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Outcomes of Children With Low-Grade Gliomas in Low- and Middle-Income Countries: A Systematic Review

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PEDIATRIC ONCOLOGY

original reports abstract

Outcomes of Children With Low-Grade Gliomas in Low- and Middle-Income Countries: A Systematic Review

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PURPOSE Pediatric CNS tumors are increasingly a priority, particularly with the WHO designation of low-grade glioma (LGG) as one of six index childhood cancers. There are currently limited data on outcomes of pediatric patients with LGGs in low- and middle-income countries (LMICs).

METHODS To better understand the outcomes of LGGs in LMICs, this systematic review interrogated nine literature databases.

RESULTS The search identified 14,977 publications. Sixteen studies from 19 countries met the selection criteria and were included for data abstraction and analysis. Eleven studies (69%) were retrospective reviews from single institutions, and one (6%) captured institutional data prospectively. The studies captured a total of 957 patients with a median of 49 patients per study. Seven (44%) of the studies described the treatment modalities used. Of 373 patients for whom there was information, 173 (46%) had a gross total or near total resection, 109 (29%) had a subtotal resection, and 91 (24%) had only a biopsy performed. Seven studies, with a total of 476 patients, described the frequency of use of radiotherapy and/or chemotherapy in the cohorts: 83 of these patients received radiotherapy and 76 received chemotherapy. The 5-year overall survival ranged from 69.2% to 93.5%, although lower survival rates were reported at earlier time points. We identified limitations in the published studies with respect to the cohort sizes and methodologies.

CONCLUSION The included studies reported survival rates frequently exceeding 80%, although the ultimate number of studies was limited, pointing to the paucity of studies describing the outcomes of children with LGGs in LMICs. This study underscores the need for more robust data on outcomes in pediatric LGG.

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INTRODUCTION

Childhood cancer survival rates have improved vastly over the past 50 years, reflecting advances in the understanding of cancer biology, the implementation of risk-adapted treatment, and the optimization of supportive care. However, it is estimated that 90% of children in whom cancer is diagnosed live in low- and middle-income countries (LMICs),[1] where effective curative and supportive care is frequently not widely accessible.[2] Currently, 90% of childhood cancer deaths occur in LMICs.[3] Importantly, childhood cancer has been increasingly recognized as a global health priority, prompting global collaboration and investment.[4] Therefore, it is important to define priorities for strengthening health systems and thereby reduce cancer-related mortality.

Pediatric CNS tumors are the second most common type of childhood cancer and the most common cause of death in children with cancer.[5] Tumors of glial origin are the most common CNS tumors in children, representing approximately 40% of all CNS tumors in this population.[6] Although children with high-grade gliomas have an overall poor prognosis despite intensive therapy, low-grade gliomas (LGGs) have much better prognoses, especially when substantial surgical resection can be achieved.[7-9] Pediatric patients with LGGs have a 10-year overall survival (OS) exceeding 90% in high-resource settings.[8] Importantly, LGG is one of the six designated index cancers of the WHO Global Initiative for Childhood Cancer (GICC), which has the goal of increasing the global survival rate to 60% by 2030.[10] The complexity of factors needed to provide quality care for LGG is substantial, with integration of comprehensive multidisciplinary care encompassing accurate pathologic and radiologic diagnosis, neurosurgery, radiotherapy, chemotherapy, and monitoring for acute complications and long-term sequelae. Many of these elements are not always available in LMICs.[11]

Understanding the outcomes of children with LGGs in LMICs is important for quantifying the gap between

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What are the outcomes of pediatric low-grade glioma in low- and middle-income countries (LMICs)?

Knowledge Generated

A comprehensive search strategy identified studies that frequently described overall survival at 5 years above 80%, although lower survival rates were reported at earlier time points. Although reported outcomes are above the goal of the WHO Global Initiative for Childhood Cancer, outcomes in most LMICs were not captured and many of the studies were limited in terms of details of management and methodology.

Relevance

This study underscores the need for more robust data on outcomes in pediatric low-grade glioma in LMICs to better understand the shortcomings of existing care and prioritize interventions to guarantee access to quality care in the future.

survival rates in low- and high-resource settings and for identifying the specific steps needed to address these disparities. It is also important if we are to track the impact of the GICC, as data on outcomes of pediatric patients with LGGs in LMICs are currently limited.[12,13] Importantly, the International Classification of Childhood Cancer-3 groups the histologic codes for LGGs and high-grade gliomas together; hence, population-based reports of pediatric LGG outcomes are scarce.[14] In the face of this paucity of data, it was determined that a systematic review of published reports of the outcomes of pediatric LGGs in LMICs, described herein, could help us to better understand the landscape of these tumors across the world.

METHODS

Search Strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[15] and was registered with PROSPERO (CRD42021262658). The search strategy included three themes: (1) LGGs, (2) pediatric patients, and (3) LMICs. Synonyms for these terms were included in the search, including specific histologic variants of LGG and all countries classified as low- or middle-income.[16] The full search strategy is included in the Appendix 1. To capture publications from diverse contexts, the following databases were interrogated: PubMed, EMBASE, SCOPUS, Web of Science, Global Index Medicus, SciELO, LILACS, IBECS, and PAHO-IRIS. Databases were searched up to June 23, 2021. The authors also screened the reference lists of identified articles.

Inclusion Criteria

To describe the outcome of children with LGG as a whole, we included criteria that would exclude studies evaluating specific presentation or management of these tumors. Inclusion criteria for studies included the following: year of publication after 2000 in a peer-reviewed journal; at least 10 patients diagnosed with LGG included; patients age 0-19 years at diagnosis; treating institution in an LMIC; examination of outcomes of frontline therapy; availability of outcome data (OS, median survival, event-free survival [EFS], and/or net survival); follow-up time of at least 1 year; and not restricted to specific populations (eg, infants), specific tumor locations (eg, optic pathways or brainstem), or a single treatment modality (eg, radiotherapy). No restrictions were placed on the publication language. If the abstracts or full texts were not available in a language understood by the authors, native speakers were sought in the Department of Global Pediatric Medicine at St Jude Children's Research Hospital.

Selection Strategy

Two authors (R.W. and H.M.J.) independently screened study titles and abstracts for potential relevance. Subsequently, full texts were assessed by two reviewers for ultimate inclusion. Conflicts were resolved by a third-party adjudicator (D.C.M.). Covidence (Veritas Health Innovation, Melbourne, Australia), a tool for systematic review management, was used for this process.

Data Extraction and Bias Assessment

Two authors (R.W. and D.C.M.) independently extracted the following data from each article, using a standardized template: treatment institution country, histologic diagnosis, age of included subjects, study sample size, treatment modalities, follow-up time, EFS number and/or percentage, and OS number and/or percentage. For studies that presented outcomes data only as survival curves, a percentage (in 5% increments) was estimated on the basis of the included figures. For studies that presented individual patient data, survival rates and/or percentages were calculated if they were not explicitly stated in the text or figures. Publishing investigators were contacted to obtain or confirm data as needed. Given that individual-level data were not available for the majority of studies and that some studies published Kaplan-Meier curves without the associated number of censorships, pooled analyses were not performed as they were deemed unreliable.

The same two authors independently assessed the risk of bias in these studies by using an assessment tool created by

combining key elements that were particularly relevant to studies analyzing survival outcomes included in published tools.[17-19] Each element was judged to have a high, low, or unclear risk of bias. Discrepancies were resolved by discussion.

RESULTS

Search Results

Our search yielded 14,977 studies, of which 110 were assessed for eligibility through full-text review. Sixteen studies met the inclusion criteria, and data were extracted from them (Fig 1).[20-35] The included studies captured data from 16 LMICs: one low-income country, five lower-middle-income countries, and 10 upper-middle-income countries (Fig 2). Two studies were included from each of Brazil, Mexico, and Turkey. One report[24] included compiled data from population-based cancer registries in the English-speaking Caribbean, representing six countries, including three high-income countries. The published studies were mainly conducted by researchers based in LMICs, although two first authors (13%) and three senior/corresponding authors (19%) were from institutions in high-income countries. Furthermore, five studies (31%) included authors from institutions in high-income countries.

Included Studies

Table 1 summarizes the data extracted from the included studies. Of these studies, 11 (69%) were retrospective reviews from single institutions and one (6%) captured institutional data prospectively. Two studies (13%) reported on population-based cancer registries. The reports were published from the specialties that care for children with LGG, including but not limited to pediatric oncology, neurosurgery, and pathology. The studies captured a total of 957 patients, with a median of 49 patients per study (range: 17-227 patients), and either reported characteristics of specific variants of LGG, such as pilocytic astrocytoma (n = 5) or subependymal giant cell astrocytoma (n = 1), or presented more general reports of multiple LGG subtypes.

Seven (44%) of the studies described the treatment modalities used. Of note, a proportion of the included studies were of more general cohorts of pediatric patients with CNS tumors; hence, it was not possible to identify the treatment used specifically for patients with LGGs. As complete resection of LGGs is frequently curative, surgical interventions were described more often than nonsurgical treatments. Of 373 patients for whom there was information on the procedures performed, 173 (46%) had a gross total or near total resection, 109 (29%) had a subtotal resection, and 91 (24%) had only a biopsy performed. The reports on seven studies, with a combined total of 476 patients, described the frequency of use of radiotherapy and/or chemotherapy in the cohorts: 83 of these patients received radiotherapy and 76 received chemotherapy. Only limited descriptions of the types and doses of radiotherapy used and chemotherapy regimens were included.

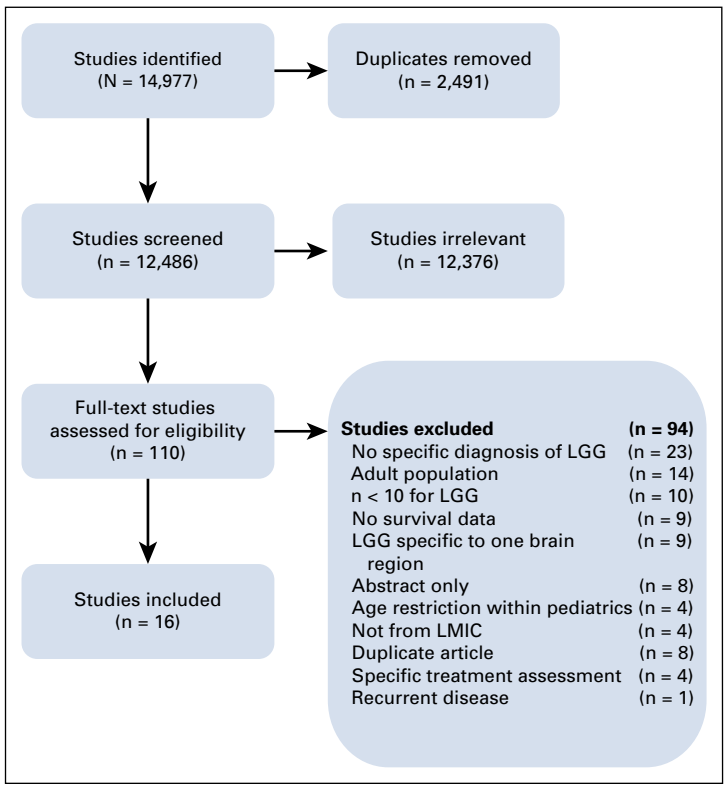

FIG 1. Study identification and selection. LGG, low-grade glioma; LMIC, lower-middle-income country.

Outcomes for LGG

In terms of outcomes for LGG, 15 (94%) of the studies included data on OS and 6 (38%) included data on EFS. In 11 of the reports (69%), the Kaplan-Meier estimator was explicitly described as the methodology of survival calculation. The follow-up time of the studies ranged from just over 1 year (above the threshold for inclusion) to 8.2 years. EFS and OS were reported at different intervals, ranging from 1 year to 5 years after diagnosis. At 5 years, EFS ranged from 55% to 70%. Furthermore, 5-year OS ranged from 69.2% to 93.5%. Lower OS was reported at earlier time points. For example, in the study from the Caribbean, the reported OS was 57.2% at 2 years, which was the lowest among the included studies. The OS included in the reports are summarized in Figure 3.

Quality Assessment

A summary of the risk-of-bias assessment is shown in Figure 4. The main source of bias lay in the fact that the studies were mainly single-center retrospective reviews of relatively small size. On the basis of our search inclusion criteria, we purposely limited selection bias by excluding studies focusing on specific populations or treatments. Limited descriptions of the treatments used, short follow-up time for LGGs, and incomplete outcome analyses make reporting bias the principal source of possible biases for the

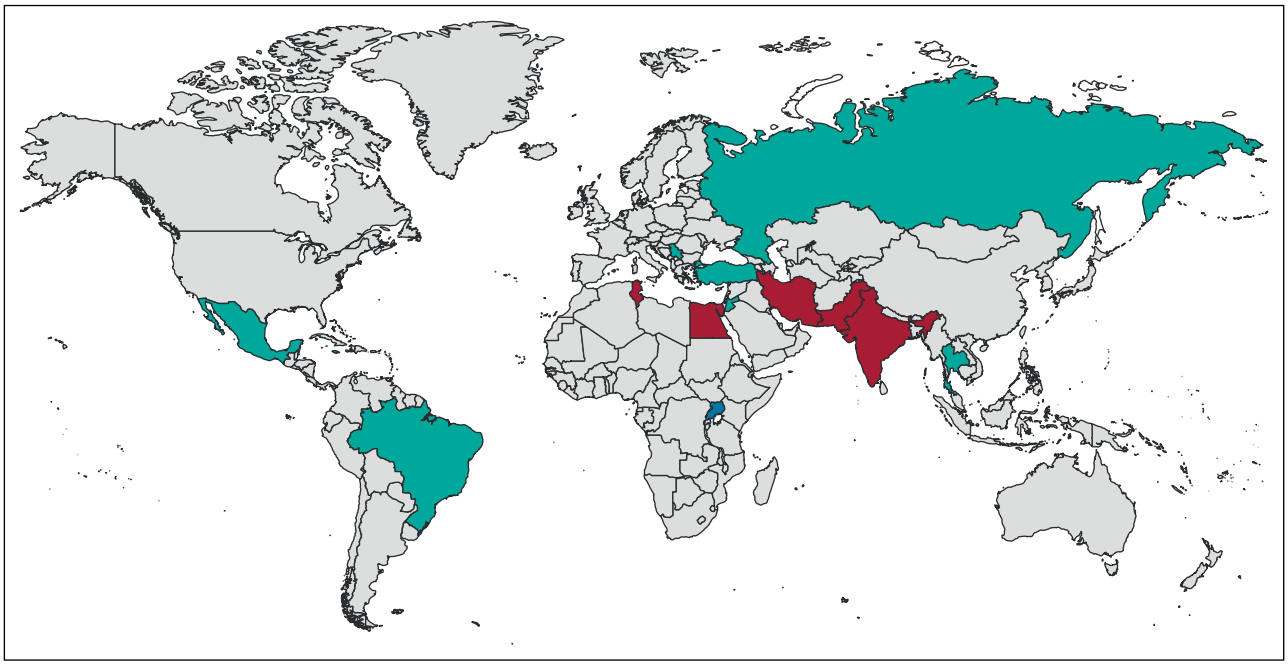

FIG 2. Map of countries included in the selected studies. Upper-middle-income countries are shown in teal, lower-middle-income countries in red, and the low-income country in blue.

included studies. Detailed results of the bias assessment for the 16 studies are included in Appendix Table A1.

DISCUSSION

Given the limited data on pediatric LGGs in LMICs, where 90% of children with cancer live, we sought to evaluate the available literature systematically and analyze the reported outcomes. Through a comprehensive search strategy, we identified 16 studies that collectively spanned the globe and included countries of different income levels. These studies captured outcomes on close to a 1,000 patients and reported survival rates frequently exceeding 80%. Nonetheless, our work identified limitations in the published studies, in terms of both the cohort sizes and the study methodologies.

The present analysis builds on recent work seeking to ascertain the burden of childhood cancer across the world and, specifically, the survival rates in LMICs. Despite these efforts, there are gaps in our understanding of the outcomes of LGGs and the factors contributing to poor survival of patients with these tumors. In almost all of the studies that were included in our review, OS at 5 years exceeded 60%, which is the goal of the WHO GICC for the six index cancers. Nevertheless, in some studies, especially those with short patient follow-up periods, the reported survival rates were lower. Interestingly, some institutions, such as the ones in Brazil and Turkey, reported outcomes similar to those in high-income countries, but others, such as institutions in the English-speaking Caribbean, Iran, and Uganda, had lower OS (57.2% at 2 years, 60.2% at 2 years, and 65% at 3 years, respectively). For single-institution experiences, neuro-oncologic capacity was not described, hence many factors contributing to these outcomes could not be evaluated. This wide range in OS leads us to believe that survival rates comparable with those in high-income countries can be obtained in LMICs, and efforts should be focused on regions with the lowest survival rates. Furthermore, studies to evaluate the elements that influence worse outcomes would be of utmost value.

Despite our comprehensive search strategy, only a small number of studies were ultimately included, pointing to the paucity of published reports and, hence, outcomes data in LMICs. Importantly, we identified only one study from a low-income country, so our understanding of outcomes of pediatric CNS tumors in low-income countries remains limited. Ultimately, we failed to identify studies from most LMICs, leaving the outcomes of LGG in these countries a matter to ponder. We can hypothesize that there is a significant barrier to publishing scientific reports in low-resource settings because of factors such as lack of protected time for research and scarcity of cancer registries. This emphasizes the need to support researchers in low-income settings in their collection and reporting of data.[36] A reporting bias may also exist, whereby poor outcomes are less likely to be included in scientific reports.

It is important to note that data on EFS or progression-free survival were largely lacking in the included studies. EFS is a valuable parameter in LGG, as close to 40% of patients will experience disease progression or recurrence, even in high-resource settings.[37] Furthermore, the functional status of survivors was rarely reported, despite this being a highly

TABLE 1. Summary of Study Characteristics, Demographics, Treatment, and Outcomes

Source	Countries of Study	Study Characteristics	Time Frame	Primary Department of Report	Diagnoses	Sample Size	Mean Age (years)	Surgical Interventions	RT	CT	Follow-Up (years)	Survival Calculation	Survival Extraction	EFS (years)	OS (years)
Araujo et al[20]	Brazil	Retrospective, single institution	2000-2006	Pediatric oncology	PA, DA	19	7.6[a]	ND	ND	ND	ND	Kaplan-Meier	Text	ND	1 year: 84% 3 years: 84% 5 years: 84%
Barragán-Pérez et al[21]	Mexico	Retrospective, single institution	2008-2012	Neurology	PA	36	5 (median age)	ND	ND	ND	ND	Kaplan-Meier	Figure	ND	5 years: 85%[b]
Becker et al[22]	Brazil	Retrospective, single institution	1984-2006	Neurosurgery	PA	31	7.8	GTR/NTR: 23 STR: 8 Biopsy: 0	0	2	5.7 (median)	Kaplan-Meier	Text	5 years: 55%	5 years: 93.50%
Bellil et al[23]	Tunisia	Retrospective, single institution	1990-2004	Pathology	PA, DA, OPG, SEGA	142	8.6	ND	ND	ND	3.0 (mean)	ND	Text	ND	5 years: 78.5%
Fawzy et al[24]	Egypt	Prospective, single institution	2007-2012	Pediatric oncology	PA, DA, SEGA, OPG, OA, GG, PXA, DIA, CG	227	6.0 (median)	GTR/NTR: 105 STR: 49 Biopsy: 55	0	26	1-5 years	Kaplan-Meier	Text	3 years: 65.5%	3 years: 87.30%
Gibson et al[25]	Caribbean[c]	Population-based cancer registry, multi-national	2011-2015	Pediatric oncology	LGG	20	5.7[a] (median age)	ND	ND	ND	1.05[a]	ND	Text	2 years: 41.9%	2 years: 57.2%
Khan et al[26]	Pakistan	Retrospective, single institution	1995-2007	Neurosurgery	PA	22	9.25	GTR/NTR: 15 STR: 5 Biopsy: 2	3	ND	3.72 (mean)	Raw number	Figure	5 years: 60% (9/15)[d]	5 years: 87% (13/15)d
Mehrvar et al[27]	Iran	Retrospective, single institution	2007-2010	Pediatric oncology	PA, DA, LGG	53	6.3	GTR/NTR: 10 STR: 4 Biopsy: 23	26	ND	1.8 (mean)	Raw number	Text	ND	2 years: 60.3% (32/53)[d]
Nikitovic et al[28]	Serbia	Retrospective, single institution	1995-2004	Radiation oncology	PA, OPG, OD	52	9.7[a]	ND	ND	ND	3.9	Kaplan-Meier	Text	ND	5 years: 92.40%
Papusha et al[29]	Russia	Retrospective, single institution	2014-2019	Pediatric oncology	PA, DA, OD, OA, GG, DIA	69	5.9	GTR/NTR: 26 STR: 37 Biopsy: 4	6	36	1.6	Kaplan-Meier	Text	2 years: 57.8%	2 years: 100%
Pongtanakul et al[30]	Thailand	Population-based cancer registry, multi-institutional	2003-2012	Pediatrics	LGG	97	6.79 ± 3.44	ND	ND	ND	ND	Kaplan-Meier	Text	ND	5 years: 69.2% 5 years: 75.7%[e]
Sevilla-Castillo et al[31]	Mexico	Retrospective, single institution	2006-2010	Pediatrics	PA, DA	17	7	ND	ND	ND	ND	Raw number	Calculated	ND	5 years: 82.4%

(Continued on following page)

TABLE 1. Summary of Study Characteristics, Demographics, Treatment, and Outcomes (Continued)

Source	Countries of Study	Study Characteristics	Time Frame	Primary Department of Report	Diagnoses	Sample Size	Mean Age (years)	Surgical Interventions	RT	CT	Follow-Up (years)	Survival Calculation	Survival Extraction	EFS (years)	OS (years)
Sharma et al[32]	India	Retrospective, multi-institutional	1979-2001	Pathology	SEGA	19	13.2	GTR/NTR: 10 STR: 9 Biopsy: 0	7	ND	3.1	Kaplan-Meier	Calculated	ND	1 year: 94.7%
Stagno et al[33]	Uganda	Retrospective, single institution	2002-2012	Neurosurgery	PA	50	6.5[a]	ND	ND	ND	1.9[a]	Kaplan-Meier	Survival curve	ND	3 years: 65%
Tihan et al[34]	Turkey, Jordan	Retrospective, multi-institutional	10 years	Pathology	PA	48	6.0 (median)[a]	ND	ND	ND	8.2[a]	Kaplan-Meier	Survival curve	4 year: 70% 4 year: 70% 4 year: 55%[f]	ND
Varan et al[35]	Turkey	Retrospective, single institution	1972-2003	Pediatric oncology	LGG	55	9.0 (median)	GTR/NTR: 10 STR: 34 Biopsy: 11	41	12	5.2[a] (median)	Kaplan-Meier	Text	ND	5 year: 93.3%

Abbreviations: CG, choroid glioma; CT, chemotherapy; DA, diffuse astrocytoma; DIA, desmoplastic infantile astrocytoma; EFS, event-free survival; GTR, gross total resection; LGA, low-grade astrocytoma; LGG, low-grade glioma; ND, not described; NTR, near-total resection; OA, oligoastrocytoma; OD, oligodendroglioma; OPG, optic pathway glioma; OS, overall survival; PA, pilocytic astrocytoma; RT, radiation therapy; SEGA, subependymal giant cell astrocytoma; STR, subtotal resection.

[a]Data for entire cohort of study, not specified for LGG.

[b]Survival data were estimated within 5% on the basis of survival curves.

[c]Bahamas, Barbados, Jamaica, St Lucia, St Vincent, and Trinidad and Tobago.

[d]Raw number.

[e]Study reported OS in two intervals: 2003-2005 and 2011-2012.

[f]Study reported independently on three institutions in Turkey and Jordan.

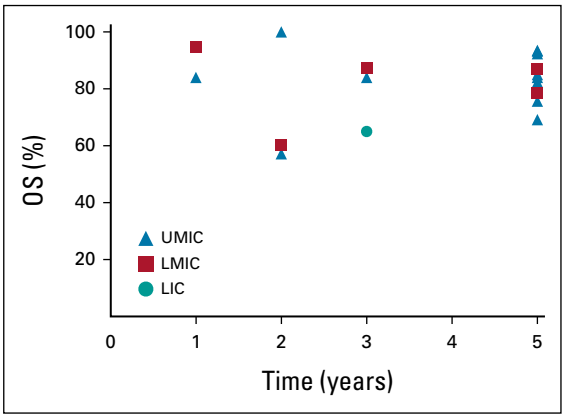

FIG 3. Reports of overall survival of pediatric patients with LGG grouped by World Bank country income classification. LGG, low-grade glioma; LMIC, lower-middle-income country; OS, overall survival; UMIC, upper-middle-income country.

relevant parameter as survivors of LGGs can have significant morbidity.[38,39]

The bias assessment of the included studies also revealed opportunities for future growth of the field. Most studies were retrospective single-institution reports of patient outcomes. As improving the outcomes of pediatric CNS tumors is an increasingly important priority, it is paramount that clinicians and researchers in LMICs increase the frequency and depth of their reporting of survival outcomes of pediatric patients with brain tumors. This suggestion aligns with the WHO GICC outline for improving pediatric cancer outcomes, which describes data collection and analysis as a first step toward improving survival outcomes.[10]

Despite their limitations, these studies provide valuable insights into current outcomes for LGGs. Although many centers in LMICs have limited resources for research, in terms of materials, infrastructure, and researcher time, it is necessary to emphasize the need for larger and more comprehensive studies, thereby enabling more generalizable conclusions.[40] As exemplified by some of the included studies, there is already ongoing international collaboration in the field, and this represents a possible mechanism to be leveraged for future studies.

Importantly, details of the therapeutic strategies used in the included reports were limited as less than half described the treatment modalities that were used. Of the studies that described surgical outcomes, $<$ 50% of the included patients had a gross total resection of the tumor. This is a major factor as gross total resection of the tumor can be curative and is a predominant predictor of long-term outcomes of LGG.[41] Outcomes of LGG are heavily influenced by neurosurgical capacity, hence a primary area of focus for possible interventions that could improve outcomes. In addition, other contributing factors to poor outcomes, such as treatment abandonment, were not mentioned in the included studies. Ultimately, these reports provide limited insight into possible factors contributing to the reported outcomes; more work is needed in this area.

This review has several limitations of its own. First, it included a relatively small number of identified studies. Despite a comprehensive search strategy that found close to 15,000 publications, only 16 were included in the review. Our inclusion criteria were strict, as we wanted to describe the overall outcome of LGG. In addition, some studies were excluded as their data were presented in such a way that we could not segregate pediatric LGGs (eg, pediatric and adult populations were combined or low-grade and high-grade astrocytomas were combined). Furthermore, although we

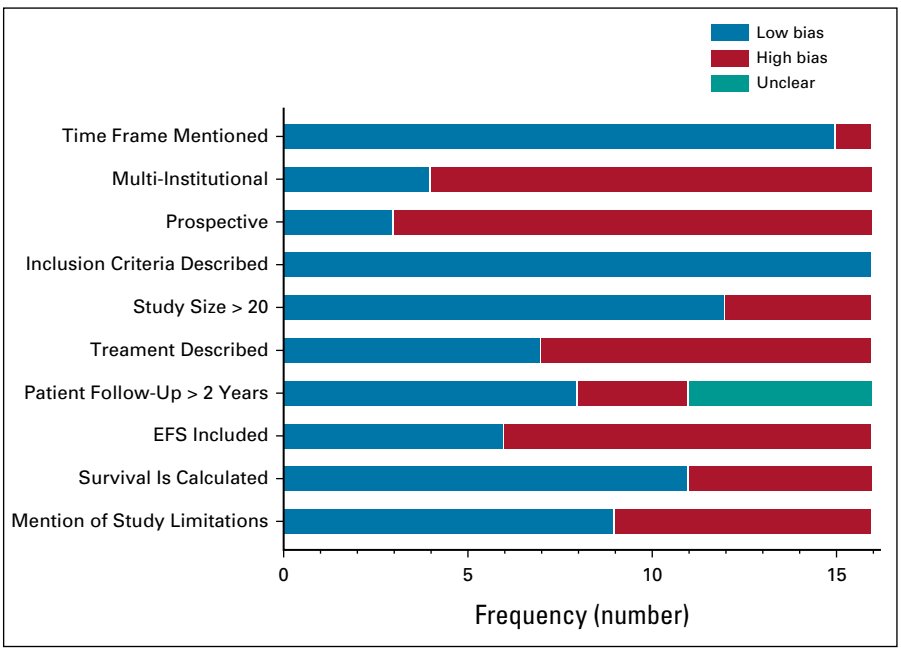

FIG 4. Summary of quality assessment results. EFS, event-free survival.

leveraged the multiple languages spoken by the authors and collaborators, literature in other languages may not have been found or was unable to be included for analysis. Finally, there was a high degree of variability in the presentation of data, which included individual-level data, tables for survival analysis, and Kaplan-Meier curves. This limited our ability to pool data and perform further analysis. Nevertheless, general conclusions on the outcomes of LGGs in LMICs can be reached on the basis of the individual studies included in this work, as we have demonstrated in Figure 3.

This study has provided insight into current outcomes of LGG in countries in different geographical regions and with different income levels. Although LGGs are only one group of pediatric CNS tumors, they represent a substantial proportion of these tumors. This study also underscores the need for more robust data on outcomes in pediatric CNS tumors. Comprehensive cancer registries that can capture clinically relevant groups will allow the field to describe the burden of LGG and pediatric CNS tumors as a whole more accurately. Only through such data is it possible to truly understand the shortcomings of care and prioritize interventions. Finally, it is important to underscore the relevance of LGG treatment in pediatric patients to the wider problem of pediatric cancer. Improvements in the outcomes of children and adolescents with LGG will depend on multiple factors, from early recognition of signs and symptoms to access to diagnostics and treatment, comprehensive multidisciplinary care, and long-term monitoring. Because of the complex care required to treat LGGs, investments in improving outcomes for patients with LGGs will undoubtedly lead to improvements in the coordination and integration of health systems, thereby benefitting the broader pediatric cancer population.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX 1. EXAMPLE SEARCH STRATEGY (PUBMED)

Element #1: ("Developing Countries"[Mesh] OR low-income OR middle-income OR global OR "limited resource*" OR LMIC* OR Afghanistan OR Benin OR "Burkina Faso" OR Burundi OR African OR Chad OR Comoros OR Congo OR Eritrea OR Ethiopia OR Gambia OR Guinea OR Guinea-Bissau OR Haiti OR Korea OR Liberia OR Madagascar OR Malawi OR Mali OR Mozambique OR Nepal OR Niger OR Rwanda OR Senegal OR Leone OR Somalia OR Sudan OR Tanzania OR Togo OR Uganda OR Zimbabwe OR Angola OR Armenia OR Bangladesh OR Bhutan OR Bolivia OR Cabo Verde OR Cambodia OR Cameroon OR Congo OR "Côte d'Ivoire" OR Djibouti OR Egypt OR Salvador OR Georgia OR Ghana OR Guatemala OR Honduras OR India OR Indonesia OR Jordan OR Kenya OR Kiribati OR Kosovo OR Kyrgyz* OR Lao* OR Lesotho OR Mauritania OR Micronesia OR Moldova OR Mongolia OR Morocco OR Myanmar OR Nicaragua OR Nigeria OR Pakistan OR Papua OR Philippines OR Tomé OR Solomon OR "Sri Lanka" OR Sudan OR Syria* OR Tajikistan OR Timor* OR Tunisia OR Ukraine OR Uzbekistan OR Vanuatu OR Vietnam OR Yemen OR Zambia OR Albania OR Algeria OR Samoa OR Argentina OR Azerbaijan OR Belarus OR Belize OR Bosnia OR Botswana OR Brazil OR Bulgaria OR China OR Colombia OR "Costa Rica" OR Cuba OR Dominica* OR Ecuador OR Fiji OR Gabon OR Grenada OR Guyana OR Iran OR Iraq OR Jamaica OR Kazakhstan OR Lebanon OR Libya OR Macedonia OR Malaysia OR Maldives OR Marshall OR Mexico OR Montenegro OR Namibia OR Paraguay OR Peru OR Russia* OR Samoa OR Serbia OR Africa OR "St Lucia" OR "St Vincent" OR Suriname OR Thailand OR Tonga OR Turkey OR Turkmenistan OR Tuvalu OR Venezuela OR Herzegovina OR Guin* OR Eswatini OR Fiji OR Maced*)

Element #2: ("Brain Neoplasms"[Mesh] OR low-grade glioma* OR benign glioma* OR WHO class I OR WHO class II OR diffuse astrocytoma* OR oligodendroglioma* OR pilocytic astrocytoma* OR subependymal giant cell astrocytoma* OR pleomorphic xanthoastrocytoma* OR angiocentric glioma* OR chordoid glioma* OR dysembryoplastic neuroepithelial tum* OR gangliocytoma* OR ganglioglioma* OR dysplastic gangliocytoma* OR lhermitte-duclos OR desmoplastic infantile astrocytoma* OR papillary glioneuronal tum* OR rosette-forming glioneuronal tum*)

Element #3: (Pediatrics [Mesh] OR pedia* OR paedia* OR child* OR infan* OR adolescent* OR "young adult")

Search: #1 AND #2 AND #3

TABLE A1. Bias Assessment for the 16 Studies Meeting Inclusion Criteria

Study	Does the Study Explicitly State the Time Frame of Observation?	Is This a Multi-Institutional Study?	Is Prospective Date Collected?	Are Selection and/or Exclusion Criteria for Cases Adequately Described?	Was the No. of Patients in the Study > 20?	Was the Treatment Regimen of Patients Explicitly Described?	Is the Median Follow-Up of Patients at Least 2 Years?	Is EFS or PFS or DFS Included in the Analysis?	Is the Survival a Calculated Analysis?	Do Authors Note Areas for Improvement in the Study?
Araujo et al[20]	Yes	No	No	Yes	No	No	No	No	Yes	Yes
Becker et al[22]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Bellil et al[23]	Yes	No	No	Yes	Yes	No	Unclear	No	No	No
Fawzy et al[24]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Gibson et al[25]	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes
Barragán-Pérez et al[21]	Yes	No	No	Yes	Yes	No	Unclear	No	Yes	Yes
Khan et al[26]	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes
Mehrvar et al[27]	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes
Nikitovic et al[28]	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes
Papusha et al[29]	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No
Pongtanakul et al[30]	Yes	Yes	Yes	Yes	Yes	No	Unclear	No	Yes	Yes
Sevilla-Castillo et al[31]	Yes	No	No	Yes	No	Yes	Yes	No	No	No
Sharma et al[32]	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No
Stagno et al[33]	Yes	No	No	Yes	Yes	No	No	No	Yes	Yes
Tihan et al[34]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Varan et al[35]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: DFS, disease-free survival; EFS, event-free survival; PFS, progression-free survival.