“Factors associated with paediatric medulloblastoma- a descriptive study of patients with medulloblastoma treated in Johannesburg (2015-2022)”

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of
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DECLARATION

I, Lucas Thapelo Mazibuko declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University

(Siganature of candidate)

05 day of May 2025 in Johannesburg

ABSTRACT

Background: Medulloblastoma is the most common malignant neoplasm of the central nervous system in children. This pathology originates from the cerebellum and predominantly impacts children aged 3 to 8 years. Notwithstanding the progress made in therapeutic approaches, medulloblastoma persists as a considerable contributor to both morbidity and mortality in children.

Objectives: This study aimed to describe the epidemiology, clinical presentation, stage, histopathology, treatment, complications and outcome of medulloblastoma in children who were treated at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 2015 to 2022.

Method: This retrospective cohort study examines all patients diagnosed with medulloblastoma from January 2015 to December 2022. The data utilised in this analysis were gathered from clinical and radiological records and histopathology reports from the National Health Laboratory Services (NHLS).

Results: A total of twenty-seven patients were diagnosed with medulloblastoma; however, only twenty patients met the study's inclusion criteria. Two patient files were missing, and five contained incomplete information. The cohort consisted of more girls than boys, with a ratio of 1.2:1. Ninety-five per cent of the children were Black, while 5% were of Indian descent. Symptoms were present for an average of four weeks before presentation. The most common presenting signs and symptoms were gait abnormalities (80%), headaches (60%), and nausea and vomiting (60%). Histopathological analysis revealed that 55% of cases were unspecified medulloblastoma, 35% were desmoplastic/nodular, and 10% were classified as classic medulloblastoma. All the patients in our cohort had debulking surgery. Sixty-five per cent of patients completed both chemotherapy and radiotherapy; 20% were referred to palliative care post-surgery, and 15% succumbed to complications such as pneumonia, surgical-site infections, and recurrent urinary tract infections. Among those who died, two of the three patients were three years old or younger, all showing advanced stages of the disease upon presentation.

Conclusion: In the cohort of patients who died, all had presented with advanced disease and residual tumours larger than 1.5 cm². This study highlights that several factors, including the size of post-operative residual tumours, the timing of diagnosis, and the completion of treatment, influence the outcomes for medulloblastoma. Early detection, complete surgical resection, and the successful execution of adjuvant therapy are vital components in enhancing patient survival rates. There is a need for future prospective studies with larger sample sizes to deepen our understanding of prognostic factors and to optimise treatment strategies in this context.

ACKNOWLEDGEMENT

I would like to thank and acknowledge the following people: My supervisors Professor G. Naidu and Professor J.R.B. Ouma, for their time and commitment to helping develop and complete this research project. Mr. Tau Mabitsela for assistance with the data.

DEDICATION

To my family, whose unwavering support has made this work possible. Your endless encouragement and patience have been invaluable throughout this journey.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DNMB	Desmoplastic/Nodular medulloblastoma
EOR	Extent of Resection
EVD	External Ventricular Drain
EFS	Event-Free Survival
GCS	Glasgow Coma Scale
GICC	Global Initiative for Childhood Cancer
GTR	Gross Total Resection
ICP	Intracranial pressure
LCA	Large Cell Anaplastic
MRS	Magnetic Resonance Spectroscopy
NHLS	National Health Laboratory Service
NTR	Near Total Resection
OS	Overall Survival
PACS	Picture Archiving and Communication System
PFS	Progression Free Survival
SHH	Sonic Hedgehog
WHO	World Health Organization
WNT	Wingless

CHAPTER 1 INTRODUCTION AND BACKGROUND

1.1 BACKGROUND

Primary brain tumours are the second most common malignancy in paediatric patients, after leukaemia, accounting for approximately 20% of all childhood cancers, and are the most common solid tumours in the paediatric population that cause cancer-related mortality (25% of the deaths) (1, 2). Medulloblastoma is the most prevalent malignant brain tumour, representing 15-20% of all paediatric brain tumours (3). However, information from low- and middle-income countries (LMICs) describes wide variations in the incidence of medulloblastoma, with reported rates ranging from 5% to 25% of all paediatric brain tumours (4). Genetic and epigenetic analyses have classified medulloblastoma into various molecular groups, with each subgroup associated with different patient characteristics and outcomes (3).

The challenge of achieving favourable outcomes for children diagnosed with medulloblastoma is particularly significant in LMICs, where overall survival (OS) rates for childhood cancer remain suboptimal (23). This situation can be attributed to various non-biological factors, including delayed diagnosis, a lack of resources, malnutrition, deeply ingrained traditional beliefs, and potentially unidentified biological variables (13, 23). In line with the World Health Organization's (WHO) Global Initiative for Childhood Cancer (GICC), the primary objective is to improve the OS rate for children with cancer in LMICs to 60% by 2030 (48). Although South Africa was not chosen to be a GICC country, the use of the St Jude Paediatric Oncology Facility Integrated Local Evaluation (PrOFILE) tool has been invaluable in the understanding of childhood cancer in South African context and exploring opportunities to improve the care of children with cancer (44).

A comprehensive audit of our patient cohort diagnosed with medulloblastoma is essential to understand patient demographics and identify the factors contributing to suboptimal outcomes. The data generated from this analysis will provide a foundation for future studies and research initiatives to enhance overall survival rates.

1.2 PROBLEM STATEMENT

Medulloblastoma, a malignant tumour that predominantly affects children, presents a complex clinical scenario characterised by differing outcomes in LMICs compared to high-income countries (HICs). This disparity highlights the urgent need to investigate the multifaceted factors associated with this condition. The primary objective is to understand the complexities surrounding medulloblastoma within various healthcare settings and identify the determinants that influence the varied survival rates. Addressing this knowledge gap is essential for developing targeted interventions to enhance health outcomes for paediatric patients diagnosed with medulloblastoma in these medical environments.

1.3 AIMS AND OBJECTIVES OF THE STUDY

This study seeks to provide an overview of the epidemiology, clinical presentation, staging, histopathology, treatment approaches, complications, and outcomes of medulloblastoma in children who received care at CHBAH and CMJAH from 2015 to 2022. This study aims to provide a comprehensive description of children treated for medulloblastoma

1.3.1 Objectives of the Study:

1. To identify and describe factors associated with mortality in children with medulloblastoma.
2. To describe the overall survival of patients with medulloblastoma.

1.4 RESEARCH QUESTIONS

What factors contribute to the overall survival of paediatric patients diagnosed with medulloblastoma at CHBAH and CMJAH?

1.5 SIGNIFICANCE OF THE STUDY

This study is important because it explains the prognostic factors associated with paediatric patients diagnosed with medulloblastoma at CHBAH and CMJAH. The findings could enhance patient outcomes by focussing on early diagnosis, improving access to histopathological diagnosis to understand the biology better, refining diagnosis and treatment, and providing better counselling, supportive, quality of life, and long-term and palliative care of medulloblastoma in our context.

1.6 RESEARCH REPORT OUTLINE

This research report has five chapters.

Chapter 1: This chapter introduces the study and provides its contextual background. It outlines the problem statement, aims, and objectives, while presenting the research questions and discussing the significance of the study.

Chapter 2: This chapter offers a comprehensive literature review on the epidemiology of medulloblastoma. It examines the clinical presentation, molecular subtypes, treatment strategies, and prognostic factors associated with the condition.

Chapter 3: This chapter details the study design, focusing on the study site, population, and sample selection. It elaborates on the data sources and collection methods, outlines the data analysis process, and identifies the outcome and predictor variables, along with the relevant ethical considerations.

Chapter 4: This chapter presents the study results in a clear and systematic manner.

Chapter 5: This chapter discusses the findings and offers conclusions based on the research outcomes.

CHAPTER 2 LITERATURE REVIEW

2.1 EPIDEMIOLOGY OF MEDULLOBLASTOMA

Medulloblastoma accounts for over 60% of embryonal brain tumours in the paediatric population, predominantly affecting individuals under the age of 10 (3, 5). The highest incidence occurs among children aged 1 to 4 years and 5 to 9 years. In the United States of America, the annual incidence in this demographic is approximately 5 cases per 1 million, with a notable male predominance, as males are affected 1.7 times more often than females (5). While medulloblastoma can occur in older patients, it represents no more than 1% of all primary central nervous system (CNS) tumours in adults (6, 7).

This information highlights the critical need for continued research and greater awareness in paediatric oncology. Significant differences in age and sex distributions are evident across various tumour subtypes, emphasising the complexity of this disease. Statistics from HICs show that medulloblastoma is the most common malignant brain tumour in children, accounting for about 20% of new cases (1, 8). Conversely, findings from LMICs indicate inconsistencies in the incidence rates of medulloblastoma among paediatric populations (4, 9, 10, 11). A retrospective study of 451 paediatric patients in Egypt, which investigated the epidemiology of intracranial neoplasms, reported characteristics consistent with existing literature. It found a male predominance (51.4%) and medulloblastoma (18.8%) as the second most common tumour after astrocytoma (35%) (9). In South India, a study conducted on 1,043 paediatric patients at a single-centre institution showed medulloblastoma (11.4%) as the second most frequent tumour after astrocytoma (47.3%), with a male preponderance (10).

To illustrate the differences in incidence across LMICs, two studies from Morocco highlighted distinctions in medulloblastoma rates. The first study, conducted at various centres, revealed through a retrospective analysis of 542 patients that medulloblastoma (34.5%) was the most prevalent brain tumour, followed by pilocytic astrocytoma (17.3%). In this study, males were more common in the 5-9 age group, while females were predominant in the 10-14 age group (11). A second retrospective study involving

633 paediatric brain tumour patients at a single institution also showed male predominance, with tumours affecting 55% of males and 45% of females (12). Additionally, pilocytic astrocytoma (23.1%) was the most frequent diagnosis.

In LMICs, survival rates for children diagnosed with cancer, especially those with brain tumours like medulloblastoma, remain alarmingly low (13, 23). A retrospective analysis within South African paediatric oncology units found that brain tumours, including medulloblastoma, had the lowest survival rates at 46.4% (13). The overall survival rate for the cohort was 52.1%, with lymphoma and nephroblastoma showing better rates at 63.9% and 62.6%, respectively (13). Neuroblastoma and retinoblastoma were similar, recorded at 5.8% and 5.7%, respectively (13). Furthermore, a comparative study of different ethnic groups revealed that white children had the highest survival rate at 62.8%, followed by children of mixed race at 53.8% (13). In contrast, Black children showed a survival rate of 48.5% (13).

In our cohort we had a total of 549 cancer paediatric patients admitted for the study period, of which CNS tumours were 125 (22,7%), and of the CNS tumours medulloblastoma were 27 (21,6%).

2.2 CLINICAL PRESENTATION

Symptoms usually appear suddenly and worsen progressively as the tumour advances, with about 76% of patients noticing them within twelve weeks. This is mainly caused by elevated intracranial pressure (ICP) due to obstructive hydrocephalus (3, 7). Research in France revealed that the average duration from the onset of symptoms to a confirmed diagnosis was 65 days (14).

The clinical presentation of medulloblastoma in patients is greatly affected by age, tumour location, and disease progression. A retrospective multicentre study conducted in a specific region of France between 1990 and 2005 examined children diagnosed with medulloblastoma, uncovering significant variations in symptoms by age group. Notably, children under three years exhibited typical symptoms such as vomiting (72%),

psychomotor regression (60%), and ataxia (60%). Alarmingly, approximately one-third of these very young patients were diagnosed only after exhibiting severe signs related to rising ICP. Conversely, older children often showed symptoms including vomiting (91%), headaches (87%), ataxia (50%), and psychological issues (28%). These psychological symptoms may manifest as poor academic performance, behavioural changes, or increased anxiety (14). This underscores the need for age-specific assessments and customised intervention strategies for the effective management of this condition.

Patients may present with cranial nerve palsies as a consequence of brainstem compression or elevated ICP (1, 6). In instances of extensive metastatic disease, cerebral metastases can precipitate seizures. Moreover, spinal metastases may lead to nerve or spinal cord compression, resulting in a spectrum of symptoms associated with the compromised nervous tissue (7). As the tumour enlarges within the posterior fossa, it can cause displacement of the cerebellar tonsils through the foramen magnum, which may irritate the upper cervical nerve roots. This irritation commonly manifests as neck stiffness, head tilt, and potential signs of impending herniation (6, 7).

2.3 MOLECULAR SUBTYPES

The 2021 WHO classification of CNS tumours recognises two ways to classify medulloblastoma: molecularly defined and histologically defined medulloblastoma (3, 15). The four molecular subtypes have subcategories that can be identified through genetic analyses, and new treatment strategies can be suggested (3).

The wingless activated medulloblastoma (WNT) subtype typically represents about 10% of all cases and is associated with a remarkable prognosis of over boasting over 95% OS at 5 years in paediatric populations (1, 5). The Sonic Hedgehog (SHH) subtype, which includes TP53 mutant and wild-type variants, constitutes approximately 30% of cases and exhibits an equal distribution across sexes. This subtype predominantly affects young children and adolescents (3). The 5-year OS for the SHH subtype ranges from 60% to 80%, with TP53 mutant variants having a worse prognosis (3, 5). The

Group 3 molecular subtype, classified as non-WNT/non-SHH, comprises around 25% of medulloblastomas and demonstrates a male predominance, particularly in infants and young children. It is characterised by the poorest prognostic outcomes of all subtypes, with a 5-year OS of approximately 50% (3, 18). In contrast, the Group 4 subtype, the most prevalent category, accounts for approximately 35% to 40% of cases. This subtype typically manifests in childhood and adolescence and is more frequent in males (3, 5, 18, 22). The 5-year OS for the Group 4 subtype is around 75% to 90% (3, 5).

2.4 TREATMENT OF MEDULLOBLASMA

Managing childhood medulloblastoma necessitates a thorough multidisciplinary strategy involving specialists in neurosurgery, neuroradiology, pathology, paediatric oncology, radiotherapy, chemotherapy, and allied health services. In LMICs, establishing such a team to treat paediatric medulloblastoma faces significant obstacles compared to HICs. These challenges include limited access to advanced diagnostic tools, such as MRI and histopathology services (23, 24), a shortage of trained healthcare professionals (46), and financial constraints that hinder the provision of comprehensive care (47). Research in Paraguay on healthcare access for paediatric brain tumour patients indicated that poor outcomes were strongly linked to insufficient resources and support systems (23).

Risk stratification in medulloblastoma is essential for assessing prognosis and customising treatment plans. The main factors impacting this classification include age at diagnosis, presence of metastatic disease, histological subtypes, and the degree of tumour resection (19). Standard-risk patients are those over 3 years old, without metastases, classified histologically as either classic or desmoplastic, and having less than 1.5 cm^2 of residual tumour after surgery (8, 19). In contrast, patients not meeting these criteria are classified as high-risk (5). Epidemiological studies indicate that standard-risk patients have an approximate 80% survival rate, while high-risk patients show notably lower survival rates, typically between 60% and 65%. This distinction in

risk highlights the necessity for personalised treatment approaches to enhance patient outcomes (5).

The emergence of molecular subtypes has improved risk stratification for medulloblastoma patients (5). This classification identifies a low-risk group, including individuals diagnosed with WNT subtype medulloblastoma under 16 years old, without metastatic spread, and non-metastatic group 4 tumours characterised by loss of chromosome 11 or gain of chromosome 17 (19). Survival rates for this low-risk cohort exceed 90% (5, 19). The standard-risk group includes SHH subtype patients who do not have TP53 mutations or MYCN amplification, plus group 4 tumours lacking chromosome 11 loss and non-MYC amplified group 3 tumours that are also non-metastatic. In contrast, the high-risk category consists of non-infant patients with TP53 wild-type tumours that are metastatic, along with non-metastatic MYCN amplified SHH medulloblastoma and metastatic group 4 tumours (19). Finally, the very high-risk classification encompasses TP53-mutated SHH medulloblastoma and metastatic group 3 tumours, indicating a significantly increased risk profile for these cases (19). It is important to note that these molecular tests are not routinely available for patients treated in the public sector in South Africa.

Surgery remains the cornerstone of medulloblastoma management, aimed at achieving safe maximal resection to facilitate histopathological and molecular assessments (1, 5). Recent analyses of resection extent indicate a notable progression-free survival (PFS) advantage of 71% linked to gross total resection compared to 53% for subtotal resection; however, no discernible benefit in PFS (77% vs 71%) or OS (85% vs 83%) is observed when comparing gross total resection to near-total resection (5,19). A retrospective study conducted in Egypt involving 405 patients evaluated the relationship between the extent of resection and patient survival outcomes in children with medulloblastoma. The findings revealed that gross total resection did not significantly enhance OS (84.6% vs 82.1%) or PFS (70.2% vs 68.4%) compared to near-total or subtotal resection (24).

Chemotherapy is vital for enhancing survival rates, particularly in younger children and those under three years of age. It helps prevent or postpone the need for radiotherapy

which reduces potential adverse effects associated with radiation therapy, which may include learning difficulties, memory deficits, challenges in social adaptation, and impaired physical development (5, 19).

In our institution the chemotherapy regimen protocol includes vincristine, etoposide, and carboplatin (VEC protocol) as follows: on day 1 we administer Vincristine 1.5mg/m^2, etoposide 100mg/m^2 IVI in 200mls over 1 hour, carboplatinum 200mg/m^2 IVI in 200mls over 2 hours. On day 2 we give etoposide 100mg/m^2 IVI, carboplatinum 200mg/m^2 IVI and on day 3 we give etoposide 100mg/m^2 IVI and carboplatinum 200mg/m^2 IVI. This is repeated monthly (i.e. 4 weekly X 6) pre DXT and post DXT.

Rutkowski et al. conducted a study to evaluate the efficacy of intensive postoperative chemotherapy as a singular treatment for young children diagnosed with medulloblastoma, particularly those under the age of three (27). This investigation involved a cohort of 43 patients who underwent surgical resection followed by three cycles of intravenous chemotherapy i.e., cyclophosphamide and methotrexate, in addition to intraventricular methotrexate. Treatment was discontinued upon the achievement of complete remission. The findings indicated that patients with complete resection demonstrated a five-year PFS of 82% and an OS of 93%. These results suggest that chemotherapy alone may serve as a promising treatment modality for this population, especially in the is an absence of metastatic disease (27). Furthermore, it has been established that individuals with SHH medulloblastoma can be effectively treated without upfront radiotherapy, with an anticipated five-year PFS exceeding 90% (28).

Radiotherapy is an essential component of the treatment for medulloblastoma following maximal safe resection in paediatric patients aged three to five years and older (39, 40). However, the application of radiotherapy in infants and children under three years of age poses significant challenges due to the potential adverse effects on their developing brains and organ systems (41). Treatment approaches guided by risk stratification can lead to neurocognitive impairments, neuroendocrine dysfunction, and difficulties with social adjustment in long-term survivors (42, 43). A study involving 88 paediatric patients with CNS embryonal tumours who received risk-adapted craniospinal irradiation in

conjunction with high-dose chemotherapy demonstrated considerable treatment-related endocrine deficiencies (29). Growth hormone deficiency was observed in 94% of these patients, while primary hypothyroidism was identified in 51% (29).

2.5 PROGNOSTIC FACTORS

Factors associated with a poor prognosis for children with medulloblastoma include tumours larger than 3 cm in diameter at presentation or those occupying more than 50% of the posterior fossa, disseminated disease at presentation, young age (under 3 years), and a residual lesion greater than 1.5 cm^2 following surgery (6). In a 2010 study conducted in HICs, histopathology emerged as a significant prognostic factor; children diagnosed with desmoplastic/nodular medulloblastoma (DNMB) represented a strong independent favourable prognostic factor, with a 5-year event free survival rate of 84% compared to 57% for those with classic medulloblastoma, even for young children with metastatic disease (30). The 2021 WHO classification of CNS tumours underscores the importance of the molecular biology of medulloblastoma in defining the prognosis and behaviour of the tumour (15).

2.6 SURVIVAL OUTCOMES

Prognosis for paediatric medulloblastoma is significantly more favourable in HICs than in LMICs. A comprehensive multi-centre study conducted in Canada from 1990 to 2009 reported an overall five-year survival rate of 69.2% for patients diagnosed with paediatric medulloblastoma (32). In contrast, a study in Paraguay, an LMIC, revealed treatment failure rates for children with brain tumours ranging from 37% to 83%. In this context, treatment failure was defined by various factors, including relapse, disease progression, abandonment of therapy, or mortality from high rates of nosocomial infections (23). A study from paediatric oncology units in South Africa highlighted persistently low OS rates for childhood cancers, recorded at 52.1% (13). This figure is particularly concerning when compared to outcomes observed in HICs (13).

Additionally, brain tumours were found to have the lowest survival rate within this population, recorded at a mere 46.4% (13).

2.7 CONCLUSION

The prognosis and outcomes for paediatric brain tumour patients in LMICs significantly differ from those in HICs. Several factors contribute to the poorer outcomes observed in LMICs, including delayed diagnosis and the resultant advanced disease at presentation. Additionally, inadequate referral and diagnostic infrastructure often hinder timely intervention. Post-neurosurgical complications, particularly infections, are more common, further complicating recovery. Moreover, delays in the initiation of adjuvant therapies, such as radiotherapy, exacerbate the challenges faced. The socio-economic disparities in these regions also play a critical role in affecting patient outcomes (23). Compounding these issues is the absence of multidisciplinary care teams and the lack of standardised, disease-specific clinical guidelines, which are essential for ensuring the quality management of brain tumour cases (33).

CHAPTER 3 METHODOLOGY

3.1 STUDY DESIGN

This study employed a retrospective cohort design to analyse the medical records of paediatric patients diagnosed with medulloblastoma from January 2015 to December 2022.

3.2 STUDY SITE

The research was conducted in two teaching hospitals affiliated with the University of the Witwatersrand: Chris Hani Baragwanath Academic Hospital (CHBAH), with a capacity of 3,200 beds, and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), which has 900 beds. Data were extracted from patient records in the neurosurgical and paediatric oncology wards.

3.3 STUDY POPULATION AND SAMPLE SIZE

The study included all paediatric patients diagnosed with medulloblastoma during the 7-year study period. A thorough diagnostic evaluation was performed, followed by surgical procedures to confirm the diagnosis and remove the tumour. Once histopathological analysis verified the medulloblastoma diagnosis, the tumour was staged, and treatment was initiated.

3.3.1 Inclusion criteria

1. Patients aged 0 to 19 years.
2. Patients with histology-confirmed medulloblastoma.

3.3.2 Exclusion Criteria

1. Patients with incomplete information from the hospital records or missing files.
2. Patients with tumour recurrence or previously treated medulloblastoma.

3.4 DATA SOURCES AND DATA COLLECTION

The retrospective study was conducted over seven years, from January 2015 to December 2022. Data were extracted from patients' clinical, radiological, and histopathological reports available through the National Health Laboratory Services (NHLS). A data collection sheet (Appendix A) served as the primary tool for gathering information. This sheet was organised to capture a wide range of variables, including demographic information, clinical presentations, radiographic characteristics, tumour phenotypes, molecular subtypes, complications and outcomes. Regular updates and reviews were conducted to include all eligible patients and maintain the accuracy of the collected data.

3.5 DATA ANALYSIS

Statistical analysis was conducted using Stata SE version 18, emphasising descriptive statistics. Continuous variables, such as age, are presented as means with standard deviations (±SD), medians with interquartile ranges (IQR), and the full range to demonstrate distribution variability. Categorical variables, including sex, are summarised with frequencies and associated percentages.

3.6 ETHICAL CONSIDERATIONS

Approval was sought from the Human Research Ethics Committee and the Neurosciences Assessor Group at the University of the Witwatersrand. Consent was

obtained from the Chief Executive Officers of CHBAH and CMJAH before the project commenced. An ethics application was submitted to the Human Research Ethics Committee (MED23041, Appendix B) to ensure compliance with ethical standards. Throughout the research process, confidentiality and anonymity were strictly maintained, with results shared exclusively with authorised personnel. The integrity of patient information was paramount; thus, personal identifiers and medical records were meticulously protected. Access to data was limited to members of the research team to ensure security. The study findings will be handled with strict confidentiality, with access restricted to authorised individuals, including the principal investigator, supervising faculty, and relevant committee members.

CHAPTER 4 RESULTS

4.1 DEMOGRAPHICS

A total of twenty-seven patients were identified with medulloblastoma; however, data from five of these patients were incomplete, and two records were unaccounted for. Ultimately, twenty patients met the inclusion criteria and were enrolled in the study across both participating hospitals. The cohort had a mean age of 6.9 years (±4.12), with ages ranging from 0.7 to 15 years. The age distribution of the patients is depicted in Figure 1. Additionally, Figure 2 shows that 55% of the paediatric cohort were female, while 45% were male. Figure 3 highlights a significant demographic finding, with 95% of patients identified as Black and 5% of Indian descent.

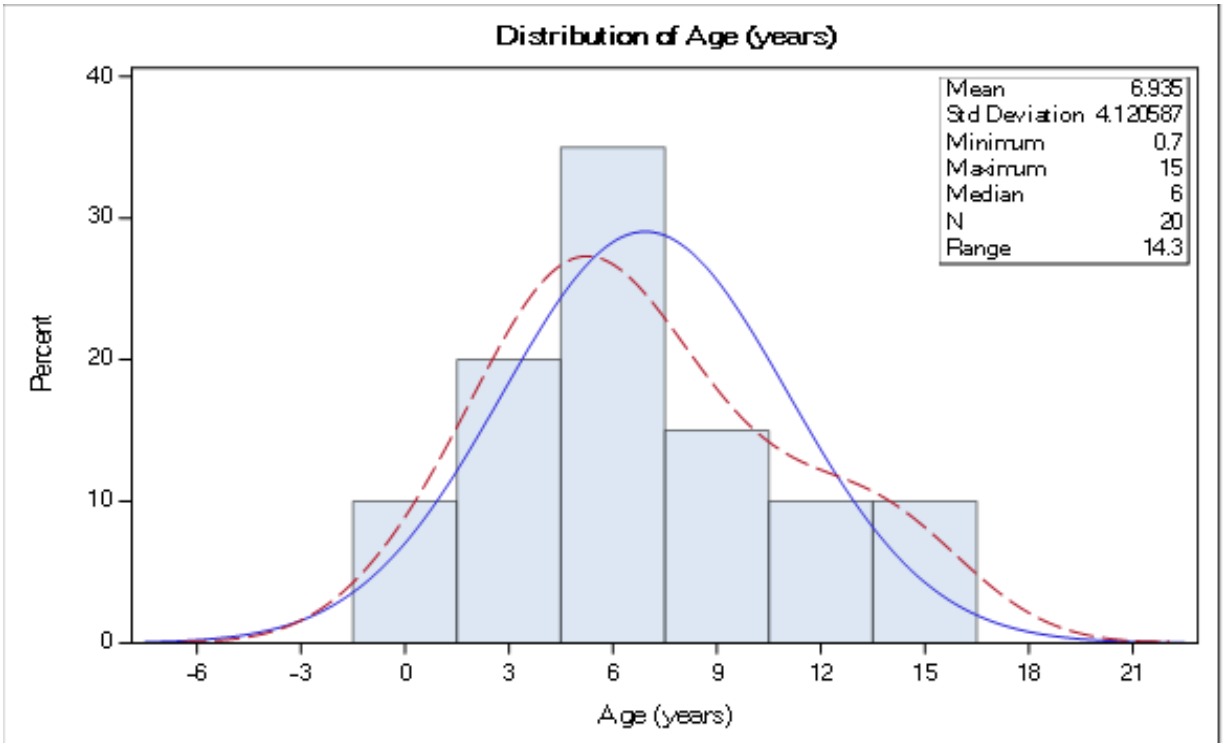

Figure 1: Age distribution of patients with medulloblastoma

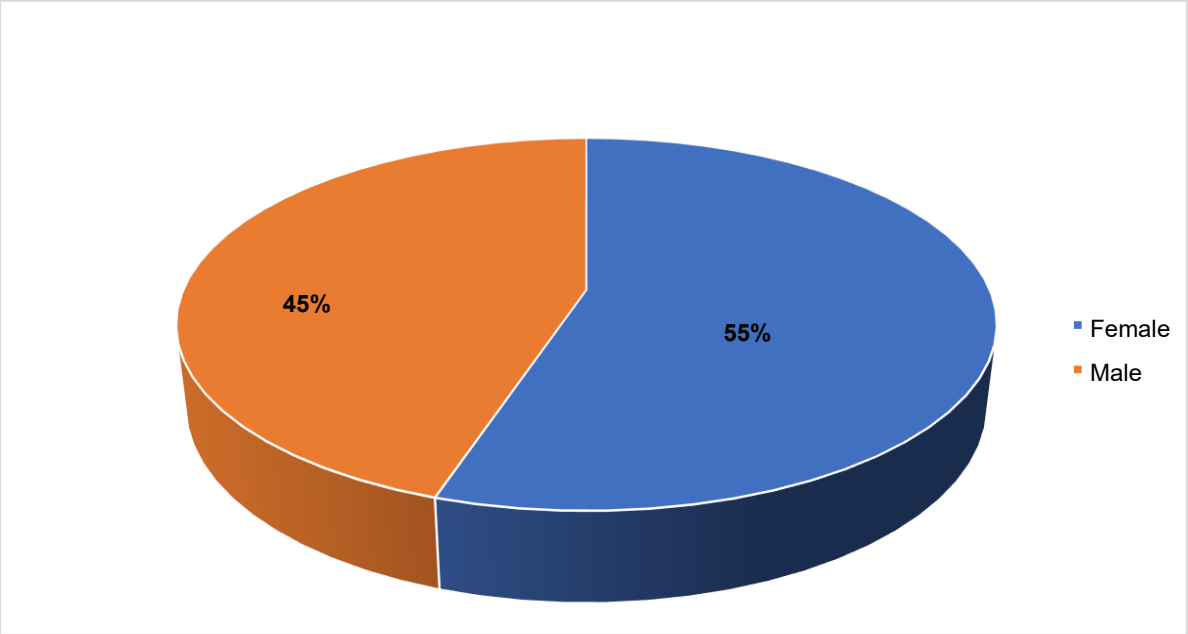

Figure 2: Sex distribution of patients with medulloblastoma

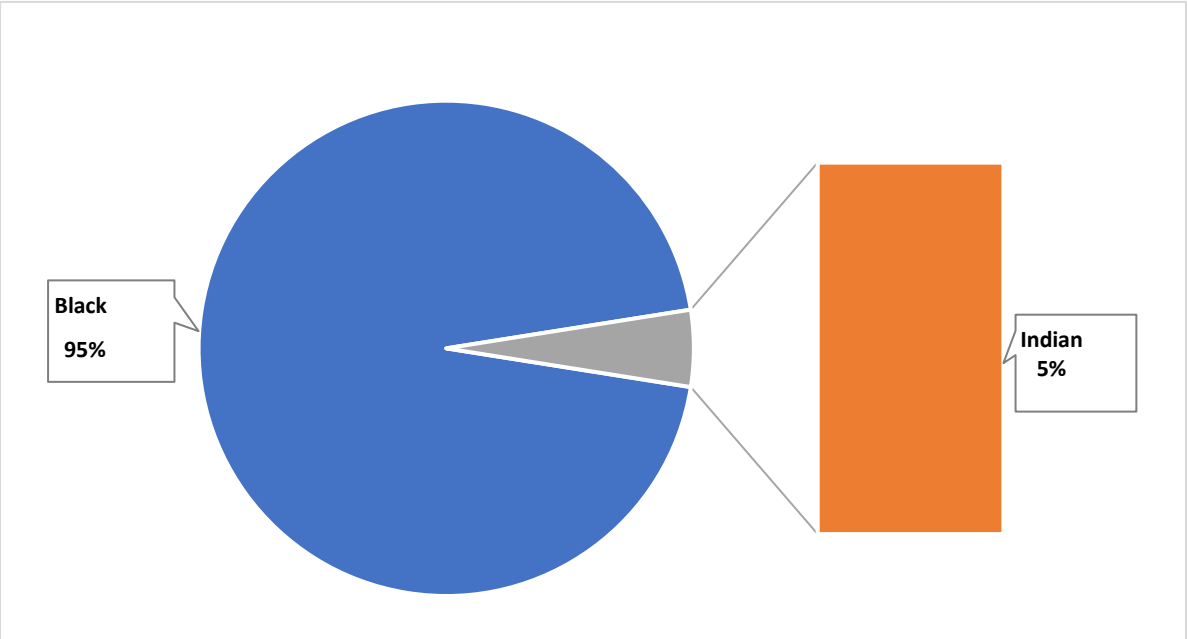

Figure 3: Race distribution of patients with medulloblastoma

4.2 CLINICAL PRESENTATION

Figure 4 illustrates the clinical manifestations observed in our cohort of 20 patients diagnosed with medulloblastoma. Among these, eleven patients (55%) exhibited two to three signs and symptoms, while (45%) presented with four or more. The most prevalent symptoms included headache and ataxic gait, reported by 16 patients (80%). Additionally, nausea, vomiting, and various behavioural changes were identified in 12 patients (60%). Other notable symptoms encompassed dizziness, visual disturbances, alterations in behaviour or personality, seizures, and fatigue. The median duration of symptomatic presentation was four weeks, spanning from 2 to 52 weeks (Figure 5).

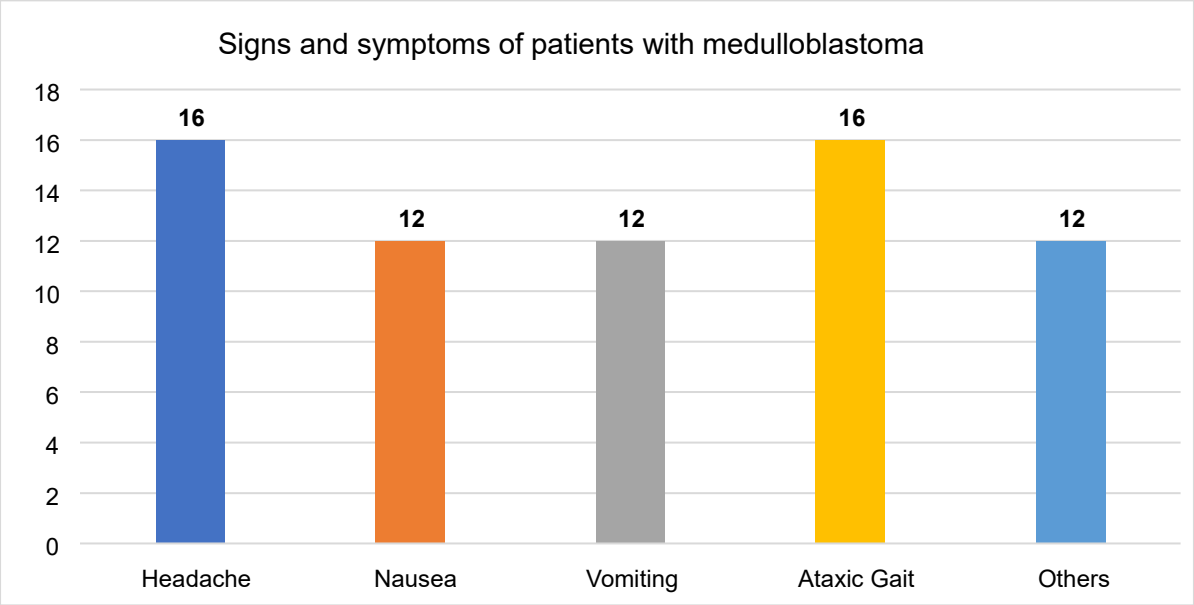

Figure 4: Signs and symptoms of medulloblastoma at presentation

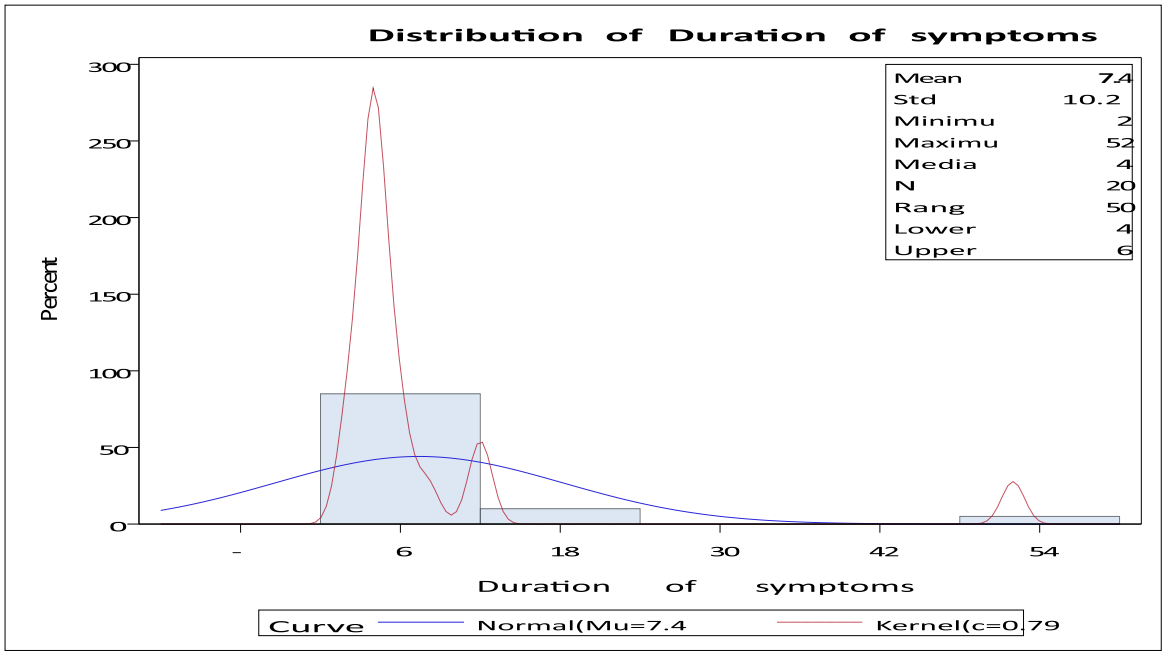

Figure 5: Duration of symptoms before presentation

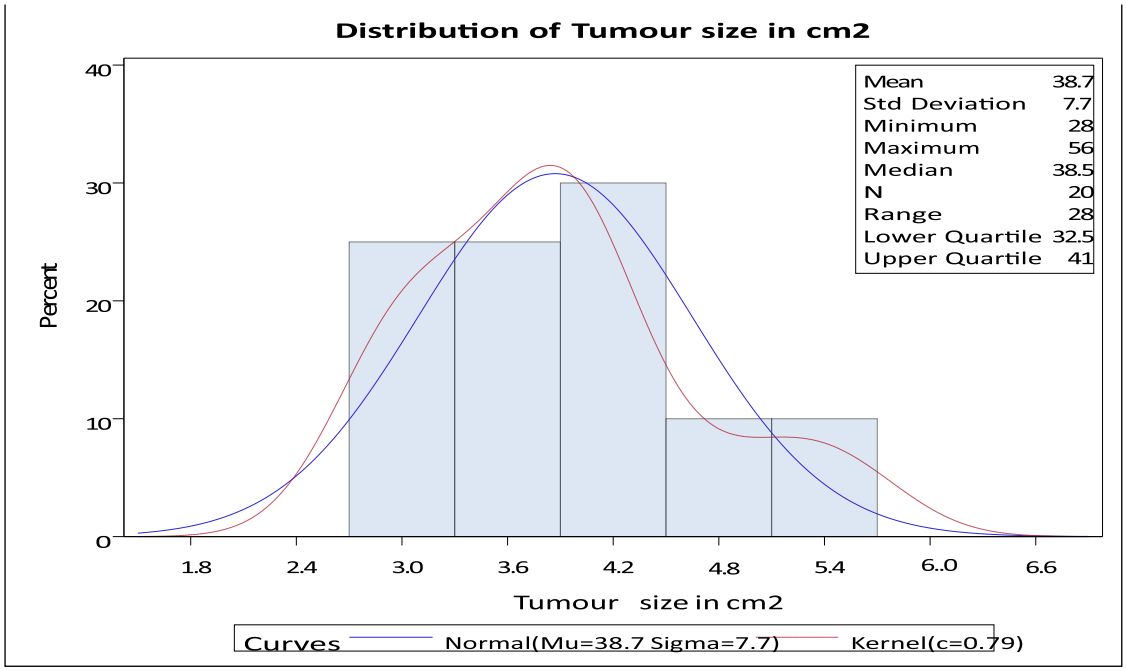

Figure 6: Tumour size (cm^2) at diagnosis

4.3 RADIOLOGICAL FINDINGS AND SUMMARY OF THE TREATMENT OF 20 PATIENTS

Table 1 illustrates the distribution of radiological characteristics and the precise localisation of tumours within the posterior cranial fossa. Table 2 presents the distribution of histopathological features within the cohort. Table 3 shows the list of all the 20 patients treated including metastatic work up, CSF and MRI.

Table 1: Distribution of radiological features and location of the tumour

Feature	**Frequency**	**Percentage**
Hydrocephalus	4	20
Spinal Drop Metastases	6	30
Location in Posterior Fossa (n=20)		
- Vermis	11	55
- Cerebellar Hemisphere	8	40
- Cerebellopontine Angle	1	5

Table 2: Distribution of histopathological findings

Feature	**Frequency**	**Percentage**
Unspecified medulloblastoma	11	55.0
Desmoplastic/Nodular	7	35.0
Classic	2	10.0

Table 3: Patients treated including metastatic workup

Age (years)	Time to diagnosis (weeks)	CSF findings	Surgery	Chemotherapy	Radiation (dose and field)	Follow up	Complications
0,6	4	Not done	Partial resection	6 VEC cycles	Delayed	Clinically stable 3 months after diagnosis	None
1	8	Malignant cells	Total resection	6 VEC cycles	Delayed	Demised 16 days after surgery	Surgical site infection
3	12	Malignant cells	Partial resection	6 VEC cycles	Radiotherapy completed	Demised 3 months later	Aspiration pneumonia
4	8	No malignant cells	Total resection	6 VEC cycles	Radiotherapy completed	Independent and coping at school a year after diagnosis	None
4	4	No malignant cells	Partial resection	4 VEC cycles	No radiotherapy	The patient did not follow up treatment a year later	Abandoned treatment
4	5	Not done	Total resection	6 VEC cycles	Radiotherapy completed	Clinically stable year later	None
5	4	No malignant cells	Partial resection	6 VEC cycles	Radiotherapy completed	Clinically stable year later	None

5	3	No malignant cells	Total resection	6 VEC cycles	Radiotherapy completed	Clinically stable year later	None
5	4	Malignant cells	Total resection	6 VEC cycles	Radiotherapy completed	Clinically stable 3 months later	None
5	5	No malignant cells	Total resection	6 VEC cycles	Radiotherapy completed	Currently in school and stable	None
7	12	No malignant cells	Partial resection	6 VEC cycles	Radiotherapy completed	Stable, however truncal ataxia	None
7	2	No malignant cells	Total resection	6 VEV cycles	Radiotherapy completed	Clinically stable 3 months later	None
7	8	Malignant cells	Total resection	6 VEC cycles	Radiotherapy completed	Clinically stable on last follow up 1 year later	None
8	6	Not done	Total resection	6 VEC cycles	Radiotherapy completed	Clinically stable 1 year later follow up	None
9	3	No malignant cells	Partial resection	No chemotherapy	No radiotherapy	The patient did not follow up after surgery	Abandoned treatment
10	3	No malignant cells	Partial resection	One cycle of VEC	No radiotherapy	The patient did not follow up on chemotherapy	Abandoned treatment
12	16	Malignant cells	Total resection	6 VEC cycles	Radiotherapy not done	Patient did not follow up	Abandoned treatment

13	3	Not done	Partial resection	6 VEC cycles	Radiotherapy completed	Palliative care	None
14	2	Malignant cells	Partial resection	6 VEC cycles	Radiotherapy completed	Demised a year later	Septicaemia
15	12	Malignant cells	Partial resection	6 VEC cycles	Radiotherapy completed	Palliative care	None

4.4 POST-OPERATIVE FINDINGS

Pre-operative imaging revealed a median tumour of 3.85 cm² (range: 3.2-5.4 cm²). Post-operative imaging data showed that twelve patients (60%) had residual post-operative tumour sizes measuring less than 1.5 cm², while eight patients (40%) had post operative residual tumours greater than 1.5 cm².

CHAPTER 5 DISCUSSION & CONCLUSION

5.1 DISCUSSION OF RESULTS

5.1.1 Demographics

In this cohort, three children died from complications related to advanced medulloblastoma and its treatment. Current literature indicates that mortality in paediatric medulloblastoma is often associated with post-operative complications, particularly in LMICs, where infection rates range from 15-40% (23). Common causes include surgical site infections, meningitis, and septicaemia, with predominant organisms being Staphylococcus aureus (35-40%) and gram-negative bacteria

including Klebsiella pneumoniae (20-25%) and Pseudomonas aeruginosa (15-20%) (23).

A three-year-old male, classified as high-risk with an unspecified WHO grade IV medulloblastoma, presented with cervical spine metastasis and a residual tumour measuring over 1.5 cm². He demised one month after surgery due to respiratory failure secondary to suspected lower cranial nerve injury and aspiration pneumonia. Sputum cultures grew Klebsiella pneumoniae resistant to first-line antibiotics.

A one-year-old female, also identified as high-risk with unspecified WHO grade IV medulloblastoma, had thoracic spine metastasis and a similar tumour burden. She demised 16 days postoperatively from septic shock following a surgical site infection. Blood cultures isolated methicillin-resistant Staphylococcus aureus (MRSA), and cerebrospinal fluid analysis showed elevated protein levels with positive culture for the same organism. These findings align with data from other LMICs, where post-neurosurgical infections significantly to mortality: meningitis (15-20%), surgical site infections (10-25%), and septicaemia (5-15%). Studies from similar settings report that MRSA accounts for 40-50% of surgical site infections, with gram-negative organisms responsible for the remainder (36, 37).

A 14-year-old female diagnosed with high-risk desmoplastic/nodular medulloblastoma, presenting with extensive cervical and thoracic spine metastases and a residual tumour exceeding 1.5 cm², underwent surgical resection of the tumour followed by chemotherapy and radiotherapy. She remained wheelchair-bound and demised from septic shock secondary to recurrent urinary tract infections approximately one-year post-treatment. Serial urine cultures consistently grew extended-spectrum beta-lactamase (ESBL) producing Escherichia coli resistant to multiple antibiotics.

In analysing the racial demographics of the patient cohort, it was found that 95% identified as black, while 5% were of Indian descent, as illustrated in Figure 3. This aligns with findings from a South African study on childhood malignancies conducted at two paediatric oncology centres, the University of the Free State and Stellenbosch University, where the predominant demographic comprised black children (58.2%), followed by those of mixed ancestry (25.6%) and white children (16.1%) (13). The study

indicated that white children exhibited the highest survival rate at 62.8%. This disparity may stem from several factors, including earlier presentation for treatment and better nutritional status among white patients. In contrast, black children and those of mixed ancestry often present later and tend to have poorer nutritional profiles, along with comorbidities such as Human Immunodeficiency Virus and tuberculosis (13). In our cohort, no patients were observed with these comorbidities. Survival rates for mixed-race children and black children were reported at 53.8% and 48.5%, respectively (13). These findings stand in stark contrast to those observed in high-income countries, where white patients are typically overrepresented in diagnoses of medulloblastoma, and other paediatric brain tumours compared to other racial groups (34). This divergence can likely be attributed to the significantly lower population of black children in high-income countries relative to the demographic landscape in Africa. Our study did not include white patients; however, this may not accurately reflect the true demographic, as some records were lost in the fire at CMJAH on April 16, 2021, and several patients consulted at Nelson Mandela Children's Hospital (NMCH).

In our study, the prevalence of medulloblastoma was notably higher among female patients than their male counterparts. This observation contrasts with existing literature that generally indicates a male predominance, with boys being affected 1.7 times more often than girls, particularly in regions such as South Asia, Europe, and the United States (4, 5). Interestingly, our findings align with a Kenyan study which reported that 90% of medulloblastoma diagnoses were in girls (35). The overall mean age of patients in our cohort was 6.9 years (±4.12), with an age range from 0.7 to 15 years. This is consistent with a population-based study involving 532 medulloblastoma cases in the United States, which reported that 57.3% of cases were diagnosed between zero and ten years of age, with a rapid decline after ten years (34). Their study showed an overall mean age of 12.9 years, which was higher than the median age of 9 years, attributable to approximately 25% of cases being older than 19 years (34).

5.1.2 Clinical, Laboratory and Radiological Findings

This study reveals that the primary symptom in children under three years old is a regression in developmental milestones. This is similar to findings from a multicentre study in the Île-de-France region, which examined 166 children diagnosed with medulloblastoma (14). In our cohort, children over three years presented predominantly with headaches (87%), vomiting (91%), and gait abnormalities (51%). Cerebellar signs were the most common neurological manifestation (58%).

Histopathological analysis indicated that 55% of the medulloblastoma cases were classified as unspecified, meaning they could not be assigned to one of the four recognised histopathological subtypes. Among the specified cases, 35% were identified as desmoplastic/nodular, while 10% were categorised as classic medulloblastoma. Notably, two patients diagnosed with WHO grade IV medulloblastoma (histology unspecified) died, as did one patient with desmoplastic/nodular histology. The patients with desmoplastic/nodular medulloblastoma demonstrated a favourable prognosis, with only one of seven patients experiencing mortality during the study period. This finding is consistent with a meta-analysis highlighting desmoplastic/nodular histology as a positive independent prognostic factor associated with better survival outcomes, even in young children with metastatic disease.

In LMICs, the shortage of subspecialty-trained neuropathologists often hampers accurate brain tumour diagnoses (23), explaining the unspecified medulloblastoma cases in our findings. A residual tumour over 1.5 cm^2 after surgery predicts poor prognosis in paediatric medulloblastoma patients (5, 6). Among eight patients with such residuals, three high-risk individuals died; factors included the residual tumour size, age under three years, and metastases presence. This is consistent with existing literature indicating worse outcomes for high-risk patients, a trend confirmed by our study (6).

5.1.3 Outcomes of patients

This study assessed treatment failure based on disease progression, treatment abandonment, relapse and mortality. Of the 20 patients in our cohort, 13 (65%) completed their prescribed chemotherapy and radiotherapy protocols. Seven patients (35%) did not complete treatment: three died during treatment, and four abandoned treatments due to disease progression.

Among those who completed treatment (n=13), two patients experienced disease progression during therapy at 6 and 8 months, respectively, and were referred to palliative care after completion of treatment, potentially due to pseudo-progression. Two additional patients showed disease progression within 3 months of completing therapy and were also referred for palliative care. At the end of the study period, these four patients in palliative care remained alive but had significant morbidity: two were wheelchair-dependent with bladder and bowel dysfunction and the other two, although they walk unaided, they also require assistance with activities of daily living and attend special needs schools.

Regarding mortality, three patients died during the treatment period: one from respiratory failure because of aspiration pneumonia with a suspected vocal cord dysfunction, at one-month post-surgery, another from surgical site infection at 16 days post-surgery, and the third from septicaemia at one-year post-treatment initiation.

Four patients abandoned treatment at different stages. One patient, after surgery and diagnosis, moved to another province and did not receive chemo or radiotherapy. Two patients, referred from North-West province, stopped after one and four chemotherapy cycles respectively and couldn't be reached for follow-up. The last patient completed six chemotherapy cycles but did not return for radiotherapy and attempts to contact them failed.

At the end of the study period (December 2022), of the original 20 patients, three had died (15%), four abandoned treatment (20%), and 13 (65%) were alive, with two of these survivors experiencing significant morbidity.

These outcomes, despite the limited sample size and relatively short duration of the study, are comparable to those reported in a 19-year Canadian longitudinal study that indicated an overall survival rate of 69.2% (32). In contrast, findings from a study conducted at two institutions in South Africa (University of the Free State and Stellenbosch University) demonstrated a lower survival rate of 46.4% among 532 paediatric patients with brain tumours, encompassing all tumour subtypes in their analysis (13).

5.2 CONCLUSION

The study examined the determinants of mortality and survival outcomes in paediatric patients diagnosed with medulloblastoma at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Hospital (CMJAH) between 2015 and 2022. The primary factors identified in this cohort study included:

- Sex: Among those who died, there were two females and one male.
- Race: All patients who died were Black, which was the predominant racial demographic in this study.
- Stage at presentation: The three patients who died presented with advanced-stage disease; notably, spinal drop metastases were identified at diagnosis during diagnostic evaluations.
- Residual tumour post-surgery: The patients who died had residual tumours exceeding 1.5 cm^2 following surgical resection.

The WHO has recognized the need to improve access to care, enhance diagnostic capabilities, strengthen healthcare systems, and develop standardized treatment protocols in LMICs, given the alarmingly low cure rate of less than 30% (15). In response, the WHO Global Initiative for Childhood Cancer aims to achieve at least a 60% survival rate for all children with cancer by 2030 through implementing these specific interventions (15).

To improve medical professional education and access to services, a structured, multifaceted approach is required. According to the PrOFILE tool evaluation across thirteen public-sector hospitals in South Africa, establishing dedicated neuro-oncology teams requires: 1) standardising multidisciplinary team reporting with consistent documentation of surgical procedures, radiology, pathology, and radiation oncology reports; 2) developing national chemotherapy safety guidelines and standard operating procedures; and 3) implementing comprehensive febrile neutropenia guidelines with protocols; and 4) forming formalized multidisciplinary teams should be formed, with neurosurgeons, paediatric oncologists, anatomical pathologists, allied health professionals, palliative care specialists, social workers, and psychologists attending regular team meetings to discuss cases (44). To sustain progress on these key priorities, the National Department of Health should support Naidu et al.'s structured approach through a dedicated childhood cancer committee. Furthermore, ongoing professional development should include specialized training opportunities and collaboration with international partners such as St. Jude Global to improve expertise in paediatric oncology care delivery.

Delayed clinical presentation is a prevalent issue among patients diagnosed with brain tumours in LMICs, a trend that aligns with our findings. It is essential to educate both parents and primary healthcare professionals on the early recognition of symptoms and the importance of prompt referral to tertiary care facilities. The St. Siluan warning signs, developed in South Africa to aid in early cancer detection, include specific neurological symptoms: persistent early morning headaches often accompanied by vomiting, visual disturbances such as squinting or white reflections (retinoblastoma) in the eye, and new onset seizures without fever. Additional warning signs include balance problems, regression in developmental milestones, and changes in behaviour or school performance (45). Increasing awareness of these signs among primary healthcare workers and community members can lead to earlier diagnoses and significantly enhance patient outcomes. The St. Siluan early warning signs have proven particularly effective in resource-limited settings, where they serve as a practical tool for healthcare workers to identify children requiring urgent referral for further investigation (45).

5.3 LIMITATIONS OF THE STUDY

Before discussing limitations, it is crucial to acknowledge that the low number of cases in our study reflects profound systemic challenges in African paediatric oncology. Only about 2% of the African population is covered by population-based cancer registries producing comparable incidence data, with striking disparities in cancer detection rates among different ethnic groups (ASR of 116.2 per million in white children versus 36.9 per million in black African children) (46). While cancer survival rates approach 80% in developed countries, approximately 80% of African children with cancer die without access to adequate treatment (47). This disparity is driven by severe healthcare budget limitations (ranging from US$17.00 per person annually in the Democratic Republic of Congo to US$819.00 in South Africa, compared to US$7,285.00 in the United States) and critical physician shortages (31 of 47 sub-Saharan African countries have fewer than 10 physicians per 100,000 population, versus 220-230 physicians per 100,000 in developed nations). Late presentation is particularly problematic; the differences in CNS tumour detection rates are approximately between white (16.1 per million) and black African (3.6 per million) children (46). About 72% of Wilms tumour cases in Nigeria and 78% in Sudan present at advanced stages (III and IV) (47). Multiple comorbidities further complicate treatment, including malaria, tuberculosis, HIV, and acute-on-chronic malnutrition (46). These challenges are particularly acute in provinces with limited healthcare resources; provinces with the highest proportion of the population with no income (55% in Limpopo and Eastern Cape) showed the lowest cancer detection rates. The dissemination of early warning signs to primary healthcare workers and public education about symptoms requiring urgent medical attention are therefore critical interventions needed to improve early detection and referral patterns, particularly in a context where childhood cancer is not yet perceived as a healthcare priority in regions struggling with other significant health challenges (46, 47).

The limitations of this study largely stem from its small patient cohort, which can be attributed to its retrospective design and the limited availability of data. The fire that occurred at CMJAH on the 16 April 2021 resulted in the destruction of the files and all the information captured, which consequently led to a reduced number of files being available for the cohort. A significant number of patients with brain tumours are also

referred to the recently opened NMCH, which likely contributed to the small sample size of the cohort. Minimal data collection occurred from the neurosurgical wards, likely influenced by age restrictions inherent in the two hospitals, where patients older than 14 years are admitted to the adult neurosurgery unit. It is worth noting that CHBAH Paediatric Oncology Unit treats children from 0-19 years. The findings from just two hospitals may not adequately represent the broader paediatric population in South Africa. Our sample size was restricted to 20 patients, which stands in stark contrast to a comprehensive 24-year study conducted in two paediatric oncology units in the Free State and Stellenbosch, involving a significantly larger cohort of 627 children with brain tumours (13).

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APPENDICES

APPENDIX A: MEDULLOBLASTOMA DATA COLLECTION TOOL

1. Patient ID: _____
2. Date of Birth: (DD/MM/YYYY)
3. Gender: (Male/Female/Other)
4. Race: _____

5. Clinical Presentation:

    Symptoms: _____

    Signs: _____

6. Radiographic Features: _____
7. Imaging Type: CT / MRI / Other: _____
8. Pre-operative Image: Yes/No
9. Tumour Characteristics: _____
10. Location in Posterior Fossa: _____
11. Evidence of Spinal Drop Metastasis: Yes/No
12. Histopathological Findings: _____
13. Molecular Subtypes:
    a. WNT Subtype: Yes/No
    b. SHH Subtype: Yes/No
    c. Group 3 Subtype: Yes/No
    d. Group 4 Subtype: Yes/No
14. Post-operative Image Available: Yes/No

APPENDIX B: ETHICS APPROVAL CERTIFICATE

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

20 August 2024

Dr Thapelo Mazibuko

Department of Neurosurgery

University of the Witwatersrand

Sent by email: thapelomazibuk008@gmail.com

Dear Dr Mazibuko,

Protocol no: M230411

Ethics Online Application Ref no. MED23-04-144

Protocol Title: Factors associated with Paediatric Medulloblastoma - A descriptive study of patients with Medulloblastoma treated in Johannesburg (2015-2022)

Principal Investigator: Dr Thapelo Mazibuko

Protocol Amendments

This letter serves to confirm that the Co-Chairman has approved protocol amendments as detailed in your letter dated 23 October 2023.

The following documents were received:

1. Motivation Letter

   - To increase sample size from 12 to 25.

   - To change data collection period from 2015-2019 to 2015-2022.

2. Latest copy of Clearance Certificate M230411

Yours sincerely,

Prof P Ruff

Chairperson

Human Research Ethics Committee (Medical)

APPENDIX C: TURNITIN REPORT

0705163J_final_article Dr Mazibuko-2.pdf

ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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2 Abd Elrhman Enayet, Mohamed Nabil, Mohamed Reda Rady, Yasser Yousef, Eman Badawy, Mohamed A. El Beltagy. "Surgical outcome of children with medulloblastoma: a retrospective study of a 405-patient series from Children's Cancer Hospital Egypt (CCHE57357)", Child's Nervous System, 2021 Publication	1%
3 Submitted to Liverpool John Moores University Student Paper	<1%
4 sa Internet Source mj.org.za	<1%

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6 Henrietta. "Pattern of paediatric cornealOmobolanle, Adio, and Nwachukwu <1% laceration injuries in the University of port

Harcourt teaching hospital, Rivers state, Nigeria", BMC Research Notes, 2012.

Publication

7 Submitted to University of Newcastle upon Tyne <1%

Student Paper

8 Emily R. Drabek-Maunder, Kshitij Mankad, <1%

Kristian Aquilina, Jamie A. Dean, Andrew Nisbet, Chris A. Clark. "Using diffusion MRI to understand white matter damage and the link between brain microstructure and cognitive deficits in paediatric Medulloblastoma

patients", European Journal of Radiology, 2024

Publication

9 Matthew T. Brown, Frederick A. Boop. "Management of Medulloblastoma in the Pediatric Population", Contemporary Neurosurgery, 2016 Publication <1%

10 Ahmad Kh Alhaj, Talal Burhamah, Fadil Mohammad, Mariam Almutawa et al. "Are the Radiological and Molecular Features of Pediatric Medulloblastomas Valuable Prognostic Indicators? A 10-Year Retrospective Review in the Middle East", World Neurosurgery, 2024 Publication <1%

11 Han Zou, Brad Poore, Alberto Broniscer, Ian F. Pollack, Baoli Hu. "Molecular Heterogeneity and Cellular Diversity: Implications for Precision Treatment in Medulloblastoma", Cancers, 2020 Publication <1%

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Bigner, Eric S Lipp, Sebastien Perreault, Yoon-

Jae Cho, Gerald Grant, Seung-Ki Kim, Ji Yeoun Lee, Amulya A Nageswara Rao, Caterina

Giannini, Kay Ka Wai Li, Ho-Keung Ng, Yu Yao,

Toshihiro Kumabe, Teiji Tominaga, Wieslawa A

Grajkowska, Marta Perek-Polnik, David C Y Low, Wan Tew Seow, Kenneth T E Chang,

Jaume Mora, Ian F Pollack, Ronald L Hamilton,

Sarah Leary, Andrew S Moore, Wendy J

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39

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