HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.htct.com.br

Original article

Are delays in diagnosis and treatment of acute leukemia in a middle-income country associated with poor outcomes? A retrospective cohort study

Yadith Karina Lopez-Garcia, Mayra Valdez-Carrizales, Jorge Adrián Nuñez-Zuno, Elia Apodaca-Chávez, Juan Rangel-Patiño, Roberta Demichelis-Gómez *

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

ARTICLE INFO

Article history:
Received 25 May 2022
Accepted 28 May 2023
Available online 7 July 2023

Keywords:
Early death
Adult
Leukemia
Cancer
Mexico

ABSTRACT

Introduction: Acute leukemias (ALs) are aggressive diseases that lead to death without medical attention. We evaluated the association between delays in diagnosis and poor outcomes in AL by evaluating the symptom onset to treatment intervals in adults with newly diagnosed AL and their effect on an early death (ED).

Methods: We assessed adults diagnosed with AL between 2015 and 2020 and evaluated baseline characteristics, the patient interval (PI), diagnostic interval (DI), treatment interval (TI) and the total time interval (TTI) to determine ED-associated factors.

Main results: We assessed 102 patients with acute lymphoblastic leukemia (ALL), 57 with acute myeloblastic leukemia (AML) and 29 with acute promyelocytic leukemia (APL). Median interval days were PI 14, DI 10, TI 4 and TTI 31.5. The TI and TTI intervals were lower in APL than in ALL and AML; TI 1 *vs.* 4 and 3 ($p = 0.001$) and TTI 21 *vs.* 31 and 35 ($p = 0.016$). The 30-day and 60-day EDs were 13.8% and 20.7%, mainly infections. ECOG > 2 (OR = 15.0) and PI < 7 days (OR = 4.06) were associated with 30-day ED; AML (OR = 2.69), high-risk (OR = 3.34), albumin < 3.5 g/dl (OR = 5) and platelets < 20 × 10^3/uL (OR = 2.71) with a 60-day ED.

Conclusion: None of the interval-delays were associated with an ED. Intervals seemed to be longer in patients without an ED, except for the TI, probably because of "the waiting time paradox." Aggressive manifestations of disease may lead to shorter diagnostic intervals, but increased mortality.

Introduction

Acute leukemias (ALs) are malignant hematological disorders with a high impact on the general population across the

* Correponding author at: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Belisario Domínguez, Tlalpan, 14080 Mexico City, Mexico.
E-mail address: roberta.demichelisg@incmnsz.mx (R. Demichelis-Gómez).

https://doi.org/10.1016/j.htct.2023.05.010

world. They are responsible for many cancer-related deaths and constitute a considerable healthcare cost burden.[1-2]

Prognostic factors in AL have changed due to risk-adapted treatment regimens, but in general, they depend on baseline characteristics, including, age, comorbidities, leukocyte count and genetic and molecular abnormalities, and show extensive disease heterogeneity.[3-6]

There is a well-described association between delays in diagnosis and poor outcomes in some solid tumors[7]; however, data gathered from those studies cannot be applied to hematological malignancies due to their rarity, insidious clinical presentation and the need for specific laboratory tests, resulting in difficult diagnostic pathways that usually require multiple primary care consultations.[8]

The AL has been associated with a shorter time to diagnosis, compared to other hematological malignancies,[9-11] but its impact on an early death (ED) or long-term outcomes in adults has not been well-established. Recently, time of diagnosis to treatment has been explored in AML and showed no relation to survival[12]; however, a previously study has shown that delaying treatment does not seem harmful in older patients, but is detrimental in younger patients.[13] Some studies on the pediatric population with AL did not show a significant association between delay intervals and an ED.[14-16]

The pathway leading to cancer diagnosis and initiating treatment has been historically longer in middle-income countries (MICs). Both are associated with advanced-stage disease and contribute to high mortality rates in these countries.[17] Mexico, like other MICs, faces many challenges in caring for patients with cancer, including the turnaround time for getting all the results and the limited availability of such tests might delay the initiation of the treatment. The number of practicing physicians is lower than that recommended by The Organization for Economic Co-operation and Development; there is < 1 hematologist/100,000 people and the medical attention is centralized in big cities.[18]

This study was performed at an academic hematology center in Mexico City and evaluated the time intervals between the first symptoms to the initiation of the treatment in adults with newly diagnosed AL and the effect on the ED.

Patients and methods

Population study

We evaluated all consecutive patients ≥ 18 years with newly diagnosed acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or acute promyelocytic leukemia (APL) by the WHO criteria[19] from January 2015 to March 2020, in the Hematology Department of the *Instituto Nacional de Ciencias Médicas y Nutrición* in Mexico City. Patients treated at the same Institution with secondary leukemia caused by the primary disease, who refused any treatment or did not have a follow-up, were excluded.

Study design

This retrospective cohort study included data extracted from the electronic medical record, baseline characteristics, such as age, with the adolescent and young adult (AYA) being < 39 years, gender, body mass index (BMI), socioeconomic level classification (low versus not low),[20] education, Charlson comorbidity index (CCI), Eastern Cooperative Oncology Group (ECOG) performance status (0–2 versus > 2), presence of comorbidities, complete blood count (CBC), blast count in bone marrow aspiration, liver function tests (LFTs), creatinine level (mg/dl), presence of symptoms, fever, infection, tumor lysis syndrome (TLS), according to the Cairo-Bishop criteria, and number of consultations after the first symptoms were recorded. The AML was classified as low-, intermediate-, or high-risk, according to the European Leukemia Net.[4] The APL was classified as low-, intermediate-, or high-risk as per the Sanz criteria.[5] The ALL was classified as high-risk, according to the presence of at least one of the following criteria: hyperleukocytosis (white blood cells 30 × 109/L for B-cell ALL or > 100 × 109/L for T-cell ALL), or a complex karyotype.[6] The chemotherapy was classified as intensive (Hyper-CVAD,[21] CALGB 10,403[22], 7 + 3 (7-day continuous infusion of cytarabine 100 to 200 mg/m2 associated with an anthracycline on days 1 to 3) and AIDA regimens[23]), non-intensive (mini-Hyper-CVAD without the antibody-drug conjugate therapy,[24] low-dose cytarabine (20 mg subcutaneous twice per day on days 1 to 10), azacytidine monotherapy (75 mg/m2 subcutaneous per day on days 1 to 7)) or palliative (support treatment only)), according to the medical decision and available institutional regimens. The support treatment included prophylactic antibiotics, according to the ASCO/IDSA guidelines[25] and the use of granulocyte colony-stimulating factor during neutropenic fever after the induction scheme, according to the treating physician. We defined the following intervals (number of days): patient interval (PI), from the first symptom to the first medical consultation (including symptomatic patients only); diagnostic interval (DI), from the first medical consultation to the diagnosis (the day of the bone marrow aspiration); treatment interval (TI), from the diagnosis to treatment initiation (including patients who received chemotherapy, or in APL patients, the day of the administration of the all-trans retinoic acid); total time interval (TTI), from the first symptom to the treatment initiation. We evaluated the complete response (CR) after the induction treatment and estimated overall survival (OS) to define the response to the treatment. The CR was established in accordance with the Cheson criteria, that states the absence of extramedullary leukemia, the lack of peripheral blood blasts, a bone marrow blast percentage below 5%, a neutrophil count ≥ 1.5 × 10^9/L, and platelets ≥ 100 × 10^9/L.[26] The OS was the time interval between the diagnosis and the patient's death or the last day of the follow-up. Interval delays refer to periods over the interquartile range (IQR) of the median time expected. The ED was defined as that which occurred within 60 days of the diagnosis. We divided the ED into 30-day mortality and 60-day mortality to analyze the associated factors because both periods have been previously reported in the literature.

Statistical analysis

Standard descriptive statistics were expressed as median and IQR or mean and standard deviation, according to the normality, or, when appropriate, absolute counts and percentages.

Differential characteristics of groups of patients according to the leukemia type and interval delay were compared by statistical tests (the $\chi 2$ test for categorical variables, Student's *t*-test and the ANOVA test for parametric variables and the Mann–Whitney U test and Kruskal–Wallis test for non-parametric variables). We considered a p-value < 0.05 statistically significant. The Kaplan–Meier approach was chosen for the OS, using the log-rank test. We calculated the odds ratio (OR) and performed a logistic regression to identify factors associated with an increased risk for an ED, including variables that were statistically significant ($p < 0.05$) in the univariate analysis. All analyses were performed with the SPSS software (version 22).

Results

Baseline characteristics

A total of 188 patients with newly diagnosed AL met the eligibility criteria and 96 (51%) of these were women, the median age was 37 years (IQR, 24–54) and 54.8% were AYA. The median BMI was 25.2 (IQR, 22.7–29.3) and 19.7% were obese (BMI > 30); 71 patients (37.8%) had at least one comorbidity; 12.2% had diabetes mellitus, 60.4% had a CCI < 3, and 95.7% (180 patients) had an ECOG of 0–2. Only 44.1% (83 patients) were residents of Mexico City; 20% (39 patients) had a university degree and 80.3% had a low socioeconomic level (LSL). Related symptoms were present in 97.3% of the patients. The patients consulted with a median of three physicians (IQR, 2–4) before consulting with a hematologist. The first medical contact was a primary care physician (63.2%) and the remaining went to the emergency room. There was no difference in the previous variables compared between AL subtypes.

The more prevalent AL was ALL in 102 patients (54.3%), followed by AML, 57 patients (30.3%) and APL, 29 patients (15.4%). According to the previously mentioned criteria, of 184 patients, 61.2% were high-risk, 31.4%, standard/intermediate-risk and 5.3%, favorable-risk; 4 patients had no risk classification due to incomplete data. The blood test, clinical characteristics and the median interval times of the ALs are shown in Table 1 and Figure 1.

Outcomes and mortality

Intensive induction therapy, according to the institutional protocol, was offered to 164 patients (87.2%), non-intensive induction therapy to 13 patients (6.9%) and palliative care to 11 patients (5.9%) (Table 2). After the diagnosis, the median hospital stay was 34 days (IQR, 26–44). The induction complications: pneumonia in 42%, blood-stream infection, 38%, septic shock, 27%, acute complicated urinary tract infection, 23%, sinusitis, 17%, soft tissue infection (STI), 16%, *Clostridioides difficile* infection, 11%, neutropenic enterocolitis, 8%, odontogenic infection, 7%; hepatotoxicity 35% (G3 - 4 in 37 patients), bleeding, 33% (G3 - 4 in 31 patients), acute kidney injury, 22% (G3 in 13 patients), ischemic stroke, 1.5%, and; appendicitis, 5%. Forty-eight patients (25.5%) required intensive care and 34 (18%), invasive mechanical ventilation.

The gram-negative bacilli (42.6%) and gram-positive cocci (8.5%) were identified in culture isolates. In total, 57 patients were suspected of having a fungal infection and, among these, 22 (12.5%) had a proven fungal infection. The previous complications that were different among the AL types are shown in Table 2.

Table 1 – Clinical characteristics of acute leukemias.

n = 188 patients (%)	ALL 102 (54.3)	AML 57 (30.3)	APL 29 (15.4)	*p*-value
Age, years (IQR)	30 (23–49)	47 (34–63)	40 (26–51)	< 0.001
AYA (%)	65 (63.7)	24 (42.1)	14 (48.3)	0.024
WBC x $10^3/\mu$L (IQR)	11.3 (2.6–72.3)	17.7 (4.4–74.3)	2.1 (0.8–24.5)	0.006
Hb g/dL (SD)	8.5 ± 3	8.1 ± 2.3	8.7 ± 2.4	NS
Platelet x $10^3/\mu$L (IQR)	35.5 (14–68)	26 (13–66)	23 (11–43)	NS
Creatinine, mg/dl (IQR)	0.86 (0.62–0.90)	0.59 (0.46–0.72)	0.80 (0.62–0–88)	NS
LDH, UI/L (IQR)	593 (294–1109)	538 (284 – 1011)	409 (224–656)	NS
Fibrinogen, mg/dl (IQR)	341 (250–447)	369 (318–460)	147 (90–212)	< 0.001
Albumin, mg/dl (IQR)	3.9 (3.4–4.2)	3.8 (3.4–4.1)	4.2 (4–4.4)	0.028
Abnormal LFT (%)	31 (30.4)	2 (3.5)	3 (10.3)	< 0.001
TLS (%)	23 (22.5)	4 (7)	2 (6.9)	0.013
Blast% (IQR)	80 (62–90)	59 (46–72)	80 (62–88)	< 0.001
High risk (%)	76 (74.5)	30 (52.6)	9 (31)	
Intermediate risk (%)	25 (24.5)	17 (29.8)	17 (58.6)	< 0.001
Favorable risk (%)	0	7 (12.3)	3 (10.3)	
PI days (IQR)	14 (7–27)	15 (5–30)	10 (6–17)	NS
DI days (IQR)	10 (5–23)	10 (6–20)	9 (6–13)	NS
TI, days (IQR)	4 (3–6)	3 (2–6)	1 (1–3)	0.008
TTI, days (IQR)	35 (22–58)	31 (18–60)	21 (16–31)	0.016

ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; APL: acute promyelocytic leukemia; IQR: interquartile range; AYA: adolescents and young adults; WBC: white blood count; LFT: liver function test; TLS: tumor lysis syndrome; TTI: total interval; TI: treatment interval; CTX: chemotherapy; WHO: World Health Organization; AKI: acute kidney injury; KDIGOs: kidney disease improving global outcomes; CR: complete response; OS: overall survival.

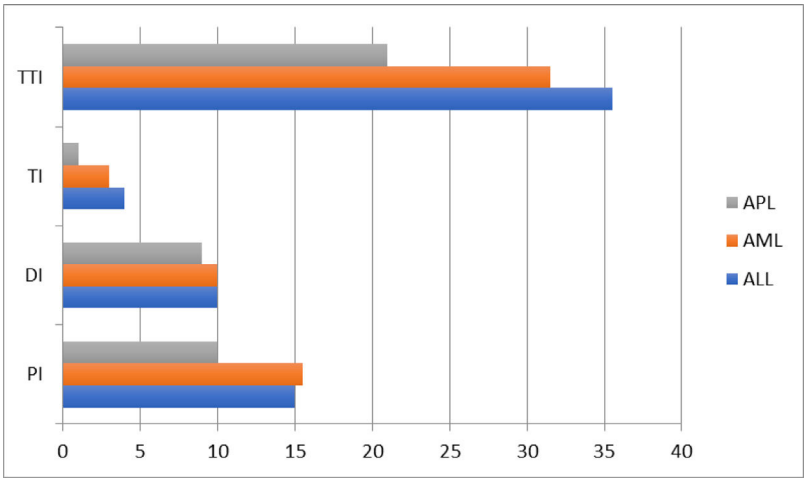

Figure 1 – Time intervals (days) of acute leukemias.PI: Patient interval; DI: Diagnostic interval; TI: Treatment interval; TTI: Total interval; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; APL: acute promyelocytic leukemia.

The CR was achieved in 76.6% of the AL patients. An ED occurred in 39 patients (20.7%). The main causes of the ED were infection in 25 patients (64%), bleeding in 5 (12.8%) and other causes in 9 (23%). Most of them (66%) died in the first 30 days. At the time of the analysis, 51.5% of the cases had survived (ALL, 47.1%, AML, 43.9%, and APL, 82.8%; $p = 0.001$), with a median follow-up of 12.9 months (IQR, 3.86 – 25.6) (Table 2). The median OS of each type of AL is shown in the Figure 2, with ALL at 19.5 months (95% CI 14.5–24.6), AML, 14 months (95% CI 2–26), and APL not reached.

Factors associated with early death

All the variables associated with an ED are shown in Table 3. In patients with an ED ($n = 39$, 20.7%), none of the intervals were statistically significant, compared to those who survived ($n = 149$, 79.3%). Among patients with an ED in the first 30 days ($n = 26$, 13.8%), compared to those who survived ($n = 162$, 86.2%), the PI was 7 days (IQR, 2–13) vs. 15 days (IQR, 7–28; $p = 0.004$), respectively.

Time intervals delays

Forty-six patients (24.4%) met the criteria for the TTI delay (> 52 days). When compared to patients without the TTI delay criteria ($n = 142$, 75.6%), we found that the main associated factors in the univariate analysis that prevented the TTI delay were the first medical contact at the emergency room ($p = 0.019$) and the presence of fever at diagnosis ($p = 0.042$).

Thirty-nine patients (21.3%) had a PI delay (> 27 days), compared to those who did not ($n = 149$, 78.7%). An infection at diagnosis ($p = 0.041$), ICU at admission ($p = 0.041$) and a lower first 30-day mortality ($p = 0.022$) were statistically significant protective factors. Furthermore, patients with a PI delay

Table 2 – Outcomes and complications between acute leukemias.

$n = 188$ patients (%)	ALL 102 (54.3)	AML 57 (30.3)	APL 29 (15.4)	p-value
Intensive induction (%)	93 (91.2)	43 (75.4)	28 (96.6)	
Non-Intensive (%)	4 (3.9)	9 (15.8)	0	0.014
Palliative care (%)	5 (4.9)	5 (8.8)	1 (3.4)	
Shock (%)	36 (35.3)	11 (19.3)	4 (13.8)	0.020
Pneumonia (%)	31 (30.4)	33 (57.9)	15 (51.7)	0.002
Blood-stream infection (%)	49 (48)	18 (31.6)	5 (17.2)	0.005
Bleeding, G2–4 WHO (%)	21 (20.6)	14 (24.6)	17 (58.6)	< 0.001
Ischemic Stroke (%)	1 (1)	0	2 (6.9)	0.042
AKI, G2–3 KDIGO (%)	11 (10.8)	16 (28.1)	4 (13.8)	0.017
Neutropenic enterocolitis (%)	5 (4.9)	9 (15.8)	2 (6.9)	NS
CR post induction (%)	85 (83.3)	35 (61.4)	24 (82.8)	0.005
30-day mortality (%)	12 (11.8)	11 (19.3)	3 (10.3)	NS
60-day mortality (%)	17 (16.7)	17 (29.8)	5 (17.2)	0.043
Infection ED (%)	11 (10.8)	10 (17.5)	4 (13.8)	
Bleeding ED (%)	3 (2.9)	1 (1.8)	1 (3.4)	NS
Other ED (%)	3 (2.9)	6 (10.5)	0	
Follow-up, months (IQR)	13.3 (5.5–23.5)	7.4 (1.8–19.9)	21 (6–40.6)	0.018

ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; APL: acute promyelocytic leukemia; WHO: World Health Organization, KDIGOs: kidney disease improving global outcomes; ED: early death; IQR: interquartile range.

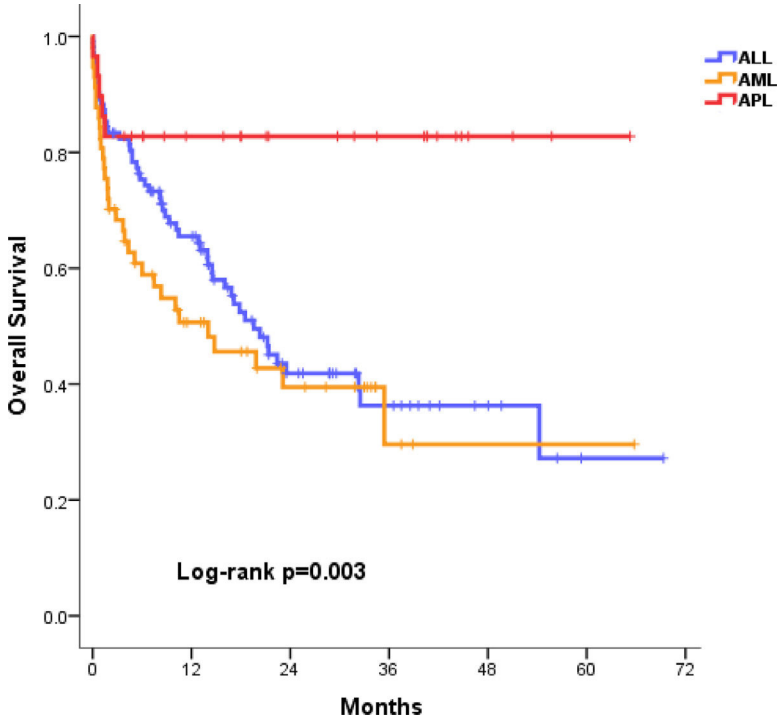

Figure 2 – Overall survival between AL types. Kaplan–Meir curve.ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; APL: acute promyelocytic leukemia.

had a longer DI (15 *vs.* 9 days; $p = 0.012$), lower hemoglobin levels (7.26 *vs.* 8.6 g/dl; $p = 0.039$), higher albumin levels (4.1 *vs.* 3.9 g/dl; $p = 0.015$), and a longer hospital stay (38 *vs.* 33 days; $p = 0.039$).

Forty-two patients (22.3%) had a DI delay (> 20 days), compared to those who did not ($n = 146$, 87.3%). The first medical contact at the emergency room ($p = 0.024$), neutropenic colitis ($p = 0.032$) and the STI ($p = 0.001$) were statistically significant protective factors. Furthermore, patients with a delayed DI had a lower BMI (24.1 *vs.* 25.9; $p = 0.038$), lower creatinine levels (0.74 *vs.* 0.86 mg/dl; $p = 0.006$) and longer TI (5 *vs.* 3 days; $p = 0.002$), compared to those who did not.

Twenty-five patients (14.1%) had a TI delay (> 6 days). None of the patients with APL were included in the group with the TI delay. Up to 46.2% of the patients who received a low-intensity chemotherapy scheme were in the TI delay group ($p = 0.001$). Patients with a TI delay had an increased association with a higher ECOG > 2 ($p = 0.008$) and septic shock ($p = 0.014$), compared to those who did not ($n = 163$, 86.9%). Furthermore, patients with a TI delay had lower hemoglobin levels (7.05 *vs.* 8.4; $p = 0.012$), lower LDH levels (330 *vs.* 565 UI/L; $p = 0.026$), a higher number of previous consultations (4 *vs.* 3; $p = 0.025$) and a shorter follow-up (227 *vs.* 442 days; $p = 0.036$), compared to those without a TI delay. When the OS

Table 3 – Factors associated with early death in acute leukemia.

Characteristic	60-day mortality				30-day mortality			
	Univariate OR (95%CI)	*p*-value	Multivariate OR (95%CI)	*p*-val.	Univariate OR (95% CI)	*p*-val.	Multivariate OR (95%CI)	*p*-value
AYA	0.24 (0.11–0.52)	< 0.001			0.25 (0.10–0.63)	0.002		
AML	2.10 (1.01–4.36)	0.043	2.69 (1.01–7.18)	0.047				
High risk	2.99 (1.29–6.95)	0.008	3.34 (1.19–9.36)	0.022				
Comorbidities	2.64 (1.28–5.42)	0.007						
Infection at diagnosis	2.19 (1.03–4.66)	0.038			3.62 (1.54–8.53)	0.002		
LSL	3.06 (1.39–6.76)	0.004			2.53 (1.02–6.26)	0.039		
ECOG >2	32.3 (3.84–272.3)	0.001			24.0 (4.53–127.0)	< 0.001	15.0 (2.20 –1 03.3)	0.006
Albumin <3.5 g/dL	6.21 (2.90–13.2)	< 0.001	5.00 (1.66–14.9)	0.004	7.11 (2.91–17.3)	< 0.001		
Platelet <20 × $10^3/\mu$L	3.07 (1.48–6.37)	0.002	2.71 (1.10–6.67)	0.030				
Creatinine >1.2 mg/dl	3.88 (1.68–8.95)	0.001			3.55 (1.40–9.00)	0.005		
PI <7 days					2.80 (1.19–6.62)	0.015	4.06 (1.30–12.6)	0.016

OR: odds ratio; CI: confidence interval; AYA: adolescent and young adults; AML: acute myeloblastic leukemia; LSL: low-socioeconomic level; PI: patient interval.

Table 4 – Previous published studies describing diagnosis and treatment intervals in adults with acute leukemia.

Type	PI	DI	TI	TTI	Reference
AML	13d (IQR, 1–47)	10 d (IQR, 5–32)	NS	41 d (IQR,17–85)	Howell DA, et al.[9] UK
	NS	NS	3 d (IQR, 2–7)	NS	Röllig C, et al.[12] DE
	4 w (range, 1–52)	NS	NS	NS	Philip C, et al.[27] IN
	15 d (IQR, 5–30)	10 d (IQR, 6–20)	3 d (IQR, 2–6)	31 d (IQR, 18–60)	This study, MX
APL	14 d	NS	NS	NS	McClellan JS, et al.[31] US
	NS	NS	1 d	NS	Rashidi A, et al.[32] US
	10 d (IQR, 6–17)	9 d (IQR, 6–13)	1 d (IQR, 1–3)	21 d (IQR, 16–31)	This study, MX
ALL	16 d (IQR, 2–26)	12 d (IQR, 3–32)	NS	32 d (IQR, 17–64)	Howell DA, et al.[9] UK
	14 d (IQR, 7–27)	10 d (IQR, 5–23)	4 d (IQR, 3–6)	35 d (IQR, 22–58)	This study, MX

PI: Patient interval; DI: Diagnostic interval; TI: Treatment interval; TTI: Total interval; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; APL: acute promyelocytic leukemia; NS: Not specified, d: days, w: weeks.

of patients with and without a TI delay was analyzed by the Kaplan-Meier method, it was not statistically significant (log rank, $p = 0.136$).

None of the interval delays were associated with an ED.

Discussion

In this study, we described the characteristics of a large young (54% AYA) and economically active population of patients with an AL who live outside of Mexico City. We found that the median interval times were: PI, 14 days (IQR, 6–27), DI, 10 days (IQR, 6–20), TI, 4 days (IQR, 2–6) and TTI, 31.5 days (IQR, 20–52).

The median interval times (PI, DI, TI, TTI) reported in our study population were not different, compared to those in other studies, or even those in high-income countries (HICs), as shown in Table 4. However, some limitations of those studies hinder the data interpretation of their results and limit the comparison to our study. In a United Kingdom study, the data were collected by questionaries delivered several weeks after the diagnosis was made. Only patients who were not severely ill (and alive) could fill them out.[9] In a study from India, only patients who received treatment (a third part) had a shorter PI.[27]

Our study demonstrated that AL patients were younger and had a slight superiority of ALL to AML, compared to HIC patients.[28] This is consistent with the epidemiology in Latin America and other developing countries.[28-29] Unfortunately, more than 1 of 5 patients in our study presented with an ED, the majority due to infections, followed by bleeding complications, similar to the data reported around the world: AML in India, 24.7%,[27] Brazil, 26%[30]; APL in the USA 17–26%,[31-32] Brazil, 20%,[33] and; ALL in Brazil, 17%.[34]

The variables at diagnosis associated with ED (60-day mortality) in the multivariate analysis were the presence of AML, a high-risk stratification, hypoalbuminemia and a low platelet count. However, we acknowledge that they may differ among leukemia subtypes. When the ED in the first 30 days was analyzed, the associated risk factors were an ECOG > 2 and a PI < 7 days. We found that a PI less than 7 days was a risk factor for an ED in the first 30 days (OR = 4.05, 95%CI 1.30–12.6; $p = 0.016$). This finding has been previously reported in a study from China, where the APL patients with an ED had a shorter interval from the onset of symptoms to the diagnosis.[35] Delays in any of the time intervals were not a risk factor for the ED. However, all the intervals, except for the TI, seem to be longer in patients without an ED. In a pediatric population with cancer (including AL), Jin *et al.* found that a longer PI had a longer OS,[36] probably because of "the waiting time paradox." An aggressive manifestation of the disease may be easier to approach, leading to shorter diagnostic intervals, but also has an increased mortality.[37] This finding was supported by our results because these patients had a higher frequency of severe manifestations, such as fever and infection at diagnosis, ICU admission and hypoalbuminemia. Other studies in AML,[27,38] APL,[32,35] and ALL[16] have also reported no association between delays in treatment initiation and death. Surprisingly, we did not find an association between interval delays and age, gender or socioeconomic level, factors that have been previously associated with hematologic malignancies in adults.[9,39]

In our study population, with patients who are younger and present more ALL and APL and have a higher probability of survival, it could be wise to adopt a navigation patient model, a promising intervention that addresses cancer disparities and allows for a reduction in times, despite the challenges of a MIC, with the lack of infrastructure, human resources and funds,[40] and with the goal of increasing survival as a result of decreasing complications.

Our study should be interpreted in the context of its limitations. First, due to the nature of the study design, there could had been bias in the data retrieval. However, since we consecutively analyzed the data of every patient with AL types diagnosed and treated at our hospital, this should be an issue. Finally, this information is from one center, although it is a reference center for hematologic diseases, we cannot effectively rule out partial population skewing.

Nevertheless, to our knowledge, this study is the first in an adult population with an AL using real-world data in a MIC setting that reports an insight on the intervals from the first symptom to the initiation of the treatment and its association with early outcomes. Furthermore, we have accounted for all possible confounders in the multivariable analysis to reduce bias to a minimum. We also thoughtfully described baseline characteristics of the AL patients and induction chemotherapy complications. In conclusion, in our adult Mexican

population with newly diagnosed AL, interval delays did not impact early outcomes.

Ethics approval

The protocol was approved by the local ethics committee (The *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* Research and Ethics Committees, reference number HEM-4063-22-22-1).

Financial declaration

The present study was partially financed by the Carlos Slim Foundation (*Becas Impulso a la Investigación en Salud*).

Conflicts of interest

No potential conflicts of interest were reported by the authors.

Acknowledgement

We thank all of the patients and their families, who trusted us and contributed to improve our knowledge on this disease, and Sergio Lozano–Rodríguez, M.D., for his critical review of the manuscript.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Redaelli A, Stephens JM, Laskin BL, Pashos CL, Botteman MF. The burden and outcomes associated with four leukemias: AML, ALL, CLL and CML. Expert Rev. Anticancer Ther. 2003;3:311–29.
3. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med. 2004;350(15):1535–48.
4. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–47.
5. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, et al. Management of acute promyelocytic leukemia: recommendations from an expertpanel on behalf of the European LeukemiaNet. Blood. 2009;113(9):1875–91.
6. Brown PA, Shah B, Advani A, Aoun P, Boyer MW, Burke PW, et al. Acute lymphoblastic leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(9):1079–109.
7. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer. 2015;112(Suppl 1):S92–107.
8. Dapkevičiūtė A, Šapoka V, Martynova E, Pečeliūnas V. Time from symptom onset to diagnosis and treatment among haematological malignancies: influencing factors and associated negative outcomes. Medicina (Kaunas). 2019;55(6):. pii: E238.
9. Howell DA, Smith AG, Jack A, Patmore R, Macleod U, Mironska E, et al. Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the haematological malignancy research network. BMC Hematol. 2013;13(1):9.
10. Chukwu BF, Ezenwosu OU, Ikefuna AN, Emodi IJ. Diagnostic delay in pediatric cancer in Enugu, Nigeria: a prospective study. Pediatr Hematol Oncol. 2015;32(2):164–71.
11. Fajardo-Gutiérrez A, Sandoval-Mex AM, Mejía-Aranguré JM, Rendón-Macías ME, Martínez-García Mdel C. Clinical and social factors that affect the time to diagnosis of Mexican children with cancer. Med Pediatr Oncol. 2002;39(1):25–31.
12. Röllig C, Kramer M, Schliemann C, Mikesch JH, Steffen B, Krämer A, et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? Blood. 2020;136(7):823–30.
13. Sekeres MA, Elson P, Kalaycio ME, Advani AS, Copelan EA, Faderl S, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. Blood. 2009;113(1):28–36.
14. Lins MM, Amorim M, Vilela P, Viana M, Ribeiro RC, Pedrosa A, et al. Delayed diagnosis of leukemia and association with morbid-mortality in children in Pernambuco, Brazil. J Pediatr Hematol Oncol. 2012;34(7):e271–6.
15. Lepe-Zuniga JL, Ramirez-Nova V. Elements associated with early mortality in children with B cell acute lymphoblastic leukemia in chiapas, mexico: a case-control study. J Pediatr Hematol Oncol. 2019;41(1):1–6.
16. Wahl SK, Gildengorin G, Feusner J. Weekend delay in initiation of chemotherapy for acute lymphoblastic leukemia: does it matter? J Pediatr Hematol Oncol. 2012;34(1):e8–e11.
17. Goss PE, Lee BL, Badovinac-Crnjevic T, Strasser-Weippl K, Chavarri-Guerra Y, St Louis J, et al. Planning cancer control in Latin America and the Caribbean. Lancet Oncol. 2013;14(5):391–436.
18. Heinze-Martin G, Olmedo-Canchola VH, Bazán-Miranda G, Bernard-Fuentes NA, Guízar-Sánchez DP. Los médicos especialistas en México. Gac Med Mex. 2018;154(3):342–51.
19. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
20. López-Romo H. Nivel Socioeconómico AMAI [Socioeconomic Level AMAI]. Mexico city: Asociación Mexicana de Agencias de Investigación de Mercado y Opinión Pública; 2008.
21. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000;18(3):547–61.
22. Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood. 2019;133(14):1548–59.
23. Sanz MA, Martín G, González M, León A, Rayón C, Rivas C, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. Blood. 2004;103(4):1237–43.
24. Kantarjian H, Ravandi F, Short NJ, Huang X, Jain N, Sasaki K, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. Lancet Oncol. 2018;19(2):240–8.
25. Taplitz RA, Kennedy EB, Flowers CR. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression:

ASCO and IDSA clinical practice guideline update summary. J Oncol Pract. 2018;14(11):692–5.
26. Cheson BD, Cassileth PA, Head DR, Schiffer CA, Bennett JM, Bloomfield CD, et al. Report of the National Cancer Institute sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. J Clin Oncol. 1990;8(5):813–9.
27. Philip C, George B, Ganapule A, Korula A, Jain P, Alex AA, et al. Acute myeloid leukaemia: challenges and real world data from India. Br J Haematol. 2015;170(1):110–7.
28. Gómez-Almaguer D, Marcos-Ramírez ER, Montaño-Figueroa EH, Ruiz-Argüelles GJ, Best-Aguilera CR, López-Sánchez MD, et al. Acute leukemia characteristics are different around the world: the Mexican perspective. Clin Lymphoma Myeloma Leuk. 2017;17(1):46–51.
29. Crespo-Solis E, Espinosa-Bautista K, Alvarado-Ibarra M, Rozen-Fuller E, Pérez-Rocha F, Nava-Gómez C, et al. Survival analysis of adult patients with ALL in Mexico City: first report from the Acute Leukemia Workgroup (ALWG) (GTLA). Cancer Med. 2018;7(6):2423–33.
30. Fernandes da Silva, Junior W, Medina AB, Yamakawa PE, Buccheri V, Velloso EDRP, Rocha V. Treating adult acute lymphoblastic leukemia in Brazil-increased early mortality using a german multicenter acute lymphoblastic leukemia-based regimen. Clin Lymphoma Myeloma Leuk. 2018;18(6):e255–9.
31. McClellan JS, Kohrt HE, Coutre S, Gotlib JR, Majeti R, Alizadeh AA, et al. Treatment advances have not improved the early death rate in acute promyelocytic leukemia. Haematologica. 2012;97(1):133–6.
32. Rashidi A, Riley M, Goldin TA, Sayedian F, Bayerl MG, Aguilera NS, et al. Delay in the administration of all-trans retinoic acid and its effects on early mortality in acute promyelocytic leukemia: final results of a multicentric study in the United States. Leuk Res. 2014;38(9):1036–40.
33. Da Silva WF, Rosa LID, Marquez GL, Bassolli L, Tucunduva L, Silveira DRA, et al. Real-life outcomes on acute promyelocytic leukemia in Brazil—early deaths are still a problem. Clin Lymphoma Myeloma Leuk. 2019;19(2):e116–22.
34. Mendes FR, da Silva WF, da Costa, Bandeira de Melo R, Silveira DRA, Velloso EDRP, Rocha V, et al. Predictive factors associated with induction-related death in acute myeloid leukemia in a resource-constrained setting. Ann Hematol. 2022;101(1):147–54.
35. Xu F, Wang C, Yin C, Jiang X, Jiang L, Wang Z, et al. Analysis of early death in newly diagnosed acute promyelocytic leukemia patients. Medicine (Baltimore). 2017;96(51):e9324.
36. Jin SL, Hahn SM, Kim HS, Shin YJ, Kim SH, Lee YS, et al. Symptom interval and patient delay affect survival outcomes in adolescent cancer patients. Yonsei Med J. 2016;57(3):572–9.
37. Gupta S, Gibson P, Pole JD, Sutradhar R, Sung L, Guttmann A. Predictors of diagnostic interval and associations with outcome in acute lymphoblastic leukemia. Pediatr Blood Cancer. 2015;62(6):957–63.
38. Bertoli S, Bérard E, Huguet F, Huynh A, Tavitian S, Vergez F, et al. Time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome of patients with acute myeloid leukemia. Blood. 2013;121(14):2618–26.
39. Obtel M, Berraho M, Abda N, Quessar A, Zidouh A, Bekkali R, et al. Factors associated with delayed diagnosis of lymphomas: experience with patients from hematology centers in morocco. Asian Pac J Cancer Prev. 2017;18(6):1603–10.
40. Bukowski A, Chávarri-Guerra Y, Goss PE. The potential role of patient navigation in low- and middle-income countries for patients with cancer. JAMA Oncol. 2016;2(8):994–5.