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GLOBAL ONCOLOGY: RESEARCH ARTICLE

# Implementing the WHO Global Initiative for Childhood Cancer in Morocco: Survival study for the six indexed childhood cancers

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## Abstract

**Background:** In 2018, the World Health Organization (WHO) launched the Global Initiative for Childhood Cancer (GICC). The goal is to achieve a global survival rate of at least 60% for all children with cancer by 2030. Morocco was designated as a pilot country for this initiative.

**Procedure:** This retrospective study included a cohort of children aged 0–15 years, with one of the six indexed cancers (acute lymphoblastic leukemia [ALL], Burkitt lymphoma [BL], Hodgkin lymphoma, retinoblastoma [RB], Wilms tumor or nephroblastoma, low-grade glioma), diagnosed between January 1, 2017 and December 31, 2019 at the six Moroccan Pediatric Hematology and Oncology units. Patients were followed-up until August 31, 2020. The Kaplan–Meier method was used to estimate survival rates, the log-rank test for comparing survival curves, and the Cox model for identifying prognostic factors.

**Abreviations:** ALL, acute lymphoblastic leukemia; BL, Burkitt lymphoma; CHI, Compulsory Health Insurance; EFS, event-free survival; GICC, Global Initiative for Childhood Cancer; HL, Hodgkin lymphoma; LGG, low-grade gliomas; MOH, Ministry of Health; OS, overall survival; PHO, pediatric hematology and oncology; RB, retinoblastoma; SMHOP, Moroccan Society of Pediatric Oncology; WHO, World Health Organization; WT, Wilms tumor.

**Results:** Data on 878 patients were included in the study. The most frequently reported cancer type was ALL ($n = 383$, 43.6%), followed by Wilms tumor ($n = 139$, 15.8%) and BL ($n = 133$, 15%). Most patients were less than 5 years of age ($n = 446$, 50.9%) and the male/female ratio was 1.46. The 1, 2, and 3-year overall survival rates were 80.1%, 73.6%, and 68.2%, respectively. In a multivariable Cox regression model, care center, cancer type, age group, and distance to the care center were statistically significantly associated to survival. Patients aged 10 years and older and patients living more than 100 km from the care center were more likely to die (respectively, HR = 1.39, $p = .045$ and HR = 1.44, $p = .010$).

**Conclusion:** The reported results represent the baseline for measuring the impact of GICC implementation in Morocco.

**KEYWORDS**
childhood cancer, survival, WHO initiative

## 1 | INTRODUCTION

With a better control of communicable diseases, cancer is becoming a leading cause of death in children and teenagers worldwide, including in low- and middle-income countries. Each year cancer is affecting globally approximately 400,000 children between the ages of 0 and 19.[1] Childhood cancers (or pediatric cancers) encompass a range of tumor types that are significantly different from that observed in the adult population. The most common pediatric cancers are leukemias, brain cancers, lymphomas, and solid tumors such as neuroblastoma and Wilms tumor (WT).[2] The 5-year survival rate of childhood cancer in high-income countries is nowadays over 80%. However, in many low- and middle-income countries, this figure is only around 20%–30%.[3] This survival gap is mainly due to a lack of diagnosis, late or erroneous diagnosis, difficulties in accessing care, treatment abandonment, treatment toxicity, and a higher relapse rates.[4]

In 2018, the World Health Organization (WHO), together with key partners that included St Jude Global and the International Society of Pediatric Oncology, launched the Global Initiative for Childhood Cancer (GICC) to provide leadership and technical assistance to governments to support them in building and sustaining high-quality childhood cancer programs.[4] The GICC objective is to achieve at least 60% survival for all children with cancer and to reduce suffering globally by 2030. Six common index cancers were identified for initial focus within the GICC:

- Acute lymphoblastic leukemia (ALL)
- Burkitt lymphoma (BL)
- Hodgkin lymphoma (HL)
- Retinoblastoma (RB)
- WT
- Low-grade gliomas (LGG)

In October 2019, Morocco was selected as a focus country for the GICC implementation. However, the lack of accurate data regarding the epidemiology and survival of childhood cancer was the first obstacle faced in the implementation of the GICC program.

According to data from the Rabat cancer registry, the number of childhood cancers from 0 to 14 years old, represented 1.7% of all cancer cases, with an annual incidence of 12.1 per 100,000 children.[5] Data from the Grand Casablanca Cancer Registry reported that childhood cancers accounted for 3% of all cancers with an incidence of 12.7 per 100,000 children.[6] However, only few data on survival rates are available at the national level. A study carried out at the Pediatric Hematology and Oncology Service (SHOP) of the Rabat University Hospital between January 2012 and December 2014 showed a 5-year overall survival (OS) rate of 63%. The main cause of treatment failure was toxic death.[7] The lack of complete national epidemiology and survival data meant the absence of baseline information on the burden and outcome of childhood cancer in Morocco. Consequently, the Moroccan Society of Pediatric Oncology (SMHOP) in collaboration with the Ministry of Health (MOH) conducted a survival study during the summer of 2020.

The objective of this study was to estimate the survival rates for the six WHO index cancers treated at the Moroccan pediatric hematology and oncology (PHO) centers between 2017 and2019. The aim of this study was to provide a baseline survival data, a key input to design the Moroccan Pediatric Oncology 2021–2030 Cancer Plan in concordance with the GICC recommendations.

## 2 | METHODS

### 2.1 | Study setting

Morocco is a North African country with a population of 33,848,242 people. It is considered a middle-income country and ranks 114th out of 169 countries in the Human Development Index. Morocco's per capita GDP is $2769, with $202 per person spent on healthcare. There are approximately six physicians and 7.8 nurses per 10,000 people.

Mortality for children 5 years of age or under is 40/1000 and life expectancy at birth is 71.8 years.[8] There are six principal units of pediatric oncology; two of them are in Casablanca, one in Rabat, one in Marrakech, one in Fes, and one in Oujda.

The incidence of cancer in patients under 15 years of age in Morocco is estimated to be 1000 new cases per year. Most pediatric cancer patients are managed by public hospitals. Thus, they are highly influenced by the Moroccan public health system, which is now considering cancer management a priority.[9]

Regarding health insurance coverage in Morocco, two basic medical coverage plans were created in 2002: the Basic Compulsory Health Insurance (CHI) and the Medical Assistance Plan (RAMED). CHI is based on the principles and techniques of social insurance benefiting employed and retired people. RAMED is based on the principles of social assistance and national solidarity with impoverished people.[10]

## 2.2 | Study population

This study retrospectively included a cohort of children aged 0–15 years, diagnosed with one of the six WHO priority diseases between January 1, 2017 and December 31, 2019 within the six Moroccan PHO units:

- Pediatric Hematology and Oncology Department of Rabat
- Pediatric Hematology and Oncology Unit at 2O August Hospital, Casablanca
- Pediatric Hematology and Oncology Unit at Abderrahim El Harouchi Hospital, Casablanca
- Pediatric Hematology and Oncology Unit of Fès
- Pediatric Hematology and Oncology Department of Marrakech
- Pediatric Hematology and Oncology Department of Oujda

The six PHO units were referenced as Care Center No. 1 to 6. Patients were monitored with active follow-up until August 31, 2020.

Children followed for other cancers, children aged more than 15 years, and duplicated patients were excluded from the study.

## 2.3 | Data collection and eligibility criteria

Data were extracted from patients' medical records, according to a standardized questionnaire for the six priority cancers. Data managers were recruited and trained for this purpose. A data collection paper form was created and used to collect data from the patients' records.

Childhood cancers were categorized according to the International Classification of Childhood Cancer, Third Edition (ICCC-3).[11]

Data variables included age, gender, place of residence, cancer type/subtype, date and type of event, survival status, and date of last contact. Vital status data were collected from parents via phone calls.

Data collection and entry were carried out by data managers at each PHO unit. The start date of the study was defined as the date of histological or radiological diagnosis of the tumor. The end point was set as August 31, 2020.

Data quality checks were maintained by the Moroccan MOH's Epidemiology and Disease Control Department through continual monitoring and validation.

## 2.4 | Statistical analysis

Initially a descriptive analysis was performed, in which the quantitative variables were represented by mean and standard deviation or median and interquartile range, while the qualitative variables were represented by headcount and percentage. We considered as events deaths, disease progression, relapse, and treatment abandonment. Abandonment was defined as missing treatment for a prolonged, consecutive period to an extent that impacts ability for cure or disease control (defined as a duration of 4 weeks in pediatric oncology).[12] Second malignant neoplasms were not considered as an event, because during the drafting of the protocol, discussions between teams did not identify any second malignant neoplasm in the follow-up of patients in the respective units. A survival analysis was performed considering the OS, abandonment-sensitive event-free survival (EFS), with abandonment considered as an event and EFS analysis in which abandonment was not considered as event. The Kaplan–Meier method was used to estimate survival rates, the log-rank test for comparing survival curves between different classes, and the Cox regression model for identifying prognostic factors. A trend was defined as statistically significant at $p < .05$. Jamovi software was used for data analysis.

## 2.5 | Ethical considerations

Ethical aspects were taken into consideration. The protocol was submitted to and approved by the ethics committee of the Faculty of Medicine and Pharmacy of Rabat.

# 3 | RESULTS

## 3.1 | Patients characteristics

We analyzed data from 899 patients followed at the six Moroccan pediatric oncology centers. After the exclusion of 21 patients, 878 patients were included in the analysis. Three hundred two patients were diagnosed in 2017, 295 in 2018, and 281 in 2019. A majority of cases were treated in Care Center 1 ($n = 270$, 30.8%) and Care Center 2 ($n = 217$, 24.7%). The cases analyzed (index cancers) represented approximately 32% for all cancer cases treated in the six units during the 3-year period (Table 1).

The most frequently reported cancer type was ALL ($n = 383$, 43.6%), followed by WT ($n = 139$, 15.8%) and BL ($n = 133$, 15%). Half of the patients were less than 5 years old ($n = 446$, 50.9%), 20% were aged above 10 years ($n = 175$) and the male/female ratio was 1.46 (Table 1).

**TABLE 1** Patient characteristics

| Characteristics | N (%) |
|---|---|
| Age (years) (*n* = 876) | |
| <5 | 446 (50.9) |
| 5–10 | 255 (29.1) |
| ≥10 | 175 (20.0) |
| Sex (*n* = 878) | |
| Male | 522 (59.5) |
| Female | 356 (40.5) |
| Medical coverage (*n* = 873) | |
| CHI | 212 (24.3) |
| RAMED | 615 (70.4) |
| None | 46 (05.3) |
| Distance from care center (km) (*n* = 877) | |
| <100 | 449 (51.2) |
| ≥100 | 428 (48.8) |
| Year of diagnosis (*n* = 878) | |
| 2017 | 302 (34.4) |
| 2018 | 295 (33.6) |
| 2019 | 281 (32.0) |
| PO center (*n* = 878) | |
| Center no. 1 | 270 (30.8) |
| Center no. 2 | 217 (24.7) |
| Center no. 3 | 66 (07.5) |
| Center no. 4 | 169 (19.2) |
| Center no. 5 | 102 (11.6) |
| Center no. 6 | 54 (06.2) |
| Cancer type (*n* = 878) | |
| ALL | 383 (43.6) |
| Burkitt lymphoma | 133 (15.1) |
| Hodgkin lymphoma | 99 (11.3) |
| Retinoblastoma | 106 (12.1) |
| Wilms tumor | 139 (15.8) |
| Low-grade glioma | 18 (2.1) |
| Events (*n* = 878) | |
| Death[a] | 124 (14.2) |
| Abandonment | 39 (04.4) |
| Relapse | 72 (08.2) |
| Progression | 35 (04.4) |

Abbreviations: ALL, acute lymphoblastic leukemia; CHI, compulsory health insurance.
[a]Death as first event.

Most patients were managed under RAMED medical coverage (*n* = 615, 70.4%). Four hundred forty-nine patients (51.2%) were living less than 100 km from the care center (Table 1).

At the most recent follow-up of the patients, 219 had died (24.9%), 39 abandoned treatment (4.4%), and 620 (70.6%) were alive at a median follow-up of 20.4 months (interquartile range: 11.5–29.5). Among the 219 deaths, 124 occurred during the first-line treatment (toxic death), with more than 70% toxic deaths occurring in ALL (*n* = 61, 49.2%) and BL (*n* = 33, 26.6%). Relapse was reported in 72 cases (8.2%) and progression in 35 (4.4%) (Table 1).

**TABLE 2** Survival rates of children included in the study

| Characteristics | 1-year survival (%) | 2-year survival (%) | 3-year survival (%) | *p* |
|---|---|---|---|---|
| **Overall survival** | 80.1 | 73.6 | 68.2 | |
| **Abandonment-sensitive event-free survival**[a] | 73.3 | 66.9 | 62.3 | |
| **Event-free survival**[b] | 76.4 | 70.3 | 66.3 | |
| **Age (years)**[c] | | | | .004 |
| <10 | 81.7 | 76.3 | 71.5 | |
| ≥10 | 74.1 | 63.5 | 54.3 | |
| **Sex** | | | | .225 |
| Male | 78.7 | 72.1 | 66.3 | |
| Female | 82.2 | 75.3 | 70.6 | |
| **Distance from care center (km)** | | | | .107 |
| <100 | 80.9 | 75.6 | 73.0 | |
| ≥100 | 79.5 | 71.4 | 62.7 | |
| **PO center** | | | | .110 |
| Center no. 1 | 85.5 | 80.1 | 76.1 | |
| Center no. 2 | 79.5 | 67.6 | 67.6 | |
| Center no. 3 | 75.4 | 75.4 | 67.8 | |
| Center no. 4 | 77.1 | 71.8 | 65.3 | |
| Center no. 5 | 72.4 | 68.2 | 61.3 | |
| Center no. 6 | 82.6 | 76.8 | 68.0 | |
| **Cancer type** | | | | <.001 |
| ALL | 79.7 | 70.0 | 61.5 | |
| Burkitt lymphoma | 58.6 | 58.6 | 53.7 | |
| Hodgkin lymphoma | 90.5 | 85.6 | 85.4 | |
| Retinoblastoma | 91.2 | 88.8 | 88.8 | |
| Wilms tumor | 86.7 | 82.9 | 81.2 | |
| Low-grade glioma | 73.5 | 73.5 | 73.5 | |

Abbreviation: ALL, acute lymphoblastic leukemia.
[a]Abandonment-sensitive event-free survival including abandonment as an event.
[b]Event-free survival not including abandonment as an event.
[c]Survival rates by age, sex, distance from care center, PO center, and cancer type are overall survival.

## 3.2 | Survival analysis

The 1-year OS was 80%, 2-year OS was 73.6%, and 3-year OS 68.2%. The abandonment-sensitive EFS was 73.3% at 1 year, 66.9% at 2 years, and 62.3% at 3 years, and the EFS not including abandonment was 76.4% at 1 year, 70.3% at 2 years, and 66.3 at 3 years (Table 2, Figure 1).

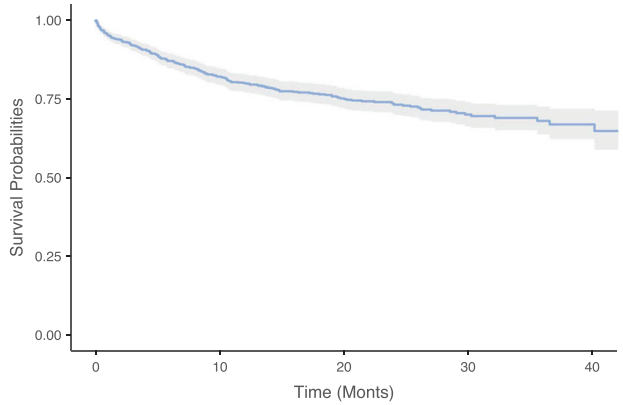


**FIGURE 1** Overall survival curve for children with cancer aged <15 years

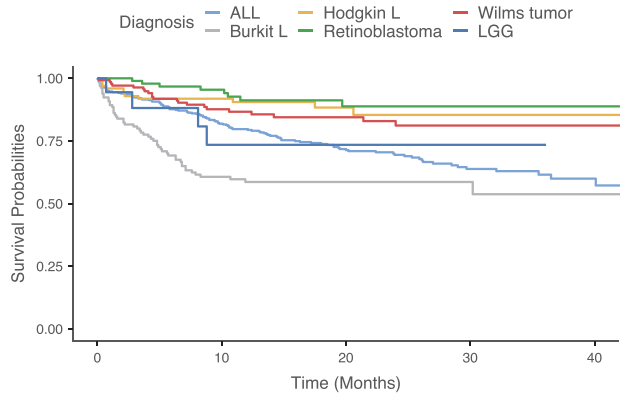


**FIGURE 2** Overall survival curves for children with cancer aged <15 years, by cancer type

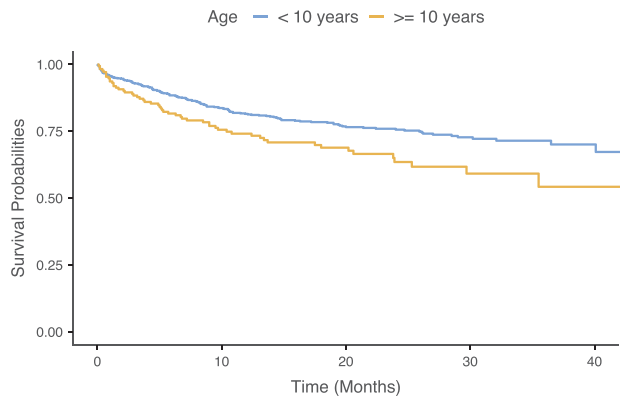


**FIGURE 3** Overall survival curves for children with cancer aged <15 years, by age group

RB and HL had better survival rates than other types of cancer (respectively, 88.8% and 85.4% 3-year OS, $p < .001$) (Table 2, Figure 2). Children aged under 10 years had better survival rates (71.5% 3-year OS) compared to children aged above 10 years ($p = .004$) (Table 2, Figure 3).

In multivariable Cox regression model, care center, cancer type, age group, and distance to the care center were statistically significantly associated to OS. Patients aged below 10 years and patients living less than 100 km from the care center were more likely to die (respectively, HR = 1.39, $p = .045$ and HR = 1.44, $p = .010$) (Table 3).

## 4 | DISCUSSION

In October 2019, Morocco was selected as a pilot country with a commitment to implement the GICC program as well as a pediatric cancer plan in 2020. A major obstacle was the lack of national data on childhood cancer incidence and survival. It was therefore decided, as a first step, to retrospectively collect national survival data focusing on the six index cancers. The implementation of this data collection process proved challenging as the majority of the centers did not have a structured archive system and, in addition, five of the six centers did not have data managers.

A data management program is essential to identify the most important areas that require improvement and to assess the impact of specific interventions on outcomes and quality of care. It is reported that quality improvement depends on a rigorous measurement of treatment results, complications, and obstacles to deliver optimal protocol-based care.[13]

Morocco, like many other LMICs, lacks functional data management systems. Furthermore, it is not possible to hire a data manager as this position is not included in the list of positions recognized by the hospital administration. To circumvent this hurdle, data managers were recruited for the duration of the study by the SMHOP with the support of an unrestricted grant from the Sanofi Espoir Foundation.

A total of 878 patients were identified in the six selected centers, representing approximately 30% of all the childhood cancer cases treated per year in each center. This is less than expected as the six WHO priority diseases are estimated to represent about 50% of the recruited cases. In the report from the PO of Rabat, hematological malignancies (acute leukemia and lymphomas) accounted for 45% of cases and renal tumors 10.3%.[7] In this study, LGG are underrepresented (2%) because pediatric brain tumors are mainly managed by neurosurgeons and thus underreported in PO series. The number of cancers reported in this study is probably underestimated; some children are treated in private sector or abroad, some may have been treated in adult units, some were not referred to our units. As a result, the data collected may not represent an accurate estimate of childhood cancer in Morocco. This finding again highlights the lack of adequate information systems and the insufficient access to quality data. This problem being known, WHO included in the "GICC CURE All" package the evaluation and monitoring, with robust information systems and research to ensure effective implementation, quality assurance, and ongoing improvement in outcomes.[14]

At the national level, setting up a childhood cancer registry was regarded as a priority. This will be implemented incrementally, starting with hospital registries to eventually become a national registry to allow the inclusion of patients treated in all public and private facilities.

Despite these limitations, the analysis of the information collected has provided crucial baseline data for the development of the national

**TABLE 3** Univariate and multivariable Cox regression model

| | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| **Characteristics** | **HR [95% CI]** | ***p*** | **HR [95% CI]** | ***p*** |
| **Age (years)**[a] | | .004 | | .045 |
| <10 | 1.00 | | 1.00 | |
| ≥10 | 1.57 [1.15–2.14] | | 1.39 [1.01–1.92] | |
| **Sex** | | .281 | | .990 |
| Male | 1.00 | | 1.00 | |
| Female | 0.86 [0.65–1.13] | | 1.01 [0.75–1.34] | |
| **Distance from care center (km)** | | .108 | | .010 |
| <100 | 1.00 | | 1.00 | |
| ≥100 | 1.25 [0.95–1.64] | | 1.44 [1.09–1.91] | |
| **PO center** | | .118 | | .003 |
| Center no. 1 | 1.00 | .051 | 1.00 | .001 |
| Center no. 2 | 1.46 [0.99–2.13] | .112 | 1.95 [1.33–2.88] | .271 |
| Center no. 3 | 1.53 [0.90–2.56] | .067 | 1.35 [0.79–2.30] | .036 |
| Center no. 4 | 1.46 [0.97–2.18] | .006 | 1.56 [1.03–2.37] | <.001 |
| Center no. 5 | 1.93 [1.20–3.11] | .401 | 2.50 [1.54–4.05] | .250 |
| Center no. 6 | 1.30 [0.71–2.39] | | 1.44 [0.77–2.68] | |
| **Cancer type** | | <.001 | | <.001 |
| ALL | 1.00 | .001 | 1.00 | .001 |
| Burkitt lymphoma | 1.75 [1.26–2.43] | .003 | 1.79 [1.27–2.53] | .001 |
| Hodgkin lymphoma | 0.39 [0.21–0.73] | .001 | 0.35 [0.19–0.65] | <.001 |
| Retinoblastoma | 0.28 [0.14–0.58] | .007 | 0.25 [0.12–0.52] | .004 |
| Wilms tumor | 0.52 [0.33–0.84] | .830 | 0.50 [0.31–0.80] | .718 |
| Low-grade glioma | 0.90 [0.33–2.43] | | 0.83 [0.32–2.56] | |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval.
[a]Cox regression model is considering the overall survival.

plan by identifying a starting point for an improvement process. The 3-year OS of 68% reported is similar to the one reported in the Rabat survival study[5] but higher than the 30% postulated survival rate in Morocco reported in 2008 by Ribeiro et al.[15]

The 3-year EFS rate was 62%, with treatment-related mortality as the most frequent event. Overtreatment in LMICs carries with it an increased risk of treatment-related mortality, defined as death from complications of treatment, as opposed to the disease itself. Finding the balance point is key to optimizing therapy and curing the maximum number of children possible. This ideal balance point depends on the malignancy in question, as well as a particular center's ability to provide supportive care to prevent and manage treatment complications.[16] Therefore, reducing treatment-related mortality is an important objective to improve the OS of children within Morocco. Improvement in supportive care modalities, including better training and preventive measures, allows a safer use of more intensive and more effective therapies.

During the recent years, the Moroccan Society of Pediatric Hematology-Oncology has decided to use adapted protocol regimens and improve in parallel to focus on quality supportive care, patient support, and data collection. The adapted treatment regimens were national protocols developed by the SMHOP, the GFAOP (Francophone African Group of Pediatric Oncology) collaborative protocols or international protocols adapted in partnership with St Jude experts (Table 4) or SIOP.

In the present study, OS rates were significantly lower in ALL (61%) and BL (53%) than those reported for WT, RB, and LGG. The survival results for ALL and BL are even lower than those reported in previous studies. As part of the GICC implementation process in Morocco, a more detailed study will be launched shortly to detail the causes of failure and identify corrective actions. Early mortality is certainly one of the major factors, but recent shortage of essential drugs may have been responsible for some treatment failures. Abandonment rate was low, which is concordant with previous reports from the SMHOP about successful strategies to reduce treatment abandonment in HL.[18] The awareness campaigns on cancer conducted by the Lalla Salma Foundation Cancer Prevention and Treatment have probably contributed to the reduction of treatment abandonment.[23]

In a multivariable analysis, a distance of more than 100 km from the care center and cancer care center appears to be a negative progno-

**TABLE 4** Protocols used by the Moroccan Pediatric Oncology teams

| Cancer type | Protocol | Institution | Reference |
|---|---|---|---|
| ALL | Marall 06 | SMHOP | 17 |
| Burkit lymphoma | MAT-II protocol | GFAOP | 18 |
| Hodgkin lymphoma | MDH-Ma 04 | SMHOP/SJCRH | 19 |
| Retinoblastoma | RB-Ma | SMHOP | 20 |
| Wilms tumor | GFA nephro | GFAOP | 21 |
| Low-grade glioma | SIOP LGG/SIOP-adapted treatment regimen | SIOP | 22 |

Abbreviations: ALL, acute lymphoblastic leukemia; GFAOP, Francophone African Group of Pediatric Oncology; SMHOP, Moroccan Society of Pediatric Oncology.

sis factor. Distance from centers as a prognosis factor emphasizes the need for an active locally funded family support system, as reported in the Recife experience.[24]

The difference in survival rates between care centers is probably due to the fact that older or larger centers are more experienced, in addition to the fact that insufficient efforts have been developed to harmonize the standard of care between Moroccan centers. Considering these findings, the next national plan for childhood cancer will include an audit and, subsequently, an upgrade of the standards of care in all centers.

In conclusion, this is the first study providing an overview of survival rates for the six WHO-indexed diseases in all Moroccan PHO units. The reported results represent the baseline for measuring the impact of GICC implementation in the country and highlight priorities such as an urgent need to set up national cancer registries, including for pediatric cancers.

## CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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