KZN Department of Health.

10.1 Study team, contributors and authorship.

Name	Department	Contribution	Author or acknowledgement
Basil Enicker	Neurosurgery	Primary investigator	Author
Colleen Aldous	School of Medicine	Supervisor	Co-Author

10.2 Participating Centres

The study will be performed in only one centre, which is the Department of Neurosurgery at IALCH.

10.3 Study Funding and Progress

No funding anticipated currently, but should the need arise in the future, funding will be sought from CHS to pay for services of a Neuropsychologist.

11. STUDY SIGNIFICANCE

There is a lack of data reporting on the prevalence of paediatric hydrocephalus in KZN. There are approximately 3.42 million people under the age of 15 years in KZN and the study will offer insight into this condition in the province. Warf et al also noted paucity of data with regards to the prevalence of paediatric hydrocephalus in Southern Africa This study will add to the body of knowledge regarding this condition in this part of the world, in particular KZN. There have been reports in the literature of the decline in the prevalence of paediatric hydrocephalus, due to decline in the incidence of congenital anomalies. This study will offer insight as to whether in 20 years, there has been an increase or decline in the prevalence of paediatric hydrocephalus in KZN or if this has remained the same. The information obtained from the study will help to draw up policies that will allow better

allocation of resources to prevent and manage paediatric hydrocephalus and its complications. The study will be used to develop clinical predictive models to help improve outcomes. The data gathered will published in peer−reviewed journals and foster further research in the field of paediatric hydrocephalus in the province. The study will also serve as a road map of decentralization of neurosurgical services in the province of KZN, as we believe patients will receive more urgent treatment, which will improve outcomes and reduce the burden of neurological morbidity in the Province of KZN. The study is towards a Doctor of Philosophy Degree in Neurosurgery.

12. DATA COLLECTION SHEETS

12.1 ANNEXURE A: RETROSPECTIVE STUDY VARIABLES

Referral Hospital		
Residential address		
Age at presentation		
Gender		
HIV exposure		
HIV status		
Method of diagnosis		
Symptoms		
Signs		
Associated congenital anomalies		
Birth weight		
APGARS		
OFC at presentation		
Time to presentation		
Co-morbid illnesses		
Nutritional status		
Temperature		
Hydration status		
Referring district		
Duration of follow-up		
Immunization schedule		
Biochemical	**Glucose level**	
	Potassium	
	Magnesium	
	Urea	
	Creatinine	
	INR	

	Sodium	
	Phosphate	
	Calcium	
	Albumin	
	Total protein	
	Haemoglobin	
	Vitamin B12	
	Serum transferrin	
	Platelet	
	WCC	
	CD4 count	
	Viral load	
	CSF polys	
	CSF protein	
	CSF glucose	
	CSF lymphocytes	
	ESR	
	CRP	
CSF diversion procedure		
Type of shunt		
Antibiotic impregnated shunt		
Day of procedure		
Time of procedure		
Level of Surgeon		
Complication		
Time to complication		
Organism cultured		
Number of days in hospital		
Number of shunts		

Number of EVD		
Number of ETV		
ETV complication		
VA shunt		
Follow up period		
Readmission		
Aetiology	**Congenital**	
	Associated with MMC	
	Aqueduct stenosis	
	Dandy−Walker malformation	
	Post−haemorrhagic	
	Post- meningitis	
	Cryptococcal meningitis	
	Tuberculous meningitis	
	Brain tumour	
	Arachnoid cysts	
	Hydranencephaly	
	Craniosynostosis	
	Traumatic brain injury	
	Holoprosencephaly	
	Idiopathic	
	Encephalocele	
	Miscellaneous	
Maternal factors	**Age**	
	Gender	
	Marital status	
	HIV status	
	Other medical illness	
	Number of pregnancies	
	Number of children alive	

	Attended ANC	
	Employment	
	Involvement of male partner	

12.2 ANNEXURE B: PROSPECTIVE STUDY VARIABLES

Referral Hospital		
Residential address		
Age at presentation		
Gender		
HIV exposure		
HIV status		
Method of diagnosis		
Symptoms		
Signs		
Associated congenital anomalies		
Birth weight		
APGARS		
OFC at presentation		
Time to presentation		
Co-morbid illnesses		
Nutritional status		
Temperature		
Hydration status		
Referring district		
Duration of follow-up		
Immunization schedule		
Biochemical	**Glucose level**	
	Potassium	
	Magnesium	
	Sodium	
	Urea	
	Creatinine	

	Phosphate	
	Calcium	
	Albumin	
	Total protein	
	Haemoglobin	
	Platelets	
	WCC	
	Vitamin B12	
	Serum transferrin	
	CD4 count	
	Viral load	
	CSF polys	
	CSF protein	
	CSF glucose	
	CSF lymphocytes	
	ESR	
	CRP	
CSF diversion procedure		
Type of shunt		
Antibiotic impregnated shunt		
Day of procedure		
Time of procedure		
Level of Surgeon		
Complication		
Time to complication		
Organism cultured		
Number of days in hospital		
Number of shunts		

Number of EVD		
Number of ETV		
ETV complication		
VA shunt		
Follow up period		
Readmission		
Anthropometry	**Body mass index**	
	Mid-arm circumference (MAC)	
	Triceps skinfold thickness (TST)	
	Mid-arm muscle circumference (MAMC)	
Aetiology	**Congenital**	
	Associated with MMC	
	Aqueduct stenosis	
	Dandy−Walker malformation	
	Post−haemorrhagic	
	Post- meningitis	
	Cryptococcal meningitis	
	Tuberculous meningitis	
	Brain tumour	
	Arachnoid cysts	
	Hydranencephaly	
	Craniosynostosis	
	Traumatic brain injury	
	Holoprosencephaly	
	Idiopathic	
	Encephalocele	
	Miscellaneous	
Maternal factors	**Age**	
	Gender	

	Marital status	
	HIV status	
	Other medical illness	
	Number of pregnancies	
	Number of children alive	
	Attended ANC	
	Employment	
	Involvement of male partner	

13. CONSENT DOCUMENT

Greetings

The Department of Neurosurgery is performing a study looking at management and outcomes of paediatric hydrocephalus. We ask your permission to have your child participate in this research study.

You have been informed about the study by **Dr. Basil Enicker.** You have been informed about any available compensation or medical treatment if injury occurs as a result of study-related procedures. You may contact Dr. **Basil Enicker** at **031-240 1133/34** any time if you have questions about the research or if you are injured as a result of the research.

The study is towards a PhD in Neurosurgery. You may contact the **Biomedical Research Ethics Office** on **031-260 4769 or 260 1074** or Email BREC@ukzn.ac.za if you have questions about your rights as a research participant.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop at any time. If you agree to participate, you will be given a signed copy of this document and the participant information sheet, which is a written summary of the research
The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate. I have been given an opportunity to ask any questions that I might have about participation in the study.

_____ _____

Signature of Participant **Date**

_____ _____

Signature of Witness **Date**
(Where applicable)

_____ _____

Signature of Translator **Date**
(Where applicable)

14. CONSENT DOCUMENT (ASSENT FORM FOR CHILDREN OVER 6 YEARS)

Greetings

The Department of Neurosurgery is performing a study looking at management and outcomes of paediatric hydrocephalus. We ask your permission to participate in this research study. You have been informed about the study by **Dr. Basil Enicker.** You have been informed about any available compensation or medical treatment if injury occurs as a result of study-related procedures. You may contact **Dr. Basil Enicker at 031-240 1133/ 34** any time if you have questions about the research or if you are injured as a result of the research.

The study is towards a PhD in Neurosurgery. You may contact the **Biomedical Research Ethics Office** on **031-260 4769 or 260 1074** or Email BREC@ukzn.ac.za if you have questions about your rights as a research participant.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop at any time. If you agree to participate, you will be given a signed copy of this document and the participant information sheet, which is a written summary of the research.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate. I have been given an opportunity to ask any questions that I might have about participation in the study.

_____ _____

Signature of Participant **Date**

_____ _____

Signature of Witness **Date**
(Where applicable)

_____ _____

Signature of Translator **Date**
(Where applicable)

Appendix 2

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

08 February 2018

Dr B Enicker (953000663)
School of Clinical Medicine
College of Health Sciences
basilenicker@yahoo.com

Dear Dr Enicker

PROTOCOL: Paediatric hydrocephalus in the Province of KwaZulu-Natal, South Africa: A study towards understanding the burden of disease and developing an integrated model aimed at improving outcomes. **DEGREE: PHD** **BREC Ref No: BE607/17**

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 09 October 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 23 January 2018 to BREC correspondence dated 02 November 2017 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 08 February 2018.

This approval is valid for one year from **08 February 2018.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **13 March 2018.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Professor V Rambiritch
Deputy Chair: Biomedical Research Ethics Committee

cc postgraduate administrator: jantjies@ukzn.ac.za
cc supervisor: Aldouse@ukzn.ac.za co-supervisor: mikedu@mweb.co.za

Appendix 3

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

HRKM Ref: 505/17
NHRD Ref: KZ_201712_011

Date: 17 January 2018
Dear Dr B. Enicker
UKZN

Approval of research

1. The research proposal titled **'Paediatric hydrocephalus in the Province of KwaZulu-Natal, South Africa: A study towards understanding the burden of disease and developing an integrated model aimed at improving outcomes'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutge

Chairperson, Health Research Committee

Date: 17/01/18

Appendix 4

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Office of The Medical Manager
IALCH

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

Reference: BE 607/17
Enquiries: Medical Management

15 November 2017

Dr B Enicker
School of Clinical Medicine
College of Health Sciences

Dear Dr Enicker

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Paediatric hydrocephalus in the Province of KwaZulu-Natal, South Africa: A study towards understanding the burden of disease and developing an integrated model aimed at improving outcomes.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

Office of the Medical Manager
IALCH

15 November 2017

Dr B Enicker
School of Clinical Medicine
College of Health Sciences

Dear Dr B Enicker

Re: Approved Research: Ref No: BE 607/17: Paediatric hydrocephalus in the Province of KwaZulu-Natal, South Africa: A study towards understanding the burden of disease and developing an integrated model aimed at improving outcomes.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For **King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH)** studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Details of any financial or human resource implications to KEH, including all laboratory tests, EEGs, X-rays, use of nurses, etc. (See Addendum 1)
5. Declaration of all funding applications / grants, please supply substantiating documentation.
6. Complete the attached KEH Form - *"Research Details"*

Once the document has been signed it should be returned to **Mrs Patricia Ngwenya:** at the Biomedical Research Ethics Administration, Room N40, Govan Mbeki Building, Westville Campus, University of KwaZulu-Natal.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:
IALCH

Investigator/s:
Principal: B Emicker
Co-investigator: _____
Co-Investigator: _____

Signature of Chief Medical Superintendent/Hospital Manager:
[redacted]
Date: 16-11-2011

Site 2 address:
_____

Investigator/s
Principal: _____
Co-investigator: _____
Co-Investigator: _____

Signature of Chief Medical Superintendent / Hospital Manager:
_____
Date: _____

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia