RESEARCH ARTICLE

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Staging at Diagnosis and Survival of Hematologic Neoplasms in Children and Adolescents in Mato Grosso, Brazil: A Population-based Study

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Abstract

Objective: To apply the Toronto Childhood Cancer Staging Guidelines (TG) and Estimate the Observed Survival Probabilities for Pediatric Patients with Leukemia and Lymphoma. **Methods:** Staging at diagnosis was conducted according to tier 2 of the TG. The study cohort included patients aged 0 -19 years from the Population-Based Cancer Registry (PBCR) of Mato Grosso, diagnosed with leukemia and lymphoma between 2008 and 2017, with follow-up until December 31, 2022. Observed 60-month survivals were calculated using the Kaplan-Meier method. **Results:** Staging was assigned in 67.3% of cases (n=239), while in 32.7% (n=116), staging could not be applied due to incomplete data. Among the cases of acute lymphoblastic leukemia (ALL), 70.7% (n=133) were staged as CNS1, with an observed survival probability of 75.0%. For acute myeloid leukemia (AML), 42.2% (n=21) were staged as CNS-, with an estimated survival of 60.0%. Most Hodgkin lymphoma (HL) cases were staged as IIA/B (37.7%, n=23) and IIIA/B (21.3%, n=13), with survival probabilities of 91.3% and 91.7%, respectively. Among non-Hodgkin lymphoma (NHL) cases, 32.1% (n=18) were staged as stage III, with a survival probability of 70.6%. **Conclusion:** The application of TG in the PBCR in Mato Grosso proved feasible, allowing for comparability of survival estimates across different stages. However, collecting tier 2 staging information will be a challenge for the PBCR due to incomplete information in medical records.

Keywords: Child and adolescent- Leukemia- Lymphoma- Stage- Population-based cancer registry

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Introduction

Childhood and adolescent cancer affecting individuals from 0 to 19 years old is rare but represents a significant global public health issue. The most common types are leukemias (34%), central nervous system cancers (18%), and non-Hodgkin's lymphoma (16%) [1, 2]. However, incidence and survival rates are still poorly understood, especially in low-and middle-income countries, due to the lack of data [3]. Despite the difficulties, studies globally have shown significant variations in rate patterns and incidence trends [4, 5]. In high-income countries, survival rates exceed 80%, while in low-and middle-income countries they range from 20% to 30% and can reach 10% in East Africa [6-8]. These data highlight the importance of population-based cancer registries (PBCR), which are critical for cancer surveillance as they can provide high-quality population-level data.

PBCRs are considered the gold standard for cancer surveillance, as they support the planning of disease control measures and etiological research. While hospital records and clinical trial-specific systems can complement PBCR data, they should not replace them. In addition, information from PBCRs can be compared internationally to assess outcomes and global disparities in cancer incidence and survival rates [9]. In this context, information regarding the staging of population-based childhood cancer is essential for epidemiological analyses and international comparison of incidence and survival [10]. However, they are not collected by the PBCR [11]. The tumor/lymph node/metastasis (TNM) system is the most commonly used system for staging tumors in adults, however, it is inadequate for assessing the extent of the disease in the child and adolescent population. On a global

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scale, there is no standardized staging system applicable for PBCR [12]. To address this gap, a consensus meeting was held in Toronto in 2014 to evaluate the possibility of standardizing pediatric tumor staging information at the population level, establishing staging systems for 16 types of tumors, which should be used by PBCRs, which was called Toronto Guidelines (TG). These systems are not intended to replace clinical staging to determine treatment and prognosis, but they do make it possible to assess the extent of the disease at the time of diagnosis [12].

This study aims to apply the TG staging system and estimate the observed survival of new cases of childhood leukemia and lymphomas through information from the PBCR of Mato Grosso from 2008 to 2017.

Materials and Methods

This is a retrospective, observational, descriptive study of the applicability of the staging system for malignant tumors in childhood to cancer registries, according to TG. Information on incidence was obtained from the databases of the PBCR in the interior of the state of Mato Grosso and in the capital, Cuiabá, which were unified and renamed PBCR Mato Grosso, covering all municipalities in the state.

This PBCR is located in the Midwest region of Brazil (Figure 1). In 2022, the estimated population, according to the demographic census was 3,658,813 inhabitants, of which 1,279,898 were in the age group of 0 to 19 years. The state is composed of 141 municipalities with a human development index of 0.736 [13]. The PBCR was implemented in 1999 by the State Department of Health and has as notifying source several public and private health establishments, according to its Norms and Routine Manual [14, 15]. Regarding data quality indicators, approximately 97.2% of cases were histologically verified and 2.7% were recorded by declaration alone (SDO), according to standards suggested by the International Agency for Research on Cancer (IARC) [16].

For this study, cases diagnosed with leukemia and lymphomas in patients aged 0 to 19 years, between 2008 and 2017 were selected, according to the diagnostic group of the third International Classification of Childhood Cancer (ICCI): Ia – acute lymphocytic leukemia (ALL); Ib – acute myeloid leukemia (AML); II – lymphomas and reticuloendothelial neoplasms; II-A – Hodgkin's lymphomas (HL); II-B – non-Hodgkin's lymphoma (NHL); II-C – Burkitt's lymphoma [17].

The stage at diagnosis was assigned according to the TG-based staging system guidelines, which can be adjusted according to the quality of the available information, facilitating the application of TG in countries with lower socioeconomic status. Tier 1 requires simpler specifications, while tier 2 requires greater detail of clinical information for staging [18, 19]. In this study, Tier 2 was used, summarized in detail in supplementary Table 1.

A total of 355 cases of hematological cancer in children and adolescents were identified in the PBCR database. The active search of medical records was carried out in two Hospital-based cancer registries (HBCR), implemented in only two high-complexity services qualified in pediatric oncology in the state, financed by the Unified Health System (SUS). These services serve most of the patients diagnosed and treated, covering 95% of the cases registered by the PBCR.

The information necessary for staging was collected by the principal investigator, trained by the National Cancer Institute (INCA), from the medical records provided by HBCR1 (n=284) and HBCR2 (n=71), as illustrated in the flowchart in Figure 2. Due to the incompleteness of the clinical information in the medical records, it was not possible to perform staging in 32.2% of cases (116 of 355), both at tier 1 and tier 2. Thus, TG was successfully applied in 67.3% of the cases (239 of 355).

Statistical analysis

Statistical analysis was performed using absolute and relative frequencies for sex, age group, sociodemographic and clinical information. Five-year survival rate was estimated using the Kaplan-Meier method, with 95% confidence intervals, according to the stage and type of neoplasm. The follow-up of the vital status of the cases was actively conducted in the medical records and in the Mortality Information System (SIM), with data available until 12/31/2022, allowing follow-up in 60 months for all cases. Survival time was calculated from the date of diagnosis to the date of death. Cases not found in SIM were considered alive and therefore censored. Differences in survival were assessed using the log-rank test, and the hazard ratio was calculated to analyze the relative risk of death between different groups. The analyses were performed using R Studio version 4.3.0.

Ethics approval

This study was approved by the Ethics Committee for Research with Human Beings at the Health Department of the Federal University of Mato Grosso (opinion No. 5,709,469) and by the Research Ethics Committee of the Mato Grosso State Department of Health (SES-MT) (opinion No. 5,779,146).

Results

In Mato Grosso, 355 cases of leukemia and lymphomas were identified. Table 1 shows the descriptive results of the cases, indicating a higher percentage in males, corresponding to 56.3 % (n= 200), a pattern observed among the diagnostic groups. The leukemia group was more frequent, accounting for 67.0% (n= 238). Most new cases were in the age group of 0 to 4 years 29.0% (n=103), and the black population represented 64.2% (n= 163), adding blacks and browns. It was found that 62.3% (n = 221) of the patients had no previous history of cancer diagnosis, and 47.9% (n = 170) had no recurrences, relapses or progression of the disease. Regarding the outcome of deaths, 11.3% (n= 40) occurred during the induction phase of treatment and 3.4% (n= 12) in the maintenance phase. With regard to vital status, 50% (n= 109) of the cases diagnosed with leukemia and 70.9% (n= 83) of the lymphoma cases were alive at the time of follow-up.

Table 1. Clinical and Diagnostic Characteristics of Children and Adolescents with Hematologic Cancer

Variables	Total		* Acute lymphoblastic leukemia and Acute myeloid leukemia		* Hodgkin lymphoma and Non-Hodgkin lymphoma	
	n (355)	%	n (238)	%	n (117)	%
Sex						
Male	200	56.3	128	53.8	72	61.5
Female	155	43.7	110	46.2	45	38.5
Age group at cancer diagnosis						
00 - 4	103	29.0	82	34.5	21	17.9
05-09	79	22.3	55	23.1	24	20.5
10-14	90	25.4	58	24.4	32	27.4
15 - 19	83	23.4	43	18.1	40	34.2
Race						
White	95	26.8	57	23.9	38	32.5
Black	228	64.2	163	68.5	65	55.6
Indians	4	1.1	2	0.8	2	1.7
Unknown	28	7.9	16	6.7	12	10.3
First previus cancer						
No	221	62.3	148	62.2	73	62.4
Yes	4	1.1	2	0.8	2	1.7
Unknown	130	36.6	88	37.0	42	35.9
Relapse/recurrence/progression						
No	170	47.9	114	47.9	56	47.9
Yes	40	11.3	29	12.2	11	9.4
Unknown	145	40.8	95	39.9	50	42.7
Deaths during induction						
Yes	40	11.3	37	15.5	3	2.6
No	178	50.1	105	44.1	73	62.4
Unknown	137	38.6	96	40.3	41	35.0
Deaths during maintenance treatment						
No	206	58.0	139	58.4	67	57.3
Yes	12	3.4	3	1.3	9	7.7
Unknown	137	38.6	96	40.3	41	35.0
Status vital						
Alive	202	56.9	119	50.0	83	70.9
Dead	153	43.1	119	50.0	34	29.1
Stage at diagnosis						
Available	239	67.3	159	66.8	80	68.4
Unknown	116	32.7	79	33.2	37	31.6

Note: * ICCC-3, International Classification of Childhood Cancer.

Regarding the application of TG, it was observed that the data necessary for the attribution of staging, both at tier 1 and tier 2, were available in the medical records in approximately 67.3% (n= 239) of the cases analyzed, however, in 32.7% (n= 116) of the cases it was not possible to apply the staging due to the incompleteness of the information in the medical records, thus classifying them as unknown staging, (Table 1).

The results obtained with the TG application, presented in Table 2, revealed that children and adolescents with ALL represented 70.7% (n=133) of cases with negative staging of the central nervous system disease (CNS1), while only 2.1% (n=4) of the cases corresponded to the (CNS2). Among patients with AML, 42.0% (n=21) of the cases were staged as (CNS-). Regarding patients with HL, most cases did not indicate advanced staging of the disease, with 37.7% (n=23) presenting staging (IIA/B). Among NHL cases, 32.1% (n=18) of the patients were diagnosed with stage (III). However, among the cases of ALL and AML, 27.1% (n=51) and 56.0% (n=28) were classified as unknown staging (X), in that order. For patients with HL and NHL, this classification represented 21.3% (n=13) and 42.9% (n=24), respectively.

In the analysis of survival observed at 60 months, they

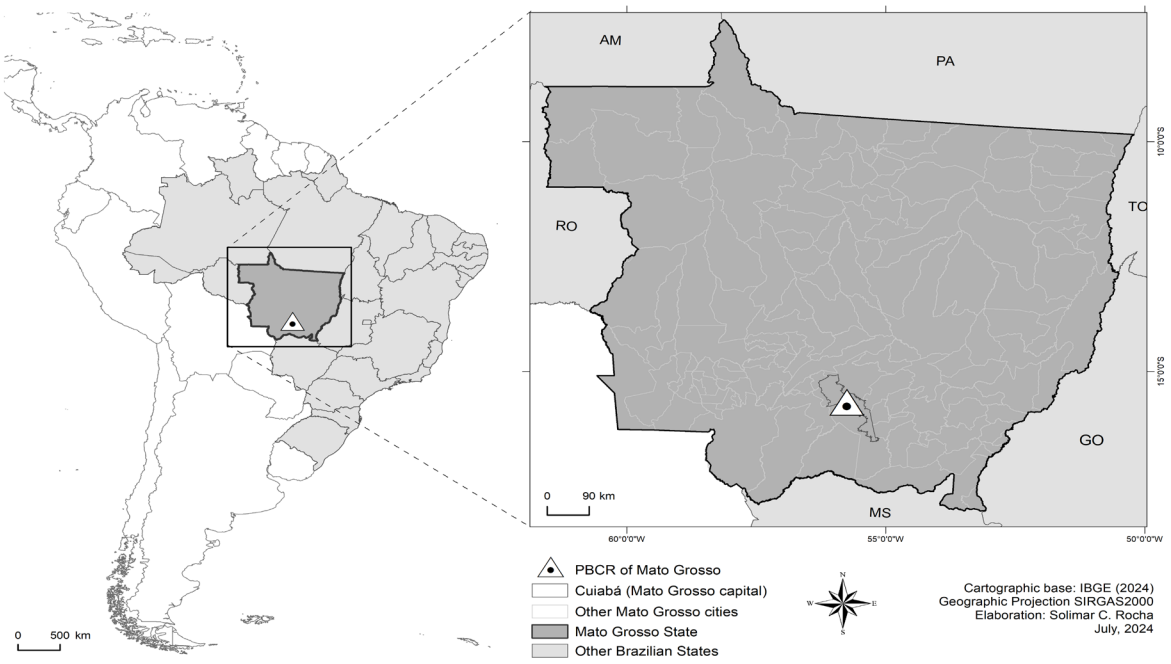

Figure 1. Map of the Location of the RCBP of Mato Grosso in Brazil.

showed that the probability of survival due to staging ALL (CNS1) was 75.0% (95%CI: 68.0; 82.8) and 60.0% (95%CI:42.1; 85.8) for cases of AML with stage (CNS-), in addition to the fact that there were no significant differences when comparing the survival curves between the staging tiers. The risk ratio between the stages for ALL was higher for the staging (CNS2) 1.40 (95%CI: 0.34; 5.78), as presented in Table 2 and Figure 3, which show the survival curves.

In relation to HL, there were no significant differences between the stagings (p=0.30), unlike what was observed for NHL (p= 0.01). It was observed that survival for HL was higher in (IIA/B) 91.3% (95%CI: 80.0; 100), followed by stage (IIIA/B) 91.7% (95%CI: 77.3; 100). Cases with stage (III) had a higher survival of 70.6% (95%CI: 51.9; 95.9), in addition to the stage (I) 66.7% (95%CI:37.9; 100) among NHL. The observed survival curves are represented in Figure 3.

Discussion

This is the first population-based study to describe the applicability of staging according to TG for childhood leukemia and lymphomas in Mato Grosso. In 32.7% of the cases, it was not possible to attribute the stage of the tumor based on the information available in the medical records. Approximately 70.7% of ALL cases and 42.0% of AML cases, as well as HL 37.7% had localized disease,

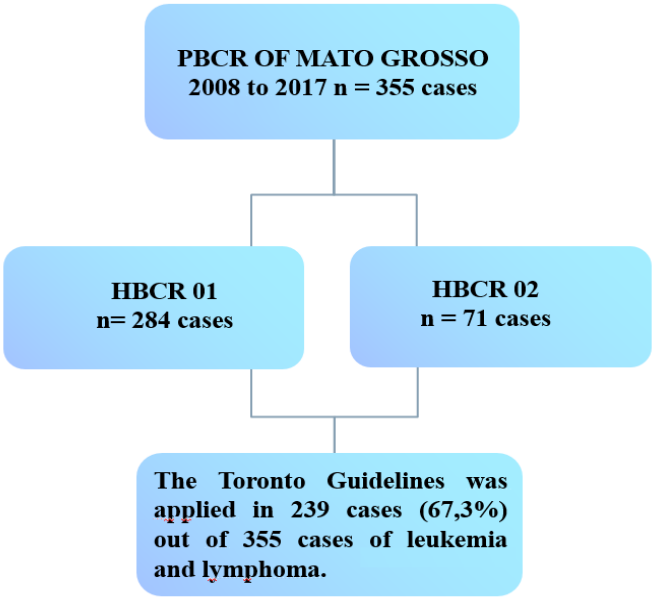

Figure 2. Flow Diagram of Case Selection for Leukemias and Lymphomas in Children and Adolescents for Applying the Toronto Guidelines, Mato Grosso PBCR.

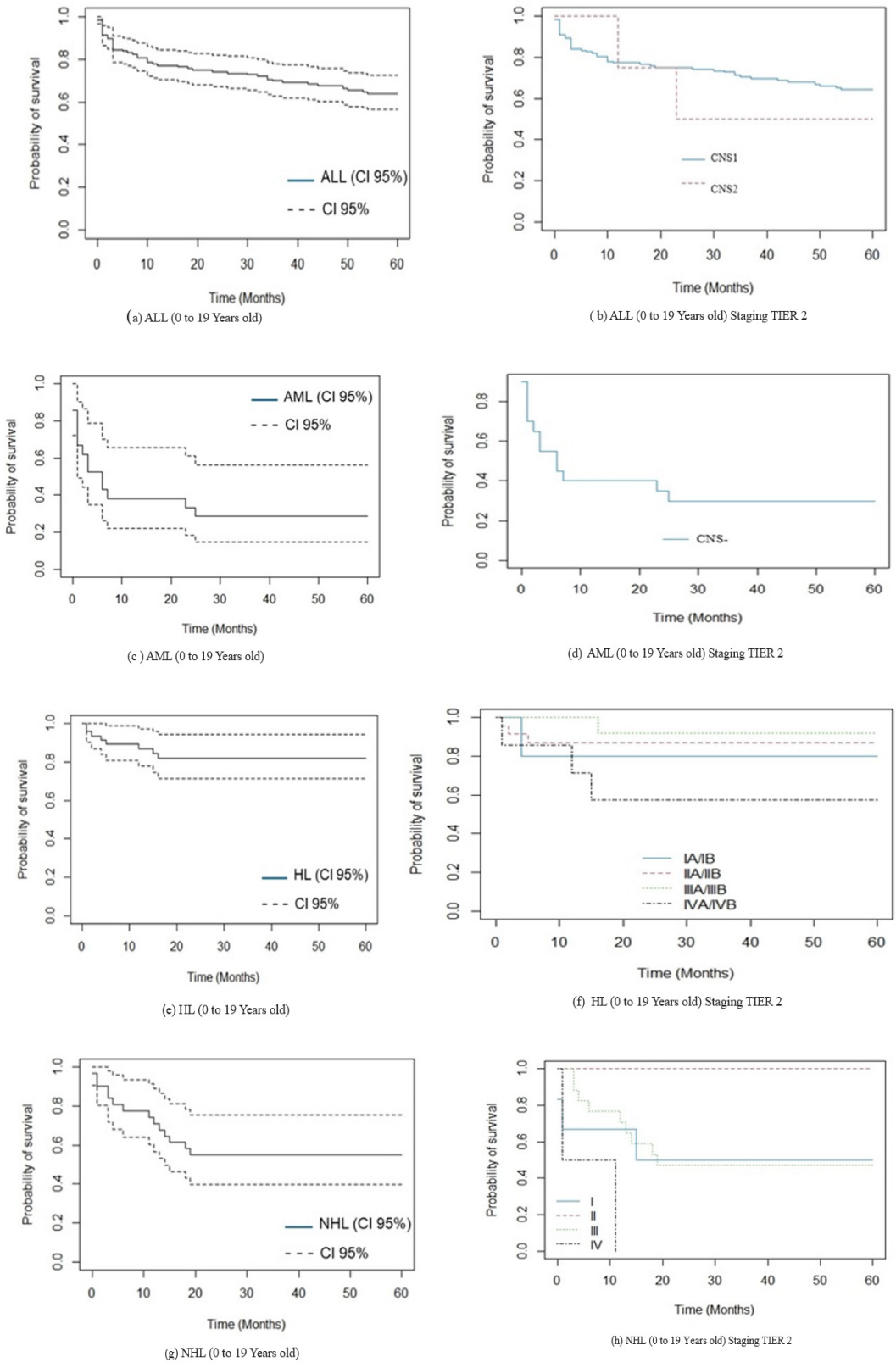

Figure 3. Survival Observed in Both Sexes According to Toronto Guidelines Tier 2 Staging. Abbreviations: HL, Hodgkin´s Lymphoma; CI 95%, 95% confidence interval

while for NHL 32.1% of cases had advanced disease. Staging was not a statistically significant predictive of survival at 60 months.

In the literature, there are few population-based studies that report survival by stage at diagnosis. To our knowledge, some have documented the proportion of cases that could be staged ranged from 85% for AML to 95% for ALL, HL, and NHL in the Australian PBCR [10], and reported that, by applying TG to records from Sub-Saharan Africa, it was possible to stage 77.8% of NHL cases [20]. The authors highlighted challenges in the complete documentation of these data in clinical settings,

Table 2. Stage Distribution byCancer Type and Observed Survival in Mato Grosso from 2008 to 2017

Cancer type	Stage Tier 2	n	%	Survival (%) CI 95%	HR CI 95%	Taste the Log-rank (p)
ALL	CNS 1	133	70.7	75.0 (68.0,82.8)	1	0.60
	CNS 2	4	2.1	62.5 (30.7,100)	1,40 (0.34, 5.78)	
	CNS 3	-		-	-	
	X	51	27.1			
AML	CNS -	21	42.0	60.0 (42.1,85.8)	1	
	CNS +	1	2.0	*	15.46 (1.34, 178.4)	0.01
	X	28	56.0	-	-	
HL	IA/B	5	8.2	80.0 (51.6,100)	1	0.30
	IIA/B	23	37.7	91.3 (80.5,100)	0.71 (0.07, 6.85)	
	IIIA/B	13	21.3	91.7 (77.3,100)	0.37 (0.02, 5.93)	
	IVA/B	7	11.5	71.4 (44.7,100)	2.34 (0.24, 22.54)	
	X	13	21.3	-	-	
NHL	I	6	10.7	66,7 (37,9;100)	1	0.01
	II	6	10.7	**	-	
	III	18	32.1	70.6 (51.9,95.9)	0.93 (0.30; 2.81)	
	IV	2	3.6	25.0 (6.25,50.0)	4.98 (1.00,24.87)	
	X	24	42.9	-	-	

Note: *, survival was zero; **, there was no censorship (death); 95% confidence interval, 95%; hazard ratio: HR

but suggested the feasibility of implementing TG staging information, unlike our results, which showed the viability of only 67.3% of eligible cases.

In another study on the application of TG, it was evidenced that accurately determining the stage of childhood cancer is challenging in low-income nations. A study involving 51 cancer registrants in Sub-Saharan Africa revealed that, after training, they were able to assign the correct stage in 71% of cases. However, there is room for improvement in guidelines and training aimed at improving information [21]. This finding is in line with our results, in which we identified a lack of complete information in medical records in cases categorized as "stage unknown," which represents a significant limitation that may hinder clinical management and treatment planning.

Identified challenges in assigning stage to diagnosis at tier 2 in hospital records from seven sub-Saharan African countries, limiting this assignment to tier 1 for most cases, except for Burkitt's lymphoma [22]. Staging at tier 2 was not feasible for leukemia due to the lack of information on the cerebrospinal fluid test, evidencing disparities in access to diagnosis. The absence of data on staging at diagnosis compromises appropriate treatment strategies, hindering improvement in clinical outcomes. However, it is important to highlight that TG was developed as a tool for cancer registries to collect comparable information on staging across populations regarding the extent of disease at diagnosis, rather than to guide individual clinical management, which is based on country-and center-specific protocols.

The proportion of cases with staging (CNS1) and (CNS-) for ALL and AML in our study was lower than that observed in an Australian study in which they reported 91.0% and 65.5%, respectively. When comparing our results of the lymphoma groups with that study, more than half of the HL cases did not have advanced disease and, for NHL, a higher proportion of cases in stage (III), corroborating our research [10]. We highlight that our results revealed that the patients did not have advanced disease, suggesting early diagnosis. However, there is a common misconception about the rarity of cancer in children, which can result in harmful diagnostic delays, as it is a risk comparable to other common diseases in this age group and where genetic factors may influence. As tumors spread rapidly in this age group, early detection is crucial, underscoring the need for greater awareness, capacity building, and guidelines for GPs [23].

The survival analysis observed in our study demonstrated that staging was not a statistically significant predictor, contrary to the results of the Australian study, which revealed statistical significance according to ALL staging (p=0.05), while for AML there was no difference in survival. In comparison, the survival reported in our study was below the estimates found in Australia for ALL (CNS - 94.1% and CNS2 89.0%). Regarding HL and NHL, there were no differences in the survival curves in our results, however, as the stage increased, the probability of survival decreased. In the Australian study, as NHL staging increased, the survival trend worsened (P = 0.04) [10]. In contrast to our results, a study in sub-Saharan Africa demonstrated that staging was a significant predictor for survival in children under 15 years of age with HLN, in addition to revealing that 52% of cases had advanced or metastatic disease [20].

Based on the findings of a survey conducted in Rwanda [24], using tier 1 TG, the 5-year survival for ALL was 44.4% (CNS-) and 15.5% (CNS+), while our study revealed a survival of 75% (CNS1). For NHL, survival was 70.0% (limited) and 5.9% (advanced), in contrast to

70.6% (stage III) in our study. These disparities highlight the importance of implementing programs for early diagnosis of the disease and ensuring access to treatment in a timely manner.

It is important to note that a considerable portion of the leukemia cases in our results evolved to deaths during the induction phase of treatment (15.5%), highlighting the need for improvement in this stage of care. On the other hand, we observed a substantial proportion of patients who did not have recurrences or progression of the disease (47.9%), which is a positive fact and may indicate the effectiveness of the available treatments. Even so, the literature has documented that about 15% to 20% of children diagnosed with ALL face recurrence, which highlights the need to adapt treatments and infection control strategies. In addition, investments in research to increase survival are essential, considering that some available medications have high toxicity, contributing to mortality in the initial phase of treatment due to infections and early recurrences [24-27].

There is also the expectation that in the future, an increasing number of people will be diagnosed with cancer annually, which will require health systems to be prepared to offer quality care. Cancer survival is an important measure of the effectiveness of health systems in managing the disease, with significant variations. In this context, global surveillance of survival estimates is essential to identify and mitigate avoidable inequalities. The evaluation of the anatomical extent of the disease/stage makes it possible to differentiate between cases diagnosed early and cases with advanced disease, making it easier to estimate the probability of survival and guide public health policies [28, 29].

Several factors contribute to global inequalities in cancer treatment outcomes, including disparities in access to diagnosis, medication, surgeries and radiotherapies, in addition to the fact that many cases are diagnosed at advanced stages of the disease. Even when medications and treatments are available, many children in countries with low-and middle-income often face disruptions due to lack of financial resources [12, 30, 31, 21].

Recently in Australia, found stability in survival to several types of childhood cancer at the population level, with the distribution of stages remaining constant in most cases, except for retinoblastoma and hepatoblastoma. In addition, they highlighted significant improvements in five-year survival, especially in advanced solid cancers such as medulloblastoma, neuroblastoma, and rhabdomyosarcoma, which historically had poor prognosis [32]. These results indicate advances in childhood cancer treatment in Australia, suggesting that this improvement is due to more effective management rather than changes in the stage of diagnosis. Global adoption of TG will allow for a comprehensive analysis of disparities in survival among countries.

The strong point of our study was the use of high-quality information on pediatric hematological cancers, made available by the PBCR of Mato Grosso, representing one of the population-based registries in the world that apply TG. This study suggests the feasibility of collecting staging data through PBCRs, highlighting the importance of standardizing data sources and collection processes. Our results are in line with those of a recent pilot study carried out in Brazil, which demonstrated the feasibility of collecting staging data using PBCRs [33]. This study also suggested the feasibility of collecting staging data using PBCRs, with the use of TG in four PBCRs, in resource-limited settings. Both studies reinforce the applicability of TG and encourage the collection of the variable for future research, promoting closer collaboration with pediatric oncologists and hospital cancer registries.

Regarding the limitations of the study, the following stand out: the high frequency of cases that could not be staged due to the absence of essential information in several medical records, especially in the documentation of the tests necessary to determine the staging. In certain cases, this lack of information reflects the age at the time of the diagnoses, which made it impossible to fully retrieve records and additional clinical information. These challenges can be attributed to diagnostic complexity and variations in clinical documentation, confirming the existing literature, which highlights barriers in the availability of staging information [20-21, 33].

The calculation of the probability of survival of cases without staging, as well as the small number of cases, may have influenced the accuracy of survival estimates and decreased the statistical capacity to identify differences.

Some initiatives were implemented such as the free electronic cancer staging tool, containing all the rules of TG, available online at: www.canstaging.org [9, 34]. In this context, reported the experience of the ChildGICR Masterclass course, which aims to address these obstacles by training health professionals in the accurate collection and standardized classification of pediatric tumor staging [35].

In conclusion, this study contributed to the understanding of the availability of information on the extent of the disease and the applicability of the TG. The feasibility of collecting this information was demonstrated, for the first time, making possible the comparison of survival between different stages at the population level of patients diagnosed with leukemia and childhood lymphomas in Mato Grosso. However, the incompleteness of medical records poses a significant challenge to the PBCR. It is necessary to invest in improvements in clinical documentation to ensure greater accuracy in staging information, facilitating future epidemiological analyses and improving clinical outcomes for patients.

Author Contribution Statement

PCFS designed the study, developed the data management, exploitation and analysis. MME, FCSL, NDG and MTBT contributed to drafting preliminary versions of the article. All the authors contributed to the critical review, the approval of the final version and agreed to be responsible for all aspects of the work.

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General

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Conflict of interest

Ethical Declaration: The authors declare no conflicts of interest.

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