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Systematic Review / Meta-analysis

Management and outcomes of low-grade gliomas in Africa: A scoping review

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ABSTRACT

Introduction: Despite recent advancements in the management of low-grade gliomas (LGGs), there is a paucity in the data within the African landscape. We aim to evaluate the epidemiology, management, and outcomes of LGGs in Africa.

Methods: Systematic searches of MEDLINE, Embase and African Journals Online were performed from database inception to January 27, 2021, for studies reporting on LGGs in Africa. Pooled statistics were calculated using measures of central tendency and spread.

Results: 554 unique studies were identified, of which 25 were included. The mean age of patients was 15.7 years (95% confidence interval (CI): 11.8–19.6) and 56.4% were male (95% CI: 55.6–62.6%). Most patients had solitary lesions (86.0%, 95% CI: 82.8–89.1%) located in the infratentorial region (71.6%, 95% CI: 66.1–77.1%). Most LGGs received histopathological diagnosis (71.7%, 95% CI: 69.2–74.2%) and astrocytoma was the most common type (81.1%, 95% CI: 78.5–83.7%). 37 patients had awake surgery (3.1%, 95% CI: 2.0–4.0%) and there were no reports of molecular pathology testing, intraoperative neuroimaging, or 5-aminolevulinic acid. Gross total resection was achieved in 74.8% (95% CI: 69.6–80.0%) and there was a recurrence rate of 1.7% (95% CI: 0.9–2.4%), with a mean follow-up of 19.4 months (95% CI: 6.9–31.9).

Conclusion: LGGs are underreported in Africa. We found a lag in the uptake of techniques established in high-income countries for improving patient outcomes. Future efforts will require further training and funding in molecular pathology testing and advanced surgical adjuncts.

1. Introduction

Gliomas are neuroepithelial tumours that derive from supporting glial cells inA the central nervous system (CNS). Historically, the World Health Organization (WHO) has classified gliomas between grades I and IV according to their histopathological and immunohistochemical features. In 2016, the WHO classification of CNS tumours started integrating molecular biology features, illustrating a shift toward genotypic profiling of tumours [1]. Low-grade gliomas (LGGs) show cytological atypia and are slow-growing [2,3] but exhibit a high potential for malignant transformation, with over 70% of tumours transforming into anaplastic glioma variants or secondary glioblastomas within a decade of presentation [4]. LGGs account for 17%–22% of total brain tumours and have a median survival time between 5.6 and 13.3 years [5].

There is no universal consensus on treatment strategy, although it is common practice to attempt surgical resection early in the disease course, as this is associated with better overall survival regardless of age, degree of disability, or histological subtype [6]. In surgical resection of LGGs, the aim is to maximize the extent of resection and minimize neurological complications. Recent advances in neuroimaging and intraoperative adjuncts have played a major role in achieving that goal, and of particular interest is the use of awake surgery for LGG resection. This allows for safe maximal tumour resection according to functional boundaries, minimizing postoperative morbidity and improving quality

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of life [7].

Furthermore, recent advances in our understanding of genomic drivers of gliomagenesis have led to more targeted interventions and better overall outcomes [5]. Key molecular drivers in LGGs include mutations in isocitrate dehydrogenase (IDH), co-deletion of chromosomes 1p and 19q, and histone mutations. Identifying these mutations has allowed for the differentiation of tumours into separate diagnostic and prognostic groups. Mutation patterns in LGGs place tumours onto a spectrum of tumour aggression, where IDH-mutant, 1p/19q co-deleted oligodendrogliomas follow the most benign clinical course, while IDH-wildtype astrocytomas are the most aggressive [8]. In addition to playing a role in prognosis, the identification of mutations in LGGs has contributed to the development of novel therapeutic approaches [9]. For example, adjunctive chemotherapy is now being guided and refined by patients' specific molecular parameters [4].

In Africa, brain tumours represent a significant burden of disease: in Sub-Saharan Africa, brain tumours represent 0.14% of disability-adjusted life years (DALYs) and 0.17% of deaths, while in North Africa, brain tumours cause 0.44% of DALYs and 0.62% of deaths [10]. However, there is a significant deficit in the literature on neurosurgical care of LGGs in Africa [11], and available reports suggest that diagnosis and management of LGGs remains a daunting task in most low- and middle-income countries (LMICs). Possible contributing factors to this deficit include the lack of access to adequate neuroimaging facilities, which prevent timely diagnosis and treatment of suspected LGG cases, the absence of surgical adjunct technologies, and lack of training in awake surgery [12].

This review aims to identify, analyse, and synthesise the relevant literature on the current state of diagnosis, management, and outcomes of LGGs in Africa, and determine where the barriers lie. This is a crucial step towards aiming interventions at the aspects of LGG care most in need, to facilitate efforts dedicated to improving patient outcomes.

2. Methods

A scoping review on the epidemiology, management, and outcomes of LGGs in Africa was conducted as per the published and registered protocol (https://doi.org/10.17605/OSF.IO/E732G; unique identifying number: E732G), available on Open Science Framework [13]. This scoping review was guided by the Arksey and O'Malley (2005) scoping review framework [14]. The work was carried out in accordance with the operational methodology outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 guideline [15].

The adequacy of the methodology of our review was also evaluated using the AMSTAR 2 criteria (electively directed at assessing the methodological adequacy of systematic reviews) [16]. The level of compliance was deemed as critically low. However, this was due to the particular type of research conducted, namely a scoping review, which requires a different methodological approach than that of a systematic review.

2.1. Search strategy

A search strategy was developed using a systematic approach that is consistent with a scoping review methodology to identify studies related to the treatment and/or outcomes of patients with LGGs in Africa, including terms describing individual African countries, LGG, therapy, and outcome. The development of the search strategy was in consultation between two authors (RdK and USK) and an expert librarian (NT). The search was conducted using several databases, including MEDLINE, EMBASE, and African Journals Online, from database inception to 27 January 2021. Appendix 1 in the protocol shows the exact content and order of the search string queries. A hand search of Google Scholar was further conducted to identify additional articles that were not captured in the above process.

2.2. Study selection

All the articles resulting from the search were exported into Rayyan [17], where duplicates were identified and deleted. Rayyan is a professional research software that is widely used by collaborators for ease of study selection decisions. The study selection process consisted of multiple steps, where a minimum of two reviewers of SZYO, RdK, NDAB, AE, DUD, MD, MK, RT, JK, DS, and USK independently screened the titles and abstracts, followed by full texts, of the identified articles based on the pre-defined inclusion and exclusion criteria. Any disagreement between the two reviewers' decisions prompted further discussion. If a disagreement persisted, a senior author (NDAB or USK) was sought to resolve the disagreement. The full texts of the remaining articles were retrieved and screened by two reviewers (of SZYO, RdK, NDAB, AE, DUD, MD, MRDT, MK, RT, JK, DS, and DYCH) independently.

2.3. Inclusion and exclusion criteria

We included studies that fulfilled the specific inclusion criteria discussed in our published protocol. Studies of interest included those that discussed the treatment and/or outcomes of LGGs, diagnosed through histology and/or radiology, in African populations. We also included various publications including journal articles, reviews, case reports, letters. There were no restrictions to the period of the publications considered to ensure that all relevant articles published from database inception to date of search were captured. Publications in English and French languages were considered.

We excluded studies that (i) did not include African populations (or did not have disaggregated data about the African population), (ii) did not discuss LGGs (or did not have disaggregated data about LGGs), (iii) did not discuss management and/or treatment and (iv) were neither written in English nor French.

2.4. Data extraction

Data extraction was performed in two stages, a pilot stage followed by a proper stage. The pilot stage consisted of having multiple authors, each going through the same 10 selected articles to extract data. This was to ensure that all participant authors were able to extract data accurately to ensure homogeneity in the reporting of the data and to ensure the data collection sheet captured all relevant and important information from the included studies.

Studies which met inclusion criteria were read in full, and the following data were extracted, summarized, and tabulated in an Excel proforma sheet: title, year of publication, name of first author, study design, study location, population size, participants characteristics (including sex, mean age and age range), neuroimaging modality used, histopathology diagnosis, molecular pathology diagnosis, type of intervention, and outcomes of care.

2.5. Data analysis

Data analysis was conducted with SPSS v.26 (IBM, USA). Pooled statistics were calculated using measures of central tendency and spread. A meta-analysis was not performed in this study due to the heterogeneity of data and study design within the articles identified.

2.6. Risk of bias assessment

The purpose of this review was to produce a systematically conducted scoping review of the available literature to provide a comprehensive overview on the management and outcomes of LGGs in Africa, hence a formal bias assessment was not done. Formal evidence grading was not conducted (given the limited and heterogenous literature body), and thus a formal bias risk assessment was deemed unnecessary for this emerging area of literature, which clearly suffers from standard biases

associated with new areas of clinical research.

3. Results

The comprehensive search returned 564 studies and we screened 554 articles (98.2%) after deduplication. The majority of papers were excluded at the title and abstract screening stage (n = 398, 70.6%) and another 131 papers (23.2%) were excluded at full text screening. Therefore, 25 articles remained for data extraction (4.4%). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flow diagram guidance [18] to illustrate the information flow through the several phases of this scoping review (Fig. 1).

The articles were published between 1985 and 2020 with a peak between 2010 and 2019 (n = 20, 80.0%). Eight (32.0%) studies were conducted in Nigeria, five (20.0%) in Egypt, and four (16.0%) in Morocco (Table 1). Each study recruited an average of 43.1 (95% CI = 9.9–76.2) patients, over a mean period of 6.5 (95% CI = 2.6–10.5) years. The patients were 15.7 years old on average (95% CI = 11.8–19.6) and most were male 56.4% (95% CI = 55.6–62.6%).

All patients had access to neuroimaging. The primary neuroimaging modality was magnetic resonance imaging [MRI, (58.0%, 95% CI = 51.5–64.4%)] and the remainder of cases were diagnosed and planned based on computed tomography scans [CT scan, (42.0%, 95% CI = 35.6–48.5%)]. Most patients had solitary lesions (86.0%, 95% CI = 82.8–89.1%) located in the infratentorial region (71.6%, 95% CI = 66.1–77.1%). The precise locations of solitary lesions were reported in a minority of cases (21.2%, 95% CI = 18.9–23.5%). Table 2 shows the distribution of LGGs. Patients with multiple LGGs (14.0%, 95% CI = 10.9–17.2%) had evenly distributed tumours: half were infratentorial (50.9%, 95% CI = 46.3–55.4%) and 49.1% were supratentorial (95% CI

Table 1
Characteristics of the low-grade glioma in Africa studies.

Characteristic	Frequency (Percentage)
Publication year	
1980–1989	1 (4.0)
2000–2009	2 (8.0)
2010–2019	20 (80.0)
2020	2 (8.0)
Study setting	
Nigeria	8 (32.0)
Egypt	5 (20.0)
Morocco	4 (16.0)
Tunisia	3 (12.0)
Uganda	2 (8.0)
Cameroon	1 (4.0)
Ghana	1 (4.0)
Kenya	1 (4.0)
Study design	
Cross-sectional	16 (64.0)
Case report	5 (20.0)
Case series	3 (12.0)
Qualitative	1 (4.0)

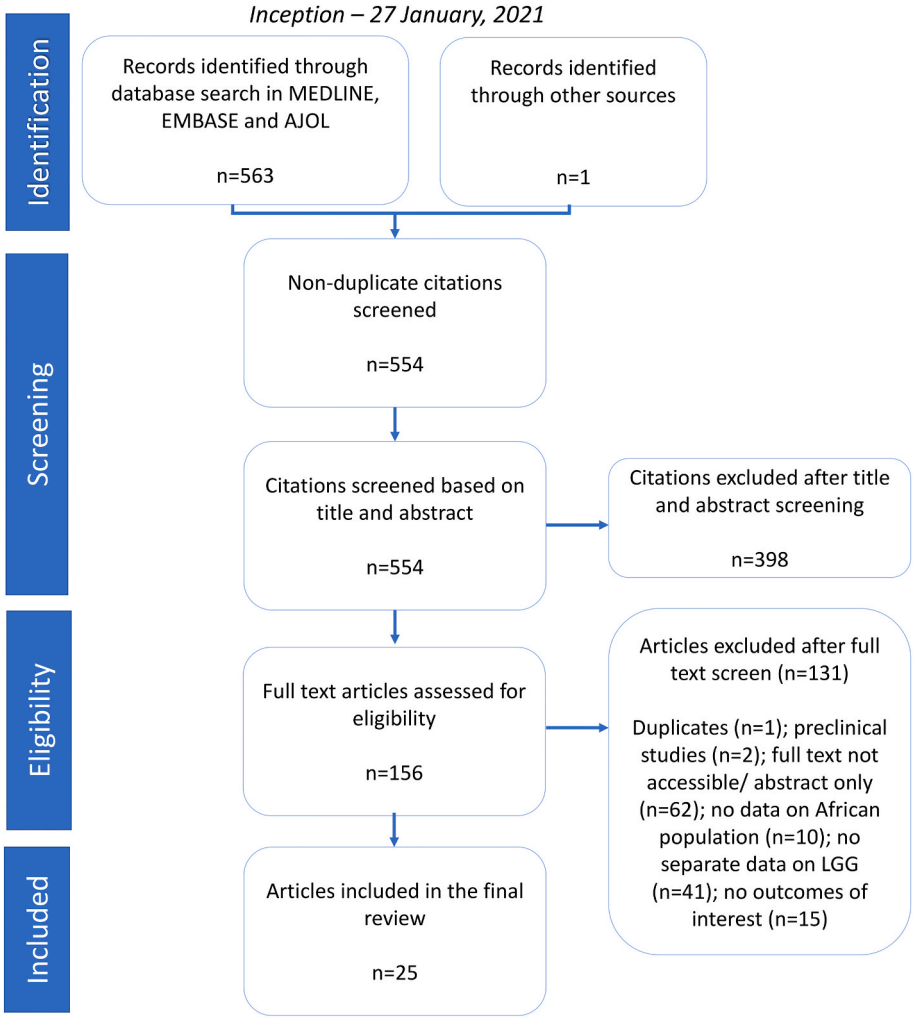

Fig. 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram for study selection.

Table 2
Precise location of LGGs in African patients.

Location	Value	Lower limit 95% CI	Upper limit 95% CI
Cerebellar	44.0%	39.5%	48.5%
Brainstem	27.6%	23.6%	31.5%
Frontal lobe	13.2%	10.1%	16.3%
Parietal lobe	7.0%	4.7%	9.3%
Temporal lobe	6.2%	4.0%	8.4%
Interlobar	1.6%	0.4%	2.7%
Occipital lobe	0.4%	−0.2%	1.0%

= 44.6–53.7%).

The majority of LGGs were sent to histopathology (71.7%, 95% CI = 69.2–74.2%), of which astrocytic tumours were the most common type (81.1%, 95% CI = 78.5–83.7%) (Fig. 2). None of the studies reported using molecular pathology.

In total, thirty-seven LGGs were operated on while the patients were awake (3.1%, 95% CI = 2.0–4.0%). Extent of resection was reported in only 262 cases, making up about one fifth of the total number of cases (21.6%, 95% CI = 19.3–23.9%). Of those reporting the extent of resection, gross total resection (i.e., 99–100% removed) was achieved in 74.8% (95% CI = 69.6–80.0%) of the cases. Subtotal resection (i.e. 90-99% removed) and partial resection (i.e. 50-90% removed) were achieved in 20.2% (95% CI = 15.4–25.1%) and 5.0% (2.3–7.6%) of cases, respectively. There were no reports of intraoperative neuroimaging, neuronavigation and 5-aminolevulinic acid use.

Forty-five (3.7%, 95% CI = 2.6–4.8%) patients were treated with chemotherapy and ten (0.8%, 95% CI = 0.3–1.3%) were treated with radiotherapy. The patients were followed-up for an average of 19.4 months (95% CI = 6.9–31.9) and had a 1.7% recurrence rate (95% CI = 0.9–2.4%).

4. Discussion

4.1. Key findings

This is the first scoping review mapping the diagnosis, management, and outcomes of LGGs across Africa. We identified and extracted data from 25 studies on LGGs from 8 of the 54 countries in Africa. Most patients had a single lesion, and this was more likely to be located in the infratentorial region. Patients with multiple lesions had them distributed equally between supratentorial and infratentorial regions. Most centres had access to histopathological diagnosis and the most common tumour type was astrocytoma. Data on surgical management was scarce, though where data was available, gross total resection was achieved in the majority of cases. The use of awake surgery was rarely reported, and there was no mention of intraoperative surgical adjuncts. These results confirm the underreported burden of LGGs in Africa, and highlight the delay in implementing novel diagnostic and therapeutic technologies.

4.2. Implications

In this review, most African patients had solitary lesions located in the infratentorial region. The precise locations of these lesions were not always reported, though our data suggests the majority were located in the cerebellum, followed by the brainstem. We hypothesize that the higher incidence of infratentorial LGGs could be due to the large proportion of paediatric patients reported on. Prior literature has shown that LGGs in children tend to occur in the infratentorial region [19], the reasons for which are still poorly understood. Another potential explanation could be the increased technical challenge of resecting tumours in this region, especially in the context of resource-poor settings, thus making its cases more publishable due to the greater educational value and interest to the global neurosurgery community.

Both histopathological and molecular features used in LGG grading provide important prognostic information and can guide the

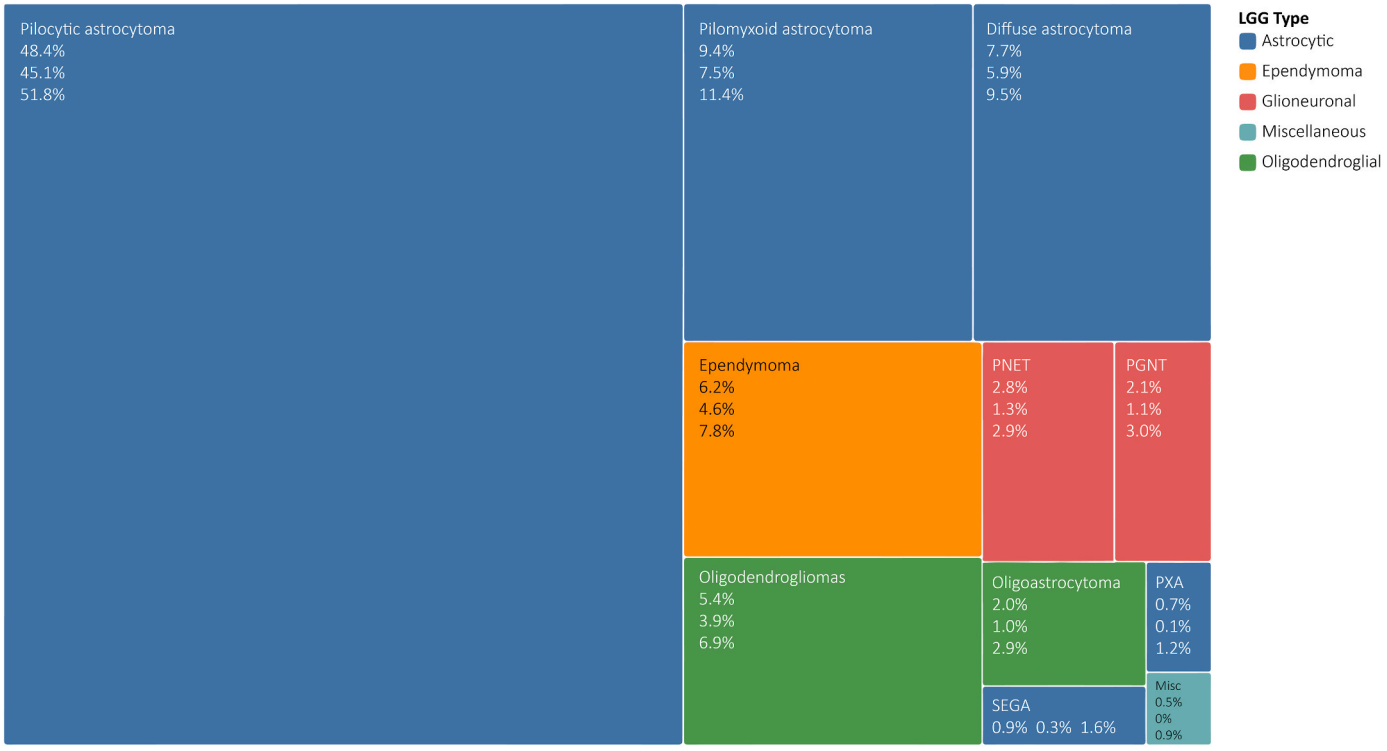

Fig. 2. TreeMap of the histopathology of low-grade gliomas in Africa by type (words at the top left corner) and showing their prevalence (first number) and corresponding 95% confidence intervals (second and third numbers represent lower and upper limits respectively). PGNT - Papillary glioneuronal tumour, PNET - Primitive neuro-ectodermal tumour, PXA - Pleomorphic xanthoastrocytoma, SEGA - Subependymal giant cell astrocytoma.

management of these tumours [20]. Our review highlights that while most patients undergo histological analysis to confirm the diagnosis of LGGs, none of the studies included in this review analysed the molecular characteristics of the tumour, highlighting the lack of availability and accessibility of qualified centres for molecular characterization of LGGs across Africa. A review by Aquilanti et al. revealed that of all of the known glioma-associated molecular alterations discovered to date, the presence or absence of an IDH mutation has the greatest prognostic significance [9], hence determining its status should be a priority. IDH mutations are noted in the vast majority of grade II and grade III gliomas, which are associated with improved survival compared with glioblastomas.

In addition to prognostic indications, the future of LGG management may see molecular characterization becoming crucial, as research into novel targeted therapies based on these genetic change's advances. The WHO 2015 Non-communicable Disease Country Capacity Survey found that only 35% of LMICs reported having pathology services generally available in the public health sector—where 'generally available' is defined as being accessible in 50% or more of health care facilities within the country [21]. The lack of molecular characterization found in our review supports this. A variety of strategies have been suggested to improve pathology services in LMICs [22]. Adequate mentorship, development of short-term visitor programs, overcoming supply-chain barriers, standardization of training and establishing the role of a pathologist in cancer screening and early diagnosis have been recommended to address this issue [23].

Technological advancements and research in the field of surgical neuro-oncology have focused on techniques, equipment and perioperative treatment modalities that aim to facilitate and optimize maximal resection of tumours. In our review, we found that many of these were not available or were not regularly practiced in Africa. None of the studies analysed in this review made use of intraoperative adjuncts in surgery for LGG resection, such as use of 5-ALA or intraoperative neuroimaging modalities like CT, MRI, and ultrasound. Such image-guided neuronavigation systems allow surgeons to better visualize brain tumours and increase both precision and safety of tumour resection, leading to smaller postoperative residual volumes that correlate with lower recurrence rates and better survival [24]. For example, intraoperative MRI has been shown to guide additional resection in up to 70% of cases with no increased risk of neurological morbidity [25].

However, these tools and equipment are scarce in resource-limited countries, adding an extra layer of difficulty to the already established barriers that neurosurgeons in Africa face. In accordance with these findings, the recent global survey by the World Federation of Neurosurgical Societies Young Neurosurgeons assessed access to image guidance systems and found that only 12.8% of LMIC clinicians had access to any of these systems, as compared to 90% of HIC surgeons [26]. Resecting infratentorial tumours requires intricate skill to circumnavigate functionally critical anatomy such as the brainstem and cerebellum, and the lack of adjuncts in Africa could explain the low rates of gross total resection observed in our study. We know that the extent of resection during primary surgery is a significant prognostic variable in LGG outcome [27], therefore we urge local policymakers and stakeholders to consider investing in these adjuncts as a cost-effective solution to improving long-term outcomes and reducing LGG recurrence rates.

Our review showed that only 3.1% of LGG patients in Africa underwent awake surgery, despite one fifth of patients with solitary lesions having their tumour in the supratentorial region, therefore being amenable to awake surgery. Given the lack of availability of surgical equipment and intraoperative adjuncts in Africa, increasing service provision of awake craniotomy may be a possible solution to improving patient outcomes. Published literature has shown that awake craniotomy is a particularly important surgical technique when resecting within eloquent areas, to preserve motor and sensory functions through real-time assessments in surgery, leading to improved functional status and quality of life after surgery [28]. The resources needed to train neurosurgeons to perform awake craniotomies may also be more cost-effective than investing in advanced technology such as neuronavigation, and its training and maintenance.

However, awake craniotomy also presents its own set of challenges in the paediatric population. Although the safety and tolerability of awake surgery in children has been established in prior literature, children remain more vulnerable and psychologically fragile [29]. Undergoing surgery can be daunting to children, let alone facing it awake. Patients undergoing the procedure must be able to cooperate with the surgical and anaesthetic team and manage their anxiety throughout the procedure, which can be especially difficult with children. Possible solutions to this would involve conducting a psychological assessment prior to surgery and reviewing the suitability of the patient on a case-by-case basis [28]. A multidisciplinary approach involving anaesthesiologists is pivotal in ensuring patients and their families fully understand the overall procedure, thus a good anaesthesiologist-patient relationship is essential in alleviating anxiety to maximize the chances of a successful procedure.

Neurosurgeons performing awake surgery require extensive training in both technical and soft skills, and neurosurgeons in low-resource settings report feeling underconfident and undertrained in awake craniotomy [30]. International training, short-term visitor programs, and mentorship may be crucial to tackle this. Published literature has revealed that the technique has been successfully adopted in multiple LMICs, including some African countries, after collaboration with neurosurgical centres in HICs [31]. Therefore, we advocate for these efforts to be extended to more African countries as a means of reducing the neurological morbidity and recurrence rates of LGG patients.

In the long term, local mentorship, with African neurosurgeons training more junior local neurosurgeons, would be economically beneficial in not only expanding the uptake of the skill across the continent, but also ensuring the sustainability of future neurosurgeons performing procedures to treat LGGs. The importance of a multidisciplinary, holistic approach also needs to be emphasized and nurtured in the neurosurgical workforce to promote teamwork among staff and to ensure all disciplines recognize the value of their roles in delivering optimal care to patients requiring care, especially in the case of awake surgery.

4.3. Limitations

Despite a systematic and extensive literature search, the quality of conclusions that can be drawn from this study are limited by the available literature, which is sparse. No randomized controlled trials were available, and a fifth of papers included were single case reports. However, this lack of available literature has served to highlight the underreporting of LGGs in Africa. Moreover, we were only able to include articles published in English or French. This means literature published in alternative languages such as Spanish and Arabic will have been omitted from our analysis. Further to the limited number of included articles, only data from Nigeria, Egypt, Morocco, Tunisia, Uganda, Cameroon, Ghana and Kenya was able to be captured in this study. Representing only 8 of the 54 countries in Africa (15%), the reported data may not be representative of the entire continent. Specifically, data from major neurosurgical hubs such as Algeria, South Africa, and Zimbabwe was not available to be included in this study.

5. Conclusion

The management of LGGs has undergone remarkable progress over the last decade, with significant advances made in the field of surgical techniques and laboratory analysis. These developments have improved the overall survival and quality of life of patients suffering from these tumours. This study has shed light on the landscape of LGG diagnosis and treatment in Africa and has highlighted a lag in adopting these novel

techniques in their practice. These delays can be explained by a lack of workforce, training, and access to technology platforms to aid diagnosis and quality of care. Future efforts should be directed at addressing these barriers.

We advocate for the improvement of technical platforms for diagnosis, particularly focused on imaging, molecular biology, and tumour genetics. We believe attention should be directed at encouraging the implementation of surgical techniques such as awake surgery to maximize excision while preserving the quality of life, and finally, further training of young neurosurgeons, neuroradiologists, and neuropathologists is crucial to provide sustainable change and improve future research, diagnosis, and management of LGGs.

Ethical approval

Ethical approval was not required for this study.

Sources of funding

No funding was received for this research.

Author contribution

Setthasorn Zhi Yang Ooi (project administration, data extraction, data analysis, writing, review and editing, data curation, visualisation), Rosaline de Koning (conceptualisation, project administration, methodology, data extraction, writing, review and editing), Abdullah Egiz (methodology, data extraction, writing, review and editing), David Ulrich Dalle (data extraction, writing), Moussa Denou (data extraction, writing), Marvin Richie Dongmo Tsopmene (data extraction, writing), Mehdi Khan (data extraction), Régis Takoukam (data extraction), Jay Kotecha (writing, review and editing), Dawin Sichimba (writing), Dokponou Yao Christian Hugues (writing), Ulrick Sidney Kanmounye (conceptualisation, methodology, data analysis, validation, review and editing, supervision), Nourou Dine Adeniran Bankole (conceptualisation, project administration, methodology, data extraction, supervision, writing, review and editing). Setthasorn Zhi Yang Ooi and Rosaline de Koning are joint first authors. Setthasorn Zhi Yang Ooi, Rosaline de Koning, and Nourou Dine Adeniran Bankole contributed equally to this paper.

Registration of research studies

1. Name of the registry: Open Science Framework.
2. Unique Identifying number or registration ID: E732G.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://doi.org/10.17605/OSF.IO/E732G.

Guarantor

Nourou Dine Adeniran Bankole.

Consent

Consent was not required for this study.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103246.

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