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ESTUDIO ORIGINAL: ESTUDIO RETROSPECTIVO

Survival analysis of patients with de novo non-promyelocytic acute myeloid leukemia in a third-level hospital in Ecuador

Análisis de supervivencia de pacientes con leucemia mieloide aguda no promielocítica de novo en un hospital de tercer nivel en Ecuador

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ABSTRACT

INTRODUCTION: There are a significant number of reports in Latin America, but there are no survival data on acute myeloid leukemia (AML) in Ecuador. We report the first survival analysis in patients with *de novo* AML from a National Reference Center.

OBJECTIVES: To evaluate overall survival (OS), relapse-free survival (RFS) and risk factors associated with survival, and clinical and laboratory characteristics at presentation.

MATERIALS AND METHODS: We retrospectively reviewed the medical records of 121 patients ≥ 15 years old, with *de novo* AML candidates for intensive chemotherapy (CT), diagnosed between Jan 2012 and Dec 2019 and followed until Dec 2021. A survival analysis (OS and RFS) was performed at 5 years. For the description of the most relevant clinical and laboratory characteristics at presentation, 260 medical records were reviewed, including patients who were not candidates for intensive chemotherapy, those who died before receiving treatment, those who did not wish to receive chemotherapy, secondary AML, or those who were referred to other centers for treatment.

RESULTS: Of the 121 patients who received intensive CT, 22.3% died during induction CT, with 74% of deaths related to multidrug-resistant (MDR) bacteria. Overall treatment-related mortality was 29.7%. The complete response (CR) rate was 41.3% with the first induction in all patients, adding the patients who achieved CR in the first and second induction, CR was achieved in 52% of cases. 12.7% of patients were considered primary refractory. The average number of days between each CT cycle, including the consolidation phase, was 50.2 days. The 5-year OS was 12.2% (median survival: 8 m) vs. 13.3 % in patients who received 7+3 induction protocol (median survival: 8 m). The 5-year RFS was 21.2% (median survival: 13 m). In the multivariate analysis, the adapted intermediate-risk cytogenetics group showed an association with OS, HR: 0.47 (p=0.036). No patient in this cohort received HSCT.

CONCLUSIONS: The very low OS rates are directly affected by the high mortality associated with treatment in the context of MDR bacterial infections as well as a serious access problem to bone marrow transplantation, which makes the OS in this study even lower than the Latin American average.

KEYWORDS: Leukemia, Myeloid, Acute; Developing Countries; Registry; Survival Analysis; Tertiary Healthcare; Drug Therapy

RESUMEN

INTRODUCCIÓN: hay un número importante de reportes en Latinoamericanos, pero no existen datos de supervivencia sobre leucemia mieloide aguda (LMA) en Ecuador. Presentamos el primer análisis de supervivencia en pacientes con LMA *de novo* en un centro de referencia del país.

OBJETIVOS: evaluar la supervivencia global (SG), la supervivencia libre de recaída (SLR), factores de riesgo asociados con la supervivencia, características clínicas y de laboratorio al debut.

MATERIALES Y MÉTODOS: revisamos retrospectivamente las historias clínicas de 121 pacientes ≥ 15 años, con LMA *de novo* candidatos a quimioterapia (QT) intensiva, diagnosticados entre ene 2012 y dic 2019 y seguidos hasta dic 2021. Se hizo un análisis de supervivencia (SG y SLR) a 5 años. Para la descripción de las características clínicas y de laboratorio más relevantes al debut se revisaron 260 historias clínicas, incluyendo pacientes no candidatos a QT intensiva, aquellos que fallecieron antes de recibir tratamiento, aquellos que no desearon recibir QT, LMA secundaria o los que fueron derivados a otros centros para tratamiento.

RESULTADOS: de los 121 pacientes que recibieron QT intensiva, 22,3% fallecieron durante la QT de inducción estando el 74% de las muertes relacionadas con bacterias multidrogo resistentes (MDR). La mortalidad relacionada con el tratamiento total fue 29,7%. La tasa de respuesta completa (RC) fue del 41,3% con la primera inducción en todos los pacientes, sumando los pacientes que lograron RC en primera y segunda inducción se alcanzó RC en el 52% de los casos. El 12,7% de los pacientes se consideró refractarios primarios. El promedio de días entre cada ciclo de QT incluyendo la fase de consolidación fue de 50,2 días. La SG a 5 años fue 12,2% (mediana de la supervivencia de 8 m) y en pacientes que recibieron protocolo de inducción 7+3 la SG a 5 años fue 13,3% (mediana de supervivencia de 8 m). La SLR a 5 años fue 21,2% (mediana de supervivencia de 13 m). En el análisis multivariable el grupo de citogenética de riesgo intermedio adaptado mostró asociación con la SG, HR de 0,47 (p=0,036). Ningún paciente de la cohorte recibió trasplante de progenitores hematopoyéticos.

CONCLUSIONES: las tasas tan bajas de SG se afectan por la alta mortalidad asociada al tratamiento en el contexto de infecciones bacterianas MDR y acceso mínimo o ausente al trasplante de médula ósea que hace que la SG de este estudio sea incluso más baja que la media latinoamericana.

PALABRAS CLAVE: Leucemia Mieloide Aguda; Países en Desarrollo; Registros; Análisis de Supervivencia; Atención Terciaria de Salud; Quimioterapia.

INTRODUCTION

Acute myeloid leukemia (AML) represents a diverse subgroup of myeloid neoplasms with genetic heterogeneity and potential clonal evolution among patients.

Its frequency of presentation increases with age, representing up to 80% of acute leukemias in adults, with the peak of presentation in Latin America being at a younger age compared to non-Latin American countries [1,2].

In Ecuador there are no data available about the clinical and cytogenetic characteristics, therapeutic regimens used and clinical results obtained.

Limited access to genetic studies that can guide treatment as well as risk stratification, added to the high rates of multidrug-resistant bacteria (MDR) and the difficult access to hematopoietic progenitor cell transplantation (HSCT), are some of the factors that would lead us to deduce that in countries like Ecuador the survival rates are low.

This work collects data from patients with de novo non-promyelocytic AML treated with intensive chemotherapy for 8 years (2012-2019), from one of the main third-level referral centers of the public health network of Ecuador, belonging to the social security of the capital of the country. This is the first national survival analysis of this pathology reported and aims to present the main clinical outcomes as well as describe the clinical characteristics and factors that could predict poor prognosis in this group of patients.

OBJECTIVES

The primary objective was to evaluate 5-year OS and RFS in patients with *de novo* non-promyelocytic AML diagnosed between January 2012 and December 2019 undergoing intensive chemotherapy. The secondary objectives were to describe the clinical variables of non-promyelocytic AML and to record complications and prognostic factors after treatment, in this population in the Hematology Unit of the Carlos Andrade Marín Hospital in a follow-up period that lasted until December 31, 2021.

METHODS

Design and patient selection

A retrospective, longitudinal, observational study was conducted in a tertiary referral center, including patients diagnosed with de novo AML between January 2012 and December 2019 who were candidates for intensive chemotherapy. Clinical and cytogenetic characteristics, therapeutic regimens, and main clinical outcomes were recorded.

All patients were diagnosed with AML if they had at least 20% blasts in blood or bone marrow since FISH or RT-PCR for the search for t(8;21) or inv(16)/t(16;16) or other translocations was not available. The origin of the myeloid cells was confirmed in all cases by immunophenotyping with flow cytometry.

We excluded patients with acute promyelocytic leukemia from the clinical description and, for the survival analysis, additionally, patients <15 years, patients who did not receive intensive chemotherapy for any reason, isolated extramedullary disease, and patients who had a diagnosis of secondary AML.

Definitions

Induction regimens in patients receiving intensive chemotherapy were classified as follows: 7+3 (continuous infusion of cytarabine [dose: 100-200 mg/m2] on days 1 to 7 and an anthracycline on days 1 to 3), 5-+2 (continuous infusion of cytarabine [dose: 100-200 mg/m2] on days 1 to 5 and an anthracycline on days 1 and 2), and 7+3 +2 (7+3 regimen associated with etoposide).

Patients receiving consolidation therapeutic strategies after achieving complete response (CR) were administered high-dose cytarabine (doses greater than 1 g/m^2 for 6 doses on alternate days). Patients who completed the consolidation phase were started on maintenance with low-dose subcutaneous cytarabine monthly. CR was defined according to the criteria of Cheson et al[3], <5% bone marrow blasts and trilineage hematopoiesis, hematopoietic recovery with absolute neutrophil count >1000/mm^3 and platelet count >100,000/mm^3; absence of peripheral blood blasts and/or extramedullary disease). Induction-related mortality was defined as death from any cause, occurring during the first month after starting intensive induction chemotherapy. Overall survival (OS) was defined as the date from diagnosis to death or last record. Relapse-free survival (RFS) was defined only for patients achieving a CR; measured from the date of CR to the date of hematologic relapse or death from any cause; patients for whom it was unknown whether they relapsed or died were censored at the date of the last recorded follow-up. The risk of conventional cytogenetics by G banding was attempted to be classified and adapted to that suggested by LEUKEMIA NET[4].

Statistical considerations

We describe absolute and relative frequencies of clinical data. Logistic regression analysis was performed for factors related to early mortality. OS and RFS results were analyzed using the Kaplan-Meier method at 5 years and comparisons of median survival times were performed using the log-Rank test. Prognostic factors associated with OS were analyzed using a Cox regression model. All analyses were performed using All analyses were conducted using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. The study was approved by the ethics and research committee of the center where this study was conducted.

RESULTS

Patient characteristics

Including the pediatric population and acute promyelocytic leukemias, during the period of this study, a total of 595 acute leukemias were diagnosed, presenting AML in 310 (52%) patients; if only patients aged 18 years or older are included, 280 (73.6%) patients had AML.

A total of 260 patients were diagnosed with non-promyelocytic AML, they had a mean age of 50.5 years (0-90 years), 147 (56.6%) were male; 217 (83.5%) patients were de novo AML, 43 (16.5%) patients were considered secondary AML. 205 pa-

tients had complete data for description, showing 22 (10.7%) patients with extramedullary infiltration at onset, with lymph nodes and spleen being the most common sites. 12 (5.8%) patients presented thrombosis associated with LMA. Of these, 9 (3.5%) were deep vein thrombosis, most of which developed at onset. Clinical demographic data are summarized in Table 1.

Table 1. Epidemiological and clinical variables.

Variable		n	(%)
Non-M3 AML		260	100
Age in years for all patients	Mean 50.5 (0-89)		
	Median 56		
Age ≥ 15 years	Mean 55.9 (15-89)		
AML >18 years		234	90
AML >60 years		135	51.9
Total AML		310	100
de novo non-M3 AML		216	69.6
M3 AML		51	16.4
AML secondary to:		43	13.8
MDS		31	
Chemotherapy		2	
Myeloid blast crisis		9	
Other CMN		1	
Total AML		310	100
AML M0		32	10.3
AML M1		49	15.8
AML M2		44	14.1
AML M3		50	16.1
AML M4		41	13.2
AML M5		36	11.6
AML M6		10	3.2
AML M7		1	0.3
Extramedullary infiltration at debut		22	10.7
Adenomegaly		7	
Splenomegaly		6	
Liver		5	
Soft tissue		4	
Central Nervous System		2	
Tonsils		1	
Intestine		1	
Skin		1	
Retina		1	
≥ 40,000/mm^3 leukocytes at onset		48	23.4
AML-associated thrombosis		12	5.9
Deep Vein		9	4.4
Arterial		3	1.5

*** Including acute promyelocytic leukemia**

AML: Acute myeloid leukemia; CMN: Chronic myeloproliferative neoplasms; MDS: Myelodysplastic syndrome.

Source: Research data. Author: Orquera A.

Sixty patients who were treated with palliative care and 59 patients excluded for different reasons (20 died before receiving chemotherapy; 12 were referred to a pediatric oncology center; 8 referred to another city or institution; 4 did not accept chemotherapy; 4 under 15 years of age; 3 with errors when filling out the medical history) were excluded from the survival analysis, in addition to the patients who were additionally diagnosed with secondary AML.

To assess OS and RFS, 121 patients with de novo AML ≥ 15 years of age who received intensive chemotherapy were evaluated. This group of patients had an average age of 51.6 years (15-83 years). 80 (66.1%) patients were older than 60 years. 86 (70.0%) patients received the 7+3 protocol (9 patients additionally received 2 days of etoposide) and the rest 5+2. 61 (50.4%) patients received idarubicin, 52 (42.9%) daunorubicin, 6 (4.9%) doxorubicin, and 2 (1.65%) mitoxantrone.

88 patients had a conventional cytogenetic report, of these 14 (15.9%) no evaluable metaphases were observed; no patient had low-risk cytogenetics; 20 (22.7%) had some intermediate-risk cytogenetic abnormality; 6 (6.8%) had some high-risk cytogenetic abnormality; 32 (36.3%) had a normal karyotype (in 29 patients at least 20 metaphases were not reached for analysis); 16 (18.1%) had a non-clonal karyotype. In our institution, during the time period of analysis of this study, FISH or molecular biology research on the genetic risk of AML was not performed regularly.

Remission, death and relapse

CR was achieved in 50/121 (41,3%) patients. CR by subgroups is shown in Table 2.

Of the 77 patients who received the 7+3 regimen, CR was achieved according to the type of anthracycline administered in 18/45 (40%) patients who received idarubicin; 14/38 (36%) patients who received daunorubicin; 2/3 (66.6%) patients who received doxorubicin.

Of the 121 patients who received intensive chemotherapy, 27 (22.3%) had induction-related deaths, with septic origin in 20 (74%) cases; bacteria were isolated in blood cultures in 11 (45.8%) patients, all (100%) of which were carbapenemase-producing *Klebsiella pneumoniae* (CKP); no other types of bacteria were isolated; 3 patients died from CNS hemorrhage, 1 from intraalveolar hemorrhage, and 4 had no cause established. 9 (7.4%) patients died during consolidation treatment, which added to the deaths during induction, this cohort presented a treatment-related mortality in 36 (29.7%) patients.

35/72 (48,6%) patients ≤ 60 years who received 7+3 first induction chemotherapy achieved CR, dying during induction chemotherapy 23.6% of patients.

In the multivariate analysis, age was shown to be a risk factor for death during induction chemotherapy (OR 1.037 [95% CI 1.003-1.072]; p=0.032). No association was found for gender, type of chemotherapy, type of anthracycline, living in the province of Pichincha, extramedullary infiltration, having 2 or more comorbidities.

Table 2. Relapse by type of chemotherapy protocol in patients who achieved complete response with the first induction

Protocolo de inducción	Total patients. n(%)	Mean age in years	CR first induction n(%)	Relapsed n(%)	Relapses < 1 year n(%)	Alive in CR n(%)	Deaths in RC n(%)
5+2	35 (28.9)	52.4	11 (31.4)	9 (81,8)	5 (55.5)	1 (9)	1 (9)
7+3	77 (66.7)	51	34 (41.5)	17 (50)	8 (47)	12 (35.2)	5 (14.7)
7+3+2	9 (7.4)	51.1	5 (55.6)	4 (80)	2 (40)	0	1 (20)
Total	121	51.6	50 (41.3)	30 (60)	15 (50)	13 (26)	7 (14)

***Remission was not evaluated in patients who failed induction or did not undergo bone marrow aspiration for other reasons. CR: Complete response. Source: Research data. Author: Orquera A.**

33 (100%) patients received reinduction chemotherapy (in this group 6 patients were not evaluated for response), 16 patients (48.4%) achieved remission and 11 patients were considered primary refractory, the latter representing 12.7% of all AML who received intensive chemotherapy and who were able to evaluate CR in bone marrow.

Adding together the patients who achieved CR in first and second induction were a total of 63, representing 52 % of cases (In the <60 years group, when patients who achieved CR in the first or second induction chemotherapy were added, the CR rate was 61.1%)

All patients received at least one cycle (1 to 4 cycles) of consolidation with high-dose ARA-C. The mean number of days between each cycle of chemotherapy that the patients received was calculated, which was 50.2 days.

39 patients completed the consolidation phase and 35 (89.7%) of these received maintenance treatment with subcutaneous low-dose cytarabine for 2 years or until losing CR.

Of the 66 patients who achieved CR with the first and second induction, 9 (13.6%) patients died in remission (all of them during consolidation treatment), 43/57 (75.4%) patients relapsed (23 [40.3%] patients relapsed before the first year of CR), 14/57 (24.5%) did not relapse.

Of the 43 patients who relapsed, 33 patients received reinduction chemotherapy (6 patients were not evaluated for response), 16/33 patients (48.4%) achieved a second remission.

A total of 104 (85.9%) patients died during the analysis period, 65/104 patients (62.5%) died from sepsis, and of these, 28/65 (43%) were able to isolate carbapenemase-producing bacteria. The causes of death of all patients in the cohort are described in Table 3.

Efficacy

The median OS of patients with de novo AML on intensive chemotherapy was 8 months (interquartile range 1-26 months), with 60 patients (49.6%) alive at that time. The 5-year OS was 12.2%. (see Figure 1). The 5-year OS in the 66 patients who achieved CR was 21.6% with a median survival of 21 months (interquartile range 1-43 months).

The median overall survival in patients who were 60 years or older and younger than 60 years were 5 months (with 23 patients

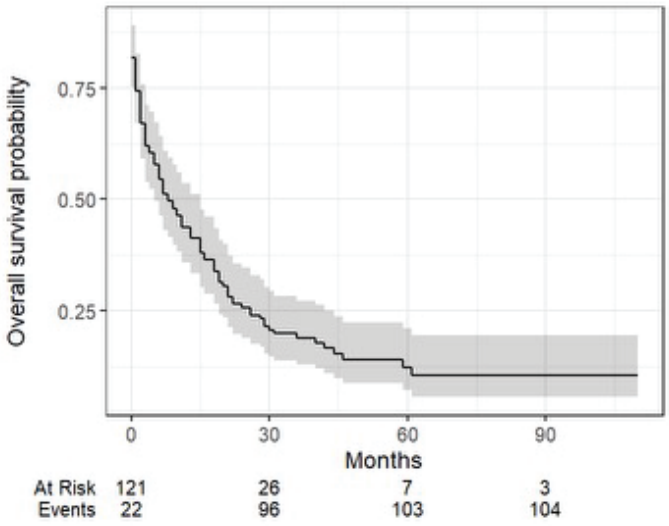

Figure 1. Kaplan Meier curve of patients with *de novo* acute myeloid leukemia, 5-year overall survival of 12.2% (median survival of 8.7 months) Source: Research data. Author: Orquera A.

alive at that time [53.2%]; interquartile range, 1-19 months) and 11 months (with 37 patients alive at that time [47.5%]; interquartile range, 2-30 months), respectively (p=0.137), between the OS of the 2 subgroups. (See Figure 2).

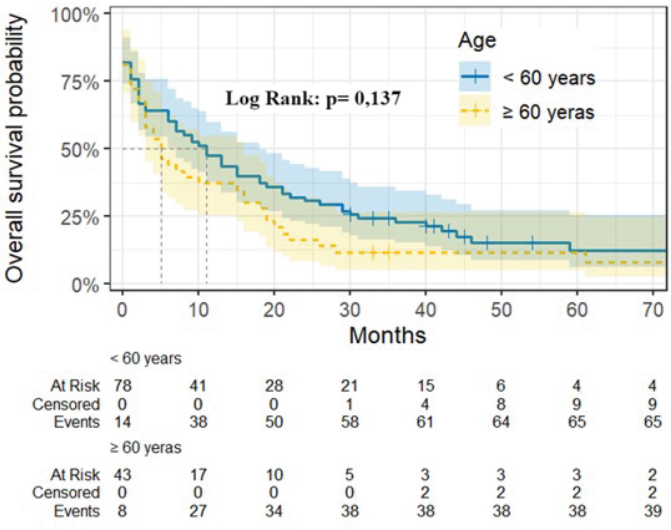

Figure 2. Kaplan Meier curve of patients with de novo acute myeloid leukemia, 5-year overall survival in patients <60 years 12.3% (median survival 11 months); 5-year overall survival in patients ≥60 years, 11.6% (median survival 5 months).
Source: Research data. Author: Orquera A.

Table 3. Cause of death in all patients with *de novo* AML who received intensive chemotherapy.

Cause of Death	n (104)	0%
Sepsis	65	53,7
Sepsis of unknown origin	22	21,1
Pulmonary sepsis	21	20,9
Abdominal sepsis	11	10,5
Perianal sepsis	7	6,7
Soft tissue sepsis	3	2,8
Urosepsis	1	0,9
Disease progression	23	22,11
Unknown cause	8	7,69
Central Nervous System hemorrhage	5	4,8
Intraalveolar hemorrhage	3	2,8

Source: Research data. Author: Orquera A.

The OS in patients residing in the capital province of the country had an OS not significantly different from that of patients who did not reside in the province of Pichincha (OS at 5 years of 7.7% vs 16.5%, [p = 0.182]). The univariate analysis of other variables is detailed in Table 4.

Table 4. Univariate analysis of patients diagnosed with *de novo* acute myeloid leukemia and its association with overall survival.

Variable	n(%)	Median OS in months	OS at 5 years	p* value
Age ≥ 60 years				p=0.137
No	78 (65)	11 [95% CI: 6.2-15.8]	12.30%	
Yes	43 (35)	5 [95% CI: 1.2-8.2]	11.60%	
≥40,000 leukocytes/mm^3				p=0.653
No	87 (71.7)	8 [95% CI: 3-13]	16.30%	
Yes	34 (28.3)	8 [95% CI: 0.8-15.1]	10.90%	
Induction protocol				p=0.238
5+2	35 (28.4)	8 [95% CI: 0-16.6]	8.80%	
7+3	86 (71.6)	8 [95% CI: 3.8-12.1]	13.30%	
Extramedullary infiltration at debut				p=0.239
No	104 (85.9)	7 [95% CI: 2.8-11.1]	10.90%	
Yes	17 (14.1)	18 [95% CI: 3.2-32.7]	23.20%	
Residents of the province of Pichincha				p=0.221
No	41 (33.8)	15 [95% CI: 10.8-19.1]	16.50%	
Yes	80 (66.2)	6 [95% CI: 2.5-19.8]	7.70%	

***Log Rank test**
OS: overall survival
Source: Research data. Author: Orquera A.

Median RFS for patients with de novo AML was 13 months (interquartile range 5–31 months), with 34 patients (51.5%) being relapse-free. The 5-year RFS was 21.2%. (See Figure 3).

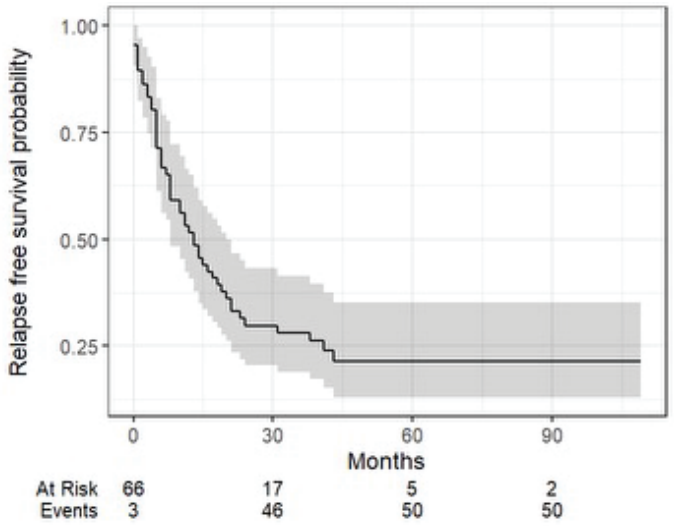

Figure 3. Kaplan Meier curve of patients with *de novo* acute myeloid leukemia, 5-year relapse-free survival of 21.2% (median survival = 13 months). Source: Research data. Author: Orquera A.

Univariate analysis of other variables for RFS is detailed in Table 5.

Table 5. Univariate analysis of clinical variables of patients diagnosed with de novo acute myeloid leukemia and their association with relapse-free survival.

Variable	n(%)	Median SLR in months	SLR at 5 years	p* value
Age ≥ 60 years				p=0.200
No	48 (72.7)	15 [95% CI: 7.2-22.8]	23.5%	
Yes	18 (27,3)	10 [95% CI: 0-24.5]	13.8%	
≥40,000 leukocytes/mm^3				p=0.374
No	47 (71.2)	13 [95% CI: 7,3-18,7]	17.2%	
Yes	19 (28.7)	15 [95% CI: 4,3-25,7]	31.5%	
Induction protocol				p=0.028
5+2	16 (24.2)	10 [95% CI: 6.1-13.8]	6.2%	
7+3	50 (75.8)	16 [95% CI: 6.9-25.1]	25.8%	
Extramedullary infiltration at debut				p=0.567
No	54 (66.4)	13 [95% CI: 7-18.9]	19.2%	
Yes	12 (33.3)	12 [95% CI: 5,2-18.8]	NR**	
Residents of the province of Pichincha				p=0.997
No	26 (39.3)	13 [95% CI: 7-18.9]	22.4%	
Yes	40 (60.7)	12 [95% CI: 2.1-21.9]	19.4%	

***Log Rank test**
****Patients censored from this subgroup did not reach the 5-year follow-up period.**
NR: Not reached; RFS: relapse-free survival.
Source: Research data. Author: Orquera A.

In the univariate analysis for conventional cytogenetics, no association was observed between OS and the different groups of cytogenetic findings. (See Table 6).

Table 6. Univariate analysis of conventional cytogenetics for overall survival in patients with de novo acute myeloid leukemia.

Variable*	n(%)	HR (IC 95%)	p* value
No evaluable metaphases	14 (15.9)	Reference	p=0.264
Intermediate risk cytogenetics**	68 (77.2)	0,61 (0.39-1.11)	p=0.104
High-risk cytogenetics	6 (6.8)	0,63 (0.22-1.76)	p=0.378

***No low-risk cytogenetic findings were obtained.**
****Patients with normal karyotype and patients with non-clonal cytogenetic alterations were included.**
Source: Research data. Author: Orquera A.

Multivariate regression analysis for the intermediate-risk cytogenetics group showed an association with OS, HR 0.47 (p=0.036); no statistically significant association found for age, leukocyte level, sex, extramedullary infiltration, induction CT intensity, residence in the Province of Pichincha, and AML subtype. (See Table 7).

Table 7. Multivariate analysis for overall survival in patients with *de novo* acute myeloid leukemia.

Variable	HR (95% CI)	p* value
Age (years)	0.99 (0,98-1,20)	p=0.949
Sex		p=0.267
Female	Reference	
Male	1.34 (0.79-2.24)	
Age ≥ 60 years		p=0.971
No	Reference	
Yes	0.98 (0.41-2.2)	
≥40,000 leukocytes/mm^3		p=0.462
No	Reference	
Yes	1.25 (0.68-2.31)	
Induction protocol		p=0.272
5+2	Reference	
7+3	0.66 (0.32-1.37)	
Extramedullary infiltration at debut.		p=0.550
No	Reference	
Yes	0.74 (0.26-2.0)	
Residents of the province of Pichincha		p=0.122
No	Reference	
Yes	1.54 (0.89-2.69)	
AML subtype		
AML M0	Reference	
AML M1	0.64 (0.31-1.32)	p=0.232
AML M2	0.52 (0.22-1.19)	p=0.123
AML M4	0.55 (0.23-1.29)	p=0.171
AML M5	0.44 (0.17-1.17)	p=0.101
AML M6	0.56 (0.17-1.18)	p=0.344
Conventional cytogenetics*		
No evaluable metaphases	Reference	
Intermediate risk cytogenetics**	0.47 (0.23-0.95)	p=0.036
High risk cytogenetics	0.51 (0.16-1.55)	p=0.235

***No low-risk cytogenetic findings were obtained.**

****Patients with normal karyotype and patients with non-clonal cytogenetic alterations were included.**

Source: Research data. Author: Orquera A.

DISCUSSION

In Latin America, as well as in this study (average age at diagnosis in ≥ 15 years of age of 55.9 years), there are several reports on de novo AML in adults[3,4] where the average age at diagnosis is lower compared to those reported in Europe such as Sweden[5] (average age of 71 years) and the USA[6] (average age of 62 years). The difference in this report, as well as those in Latin America, could be explained, first by a different population pyramid in Ecuador than in developed countries, with an average age of 27.9 years[7] which is lower when compared to the USA, whose average age is 38.3 years[8] and second by the greater probability of underdiagnosis of older adult patients diagnosed with AML who do not access reference centers that treat oncohematological diseases, perhaps because they are very sick at the time of diagnosis.

Regarding treatment-related AML, myelodysplastic syndrome (MDS) and chronic myeloproliferative neoplasms (CNM) in this study accounted for 0.8%, 10%, and 0.42% (only one patient had a Philadelphia chromosome-negative CNM), respectively. The rate of treatment-related AML in this cohort is very low compared to that reported by Morten et al.[9], who mention that treatment-related AML accounts for 10% to 15% of all newly diagnosed AML; this may be explained by an overall lower survival rate in solid cancers in Ecuador as well as a lower rate of access to chemotherapy for solid tumors in general. Regarding AML secondary to MDS, Szotkowski et al [10] reported a 10% rate of AML associated with MDS, a rate similar to that of this cohort, although the definition of AML secondary to MDS in this analysis was based on the patient having a previous diagnosis of MDS or the presence of previous cytopenias.

Extramedullary infiltration was present in 10.7% of patients. Although the exact frequency of extramedullary involvement of AML is generally unknown, Solh et al[11] mention an estimate of involvement at onset of between 2 and 9%. In this cohort there could perhaps be an overestimation given that liver or lymph node involvement was not documented by biopsy. The literature reports a rate of venous thromboembolism (VTE) events at any time since the diagnosis of AML of between 5-8.7%[12-14], rates somewhat higher than that of this cutoff, in which 4.4% of VTE events were found, while 1.5% of arterial thrombotic events were found, this rate also being somewhat lower than that reported in other registries that showed rates of between 2-7%[15-17] of arterial thrombotic events.

In this study, it was decided to adapt a conventional anarchic cytogenetic risk grouping (Table 7), in the sense that most of the tests did not obtain a representative number of metaphases for analysis, since although all the studies had at least 2 analysable metaphases, only 3 studies reached a number of at least [20] metaphases for analysis, a condition that must be met to define normal karyotype and non-clonal karyotype[18], findings that were the most frequent in this cohort. In this context, it was decided to do an exploratory analysis including non-specific findings, such as those tests where evaluable metaphases could not be obtained (a finding associated with low survival)[19] as well as including the findings of non-clonal karyotypes in the intermediate risk

group as a similarity to the normal karyotype, the latter being considered as an intermediate risk cytogenetic finding[20]. Taking into account the above, it is striking that in the multivariate analysis, the intermediate-risk cytogenetic group did achieve an advantage in OS in relation to the high-risk group and tests with non-evaluable metaphases, so we could conclude that despite the limitations noted, the cytogenetic study of this cohort could be useful to assess the risk of the patients in this study.

Regarding mortality related to induction chemotherapy, the rate varies depending on the care center. In the records of Torres J, et al. (Mexico, 2020)[21], Demichelis R, et al. multicenter registry (Mexico, 2020)[4], Lovato P, et al (Cuba, year 2008)[22] and the Indian Acute Leukemia Research Database registry (year 2019) report variable rates of 7%, 17%, 18% and 6.1% to 43% respectively[23]. In this study, the mortality rate related to induction is higher (22%) and even more so when compared to the rates reported in the SWOG and the MD Anderson Cancer Center between 1991 and 2009, where they recorded a decrease in treatment-re lated mortality, from 18 to 3% at SWOG and from 16 to 4% at MD Anderson[24]. If we start from the premise that there were no changes from 1991 to 2009, in the chemotherapy treatment of AML, it can be stated that the improvement of the SWOG and MD Anderson centers in the mortality rates related to the treatment are given by improvements in the support and direct care of the patient and underlines the problems that the medical units of Ecuador in general have to face in the direct care of the patient if they want to reduce mortality, problems that range from the delay in the patient referral systems, lack of constant availability of drugs and examination platforms, lack of trained human talent and an infrastructure with difficulties both in the structural aspect and in achieving constant preventive maintenance in the context of a saturated health system.

It is important to note that 74% of patients who died during induction chemotherapy did so due to sepsis and in the 11 cases where a germ was isolated in the blood cultures, in all cases carbapenemase-producing bacteria were isolated, bacteria that are associated with high mortality rates and probability of admission to a critical care unit. In Ecuador, we consider that the protocols for the prevention of infections associated with health care are complied with as far as possible, but this will not be sufficient to control infections caused by MDR bacteria in the context of units that were not built for the treatment of cancer patients, but rather were adapted for the care of these patients, since, for example, they do not have individual rooms where patients often have to share sanitary facilities. This is one of the explanations for the high levels of MDR bacteria, as is the case in this cohort, which is added to other problems related to infrastructure or lack of human resources.

In the Swedish national registry (median age 72 years)[5] a CR of 68% is reported in patients with de novo AML, a population considerably older than that of this cohort (median age 56 years) where a CR of 41,3% was achieved with the first induction and 52.0 % with a second induction chemotherapy in the context that they received both induction protocols with 7 + 3 and 5 + 2. In the Brazilian registry of Campos et al (median age 44 years and secondary leukemias were included)[25], a CR rate of 54% and partial response of 12% is reported while Demichelis R, et al (median age 44 years and secondary leukemias were included)[4] in their Mexican multicenter registry reports CR with one or two induction cycles in 71.3% of patients and if only the first induction cycle was considered, the CR rate was 53.9%. In relation to CR, it is difficult to compare the CR rates of this study, given that the populations of the different real-world registries are different from the population of this cohort, either in age or in that secondary leukemias were not included. In this sense, the CR rates of this study are lower than the average of other real-world registries, which we believe is largely influenced by this unacceptably high rate of induction-related mortality (22.3%).

In this study, 12.7% of patients were considered to have primary refractory de novo AML, a rate similar to that reported in the literature, which indicates a rate of 10-40% for primary refractory AML[26-28]. 40.3% of patients relapsed in the first year, a figure that is interesting in the context that in this cohort none of the patients benefited from hematopoietic progenitor cell transplantation (HSCT), in addition to presenting an average between chemotherapy cycles of 50 days (decreased intensity), long periods between chemotherapy that were aggravated not only by the expected clinical complications, but also by the lack of physical space in the Hematology Unit due to saturation of the hospital bed capacity; if these data are compared with one-year relapse rates mentioned in the literature of around 40%[29,30] they are similar to that of this study, but in populations that did have access to HSCT. These data do not in any way doubt the benefit of HSCT in AML, especially in high-risk patients, but rather show the limitation of the data in this study due to the lack of knowledge of the risk group rates due to the lack of access to genetic/molecular tests in the institution and thus being able to more objectively discern the disadvantage of not having access to HSCT according to the risk group.

In this cohort (no patient underwent HSCT) the median survival in de novo AML with intensive chemotherapy reached 8 months and a 5-year OS of 12.2%, a very low rate if we compare it with registries such as the Swedish one31 which reaches a median OS of 20.7 months or with the Canadian registry32 which reaches a 5-year OS of 43% in adult patients under 18 years of age 65 years. Latin American registries such as the multicenter report in different centers in Latin America reported by Reggo et al (24% of patients underwent HSCT)28 and the multicenter Mexican registry reported by Demichelis R, et al (8% of patients underwent HSCT and included secondary AML)4, achieved median OS in patients with intensive chemotherapy of 11.9 months, 14.9 months respectively. Lovato et al22, in Cuba, performed an analysis in patients < 60 years with AML, excluding patients with HSCT, reporting a median OS similar to that of this cohort (median OS 11 months and 5-year OS of 12.3% in ≤ 60 years) of 11 months and an OS of 17.8% in patients with de novo AML with intensive chemotherapy.

With the different points noted above, the information generated in this study points out the different problems and challenges to solve them, aimed at improving an OS that is too low:

1.- Reduce mortality related to induction by implementing a national system of early referral in patients with clinical suspicion of leukemia, added to health policies with a greater hospital investment that generates an improvement in the infrastructure with the construction of true Hematology Units that are equipped for the care of patients with leukemia, as well as in the strengthening of human talent trained for patient care; all this would have a direct influence on the decrease of MDR bacteria that are the main cause of death in hematological patients, since currently the efforts to reduce infections by MDR germs are only limited to the strengthening of programs for the prevention of intrahospital infections.

2. Improve risk stratification through a wide implementation of cytogenetic and molecular analysis. In the context that would help decision making and focus on patients who do benefit from allogeneic HSCT, it would also help implement targeted treatments such as FLT3, KIT, IDH1 and IDH2 inhibitors, as well as being able to identify high-risk populations such as AML associated with TP53, which has a different management and is clearly underdiagnosed in this cohort.

3. Accessibility to HSCT is too limited in our setting, taking as an example that none of these patients benefited from transplantation in this study, which points to the need for government level to prioritize the creation of bone marrow transplant programs with the aim of improving OS rates in patients with leukemia in Ecuador.

The main strength of this study is that it is the first Ecuadorian survival analysis in AML and its main limitation is the retrospective nature of the analysis, given that the effect of treatment on the outcome is greatly affected by other uncontrolled factors.

CONCLUSIONS

The very low OS rates are directly affected by the high mortality associated with treatment in the context of MDR bacterial infections (as well as the low reported CR rate) as well as a serious problem of little or no access to bone marrow transplantation, which makes the OS in this study even lower than the Latin American average, figures that do not seem to be different in other centers of the public health system throughout the country, given that they present similar problems in the care of oncohematological patients to those stated.

ABBREVIATIONS

AML acute myeloid leukemia

CNM chronic myeloproliferative neoplasms

CKP carbapenemase-producing Klebsiella pneumoniae

CR complete response

HSCT hematopoietic progenitor cell transplantation

MDR Multidrug-resistant

MDS myelodysplastic syndrome

OS overall survival

RFS Relapse-free survival

VTE venous thromboembolism.

AUTHORS' CONTRIBUTION

OA. ML: Research conceptualization and design.

OA, PV: Analysis and data interpretation.

AO, PV: Manuscript writing.

AO, PV, JC: Critical review of the Manuscript.

OA, ML, MG, AM: Data collection.

All of the Authors read and approved the final version of the article.

AVAILABILITY OF DATA AND MATERIALS

Free and limited bibliographic resources were used. The collected information is available upon request.

ETHICS COMMITTEE APPROVAL AND CONSENT TO PARTICIPATE IN THE STUDY.

The scientific article was approved by peers and by the Human Research Ethics Committee – CEISH/HECAM.

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The authors reported not having any personal, financial, intellectual, economic or corporate conflicts of interest.

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