Analysis of Survival of Pediatric Patients with Leukemias and Lymphomas in the Oncological Context: Epidemiological Study in the State of São Paulo, Brazil, 2000-2022

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Análise de Sobrevivência em Pacientes Pediátricos com Leucemias e Linfomas no Contexto Oncológico: Estudo Epidemiológico no Estado de São Paulo, Brasil, 2000-2022

Análisis de Supervivencia en Pacientes Pediátricos con Leucemias y Linfomas en el Contexto Oncológico: Estudio Epidemiológico en el Estado de São Paulo, Brasil, 2000-2022

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ABSTRACT

Introduction: The time taken for screening, detection and initiation of treatment is a determining factor for therapeutic management in oncology. The availability of reliable data guides decisions for public policies and evaluates compliance with these policies. **Objective:** To analyze the survival and outcomes of pediatric patients with leukemia and lymphoma from 2000 to 2022. **Method:** Epidemiological, descriptive study, with data extracted from *Fundação Oncocentro do Estado de São Paulo*, according to the International Classification of Childhood Cancer (ICCC). The time elapsed between the first consultation and diagnosis was evaluated, between diagnosis and the start of oncological treatment, and the survival of these patients, calculated according to the Peto-Peto test. **Results:** 12,030 cases were analyzed, 6,994 in males and 7,292 with leukemia. The probability of the time between consultation and diagnosis exceeds 30 days was 49.29% for leukemias and 76.31 for lymphomas, a significant result for treatment and relapses ($p < 0.001$) but not in relation to sex; the time between diagnosis and treatment exceeding 60 days was 38.04% for leukemias and 71.97% for lymphomas. Not undergoing treatment was significant ($p < 0.001$) while waiting for diagnosis after consultation for patients with leukemia and lymphomas, except surgery, chemotherapy and radiotherapy combined. **Conclusion:** Despite the advances, a considerable percentage of patients wait longer than expected for diagnosis and initiation of treatment, impacting their survival rates.

Key words: Survival Analysis; Diagnosis Leukemia; Diagnosis Lymphoma; Time-to-Treatment.

RESUMO

Introdução: O tempo no rastreio, detecção e início do tratamento é fator determinante para o manejo terapêutico em oncologia. A disponibilidade de dados confiáveis orienta decisões para políticas públicas e avalia o cumprimento dessas políticas. **Objetivo:** Analisar a sobrevivência e desfechos de pacientes pediátricos com leucemias e linfomas de 2000 a 2022. **Método:** Estudo epidemiológico, descritivo, com dados extraídos da Fundação Oncocentro do Estado de São Paulo, segundo a Classificação Internacional de Câncer na Infância. Avaliou-se o tempo decorrido entre a primeira consulta e o diagnóstico; entre o diagnóstico e o início do tratamento oncológico; e a sobrevivência desses pacientes, calculada conforme o teste Peto-Peto. **Resultados:** Foram analisados 12.030 casos, com prevalência no sexo masculino 6.994; 7.292 corresponderam às leucemias. A probabilidade de o tempo entre a consulta e o diagnóstico ter sido superior a 30 dias foi de 49,29% para as leucemias e de 76,31 para os linfomas, significativo para o tratamento e recidivas ($p < 0,001$) e não por sexo; o tempo entre o diagnóstico e tratamento, superior a 60 dias, foi de 38,04% para as leucemias e de 71,97% para os linfomas. Não realizar tratamento foi significante ($p < 0,001$) na espera entre a consulta e o diagnóstico para os pacientes com leucemias; o mesmo para os linfomas, exceto para a combinação de cirurgia, quimioterapia e radioterapia. **Conclusão:** À despeito dos avanços obtidos, uma porcentagem considerável de pacientes aguarda um tempo maior do que o esperado para o diagnóstico e o início do tratamento, repercutindo nas taxas de sobrevivência desses pacientes.

Palavras-chave: Análise de Sobrevida; Diagnóstico Leucemia; Diagnóstico Linfoma; Tempo para o Tratamento.

RESUMEN

Introducción: El tiempo necesario para el *screening*, detección e inicio del tratamiento es un factor determinante para el manejo terapéutico en oncología. La disponibilidad de datos confiables orienta las decisiones de políticas públicas y evalúa el cumplimiento de estas políticas. **Objetivo:** Analizar la supervivencia y desenlaces de pacientes pediátricos con leucemia y linfoma en el período de 2000 a 2022. **Método:** Estudio epidemiológico, descriptivo, con datos extraídos de la Fundación Oncocentro del estado de São Paulo, según la Clasificación Internacional del Cáncer Infantil. Se evaluó el tiempo transcurrido entre la primera consulta y el diagnóstico; entre el diagnóstico y el inicio del tratamiento oncológico, y la supervivencia de estos pacientes, calculada según la prueba de Peto-Peto. **Resultados:** Se analizaron 12 030 casos, con una prevalencia masculina de 6994; 7292 correspondieron a leucemia. La probabilidad de que el tiempo entre consulta y diagnóstico sea mayor a 30 días fue del 49,29% para leucemias y del 76,31 para linfomas, significativa para tratamiento y recaídas ($p < 0,001$) y no para sexo; para el tiempo entre diagnóstico y tratamiento, superior a 60 días, fue del 38,04% para las leucemias y del 71,97% para los linfomas. No recibir tratamiento fue significativo ($p < 0,001$) en la espera entre la consulta y el diagnóstico en pacientes con leucemia; lo mismo para los linfomas, excepto la combinación de cirugía, quimioterapia y radioterapia. **Conclusión:** A pesar de los avances logrados, un porcentaje considerable de pacientes espera un tiempo más de lo esperado para el diagnóstico y el inicio del tratamiento, impactando en las tasas de supervivencia de estos pacientes.

Palabras clave: Análisis de Supervivencia; Diagnóstico Leucemia; Diagnóstico Linfoma; Tiempo de Tratamiento.

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INTRODUCTION

Childhood cancer is a heterogeneous group of malignant neoplasms with particularities, reflecting in their occurrence, etiology, therapy, overall survival and the risk of treatment-related acute and late toxic effects[1].

In Brazil, the estimated number of new cases of leukemia for each year of the triennium 2023 to 2025 is approximately 11,540 cases, ranked as the 10th most frequent type of cancer. On the other hand, the estimated number of new cases of Hodgkin's lymphoma (HL) for each year of the same triennium, is around 3,080 cases and for non-Hodgkin's lymphoma (NHL), it is nearly 12,040 new cases[2].

The State of São Paulo, due to its demography, is home to about 24.0% of the total estimated cases and 12.0% of all deaths in the country, the State with the highest cancer morbidity and mortality rate in this age group[3].

Leukemias are a heterogeneous group of malignant neoplasms that develop in different cell lineages of the bone marrow, with predominance in leukocytes, while lymphomas originate in the lymphatic system, more specifically in lymphocytes, which undergo malignant transformation in lymph nodes and subsequent dissemination[4].

Due to socioeconomic differences, not all children and adolescents benefit from advances in oncology, hematology, and precision medicine[5,6]. It is possible to affirm that pediatric hematological tumors is a neglected global public health disease, but can be prevented and early detected[7].

In this scenario, on November 12, 2012, Law 12.372[8] – the 60-days law – was sanctioned and later amended by Law 13.685[9] of June 12, 2018; it determined that the first treatment should start within 60 days from the diagnosis at the National Health System (SUS). However, due to socioeconomic and socio-regional disparities, problems of equal access and equity are a Brazilian reality. For cases of acute leukemia, the treatment needs to commence earlier since the onset of the first symptoms, due to tumor aggressiveness and refractoriness[10].

The quality and timeliness of cancer records are essential to provide precise information about each phase of the treatment[3].

It is evident that, depending on the type of neoplasm affecting children and adolescents, survival rates can be compromised, even with timely and correct therapy, given the risk of recurrence, aggressiveness and resistance of the primary tumor, further to the risk of developing a second primary tumor, with concomitant evolution of chronic diseases and the appearance of functional deficiencies. In these cases, time is of essence for screening, detection and initiation of the treatment[11].

This article aimed to analyze the survival and clinical outcomes of pediatric patients with leukemias and lymphomas in the State of São Paulo.

METHOD

Epidemiological, descriptive study, with data from *Fundação Oncocentro do Estado de São Paulo (FOSP)*, from January 2000 to December 2022.

Data from patients up to 19 years old entered at the FOSP database, referred by 77 institutions registered in the State of São Paulo, were included. The neoplasms analyzed were selected according to groups I and II of ICCC[12], respectively. For the purposes of data presentation, group I included leukemias (myeloproliferative and myelodysplastic diseases) and group II, lymphomas (Hodgkin's and Non-Hodgkin's lymphomas and reticuloendothelial neoplasms).

Data were extracted from FOSP database on February 7, 2023 and exported in Data Base File to R[13] a software for statistical computing and graphics.

As outcome variables, the time elapsed between the doctor visit and the oncological diagnosis and the time between the diagnosis and the beginning of the oncological treatment were evaluated. To study these periods of time, survival analysis was conducted[14,15], where the event of interest (here considered as a failure) is the occurrence of death by cancer. The study cutoff is 180 days, three times the period to start treatment after diagnosis according to the current legislation.

As independent variables, isolated or combined treatment (surgery, surgery + chemotherapy, surgery + radiotherapy + chemotherapy, surgery + radiotherapy + chemotherapy + hormone therapy, surgery + radiotherapy, no treatment performed, other treatment combinations, chemotherapy, radiotherapy, radiotherapy + chemotherapy), sex (male, female), recurrence (yes, no). The analyzes performed were stratified by group. Furthermore, the Federative Unit (FU) of birth and residence and the Regional Health Department (DRS) were the treatment occurred were analyzed.

For the descriptive analysis of the outcome variables, measures of central tendency, as mean and median, and dispersion, as standard deviation, minimum and maximum values were used. In addition, for the independent variables, the frequency and percentage were considered.

The Peto-Peto test was utilized[16] to compare survival periods for treatments, sex and relapse. The variance of the Peto statistic (non-parametric estimation) is equal

to the variance of the log-rank test, in which each time interval is weighted by the square of the survival function. Greater weight is attributed to differences (or similarities) at the beginning of the curve, where there is greater concentration of data, therefore, more informative. An S(t) weight is used in the estimator, incorporating censorship without assumptions about the time distribution. The Peto statistic follows a $\chi 2$ distribution with k – 1 degree of freedom approximately.

In cases where differences between the groups evaluated were found for the variable treatment, the procedure of multiple comparisons by Benjamini and Hochberg[17] was used. All the analyzes were performed with a significance level of 5.0% with the software R[13], version 4.1.2.

Approval by the Research Ethics Committee was waived because only secondary and public data were utilized[18].

RESULTS

A total of 12,030 (100.0%) cases were analyzed in groups I and II, of which 6,994 (58.1%) were males and 5,036 (41.9%), females. Also, 7,292 (60.6%) encompassed the group of leukemias, 410 (3.4%), of myelodysplastic diseases (CICI – IA, IB, IC, ID, IE) and 4,328 (36.0%), lymphomas and reticuloendothelial neoplasms (CICI – IIA, IIB, IIC, IID, IIE).

Most of the cases were reported in the States of São Paulo, 9,476 (78.8%), Minas Gerais, 673 (5.6%) and Bahia, 221 (1.8%); 10,448 (86.8%) lived in São Paulo, 616 (5.1%) in Minas Gerais and 84 (0.7%) in Goiás. The Regional Health Departments (DRS) with the highest percentage of assistance were DRS 01 (Greater São Paulo) with 4,309 (41.2%) cases, followed by DRS 07 (Campinas) with 1,192 cases (11.4%) and DRS 17 (Taubaté) with 779 cases (7.5%).

The overall mean time between the consultation and diagnosis was 14.01 days (± 30.00), for 5.00% of the patients the waiting interval was 66 days and another 180 days for 1.00% of them. Due to data variability, the overall median was 82 days, 29 days for group I (leukemias) and 180 days for group II (lymphomas).

Figure 1 portrays the survival curves by groups (I and II), considering the cut-off of 180 days, while waiting for the oncological diagnosis after the doctor visit and the beginning of the treatment.

The curves show distinct behavior of different groups of neoplasms. For the leukemia group, the probability of survival of 50.0% was around 20 to 30 days and, for patients with lymphomas more than 50.0% were still alive in 180 days, (Figure 1). The overall probability that the time between the doctor visit and diagnosis was greater than 30 days was 0.6165 [95%CI:(0.6303;0.6030)]. The probability for group I was 0.4929 [95%CI:(0.4733;0.5133)] and 0.7631 for group II [95%CI:(0.7452;0.7813)].

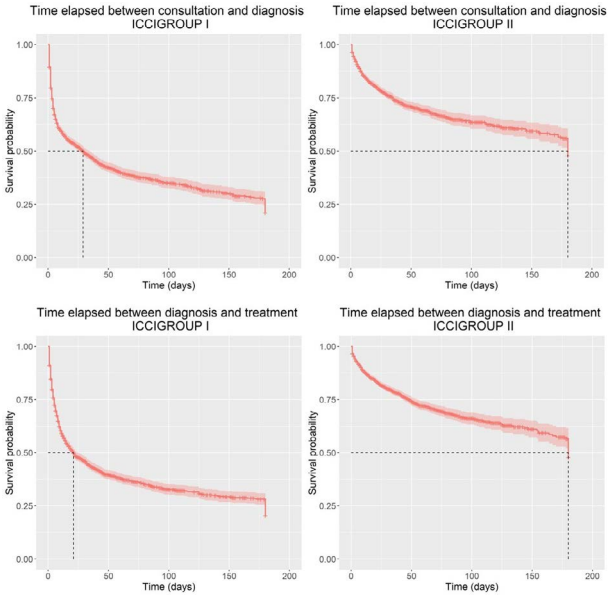

Figure 1. Survival curve of patients in relation to the time elapsed between doctor visit and diagnosis, and between diagnosis and initiation of treatment, by group of neoplasms

Captions: myeloproliferative leukemias and myelodysplastic diseases (ICCI group I); lymphomas and reticuloendothelial neoplasms (ICCI group II).
Source: FOSP[19].

The overall mean time between diagnosis and initiation of cancer treatment was 17.23 (± 32.45), for 5.00% of the patients this interval was 80 days and another 180 days for 1.00% of them. In less than 25 days, patients in group I had a 50.0% probability of survival during this waiting time, while those in group II, more than 50.0% were still alive in 180 days.

The overall probability that the time between diagnosis and treatment was greater than 60 days was 0.5493 [95%CI:(0.5338;0.5653)]. The probability for group I was 0.3804 [95%CI:(0.3584;0.4037)] and for group II it was 0.7197 [95%CI:(0.6985;0.7414)].

Figure 2 shows the survival curves by group and sex.

Distinct survival curves per sex can be seen in groups I and II, better for females, except in group II after approximately 120 days, where an inversion occurred. In general, the survival of patients in group I in nearly 25 to 30 days drops to 50.0% while waiting for the oncological diagnosis, more pronounced in males and, even lower, around 20 days, for those in group I while awaiting treatment.

The analysis of treatment and recurrence rate for both groups was statistically significant ($p < 0.001$) between the doctor visit and the diagnosis, but not for sex ($p = 0.7396$ for group I and $p = 0.9028$ for group II).

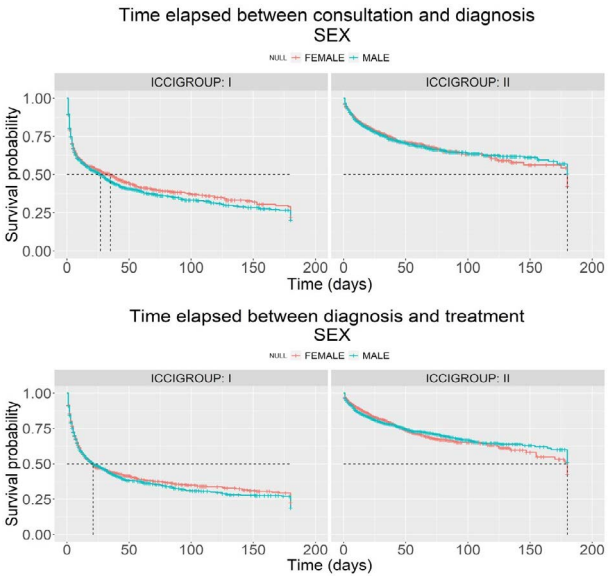

Figure 2. Survival curve of patients in relation to the time elapsed between doctor visit and diagnosis, and between diagnosis and initiation of treatment, by gender

Captions: myeloproliferative leukemias and myelodysplastic diseases (ICCI group I); lymphomas and reticuloendothelial neoplasms (ICCI group II).
Note: FOSP[19].

Chemotherapy was the most common treatment for 8,202 (68.20%) patients of both groups, followed by the combination of radiotherapy plus chemotherapy for 1,474 (12.30%), 1,323 (11.00%) in different combination of treatments, 424 (3.50%) for surgery plus chemotherapy, 116 (1.00%) for surgery plus chemotherapy and radiotherapy, 85 (0.70%) for surgery, 3 (0.00%) for surgery plus radiotherapy, chemotherapy and hormone therapy and 5 (0.00%) for surgery plus radiotherapy carried out in a hospital. A considerable number of patients, 349 (2.90%), in the cutoff period.

When the time between diagnosis and beginning of the most common treatment is analyzed separately for the leukemia group, without considering clinical staging, the median waiting time to start chemotherapy was 17 days (0.5218;0.4790) for radiotherapy plus chemotherapy, 34 days (0.5889;0.4283) and 44 days (0.5497;0.4552) for other combination of treatments. More than 18.73% [95%CI:(0.2285;0.1536)] of the patients waited more than 180 days to start chemotherapy, 23.72% [95%CI:(0.3670;0.1534)] for radiotherapy plus chemotherapy and 25.20% [95%CI:(0.3230;0.1966)] for other combinations of treatment.

For the lymphoma group, the same analysis – separate analysis of the time between diagnosis and most common treatment – revealed that the median waiting time to start chemotherapy was 125 days (0.5682;0.4533), 178 days (0.6476;0.4026) for other combinations of treatment. In general, 39.52% [95%CI:(0.4928;0.3169)] of the patients treated with chemotherapy waited more than 180 days, 64.34% [95%CI:(0.8326;0.4971)] for those treated with radiotherapy plus chemotherapy and 39.05% [95%CI:(0.5569;02738)] for other combinations of treatment.

Figure 3 shows the survival curve of groups I and II while waiting to start the treatment.

The survival curve of the patients while waiting for the beginning of the treatment was different in the two groups, with a worse survival profile for patients in group I (leukemia). In group I, for those who needed chemotherapy alone, the survival dropped 50% in less than 25 days, in less than 30 days for the combination of radiotherapy and chemotherapy, and in less than 50 days for other combination of treatments. For group II (lymphomas), the survival for 50.0% of the patients undergoing chemotherapy alone was greater than 125 days and greater than 180 days for more than 75.0% of patients undergoing the combination of radiotherapy with chemotherapy and for more than 50.0% of those who received other combinations of treatment.

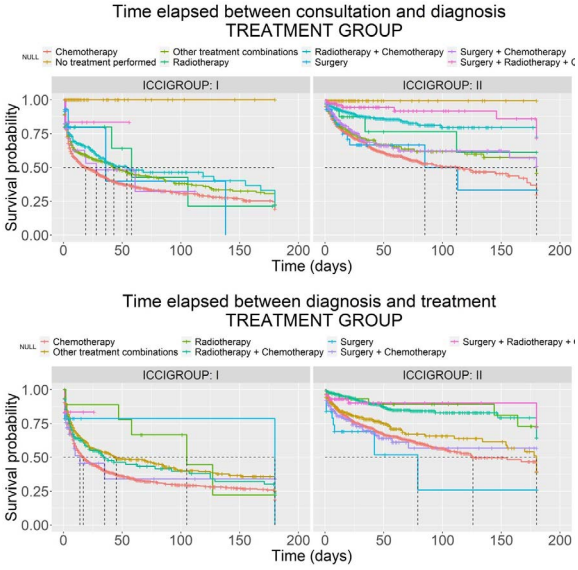

Figure 3. Survival curve of patients in relation to the time elapsed between the doctor visit and the diagnosis, and between the diagnosis and initiation of treatment, by groups of neoplasms and treatments performed

Captions: myeloproliferative leukemias and myelodysplastic diseases (ICCI group I); lymphomas and reticuloendothelial neoplasms (ICCI group II).
Note: FOSP[19].

The Peto-Peto test was significant for the waiting time between the diagnosis and the beginning of the treatment of the patients when analyzing the treatment and disease recurrences ($p < 0.001$), but not significant by sex ($p = 0.3732$ for group I and $p = 0.4201$ group II).

On the other hand, the survival curves of the patients submitted to surgery, a barely used strategy, dropped significantly for patients with lymphomas.

The data of the variable treatment between the two groups is shown in Table 1.

The waiting time between the doctor visit and diagnosis was statistically significant (p = 0.002) after analyzing its impact on treatments of group I (leukemia) comparing chemotherapy alone with other treatments and chemotherapy with radiotherapy (p = 0.002) different than group II (lymphomas), where the time impacted more other therapies (Table 1).

The waiting period between diagnosis and treatment, when comparing the treatments, was not statistically significant in the leukemia group, but surgery was not statistically significant only compared to surgery and chemotherapy for the lymphoma group (p = 0.826) (Table 1).

However, 11,088 (92.2%) patients had no local recurrence, 11,854 (98.5%) had no regional recurrence, and 11,976 (99.65) had no distant recurrence. Of those with local recurrence, the curves showed different behaviors, with more pronounced drops for leukemias. In the upper quadrants, when analyzing the influence on patient survival and local recurrences, the neoplasms in group I tended to appear earlier, reaching 25.0% in nearly 10 days (Figure 4).

Table 1. Multiple comparisons between the ICCI groups (I and II), at different times (Doctor visit - Diagnosis; Diagnosis - Treatment) for the treatments performed (n = 12,030). São Paulo, 2023

Variables	Surgery	Surgery + Chemotherapy	Surgery + Radiotherapy + Chemotherapy	Other treatment combinations	Chemotherapy	Radiotherapy
Doctor visit Diagnosis – ICCI – Group I						
Surgery + Chemotherapy	0.6992	-	-	-	-	-
Surgery + Radiotherapy + Chemotherapy	0.8348	0.5761	-	-	-	-
Other treatment combinations	0.8666	0.8348	0.5761	-	-	-
Chemotherapy	0.6992	0.8348	0.4202	0.0022*	-	-
Radiotherapy	0.9445	0.8348	0.8348	0.8666	0.6992	-
Radiotherapy + Chemotherapy	0.9526	0.6992	0.6757	0.4829	0.0002*	0.9526
Doctor visit Diagnosis – ICCI – Group II						
Surgery + Chemotherapy	0.4177	-	-	-	-	-
Surgery + Radiotherapy + Chemotherapy	0.0001*	0.0002*	-	-	-	-
Other treatment combinations	0.5701	0.4866	0.0001*	-	-	-
Chemotherapy	0.9451	0.0445*	0.0000*	0.1576	-	-
Radiotherapy	0.1766	0.4177	0.1494	0.3145	0.1494	-
Radiotherapy + Chemotherapy	0.0002*	0.0000*	0.1894	0.0000*	0.0000*	0.4342
Diagnosis- Treatment ICCI – Group I						
Surgery + Chemotherapy	0.7722	-	-	-	-	-
Surgery + Radiotherapy + Chemotherapy	0.8526	0.7722	-	-	-	-
Other treatment combinations	0.9434	0.6180	0.8326	0.7722	-	-
Chemotherapy	0.7722	0.8326	0.7722	0.8526	0.7722	-
Radiotherapy	0.8326	0.6223	0.8326	0.9434	0.6180	0.8326
Radiotherapy + Chemotherapy	0.8326	0.7620	0.8326	0.7722	0.8326	0.7722
Diagnosis- Treatment – ICCI - Group II						
Surgery + Chemotherapy	0.0826	-	-	-	-	-
Surgery + Radiotherapy + Chemotherapy	0.0005*	0.0076*	-	-	-	-
Other treatment combinations	0.0108*	0.1362	0.0277*	-	-	-
Chemotherapy	0.0040*	0.1032	0.0169*	0.2410	-	-
Radiotherapy	0.0075*	0.0286*	0.9070	0.0299*	0.0112	-
Radiotherapy + Chemotherapy	0.0000*	0.0000*	0.4835	0.0000*	0.0000*	0.7110

(*) Benjamini-Hochberg test[17].

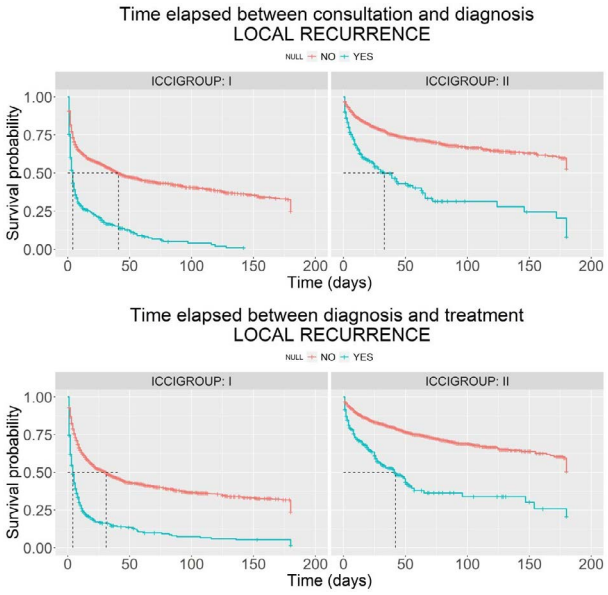

Figure 4. Comparative analysis between the time elapsed between first visit and diagnosis and between diagnosis and treatment according to local recurrence by neoplasm group

Captions: myeloproliferative leukemias and myelodysplastic diseases (ICCI group I); lymphomas and reticuloendothelial neoplasms (ICCI group II).
Note: FOSP[19].

According to the last update, 6,264 (52.1%) of the patients were alive, without evidence of the disease, 2,134 (17.7%) were alive with cancer, 3,239 (26.9%) had died due to cancer and 393 (3.3%) for other causes.

DISCUSSION

In this study, 12,030 (100.0%) cases of neoplasms for groups I (leukemias) and II (lymphomas) were analyzed, predominantly in males (58.1%), similar to national and international studies. A study with a similar population[20], where 92,085 patients with leukemias and 33,273 with lymphomas were analyzed, showed that the incidence was slightly higher in males and this difference is greater in a certain age group.

In relation to leukemias, there was predominance of diagnosis of lymphoid leukemias (4,991, 41.5%), followed by acute myeloid leukemias/acute non-lymphocytic leukemias (1,755, 14.6%), corroborated by the literature. According to a study that analyzed different leukemias, the authors observed a higher prevalence of cases of lymphoid leukemia, followed by acute myeloid leukemia[21]. Burkitt's lymphoma (1,360, 11.3%) (Table 1), data that are convergently related to the findings in the international literature[22].

In relation to the FU of birth and origin, these data are corroborated by a national study that analyzed cancer care among children and adolescents and the origin-destination flow between the FU of birth and residence[23]. The authors showed that six out of 10 children are assisted locally, especially in the states of São Paulo and Minas Gerais, and most of them had access to medical assistance in the same health regions where they lived.

The highest percentage of attendance was found in DRS 01 (Greater São Paulo) with 4,309 (41.2%) patients, followed by DRS 07 (Campinas) with 1,192 (11.4%) and DRS 17 (Taubaté) with 779 (7.5%) patients. These data show the strategic importance of the DRS and its correlation with patient travel flows. However, a study that mapped these flows showed that around 15.0% of the origin-destination displacement takes place outside the State of São Paulo, indicating that these flows need to be better studied and understood[23].

Overall, the median was 82 days, 29 days for group I (leukemias) and 180 days for group II (lymphomas). According to a study carried out in the State of Paraíba[24] with 0-19 years 104 children with hematologic malignancies, the waiting in average was 6.1 days (± 9.5). Both the sample size and the coverage of the service network may have caused this difference.

The drop of survival curves of leukemia shown in Figures 1 and 2 was more pronounced, showing that 50.0% of patients were not alive after nearly 25 days. For lymphomas, the drop was less pronounced and in 180 days, more than 50.0% of patients were still alive. The analysis involved all the patients with leukemias and lymphomas, without discriminating the subtypes of the diseases or clinical staging.

In less than 25 days, patients in group I had a 50.0% probability of survival in the cutoff period while those in group II in the same period, more than 50.0% were still alive. In a study that analyzed the epidemiological profile of children and adolescents assisted at a reference center in the west of the state of Pará, the most frequent neoplasms were leukemias, the waiting time between the onset of symptoms and the diagnosis was from one to two months and, for the start of treatment, an average of 15 days[25], different from the present study, according to the scope of the investigation.

The causes of delay in diagnosis and treatment of patients were not explored in this study. Additional information about the appearance of the first signs and symptoms, access to health services as well as referrals within the health system should be addressed in other studies[26]. More specific interventions can be implemented. The overall probability of the time between the doctor visit and the diagnosis greater than 30 days was 61.65% and between the diagnosis and treatment greater than 60 days was 54.93%, possibly indicating that many patients wait longer than the time frame determined by the current

legislation in the State of São Paulo. Understanding where the greatest delay occurs is relevant for an assessment of the Care Network for these patients.

These data reflect serious implications in the short, medium and long term, since the longer the delay in terms of early detection of the neoplasm, from doctor visit and diagnosis and its relationship with local recurrence of the tumor (progression or non-progression of the neoplasm), lower are the chances of cure[27].

In a study published in 2022[28], 74.0% of children and adolescents between 0 and 19 years of age underwent treatment early, that is, before the maximum period stipulated by the current legislation[8]. And, in another national study[29], it was shown that age-adjusted mortality rates presented a tendency towards stability throughout the country.

Delays in starting cancer treatment were also observed in developed countries as Canada, as the mean time from the onset of the first signs and symptoms to start the treatment was 173 days[30]. Despite the time gap, it is important to emphasize that the delay in starting treatment is decisive in having a major impact on the course of the treatment that the patient will undergo, as well as on their morbidity and mortality rates[31]. In another study, 25.0% of children and adolescents with hematological malignancies (leukemias and lymphomas) died, 1.0% before starting treatment[32].

The findings regarding the choice of chemotherapy as the first line of treatment is a reality in treatment protocols for both leukemias and lymphomas, when compared with surgery, radiotherapy and the combination of other therapeutic approaches[33].

For patients who did not submit to treatment in the cutoff period, the probability of survival was higher in both groups (Figure 3). Among leukemias, there was no significant difference between the treatments, which showed a better survival curve and for lymphomas, surgery was not significant only in relation to the combination of surgery and chemotherapy, with worse survival curves.

Survival of patients in group I is lower than in group II, regarding the time between diagnosis and initiation of treatment (Figure 3). A study published in 2022 showed that mortality rates by leukemia remained stable from 2001 to 2019 and, for lymphomas, important reductions in the age group from 0 to 20[34] were found. In another study, it was observed that there was a significant reduction in the percentage of mortality by leukemia and lymphomas in children and adolescents between 1980 and 2015[35].

It is known that the initiation of cancer treatment and, consequently, its continuation will determine the quality of life over time, in addition to interfering with the risk of relapses and the refractoriness of the disease[36]. The delay in therapy can happen due to several factors, as uncertainty of the diagnosis, waiting time for the first consultation with an oncologist and decentralization of care which entails intercity or interstate travel and referrals to specialized counter-referral services[37].

One of the study biases was the sampling, since only part of the population was investigated. Another bias of sampling since not all institutions that treat pediatric cancer patients in the state are registered. And the years 2017, 2018, 2019, 2020, 2021 and 2022 still have ongoing cases, according to FOSP and are subject to periodic update.

The present study is characterized by certain limitations inherent to its characteristics, susceptible to various biases. Some institutions enter information about a year late, which can lead to errors in interpreting the data presented, such as the type of treatment performed, and interfering with the survival curves.

The possibility of families changing residence to be near the center providing pediatric treatment introduces a potential source of bias. Furthermore, the geographic distribution of technological resources and the capacity the system has to solve this issue may have significantly influenced the results.

The inaccuracy in residence addresses can impact the reliability of data, especially for assistance. Although many important information can be found at the databases, more precise information as hematological cell count at diagnosis, type of treatment with medications or combinations used in each stage of the disease would contribute for a more accurate portrait of oncological treatment.

CONCLUSION

The patient survival curves were different for the two groups. Patients in group I (leukemias) had a survival probability of 50.0% in nearly 25 days, while group II (lymphomas), 50.0% were alive in 180 days (censored).

The probability that the time between doctor visit and diagnosis exceeded 30 days was 0.4929 [95%CI:(0.4733;0.5133)] for the leukemia group and 0.7631 for the lymphoma group [95%CI:(0.7452;0.7813)]. This difference was significant when analyzing treatment and disease recurrences for both groups ($p < 0.001$).

The probability that the time between diagnosis and treatment exceeded 60 days was 0.3804 [95%CI:(0.3584;0.4037)] for the leukemia group and, for the lymphoma group, of 0.7197 [95%CI:(0.6985;0.7414;)] a significant difference when treatment and disease recurrences ($p < 0.001$) were analyzed.

None of the periods analyzed (consultation and diagnosis and between diagnosis and treatment) showed statistical significance for sex in both groups.

These data show that there is a considerable percentage of patients with leukemias and an even greater number of patients with lymphomas waiting more time than expected. However, the waiting time may be essential for the outcome of cancer treatment and the findings show that they failed to comply with the current legislation, even in a State with a structured oncology care network.

Chemotherapy was the treatment of choice for 8,002 patients (66.5%), still the first option for different phases of treatment of leukemias and lymphomas.

Part of the research was carried out in the state of São Paulo, where there is a concentration of specialized oncological services and diagnostic support and high technological density (hard technologies). Even in this scenario, it is necessary to review the patients' flow at different levels of complexity of the Health Care Network. Furthermore, the flow should be based on early recognition of the main critical signs and symptoms and differences of the natural course of the neoplastic disease.

Complementary studies evaluating economic, social and technological indicators offered by the Oncology Network can contribute to achieve better survival rates for patients with pediatric cancer, as they would map critical topics for more specific and relevant interventions.

CONTRIBUTIONS

Pedro Emílio Gomes Prates and Ricardo Alexandre Arcêncio contributed to the study design, acquisition, analysis and/or interpretation of the data, wording and/or critical review. Jonas Bodini Alonso and Emília Campos de Carvalho contributed to the acquisition, analysis and/or interpretation of the data, wording and/or critical review. All the authors approved the final version to be published.

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DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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