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ORIGINAL ARTICLE

OVERALL SURVIVAL IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH PROTOCOL CALGB 9511 AT A TERTIARY HOSPITAL IN THE NORTHEAST OF BRAZIL

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ABSTRACT

Introduction: Acute lymphoblastic leukemia (ALL) is the most common neoplasm in childhood and has high survival rates. In adults, due to the biological characteristics of the disease and chemotherapy-related toxicity, survival is lower. CALGB 9511 is a chemotherapy protocol based on pediatric regimens with high remission rates after induction. **Objectives**: To evaluate the survival of patients with ALL undergoing the CALGB 9511 protocol at Walter Cantídio University Hospital (HUWC); to describe the impact of risk factors: presence of measurable residual disease, BCR-ABL fusion gene status, and allogeneic bone marrow transplant (BMT) on the survival of this group. **Methodology**: Retrospective evaluation of medical records of patients with ALL treated with this protocol between 2011 and 2022. Statistical analysis was performed using the Kaplan-Meier method to estimate survival probability. **Results**: 79 patients were eligible; 19% were BCR-ABL positive; the mean 2-year overall survival was 44%; The 2-year survival rate for patients undergoing HSCT was approximately 78%.. **Conclusion**: The survival curves of the study conducted at HUWC are similar to those described in the literature and corroborate the severity of the disease. Accessibility to new therapeutic modalities is a strategy that can improve the survival of these patients.
Keywords: Leukemia. Disease. Drug Therapy.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common hematologic neoplasm in childhood, with an overall five-year survival rate of approximately 90%. Survival in adults is lower due to the biological characteristics of the disease itself and the toxicity of chemotherapy regimens.[1,2,3]

Multiple induction regimens have been developed for the treatment of ALL in adults, many of which are based on pediatric protocols that include the use of corticosteroids, anthracyclines, alkylating agents, asparaginase, and central nervous system prophylaxis.[4,5,6]

Around 80% of patients undergoing intensive induction regimens achieve complete remission, however more than half will experience disease recurrence during or after chemotherapy, leading to reduced overall survival. Risk stratification is essential to define which patients should be referred to a specialized bone marrow transplant center after the first remission.[7]

The CALGB 9511 protocol was developed based on intensive pediatric regimens. This protocol is divided into the phases of Induction, Intensifi-

cation, Central Nervous System Prophylaxis, and Maintenance. The results demonstrated high rates of complete remission after Induction and progression-free survival, especially in younger patients without comorbidities[8].

The treatment of ALL in adults remains challenging, particularly within the public health system. Early access of patients to a specialized oncology-hematology center, with support for possible complications during treatment and adequate infrastructure, are still obstacles to be overcome.

This retrospective study aims to report the outcome of adult patients with ALL treated with the CALGB 9511 protocol at an oncology-hematology center in the state of Ceará.

MATERIALS AND METHODS

Study design and patients

This is a descriptive retrospective observational study aimed at evaluating the group of patients diagnosed with Acute Lymphoblastic Leukemia treated at the Hematology Service of Walter Cantídio University Hospital (HUWC-UFC). Adult patients aged 18 years or older diagnosed with Acute Lymphoblastic Leukemia were evaluated from March 1, 2011, to December 31, 2022. Patients under 18 years of age, diagnosed with biphenotypic acute leukemia or mixed lineage leukemia, and those with a previous diagnosis of Chronic Myeloid Leukemia were excluded from the study.

High-risk criteria were based on the CALGB 8811 protocol. High-risk patients were those with a white blood cell count greater than 30,000/mm^3 for ALL-B and greater than 100,000/mm^3 for T lineage; age greater than 35 years, BCR-ABL positive, and complex karyotype (more than 3 chromosomal alterations).

Indications for allogeneic bone marrow transplantation were high-risk ALL and patients with relapsed ALL.

Disease assessment

The definition of ALL was based on the 2016 WHO classification. Lineage identification was performed through flow cytometry. BCR-ABL analysis was conducted by PCR, and karyotype analysis was performed through classical cytogenetics in Giemsa.

Patients in complete remission after induction had <5% blasts in bone marrow aspirate. Measurable residual disease (MRD) was assessed at the end of induction by flow cytometry in BCR-ABL negative ALL patients and by flow cytometry and PCR in BCR-ABL positive ALL.

Statistics

For descriptive statistics, the mean, median, and standard deviation were calculated for continuous quantitative variables, and relative and absolute frequency were calculated for qualitative variables. Data analysis was performed using the R program. Results with $p < 0.05$ were considered statistically significant. Survival probability estimation was conducted using the Kaplan-Meier method, and a log-rank test was performed to compare the observed differences between the survival curves of the groups.

RESULTS

Between March 2011 and December 2022, a total of 79 patients were eligible (Table 1). The average age at diagnosis was 36 years, with 48.1% (38/79) being female and 51.9% (41/79) being male. Regarding the immunophenotype at diagnosis, 82.3% (65/79) had markers defining them as B-lineage, and 17.7% (14/79) were classified as T-lineage.

As for the mutational status of BCR-ABL, analyzed only in acute lymphoblastic leukemias of B-lineage, 50.6% (40/79) did not have the fusion gene, and 19% (15/79) tested positive for the gene in question. Additionally, 30.4% (24/79) did not undergo mutational status evaluation due to reasons such as early death or unavailability of molecular biology assessment at the time. Of the patients, 69% (55/79) were classified as high-risk ALL, and 30.4% (24/79) as standard-risk.

After the completion of induction chemotherapy, during the follow-up assessment with bone marrow aspiration, 78.5% (62/79) were in remission, and 21.5% (17/79) were refractory or had early death. Among those who achieved remission, 14.8% (9/62) had positive measurable residual disease post-induction, and 41% (25/69) had negative MRD; 10.1% of patients (8/69) had central nervous system infiltration at diagnosis or during the course of treatment.

Of the patients who achieved remission after induction chemotherapy (Table 2), 45.2% (28/62) experienced disease recurrence during treatment (relapse), and 31.6% (27/79) of patients underwent bone marrow transplantation.

Regarding the primary outcome (Table 2), 65.8% (52/79) deceased and 34.2% (27/79) survived. The overall survival at 2 years was 44% (95% CI 0,34 – 0,56), and the median survival was 1.4 years (Figure 1). Progression-free survival at 1 year was 67.3%

(95% CI 0.575 – 0.787) and at 2 years was 40.1% (95% CI 0.302 – 0.532) (Figure 2).

Regarding the secondary outcome, the median survival of patients diagnosed as having the BCR-ABL positive gene showed a survival rate above 75%, while BCR-ABL negative patients had a median survival of 19.9 months (p=0.06) and an overall survival at 2 years of 50% (Figure 3).

The probability of survival at 2 years for patients undergoing allogeneic bone marrow transplant was 78% (95% CI 0.62 – 0.97), while for those who were not transplanted, it was 27,5% (95% CI 0,17 – 0,43) (Figure 3). Regarding the reasons for not undergoing transplantation, 73% of patients were due to treatment refractoriness, 6% due to being classified as standard risk, 4% due to patient's preference, 8% due to lack of a donor, and 9% due to clinical comorbidities contraindicating the procedure.

The presence of measurable residual disease was assessed after 100 days post-transplant, with negative results in 29,6% of patients, positive in 3.7%, inconclusive in 7.4%, not performed due to early post-transplant relapse in 11.1%, and not performed due to unavailability of the test in the facility in 48,2%.

DISCUSSION

Acute lymphoblastic leukemia is the most common cancer in children, with survival rates exceeding 90%. Beyond this age range, adolescents and young adults have poorer outcomes compared to the pediatric population, with a five-year overall survival between 54% and 74%. The use of pediatric protocols has improved survival rates; however, in older adults, outcomes remain discouraging, with cure rates below 20%.This is possibly due to increased therapy-related toxicity, leading to dose reductions and treatment delays. Additionally, adverse genetic risk characteristics are more common in this population, resulting in shorter remissions and frequent relapses.[1,2,3]

The CALGB protocol is based on pediatric regimens and includes high doses of glucocorticoids, asparaginase, and vincristine, along with frequent central nervous system prophylaxis. Conventional protocols for adults use more myelosuppressive drugs, and central nervous system prophylaxis is delayed. When compared to traditional protocols, CALGB shows a median event-free survival of 78.1 months versus 30 months and a three-year overall survival of 73% (95% CI, 68%-78%) in patients under 30 years old.[1,2,3]

In this study, patients diagnosed with ALL and undergoing chemotherapy at a tertiary hospital in Northeast Brazil were evaluated. Regarding the primary outcome, the overall survival at 2 years was 44% with a median survival of 1.4 years. These results confirm the severity of the disease and the more unfavorable prognosis in patients over 50 years old, where overall survival is reduced to less than 25%. The two-year progression-free survival was 40%, which is comparable to other historical cohorts in the literature, confirming that despite high rates of remission post-induction, the incidence of relapse during treatment remains high, leading to a worse prognosis in those patients who relapse.[9,10]

Risk factors such as age, leukocyte count, complex karyotype, and some genetic alterations, such as the BCR-ABL fusion gene status, are known markers of poor prognosis. The Philadelphia chromosome t(9;22) is present in approximately 25 to 30% of ALL cases in adults. Historically associated with adverse prognosis, the development of targeted therapies such as tyrosine kinase inhibitors (TKIs) has resulted in prolonged remissions in young adults and older patients, negating their adverse prognosis.[1,2,3] In this study, the two-year overall survival of BCR-ABL positive ALLs was above 75%, while that of BCR-ABL negative ALLs was below 50%, with a median survival of 19.9 months, corroborating with the most current literature data even when using first-generation tyrosine kinase inhibitors (Imatinib) due to the difficulty of accessing second or third-generation TKIs.

Central nervous system infiltration in ALL is common both at diagnosis and relapse and indicates a worse prognosis. Pediatric protocols tend to perform central nervous system prophylaxis earlier to reduce the incidence of this event, preventing future CNS relapses. Central nervous system prophylaxis in this study was administered to 68.4% of patients, an important step in the treatment course and a pre-transplant strategy due to the unavailability of total body irradiation as pre-HSCT conditioning.

Despite the emergence of new targeted therapies, bispecific antibodies, and CAR-T cells, allogeneic bone marrow transplantation remains an important tool for durable remissions and cure in ALL, especially in a scenario of unavailability of these new therapies within the public healthcare system.

Indications for allogeneic transplantation in first remission vary according to the literature. Measurable Residual Disease positivity is one of the main prognostic markers currently and is the main transplant indicator in first remission. MRD post-induction is

related to long-term survival, and MRD post-consolidation is related to early relapse and chemotherapy refractoriness. At Walter Cantídio University Hospital, the transplant service is linked to the hematology service, allowing for communication and facilitated access to patients who are candidates for transplant in the service.

In this study, the overall survival of patients undergoing HSCT was compared to those who did not undergo this consolidation therapy. Our results showed a survival rate above 75% in the HSCT arm and approximately 25% in those who did not undergo transplantation. This strengthens the need for early referral of patients in first remission for evaluation by the transplant team and the search for alternative donors in the absence of matched donors.

Access to healthcare in the public service in developing countries like Brazil, especially in the Northeast region, is still precarious. Difficulty in obtaining medical care, particularly in rural areas, is still a reality, and many patients receive specialized care late, contributing to delayed diagnosis, early death, and poorer outcomes compared to first-world countries.

The results in this study were comparable to other historical cohorts, confirming the impact of using pediatric protocols on the survival of patients with ALL and better survival after the development of targeted therapies for BCR-ABL positive ALL patients. Allogeneic HSCT is an important consolidation tool, reducing mortality and increasing the chances of cure for these patients.

Despite many advances, such as increased access to measurable residual disease testing, which is a known important prognostic factor, there are still obstacles to be overcome: the difficulty of conducting comprehensive mutational profiling to identify characteristics of higher risk that may predict non-response to induction chemotherapy or early relapse, the availability of hematological beds for adequate treatment, and access to new drugs, especially in the setting of refractory disease.

CONCLUSION

Significant progress has been made in the treatment of ALL. Treatment in the public health system in developing countries remains challenging due to difficulties in accessing specialized services, bed availability, and access to new therapies. The results of this study reinforce the severity of the disease and the need for increased resources that can lead to improved survival in this patient population.

TABLE 1: Baseline characteristics of study patients. (Data expressed as absolute frequency (n) and relative frequency (%) for categorical variables and mean, standard deviation, and range for quantitative variables)

VARIABLES	N(%)
Age	36 ± 15 (33)*
Sex	
Female	38 (48,1%)
Male	41 (51,9%)
Risk Stratification	
High	55 (69,6%)
Standart	24 (30,4%)
Immunophenotype	
B ALL	65 (82,3%)
T ALL	14 (17,7%)
BCR-ABL	
Negative	40 (50,6%)
positive	15 (19%)
Not avaliable	24 (30,4%)
Karyotype	
Complex	10 (12,6%)
Hypoploidy	1 (1,2%)
Hyperploidy	1 (1,2%)
Normal	6 (7,6%)
Not performed	61 (77,2%)
***Mean ± Standard Deviation (Median); n (%); Range**	

TABLE 2: Summary of Primary Outcome (Data presented as absolute frequency (n) and relative frequency (%) for categorical variables)

VARIABLES	N(%)
Remission post-Induction	
Yes	62 (78,5%)
No	17 (21,5%)
MRD post-induction	
Positive	9 (14,5%)
Negative	25 (40,3%)
Not performed	28 (45,2%)
Central Nervous System Prophylaxis	
Yes	54 (68,4%)
No	9 (11,4%)
Not performed due to early demise	16 (20,3%)
Central Nervous System Infiltration	
Yes	8 (10,1%)
No	71 (89,9%)
Relapse	
Yes	28 (45,2%)
No	34 (54,8%)
Bone Marrow Transplant	
Yes	27 (31,6%)
No	14 (20,3%)
Not due to therapeutic refractoriness	38 (48,1%)
MRD D+100	
Inconclusive	2 (7,4%)
Positive	1 (3,7%)
Negative	8 (29,6%)
Not performed due to early demise	3 (11,1%)
Not available	13 (48,2%)
Decease	
Yes	52 (65,8%)
No	27 (34,18%)
Decease post-HSCT	
Yes	10 (37%)
Due to post-HSCT relapse	4/10 (40%)
Infeccion	5/10 (50%)
Other causes	1/10 (10%)
No	17 (63%)

FIGURE 1: **Overall survival at 2 years for patients with ALL undergoing protocol CALGB**

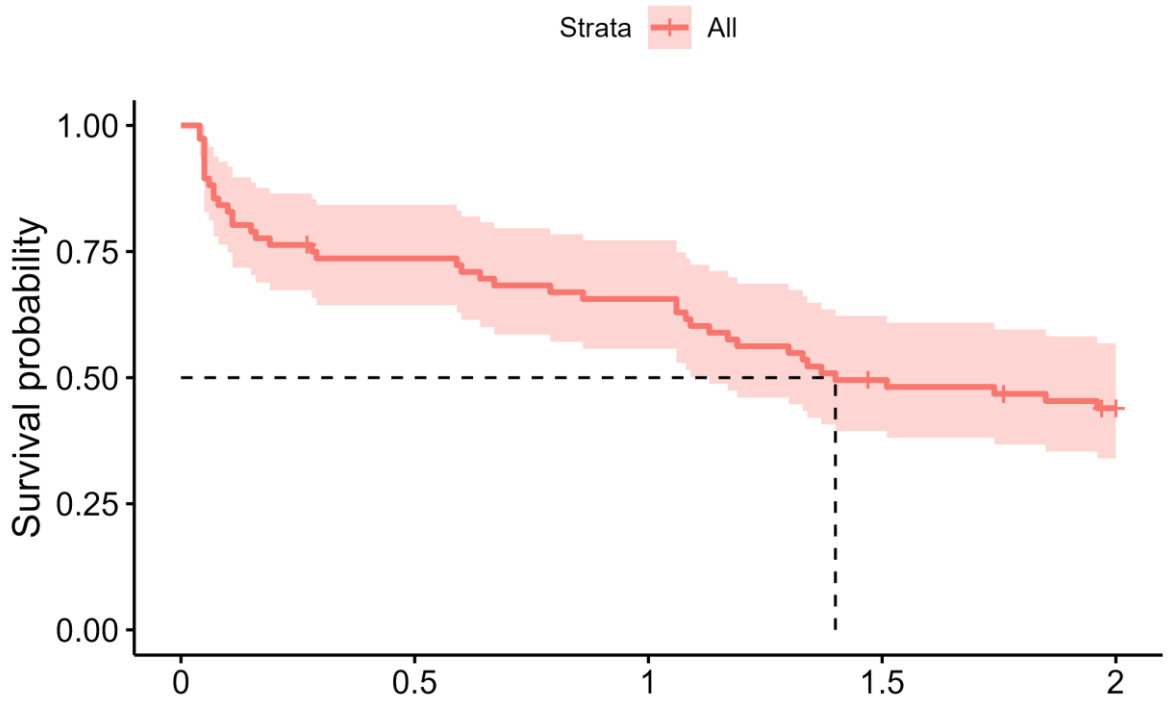


FIGURE 2: **Progression-free survival at 2 years**

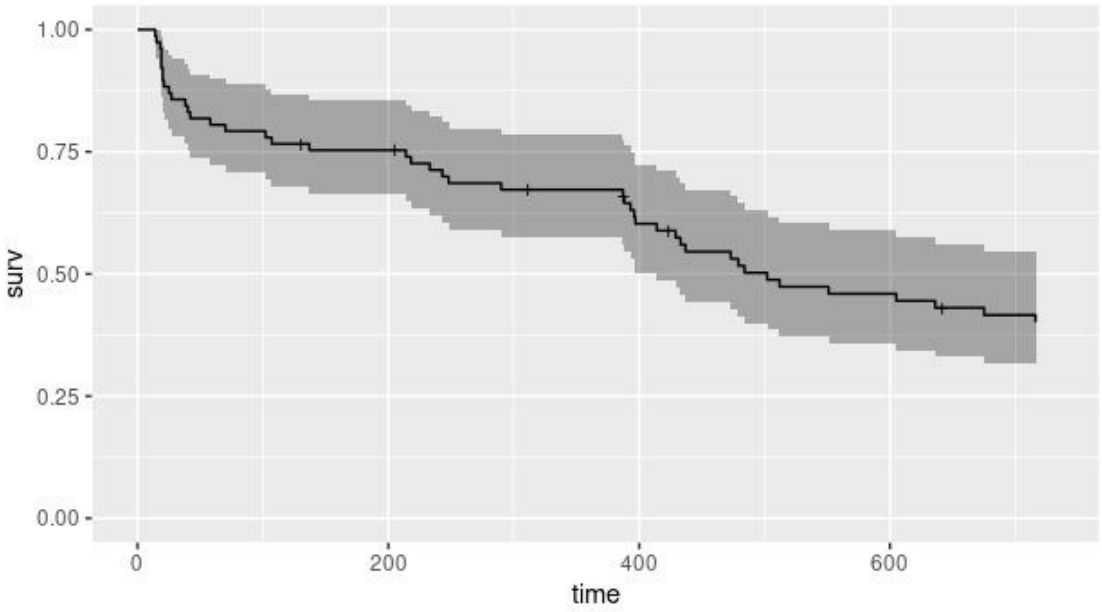


FIGURE 3: Probability of survival according to BCR-ABL fusion gene mutational status

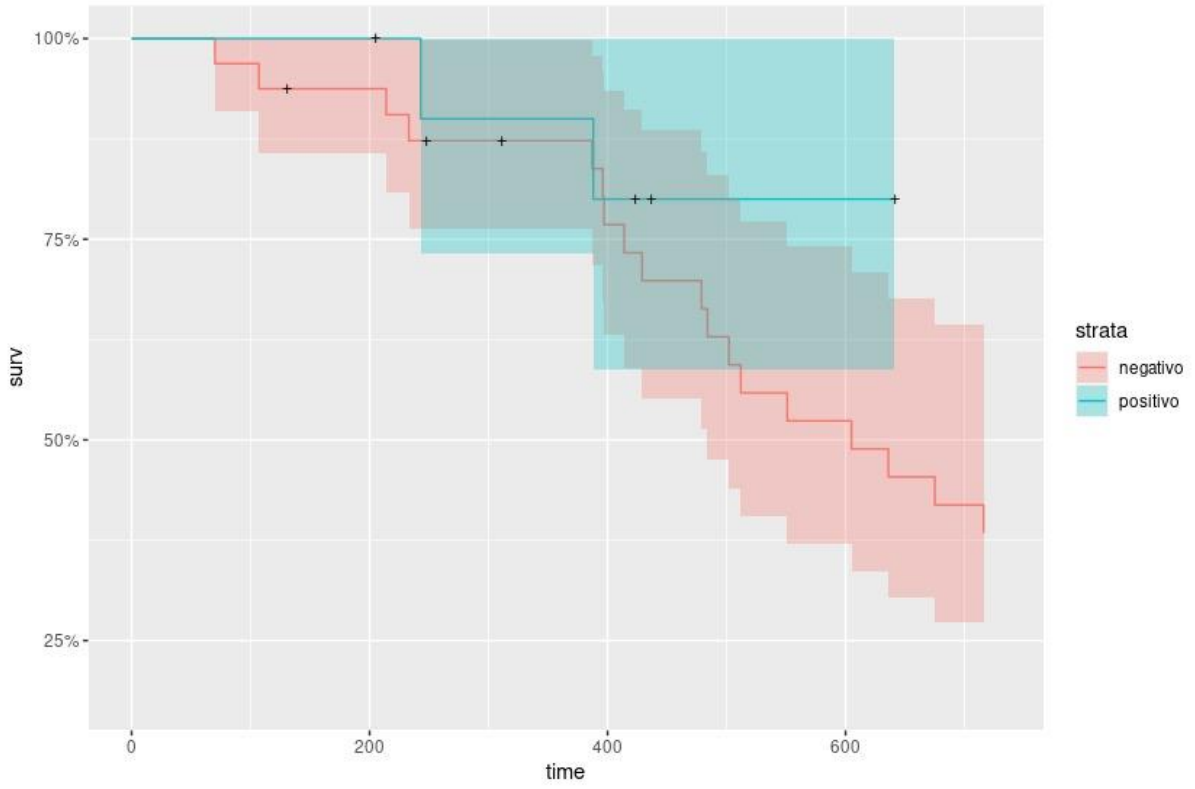
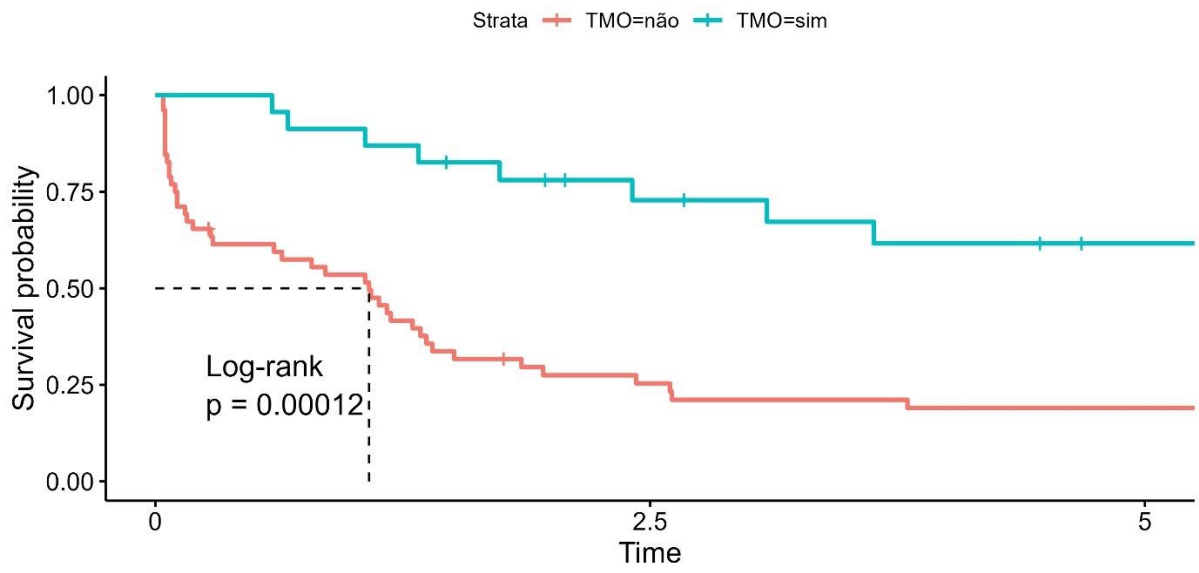


FIGURE 4: Overall survival in patients undergoing HSCT



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