A Systematic Review of Survival of Children with Solid Tumors in Low- and Middle-Income Countries

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Abbreviations	
LMIC	Low- and middle-income countries
OS	Overall survival
CNS	Central nervous system
AHOPCA	Asociación de Hemato-Oncología Pediátrica de Centro América
GCT	Germ cell tumors
ALL	Acute lymphoblastic leukemia
CI	Confidence interval
GBD	Global Burden of Disease Study
GCC	Global Childhood Cancer microsimulation model

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Abstract

Population-level estimates of the survival of children from low- and middle-income countries diagnosed with solid tumors do not currently exist, in contrast to outcomes of hematologic and central nervous system cancers, which have been collated from population-based cancer registries and published by the CONCORD Programme. To fill this knowledge gap, we conducted a systematic review of PubMed Legacy, Embase, Web of Science, Cochrane Central Registry of Controlled Trials, and three regional databases for publications that reported survival of children diagnosed age 0-14 years with any malignancy from January 2011 to December 2016. The search identified 4695 original records; 51 articles met inclusion criteria. The range of survival reported was broad; for instance, 5-year overall survival for retinoblastoma ranged from 48% in Central America to 98% in China. However, the paucity of published statistics prevented approaches for meta-analyses and emphasizes the need for more standardized data collection and reporting.

Introduction

As mortality during childhood due to infectious diseases continues to drop, addressing the unnecessary deaths due to childhood cancer has become more prominent on the public health agenda.[1] Indeed, in September 2018, the World Health Organization's Global Initiative for Childhood Cancer set a goal to achieve at least a 60% survival rate for children with cancer by 2030.[2] Because many low- and middle-income countries (LMIC) are implementing universal health care coverage, it is important to make the case to include treatment of childhood cancer so that these preventable deaths can be addressed. A key underpinning of this case is to understand how investment in childhood cancer treatment could narrow the survival gap between low,

middle, and high-income countries and provide return on investment due to lives saved. A first step in this calculation is to determine the cumulative probability that children in LMIC survive up to a given time (e.g. 5 years) after a diagnosis of childhood cancer.

The most accurate and unbiased estimate of childhood cancer survival comes from the data reported at the population level, by population-based cancer registries (PBCR). The CONCORD Programme reported the 5-year net cancer survival from 322 population-based cancer registries in 71 countries, reviewing the registry reports of incidence and survival among children diagnosed with either a hematologic malignancy (leukemia or lymphoma), or a central nervous system (CNS) tumor.[3] Notably, this study did not report the data from the registries on the survival of children with non-CNS solid tumors, which together account for 40% of childhood cancer diagnoses. To fill that gap, a systematic review of case-series and clinical trials published between 2011-2016 on survival of children diagnosed with a solid tumor and treated in a LMIC was undertaken.

Methods

Seven databases - PubMed Medline (Legacy version), Embase (Elsevier interface), Web of Science, Cochrane Central Registry of Controlled Trials (Wiley interface), Index Medicus for the Eastern Mediterranean Region (IMEMR), Latin American & Caribbean Health Sciences Literature (LILACS), and Scientific Electronic Library Online (Latin American – SciELO) – were searched by a medical librarian from January 2011 to December 2016. The original search was completed in July 2016, and was updated on December 19, 2016. There were no language or study design restrictions applied to the search (Supplementary Materials). The search strategies were peer reviewed by another librarian. The search strategies used a combination of controlled

vocabulary terms and free text terms for childhood cancer, specific cancer types, and pediatrics; LMIC countries; and survival and prognostic terms when applicable.

Independent review of the retrieved titles and abstracts was conducted in teams of two, which consisted of one student co-author and one physician or professor coauthor. Disputes in inclusion/exclusion were discussed between independent reviewers of the team, with any final decisions determined by the project leadership (Leslie R. Robison & A. Lindsay Frazier). Full text articles were also independently screened for the articles that met inclusion criteria.

The full search strategies for each database can be found in the Supplementary Materials. Included papers reported OS or event-free survival (EFS) in children ages 0-14y from a LMIC as defined by the 2015 World Bank List of Economies.[4] The original search strategy encompassed all childhood cancer diagnoses, but was adjusted in July 2016 to focus on the following solid tumors: retinoblastoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, Kaposi sarcoma, neuroblastoma, Ewing sarcoma, osteosarcoma, germ cell tumors (GCT), Wilms tumor, and hepatoblastoma. The less common childhood solid tumors, such as melanoma or adrenocortical carcinoma, were not included in this review. Each publication was required to be either a sequential case series or a report of a clinical trial and to include at least 20 pediatric patients age 0-14y in a single disease category. Additionally, more than 50% of the patient sample in the article had to have been treated after January 1, 2000 and median follow-up had to be at least 1 year. Because many articles reported only a subset of the expected disease incidence (e.g. only parameningeal rhabdomyosarcoma), studies that reported on a selected population were included only if the report included at least 75% of the total population that would have been diagnosed with the disease.

Conference proceedings and abstracts were excluded, as were single patient case reports and reports of a procedural or surgical outcome. If the full article was unavailable through institutional access or interlibrary loan, the median follow-up was not reported, an outcome of treatment other than primary treatment was studied, or the time point for a survival statistic was missing, the paper was excluded. From the included publications, the total number of patients under 14 years of age, the years the patients were treated, and the median (and range) age at diagnosis and follow-up were abstracted. If the survival was reported only by risk group, the results for each risk group were abstracted. Reported EFS and OS were collected at each time point recorded in the article. The remainder of this review focuses on reporting only OS collected from the included articles because many articles reported only OS and not EFS.

Results

The search identified 4695 original records on survival of children with cancer; 4231 were excluded after review of the abstract (Figure 1). The principal reasons for exclusion were conference proceedings, unavailability of the full article through institutional or interlibrary loan, single case reports, reporting the outcome of a treatment other than primary treatment, and a lack of time point for survival statistics. Of the 464 selected abstracts, 238 described outcomes of children with either hematologic or CNS malignancies, but did not include data on survival of children with solid tumors and were therefore excluded. The full text of the remaining 226 articles were obtained and further screened for eligibility. The most common reasons for excluding 175 of these articles were the reporting of only a subset of patients (i.e. only head and neck rhabdomyosarcoma) or a focus on rare cancer(s) not encompassed by this review. The remaining 51 articles were retained to be included in the descriptive synthesis.

Among these 51 publications, 20 individual countries plus the regional Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) were represented (Figure 2).[5–55] China, an upper-middle income country, contributed 12 articles, the largest country-specific contribution. Four low income countries contributed data: Malawi (3 studies), Botswana (1 study), Senegal (1 study), and Uganda (1 study), making up 11.8% of all publications included in this systematic review. Eleven publications (21.5%) were from lower-middle income countries and 34 publications (66.7%) were from upper-middle income countries. The number of included articles by disease ranged from 2-15 articles (Figure 3). Retinoblastoma survival was reported in the largest amount of publications (15). GCT, Ewing sarcoma, hepatoblastoma, Kaposi sarcoma, and non-rhabdomyosarcoma soft tissue sarcoma survival were estimated by the least number of reports (2 each).

Survival varied substantially across disease, country, and country income-level (Table 1 and Figure 4). In retinoblastoma, OS (not stratified by risk group) ranged from 48% at 5 years from AHOPCA[12] to 98% at 5 years in China.[7] Additionally, a publication from China reported 74.8% OS at 10 years.[6] A publication from Turkey reported 99% and 60% OS at 4 years for intraocular and extraocular risk groups, respectively.[8] Only one article from Tunisia reported GCT OS (75% at 5 years)[20]; other articles only reported risk group survival but not overall survival. For hepatoblastoma, a publication from China reported 83.3% OS at 5 years[22] and a publication from Brazil 86% at 5 years. [23] Rhabdomyosarcoma OS not stratified by risk group ranged from 56.9% at 5 years in Egypt[28] to 83% at 5 years in Lebanon.[29] A publication from Turkey reported 40% OS at 5 years for an actinomycin-D treatment group and 68.2% OS at 5 years for a carboplatin treatment group.[24] Minimum OS in osteosarcoma at 5 years was 37.9% in Thailand[30] and maximum was 61.8% in China.[33] Ewing sarcoma 5-year OS was reported by two

publications: 54.4% in Brazil[34] and 69% in Lebanon.[35] Kaposi sarcoma OS was reported by two publications: 58% at 2 years in a 2016 publication from Malawi[36] and 43% at 1 year in a 2013 publication in a combined cohort from Malawi and Botswana.[37] Non-rhabdomyosarcoma soft tissue sarcoma was reported by two publications: 10% at 5 years in Cambodia[43] and 72% at 5 years in Argentina.[44] Neuroblastoma 5-year OS ranged from 30.8% in Iran[40] to 60.7% in India.[41] A publication from Egypt showed a difference in 2-year OS in neuroblastoma between males and females (47.6% in males and 10.4% in females).[39] Wilms Tumor OS not stratified by risk group ranged from 46% at 3 years in Malawi[54] to 89.9% at 5 years in Chile.[45]

Discussion

Because of the absence of population-based survival estimates for children with non-CNS solid tumors in LMIC, a systematic review of case-series and clinical trials was undertaken. The most striking aspect of this systematic review is the paucity of published data on pediatric solid tumor patients in LMIC. An initial search of childhood cancer survival publications retrieved 4695 records from the 5-year period January 2011 to December 2016, however, only 51 fulfilled the inclusion criteria and were included in the descriptive synthesis. Among these publications, only one third were from low or lower-middle income countries. Because of the variability in methods and reporting, a synthetic meta-analysis was not possible. The sparsity of these publications contrasts with what exists in the literature on survival of children with acute lymphoblastic leukemia (ALL) in LMIC. For example, a systematic review and meta-analysis on abandonment of therapy in children with ALL included 157 articles in the descriptive synthesis and 40 articles in the meta-analysis.[56] Although non-CNS solid tumors account for 40% of childhood malignancies,[57] the challenge of reporting outcomes is that solid tumors represent a

broad range of many diseases and hence sample size per disease limits sufficient data to warrant reporting.

Previous publications on childhood cancer survival in LMIC have illuminated several important factors to consider when considering reports of survival. Studies differ in methods and data sources for survival estimation that require nuanced interpretation. For instance, in terms of "data source", population-level survival can only be directly estimated from population-based cancer registries[3,57] or extrapolated from public health data, and will likely be different than that observed in a single center, or on a clinical trial .[58,59] Additionally, patients who abandon care are not always included in the calculation of survival, and the decision to include/exclude patients who abandon care is often not explicitly stated in the methods. But abandonment of care varies dramatically across sites; for instance, a systematic review and meta-analysis on pediatric ALL abandonment of therapy rates in LMIC reported a range from 0% to 74.5%[56], and will thus have a significant effect on survival and interpretation of reported results. In the present systematic review on the survival of children with solid tumors in LMIC, abandonment of therapy was rarely reported as an event and thus not incorporated into this synthesis; a strong recommendation is that studies of the future specifically record abandonment as an event.

Other prior studies have used data on survival in population-based registries to highlight gaps in survival as a function of geographic residence. The CONCORD programme harnessed the data available in population-based registries to provide an estimate of the "survival gap" between LMIC and high-income countries for ALL, lymphoma, and CNS tumors.[57] For example, age-standardized 5-year net survival of children diagnosed with ALL ranged from 51.5% (Colombia, 2005-2009, 95% CI: 44.9%-58.0%) to 94.0% (Germany, 2000-2004, 95% CI: 90.7%-97.3%) based on reports from 254 registries in 61 countries.[57] Our results contribute

another dimension to these data and suggest a need to expand the assessment of childhood cancer survival in LMIC population-based registries to include non-CNS solid tumor.

Two studies have previously extrapolated the outcomes of children with solid tumors in LMIC: the Global Burden of Disease Study (GBD)[58] and the Global Childhood Cancer (GCC)[59] microsimulation model. Neither study is directly comparable to the data contained in this systematic review. The 2017 report from GBD used vital registration system data, verbal autopsy reports, and information from population-based cancer registries to calculate mortality to incidence ratios, a measure that may not correlate with reported population-based survival rates.[60] Furthermore, because the GBD 2017 study used primarily anatomic site-based coding to report cancer burden, many childhood solid tumors were included under "uncategorized cancers."[61] This hinders our understanding of survival for specific solid tumors, each of which are unique in diagnosis, prognosis, and treatment methods.

The GCC study simulates the survival of children with cancer, based upon estimates of treatment availability, treatment completion and quality of care.[59] The model parameters were calibrated to be consistent with the survival observed by the CONCORD programme for non-solid tumors. Where data were unavailable, GCC used a hierarchical approach to infer parameters. Thus, the survival of all solid tumors were "inferred" by the model, since the CONCORD studies only collected registry data on hematologic and CNS malignancies. The net survival estimated by GCC reflects the survival of the entire population within a country or region. For example, 5-year net survival of neuroblastoma estimated by GCC ranged from 6.7% (95% uncertainty interval (UI) 3.2-12.4) in Africa to 81.5% (95% UI 58.3-96.8) in North America.[59] Likewise, simulated retinoblastoma 5-year net survival in GCC was 5.2% (95% UI 3.4-7.7) in Africa, 32.1% (95% UI 24.3-40.5) in Asia, and 54.8% (95% UI 45.0-64.2) in Latin

America and the Caribbean.[59] Publications included in this systematic review, however, represent patients included in a trial at a given treatment center. Therefore, estimates from this systematic review may overestimate general population estimates.

Similarly, overall 5-year survival obtained from this systematic review (Table 1) was generally higher than population averages simulated by GCC in retinoblastoma (Figure 5). This trend is less pronounced in neuroblastoma (Figure 6). Survival estimates for this systematic review likely represent "best case" scenarios of those children fortunate enough to have been treated at an institution(s) with the resources to gather clinical data on outcomes and publish a manuscript. However, even though the case series reports are not generalizable to the entire population in a country, the case-series reports serve as an informative benchmark against which to understand the effectiveness of interventions designed to increase the survival of children with solid tumors in LMIC.

This systematic review was limited in drawing conclusions because the variability in the methodology and reporting of survival estimates across studies hindered efforts to summarize the data. For example, survival was not often reported at a standard time-point (1y, 5y, or 10y), preventing comparisons of estimates across studies. Oftentimes, survival was not presented for the disease as a whole, but only stratified by risk or treatment group. Calculation of the standard error of the estimate was inconsistent, also preventing a meta-analysis of the published survival estimates. In addition, the scarce number of articles in any one disease category limited the ability to draw conclusions from summaries of the data. We suggest that a checklist of standardized reporting be developed to guide both authors and editors in the preparation and selection of articles for publication. This list would include the reporting of median follow-up time and survival at pre-specified intervals for comparability of results, the inclusion of

calculation of the standard errors around the survival estimate, the inclusion of pediatric cancer stage, using the Toronto Staging Guidelines[62] to truly understand differences in survival across jurisdictions, and to report survival of the overall cohort of all patients diagnosed with a certain disease regardless of risk or treatment group. With the incorporation of these approaches to reporting survival, we may develop a better understanding of survival of children with solid tumors in LMIC en route to achieving the goal set forth by the World Health Organization's Global Initiative for Childhood Cancer of a 60% survival rate by 2030.[2]

Conflict of Interest

A. Lindsay Frazier is a consultant for Decibel Therapeutics. All other authors have no conflicts of interest to declare.

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Legends

FIGURE 1 Systematic review phases for the inclusion and exclusion of articles.

FIGURE 2 Frequency and income level of countries represented in the 51 publications that met the eligibility requirements. Most publications were contributed by upper-middle income countries. One publication included a combined cohort from both Malawi and Botswana. Income level was defined by the 2015 World Bank List of Economies.[4] The study from the Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) included Nicaragua, El Salvador, Guatemala, and Honduras.

FIGURE 3 Frequency and income level of articles for each disease represented in the 51 publications that met the eligibility requirements. Most publications were on retinoblastoma survival (15). Income level was defined by the 2015 World Bank List of Economies.[4]

FIGURE 4 Five-year overall survival reported by included articles. Of the 51 included articles, 34 reported overall survival (OS) at 5 years. The study from the Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) included Nicaragua, El Salvador, Guatemala, and Honduras. The rhabdomyosarcoma publication from Turkey reported two 5-year OS metrics: 68.2% (shown) for patients undergoing a carboplatin treatment regimen and 40% (not shown) for patients undergoing an actinomycin-D treatment regimen.

FIGURE 5 Survival estimates of children with retinoblastoma from the Global Childhood Cancer microsimulation model study (GCC)[59] and this systematic review. The study from the Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) included Nicaragua, El Salvador, Guatemala, and Honduras.

FIGURE 6 Survival estimates of children with neuroblastoma from the Global Childhood Cancer microsimulation model study (GCC)[59] and this systematic review. Error bars represent 95% confidence interval.