ORIGINAL ARTICLE

DOI: 10.46765/2675-374X.2024V5N2P245

10-YEAR REAL-WORLD DATA ON ACUTE MYELOID LEUKEMIA: THE PARADIGM OF A PUBLIC HEALTH CENTER IN BRAZIL

Camilla Campos[1] - ORCID: https://orcid.org/0000-0002-5172-192X
Alini Maria Orathes Ponte Silva[1] - ORCID: https://orcid.org/0009-0001-4864-2112
Felipe Feistauer[1] - ORCID: https://orcid.org/0009-0004-9786-0134
Lais Teixeira da Silva[1]- ORCID: https://orcid.org/0000-0003-0672-0079
Marco Aurélio Salvino[1] - ORCID: https://orcid.org/ 0000-0001-5885-869X
Thiago Favano[2] - ORCID: https://orcid.org/ 0000-002-3927-2025

1 Federal University of Bahia
2 Mink Therapeutics, USA

Corresponding author: Camilla Campos (e-mail: camillacorreiap@gmail.com)

Received: 03 Sep. 2024 • Revised: 17 Sep. 2024 • Accepted: 16 Oct. 2024.

ABSTRACT

Introduction: Despite advances in Acute Myeloid Leukemia (AML) diagnosis and treatment, the outcomes in low- and middle-income countries (LMIC) are far apart from those in high-income countries (HIC). **Objective:** To describe the clinical features and outcomes of AML patients in Brazil's public health system, we conducted a retrospective analysis of all cases of non-promyelocytic AML diagnosed within 10 years (2007- 2017) in northeastern Brazil, Bahia. **Methodology:** We analyzed the real-life outcomes of 62 patients diagnosed with non-promyelocytic AML between 2007 and 2017 at a university hospital in Northeast Brazil. We classified patients using the European LeukemiaNet 2022 guideline into favorable (n=8), intermediate (n=18), and adverse risk (n=7) groups. Twenty-nine were not otherwise classified because no cytogenetic and/or molecular tests were available at diagnosis. **Results:** Allogeneic bone marrow transplant (alloBMT) was performed in 16 patients (37%). Median overall survival (mOS) was seven months. Among patients receiving alloBMT, mOS was 49 months, while for the chemotherapy group, it was six months (P = 0.003). For 10-year real-life data, we found complete remission of 53%, 5-year OS of 27%, and a mortality rate during induction therapy of 27%, inferior to HIC. **Conclusion:** Inferior outcomes found in LMIC result from a multifactorial scenario and an unmet need in the worldwide panorama of AML.

Keywords: Leukemia, Myeloid, Acute. Leukemia. Developing Countries.

INTRODUCTION

Acute Myeloid Leukemia (AML) is the most frequent acute leukemia in adults, accounting for 80% of cases, and the incidence increases with age. AML originates from several genetic and epigenetic modifications in hematopoietic precursor cells, generating a clone of proliferating leukemic cells that do not differentiate in mature cells[1].

The pathogenic mechanisms associated with chromosomal and molecular modification in blast cells generated the European Leukemia Net (ELN) 2022 classification[2] based on parameters involving clinical and prognostic characteristics. According to molecular and cytogenetic profiles, AML is diagnosed into favorable, intermediate, and adverse-risk groups. Secondary AML (*s*AML), arising from a prior hematological condition or after chemotherapy for solid tumors, is a distinct subgroup involving the worst outcomes.

For many years, the treatment of Acute Myeloid Leukemia (AML) primarily relied on chemotherapy, hypomethylating agents, and bone marrow transplant (BMT), particularly allogeneic BMT (alloBMT) after relapse and based on risk stratification. Recently, however, the landscape has shifted with the advent of targeted therapies. Agents targeting FLT3, BCL2, IDH1, IDH2, and hedgehog pathways have notably improved treatment options[2]. These new therapies have shown promising results with reduced toxicity and have been explored both in initial treatment and in relapsed settings, used either as standalone treatments or in combination with other drugs.

The impact of targeted therapy on AML has been particularly transformative for specific patient groups. These include patients with adverse-risk profiles, secondary AML (sAML), and elderly patients who are often ineligible for intensive treatment due to their inability to achieve complete or long-term responses with conventional chemotherapy. With these advancements, there is a significant shift in the management and prognosis of these traditionally challenging cases of AML.

Novel exams and drugs are expensive and not readily available worldwide, especially in low and middle-income countries (LMIC) where distinct differences between private and public care are observed. Brazil is a country of continental size facing relevant socio-economic inequalities, especially in northern and northeastern regions. Three-quarters of the Brazilian population rely on the public health care system[3] and can only access novel treatments if included in clinical trials. Previous Brazilian data reported that up to half of the study subjects[1,4,5] could not be stratified using a comprehensive cytogenetic-molecular model (e.g., ELN). This scenario affects clinicians' ability to offer the best prognostic estimates to patients. In addition, decision-making involving therapeutic strategies and indication of allogeneic BMT in patients' first remission cases with missing prognostic data are equally affected.

To describe the clinical features and outcomes of AML patients in Brazil's public health system, we conducted a retrospective analysis of all cases of non-promyelocytic AML diagnosed within 10 years (2007- 2017) in northeastern Brazil, Bahia[6]. Our study is the first, to our knowledge, to look at the clinical features and outcomes of AML patients in this region.

METHODS

This retrospective single-center cohort was conducted at Professor Edgar Santos University Hospital from the Federal University of Bahia. All data collection followed the institutional ethical review committee (CAAE: 98938818.4.0000.0049).

The study population comprises patients older than 16 years diagnosed with non-promyelocytic AML in our center between January 2007 and December 2017. Each patient's data was collected from an internal database for ICD-10. A total of 62 patients were included. We used the ELN 2022 guideline for risk stratification adapted to the available data. Patients who did not perform molecular or cytogenetic tests were classified as unknown risk.

STATISTICAL ANALYSIS

Descriptive analyses were performed for patient baseline characteristics. Continuous variables were described as median and interquartile range (IQR) or mean and standard deviation (SD) according to a normal distribution. We used logistic regression for univariate and multivariate data analysis, assessing death as the outcome. The variables analyzed were age, sex, hemoglobin (Hb), white blood cell (WBC), platelets, splenomegaly, hepatomegaly, adenopathy, mucocutaneous involvement,

AML origin (de novo x secondary AML), risk stratification and alloBMT. The multivariate analysis included AML origin, risk stratification, and alloBMT as predictor variables.

Survival curves were estimated using the Kaplan-Meier method, and group comparisons using a log-rank test. The impact of BMT on the overall survival of patients eligible for intensive treatment was assessed using a Cox proportional hazards model.

Overall survival (OS) was defined as the timespan from diagnosis to death from any cause; those alive or lost to follow-up were censored at the date last known as alive. Early mortality was defined as death occurring within one year of diagnosis. Relapse-free survival (RFS) was defined as the time from complete remission (CR) to the first relapse. The overall response was considered CR, CR with incomplete hematologic recovery (CRi), and partial remission (PR). CR, CRi, and PR were based on ELN 2022 guidelines.

Statistical significance was set as p-value <0.05. Statistical analysis and modeling were performed in R version 4.1.0 and SPSS version 25.

RESULTS

A total of 62 patients were included, but one patient died of intracerebral hemorrhage before receiving any treatment. The median age at diagnosis of the total cohort was 44 (ranging from 16-83 years), and 42 patients (68%) were diagnosed with *de novo* AML (Table 1). The median age for *de novo* AML was 32 years (range 16-61), and for sAML, it was 64 years (range 23-83). A total of 13 (21%) patients were ≥ 60 years old. Thirty-six patients (58%) were female. Baseline characteristics are described in Table 1.

TABLE 1. Baseline characteristics of the total cohort (n=62)

Variables	Results
Age	
Years(1)	44 (24-56)
≥ 60 years	12 (21%)
Female sex	36 (58%)
de novo AML	42 (68%)
Secondary AML	20 (32%)
Myelodysplastic syndrome (MDS)	10 (50%)
Chronic myeloproliferative disease (CMD)	8 (40%)
MDS/CMD	1 (5%)
Prior chemotherapy for solid tumor	1 (5%)
Laboratory data	
Hemoglobin (g/dl) (2)	6,8 (±1,8)
WBC (mm3) (1)	10.890 (3.357-35.777)
Platelets (mm3) (1)	30.500 (12.500 – 72.500)
Clinical data	
Splenomegaly	11 (18%)
Hepatomegaly	10 (16%)
Adenopathy	16 (26%)
Mucocutaneous involvement	8 (13%)

Median, IQR - Mean, SD

Based on the ELN 2022 guideline, eight patients (13%) were classified into a favorable risk group, 18 (29%) as intermediate, 7 (11%) as an adverse-risk group, and 29 (47%) as an unknown risk group. Only 13 patients (21%) underwent molecular mutation tests, which included FLT3, NPM1, CEBPA, and c-KIT. Thirty-seven patients (60%) were submitted to a karyotype analysis at diagnosis.

Of the 61 treated patients, 52 (85%) received intensive induction therapy, 7 (11%) non-intensive regimens, and 2 (3%) received palliative care without chemotherapy (e.g., hydroxyurea). As for patients who received intensive induction regimens, the majority (47 patients; 90%) received the 7+3 protocol. Alternative schemes (5+2, high dose cytarabine) were chosen according to clinical judgment following advanced age and morbidities. The death for intensive induction therapy was 19% (10 patients). The primary cause of death was infection (9 patients; 90%), and one patient died from disease progression. The overall induction response was 67%; 23 patients (55%) had complete remission, and 5 (12%) had partial remission. 13 (31%) were primary refractory AML, and one patient had no record of response in his chart.

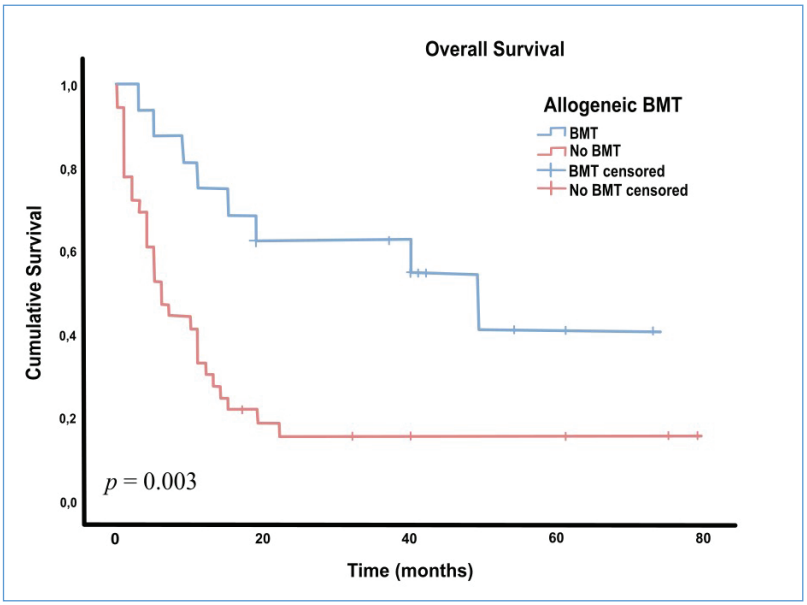
Comparing the data of *de novo* and *s*AML, *de novo* patients received intensive induction therapy, while only 10 (60%) *s*AML were eligible. The overall response rate after induction was 71% and 50%, respectively.

During the follow-up, 12 patients (29%) relapsed, and one of them twice. The median time to relapse was eight months. Analyzing patients with refractory and/or relapsed disease (n=27), 8 (30%) were classified as an unknown risk group, 6 (22%) as an adverse risk group, 9 (33%), and 4 (15%) as intermediate and low risk, respectively.

In the context of refractory or first relapsed cases, all intensive chemotherapy-eligible patients received FLAG (with or without anthracycline) as the rescue regimen (21 patients, 78%). Five cases (19%) had exclusive palliative care, and one patient used azacytidine. The mortality rate of the FLAG regimen was 24% (n=5). 11 patients (55%) achieved complete response. Four patients were submitted to a second rescue, 3 received MEC protocol, and 1 received FLAG-Mitoxantrone (15 months after the first FLAG scheme). All patients who had a third line of high-dose chemotherapy died within 60 days (N=4).

Of the 42 patients surviving induction, 16 (38%) were submitted to alloBMT. We found a survival advantage (hazard ratio, HR: 0.32, 95% CI: 0.15-0.71; p=0.005) in transplanted patients, with superior median overall survival (mOS) of 49 months compared to the chemotherapy group (6 months) (*P* = 0.003; Figure 1). Most patients (n=9, 56%) were transplanted as second-line therapy after a second remission. Autologous BMT was performed in 3 cases, and all patients died from infection, two of them in the context of graft failure.

FIGURE 1. Overall survival between BMT patients and no-BMT.



The median time from diagnosis to bone marrow transplant (BMT) was seven months. For the last date of chemotherapy, the median time was three months. Three alloBMT patients experienced a relapse after the transplant. Regarding risk stratification, one patient was classified as an adverse risk group, and the other two were unknown. The median relapse after alloBMT was eight months. All patients were submitted to a second alloBMT, but the mortality was 100%.

A total of 48 (77%) patients died during the follow-up, and most deaths (n=39, 81%) were in the first year of diagnosis (early mortality). Only 23% (n = 14) were alive during our analysis. The primary cause of death was infection (n=25, 52%), where 20% (n=5) of the cases were of fungal origin, followed by leukemia progression (n=16, 33%). Analyzing death between the intensive treatment group, 76% (n=29) died with active AML.

We performed a univariate analysis of clinical and laboratory characteristics with time of death as an outcome (Table 2) and found no association.

TABLE 2. Association between clinical and laboratory features with death

	Odds ratio (OR)	Confidence Interval (CI) 95%	P value
Age	1.0	1.0-1.1	0.06
Male sex	0.3	0.7-1.2	0.08
Hemoglobin	0.9	0.7-1.4	0.97
WBC	1.0	1.0	0.10
Platelets	1.0	1.0	0.66

Using a multivariate analysis, including AML origin, stratification risk, and alloBMT as predictor variables, we could see alloBMT's protective power (Table 3).

TABLE 3. Adjusted and unadjusted associations between alloBMT, risk stratification, and de novo AML with death as an outcome.

	Odds ratio (Confidence Interval 95%)			
	Unadjusted	p-value	Adjusted*	p-value
alloBMT	0.2 (0.05 - 0.73)	0.02	0.14 (0.03 - 0.58)	0.01
Risk stratification	1.58 (0.92 - 2.81)	0.11	1.91 (1.04 - 3.81)	0.45
De novo AML	1.6 (0.34 - 11.63)	0.59	1.18 (0.2 - 9.94)	0.86

*Each difference is adjusted to the other variables.

The mOS of the entire cohort was seven months (CI: 3.14-10.85). The mOS was shorter in patients in the unknown and adverse-risk groups (3 and 5 months, respectively) than in favorable and intermediate-risk groups (22 and 11 months, respectively, $P = 0.05$; Figure 2). The median relapse-free survival (RFS) was seven months (CI: 2.47-11.52). The patients with sAML had mOS of 3 months versus 11 months for *de novo* AML ($P = 0.024$; Figure 3).

As for patients alive during the follow-up (n=14), 8 (57%) underwent alloBMT transplant. Of the six patients who had not been submitted to transplant and survived, three were in the adverse risk group, two were in the intermediate risk group, and one was in the unknown risk group.

FIGURE 2. Overall survival according to risk classification.

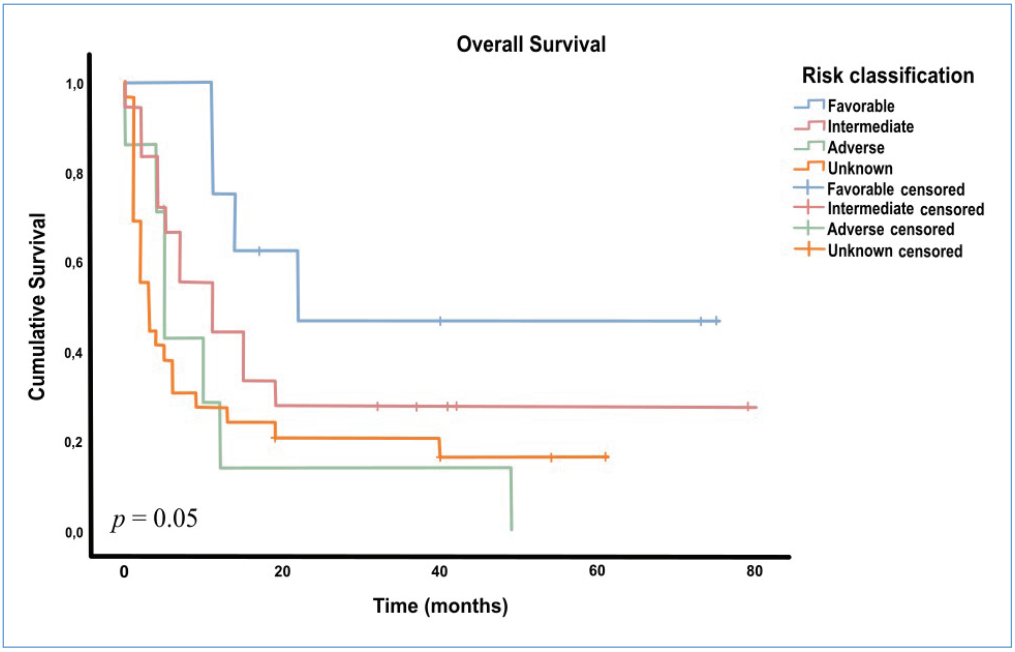
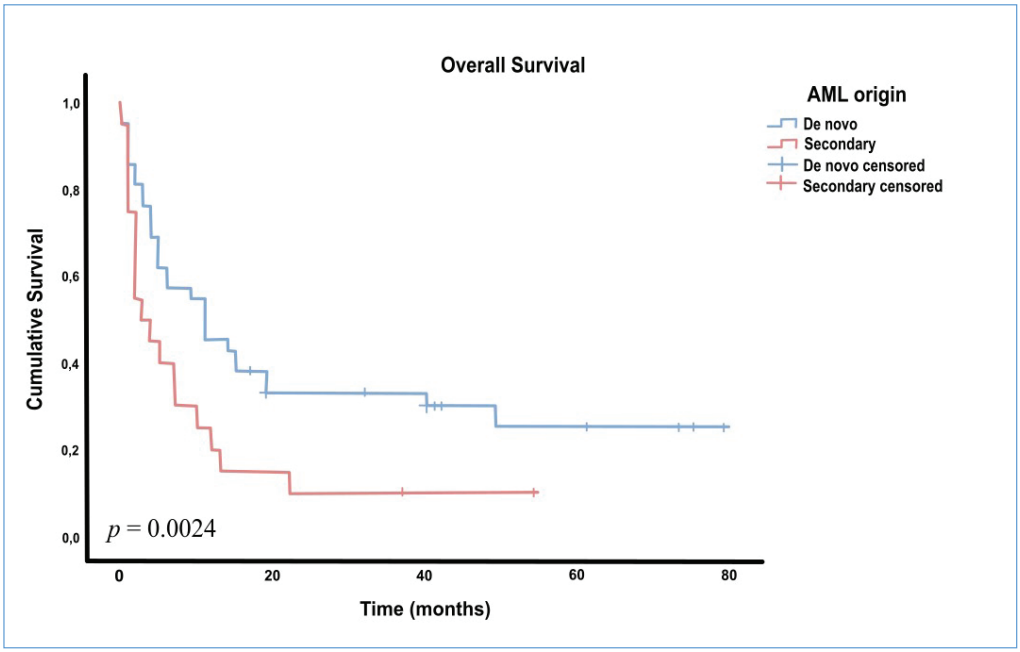


FIGURE 3. Overall survival according to AML origin.



DISCUSSION

We show real-life data for 10 years involving non-promyelocytic AML outcomes at a university hospital in Northeast Brazil, the only transplant center in the state. The results show patients' OS among AML, including favorable and intermediate-risk groups and for those receiving alloBMT. Our findings for CR (53%), 5-year OS (27%), and mortality rate during induction therapy (27%) were similar to other studies in Brazil, ranging from 48-73%, 17-25%, and 10-42% (median of 29%) respectively[4,5,7–13]. Nevertheless, our data is inferior to trials from Europe and North America[14–16], especially for *s*AML under targeted therapy, where CR rates are around 65%[17], as well as for relapsed cases.

The survival advantage among transplanted patients (mOS 49 x 11 months) was comparable to another Brazilian cohort (mOS 26.8 x 12 months) involving transplanted and non-transplanted patients, respectively[9]. The small number of patients submitted to alloBMT [17] results from inaccessibility to transplants due to the small number of available beds and the challenge of finding matched unrelated donors in a racially mixed population.

The low median age found in our cohort could reflect the problematic access to a hematologic center and a higher rate of early death of older patients before referral to a specialized hospital. Additional data is necessary to confirm this hypothesis. Although there are no randomized trials to our knowledge comparing high-income countries (HIC) with socioeconomic aspects of AML treatment, data suggest a trend of higher mortality in remission induction among patients with less favorable social conditions[11].

The higher mortality rate in our country, compared to those in higher-income countries, involves several factors: inadequate diagnostic tools, subpar hospital infrastructure characterized by a limited number of beds, overcrowded wards, and a scarcity of specialized facilities such as positive pressure beds. This scenario is prone to a higher incidence of infections and the need for effective treatments.

AML is a heterogeneous disease involving distinct molecular pathways and clinical outcomes. Several trials in HIC countries evaluate these outcomes. However, retrospective data from LMIC countries frequently describe poor outcomes. Brazil, a vast nation, experiences disparities in healthcare access across its states and between private and public sectors. Salvador, the capital of Bahia, has an estimated population of 14 million and a Human Development Index (HDI) of 0.660. This places it in the 22nd position out of the 27 states in Brazil[6].

An alarming finding here was the high number of patients not adequately stratified (39%) due to an absence of cytogenetic and molecular tests. Real-life data from university hospitals in Brazil demonstrate that 26% of patients are non-stratified[5]. Another study evaluating a few Brazilian BMT centers pointed out that 57% of the patients referred from other services did not have a karyotype test at diagnosis[4].

Recently, a Brazilian group implemented a novel scoring system that integrates clinical and laboratory characteristics (age, serum albumin, and WBC) with cytogenetic-molecular data for cases with missing information, preventing using ELN classification[2]. In the Brazilian public health system, access to real-life data and cytogenetic and molecular tests is limited, primarily due to the high costs associated with setting up a molecular biology laboratory and the challenge of having inadequately trained staff. Our study found that patients categorized as unclassifiable risk (UR) exhibited outcomes similar to those in the adverse risk groups, indicating that a significant portion might have been undertreated. The presence of a UR group is a common expectation in LMICs like Brazil. Therefore, treating these patients appropriately, considering their risk stratification, is crucial. Implementing therapeutic strategies typically reserved for non-favorable risk groups can significantly improve outcomes for UR patients. Statistically, UR group patients are more likely to belong to intermediate or adverse risk groups rather than favorable ones.

A clear-cut, real-life strategy for cases in unclassifiable risk groups is urgently needed. Therefore, every center should know its population survival curves to individualize the best treatment. We suggest that patients with inadequate risk assessment undergo consolidation therapy with alloBMT in first complete remission (CR1) as this remains the primary curative intervention and the main outcome in the real-world setting of LMIC. Although novel target drugs optimize treatment response rates, they are not universally available in public health centers.

Our study's limitations involve its retrospective nature and the small number of participants. As a suggestion, a prospective multicenter study with the collaboration of other regions of Brazil to compare outcomes and access to treatments will minimize the differences and improve the service provided by the Brazilian public healthcare system (SUS).

Finally, understanding AML pathogenesis and developing potent new treatments leads to increasingly divergent outcomes between LMICs and HICs. Consequently, the gap between diagnostic techniques and therapy remains a significant challenge in LMICs. Establishing dedicated teams and centers for acute leukemia in these regions is vital for improving patient outcomes. Such specialized centers will enhance treatment and play a crucial role in gathering valuable data for developing more effective treatment strategies for AML.

ACKNOWLEDGMENTS

The authors thank the Federal University of Bahia and the Professor Edgar Santos University Hospital.

AUTHORS CONTRIBUTION

Camilla CAPC: conception and design of the study, acquisition of data, analysis and interpretation of data, drafted the article and revised it critically, and final approval of the version to be submitted. **Marco AS**: conception and design of the study, acquisition of data, analysis and interpretation of data, drafted the article and revised it critically, and final approval of the version to be submitted**. Lais TS:** Drafted the article, revised it critically, and gave final approval of the version to be submitted. **Alini MOPS**: Drafted the article and revised it critically, and final approval of the version to be submitted. **Thiago F**: drafted the article, revised it critically, and gave final approval of the version to be submitted. **Felipe F**: drafted the article, revised it critically, and gave final approval of the version to be submitted.

FUNDING

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY

The data are available from the corresponding author upon reasonable request.

REFERENCES

1 Silveira DR, Quek L, Santos IS, et al. Integrating clinical features with genetic factors enhances survival prediction for adults with acute myeloid leukemia. Blood Adv. 2020;4(10):2339–50.

2 Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–77.

3 Ministry of health (BR). Mais saúde : *direito de todos :* 2008-2011 [Internet]. Brasília; 2008 [cited 2024 Jan. 17]. Available from:.

4 Helman R, Santos FP, Simões B, et al. Acute myeloid leukemia: update in diagnosis and treatment in Brazil. *Einstein* 2011;9(2): 179–83.

5 Benicio MT, Ribeiro AF, Américo AD, et al. Evaluation of the European LeukemiaNet recommendations for predicting outcomes of patients with acute myeloid leukemia treated in low- and middle-income countries (LMIC): A Brazilian experience. Leuk Res. 2017;60:109–14.

6 IBGE. Portal do IBGE [Internet]. Brasília; 2024 [cited 2024 Jan. 17]. Available from: https://www.ibge.gov.br/.

7 Pulchieri W, Spector N, Nucci M, et al. The treatment of acute myeloid leukemia in Brazil: progress and obstacles. Hematologica. 1995;80(2):130–5.

8 Bittencourt R, Fogliato L, Daudt L, et al. Leucemia Mielóide Aguda: perfil de duas décadas do Serviço de Hematologia do Hospital de Clínicas de Porto Alegre - RS. Rev Bras Hematol Hemoter. 2003;25(1):17–24.

9 Datoguia TS, Velloso ED, Helman R, et al. Overall survival of Brazilian acute myeloid leukemia patients according to the European LeukemiaNet prognostic scoring system: a cross-sectional study. Medical Oncology. 2018;35(11):141.

10 Rego MF, Pinheiro GS, Metze K, et al. Acute leukemias in Piauí: comparison with features observed in other regions of Brazil. Brazilian Journal of Medical and Biological Research. 2003;36(3):331–7.

11 Fagundes EM, Rocha V, Glória AB, et al. De novo acute myeloid leukemia in adults younger than 60 years of age: Socioeconomic aspects and treatment results in a Brazilian university center. Leuk Lymphoma. 2006;47(8):1557-64.

12 Lima AS, Mello MR, Fernandes E, et al. Clinical outcomes of patients with acute myeloid leukemia: Evaluation of genetic and molecular findings in a real-life setting. Blood. 2015;126(15):1863-5.

13 Silva AL, Alves FS, Kerr MW, et al. Acute lymphoid and myeloid leukemia in a Brazilian Amazon population: Epidemiology and predictors of comorbidity and deaths. PLoS One. 2019;14(8): e0221518.

14 Shah A, Andersson TM, Rachet B, et al. Survival and cure of acute myeloid leukaemia in England, 1971-2006: a population-based study. Br J Haematol. 2013;162(4):509–16.

15 Röllig C, Bornhäuser M, Thiede C, et al. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European leukemianet recommendations: Evaluation of the proposed reporting system. J Clin Oncol. 2011;29(20):2758-65.

16 Alpermann T, Kern W, Schnittger S, et al. Evaluation of the proposed reporting system of the European LeukemiaNet and recommendations for prognosis of acute myeloid leukemia. Leuk Res. 2013;37(2):197-200.

17 DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med . 2020;383(7):617-29.