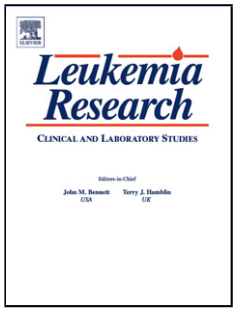

Acute undifferentiated leukemia: data on incidence and outcomes from a large population-based database

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Acute undifferentiated leukemia: data on incidence and outcomes from a large population-based database

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Keywords
acute; undifferentiated; leukemia; incidence; prognosis

Highlights

- SEER data for acute undifferentiated leukemia (AUL) 2000- 2016
- AUL is rare and occurs mostly in older patients
- AUL has decreased in incidence
- The prognosis of AUL is often poor, but has improved
- In the pediatric age group, the prognosis is comparable to ALL

ABSTRACT

Acute undifferentiated leukemia (AUL) is rare and defined by the absence of bona fide myeloid and lymphoid markers. Little is known about its incidence, survival and optimal management in the recent time period. Based on a case observed in our clinic, we queried the Surveillance, Epidemiology, and End Results database between 2000 and 2016. A total of 1,888 cases of AUL were diagnosed (1.34 per million person-years). The incidence of AUL has significantly decreased over time. Compared to other acute leukemias, patients with AUL have the highest median age (74 years); in contrast to acute myeloid leukemia (AML, 65) and acute lymphoblastic leukemia (ALL, 12). Excluding patients with preexisting malignancies, 1,444 patients with AUL were analyzed for survival. Only 35% of AUL patients had received chemotherapy. Comparatively, 94% of ALL and 71% of AML cases received chemotherapy. Among AUL patients who received chemotherapy, the median survival was 12 months as opposed to 1 month in the group who did not receive chemotherapy (or unknown status). Among adults, AUL patients had the worst prognosis, with a median overall survival (OS) of 9 months, compared to 27 months in ALL and 13 months in AML. Among children, the median OS was superior for all three groups of leukemias, the OS of AUL patients being better than in AML and very similar to ALL. On multivariate analysis older age and time period were associated with worse outcome. We describe here the largest series of cases with AUL published to date.

Key Points:

- Acute undifferentiated leukemia is rare, occurs mostly in older patients and has decreased in incidence.

- The prognosis of undifferentiated leukemia is often poor, but has improved, especially in younger patients treated with chemotherapy

1. INTRODUCTION

The last three or four decades have seen significant progress in the diagnosis and treatment of acute leukemias.[1,2] No longer a universally fatal disease, acute leukemia has become treatable and, in many instances, curable. Using immunologic and molecular markers, many different prognostic types of acute leukemia are recognized. Acute undifferentiated leukemia (AUL) is rare and has neither lymphoid nor myeloid lineage specific markers. In the 2016 update of the World Health Organization (WHO) classification of myeloid neoplasms, AUL is listed as a subcategory of mixed phenotype acute leukemia.[3] In an earlier epidemiologic study, an incidence of 1.6 cases per 1 million person-years was described.[4] Based on a case of AUL observed in our clinic, we queried the Surveillance, Epidemiology, and End Results (SEER) registry database and reviewed the pertinent literature.

2. PATIENTS AND METHODS

Case

A 62-year-old male patient presented to the emergency room in December of 2018 with complaints of abdominal pain and increasing fatigue. A complete blood count revealed mild thrombocytopenia. A computed tomography scan of his abdomen revealed splenomegaly and peripheral blood smears identified circulating blasts. Other than hyperlipidemia, the patient had no other chronic medical conditions. The physical examination was normal without palpable lymphadenopathy or hepatosplenomegaly. A bone marrow biopsy was performed (A summary of his laboratory features is shown in Table 1). Figure 1A shows a high-power view of the blasts. Figure 1B shows the expression of selected surface markers. Using a complete leukemia panel, no lineage-specific markers were expressed. Therefore, the diagnosis of AUL was made. He was treated with the "7+3" protocol (cytosine arabinoside 100 mg/m^2 continuous intravenous infusion days 1-7 and daunorubicin 60 mg/m^2 day 1-3). However, the day-14 follow-up bone marrow biopsy showed persistent leukemia with 30% blasts. Therefore, the decision was made to switch chemotherapy to hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD). The patient achieved complete remission after cycle 1A. However, his performance status declined and his tolerance of further hyper-CVAD cycles was questioned. Given the presence of *GATA2*, *NF1* and *BCOR* mutations, which suggested myeloid lineage, consolidation therapy with high-dose cytosine arabinoside was given. He achieved complete molecular remission by next-generation sequencing (NGS) after two cycles. Unfortunately, he developed cerebellar toxicity after the second cycle. Subsequently, three cycles of decitabine maintenance were given without major complications. Because of chemotherapy toxicities and lack of social support, the patient was not deemed to be an appropriate candidate for allogeneic stem cell transplantation. He continues regular follow-up in our clinic and remains in complete remission eleven months after his initial diagnosis.

Patients in the SEER registry

We used data obtained from registries participating in the National Cancer Institute's SEER registry that covers 27% of the population in the United States (U.S.).[5] The SEER registry database was used to identify all AUL diagnoses between 2000 and 2016 (SEER*Stat Database named: "Incidence - SEER 18 Regs Custom Data, with additional treatment fields, Nov 2018 Sub (2000-2016) <Katrina/Rita Population Adjustment>). All cases were microscopically confirmed as per SEER criteria. All newly diagnosed cases (n = 1,888) were included to estimate incidence rates.

However, in order to reduce bias, patients with a preceding different malignancy (n = 444) were excluded from survival analysis. In order to compare survival, patients diagnosed with microscopically confirmed acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) in the same period and not having preceding different malignancy were also included for comparative purposes. Table 2 summarizes The International Classification of Diseases for Oncology codes that were included to identify the cases of each group.

Statistical analysis

The baseline characteristics of the three groups of patients were compared. Median age was compared using Kruskal-Wallis test. Age group, sex, race/ethnicity, year of diagnosis and use of chemotherapy were compared using Fischer-exact test. Incidence rates of AUL were calculated and age-adjusted according to the 2000 U.S. Standard Population (19 age groups – census P25-1130). Annual percentage change was estimated using the weighted least square method to measure trends of AUL over the time period between 2000 and 2016. For survival analysis, the follow-up time was limited to 60 months and was calculated based on date of diagnosis and date of last contact. The patients were further divided into two separate subgroups: pediatric (age < 18 years) and adult (age ≥18 years). Survival function was estimated using the Kaplan-Meier method and comparisons were made using the long-rank test. All factors with p-values <0.1 in univariate analysis were entered in a backward-method multivariate Cox proportional hazard ratio model. All statistical analyses were performed using the MedCalc® 18.11.6 and SEER*Stat® 8.3.5 software.

3. RESULTS

Incidence rates and baseline characteristics

Between 2000 and 2016, a total of 1,888 cases of AUL were diagnosed corresponding to an age-adjusted incidence rate of 1.34 per 1,000,000 person-years. The incidence of AUL has decreased significantly over time, with an estimated annual percentage change of –7.37% (95% confidence intervals [CI]: –8.91% to –5.80%), p < 0.0001. Overall, and similar to other acute leukemias, AUL is much more frequent in older age groups. The incidence rates per age and sex is presented in Table 3 and the trend over time is shown in Figure 2.

Patients with AUL have the highest median age (74 years old) compared to patients with acute myeloid leukemia (AML) (65 years) and patients with acute lymphoblastic leukemia (ALL) (12 years). Seventy one percent of the patients with AUL were 60 years or older. Sex was comparable among the three groups. With regards to year of diagnosis, 44% of the AUL cases were diagnosed between 2000 and 2004. By comparison, only 29% and 27% of the AML and ALL cases were diagnosed in the same period, respectively. Only 35% of AUL patients were coded as "received chemotherapy" (versus no chemotherapy or unknown). On the other hand, 71% and 94% of AML and ALL cases were coded as received chemotherapy. The baseline characteristics of all patients are shown in Table 4.

Survival analysis for AUL

Among all patients with AUL as a whole group (n = 1,444), the median OS was two months (CI: could not be calculated). Age was a very strong predictor of OS. If adults (age ≥18 years, n =1,328) and children (age < 18 years, n=116) are analyzed separately, the median OS for patients whose age is 18-39 years was 19 months (CI: 13-30) compared to six months (CI: 4-10) and one month (CI: 1-2) among those whose age was 40-59 and 60+, respectively. The one-year OS among the

three age groups was 64%, 39%, and 11%, respectively. On the other hand, in the pediatric age group (age < 18 years, *n* =116), the median OS was not reached. Patients aged 10 to 17 years had a trend towards worse 3-year OS compared to those who were younger than 10 years (82% vs 76%, respectively, HR= 2.32 [0.99-5.41]). Figures 3A and B show the Kaplan-Meier survival curves according to age for patients with AUL.

Among the AUL patients labeled as received chemotherapy (*n* = 502 patients), the median OS was 13 months (CI: 11-15) compared to 1 month in those patients whose chemotherapy status was labeled as "No/Unknown", HR = 3.45 (CI: 3.01-3.95) (Fig. 4). There has been improvement in prognosis of AUL with time. Patients diagnosed between 2000 and 2004 had a worse survival in comparison to those diagnosed between 2010 and 2016, HR = 1.29 (CI: 1.13-1.47). This improvement over time was more pronounced when only patients labeled as having received chemotherapy were analyzed (Fig. 5A and B). Using multivariate Cox regression analysis among AUL, older age was the strongest factor associated with worse survival followed by earlier year of diagnosis (see Table 5).

Comparative survival analysis for AUL with other acute leukemias

We compared the survival of AUL patients treated with chemotherapy with ALL and AML. Given dissimilarities between the adult and pediatric populations with regards to disease biology, pathophysiology and incidence, we analyzed them as two separate subgroups. With regards to the adult population (age 18≥ years and received chemotherapy, *n* = 32,536), AUL patients had a worse prognosis, with a median OS of 9 months (CI: 6-11), compared to 27 months (CI: 26-28) in ALL patients and 13 months (CI 12 months to could not be estimated) in those with AML, $p < 0.0001$. The 36-months OS percentages among ALL, AML and AUL were 44%, 28%, and 21%, respectively. In the pediatric population (age < 18 and treated with chemotherapy, *n* = 15,027), the median OS was not reached for any of the three groups of leukemias. However, and keeping in mind the small number of patients in the AUL group, the OS of AUL was better than AML but similar to ALL. The 36-months OS rates among ALL, AML and AUL were 91%, 67%, and 85% respectively. Figure 6 A and B shows the survival curves of adult and pediatric patients who were treated with chemotherapy. Figure 7A and B shows the adjusted survival curves for the three types of leukemia in both the adult and pediatric subgroups.

Finally, we constructed a Cox multivariate analysis model to adjust for age, sex, race, and ethnicity. In both groups (adult and pediatric), older age, non-White Race, Hispanic ethnicity and earlier period of diagnosis were predictive of worse outcomes (data not shown). Male sex was predictive of worse outcomes, but only in the adult subgroup. When AUL in adults was compared to ALL and AML in a multivariate model, it had worse outcomes with 47% and 35% increased risk of death, respectively. By comparison, pediatric AUL had similar outcomes to ALL but better survival than AML, with a 65% reduced risk of death. Table 6 shows the results of multivariate Cox regression analysis for the 3 groups of acute leukemias.

4. DISCUSSION

Our analysis confirms that AUL is rare and its incidence is decreasing. In a classic study of acute leukemias predating modern immunodiagnostics, 15/126 cases with a lymphoid morphology, but without B or T cell markers, were deemed to be undifferentiated (11.9%).[6] In a survey of acute leukemia cases registered by SEER between 2001 and 2007, only 825/ 29,672 were

undifferentiated (2.7%). This resulted in an incidence ratio of 1.6 cases per 1 million person years.[4] We show here that the incidence of AUL continues to decrease (See Fig. 2). Overall, the incidence of AUL is higher than the incidence of mixed-phenotype acute leukemias (MPAL) (with 0.35 cases per 1 million person years).[7] As in all other cases of acute leukemias, the incidence of AUL is higher in the older population (Table 3). The reasons for the decreasing incidence of AUL are probably not a different etiology or pathogenesis but the more sensitive diagnostic tools assigning patients either to the myeloid or lymphoid lineage.

We describe here the largest series of patients with acute leukemia without lineage defining markers (n=1,888). In a previous survey of acute leukemia patients older than 65 years treated between 1992 and 2010, 670 cases were included.[8] In the earlier series, the survival was universally poor (median survival one to six months depending on treatment with chemotherapy or palliative management only) [4,8]. In our study, a more differentiated picture emerges. In young patients and in children, the prognosis may be good or not much different from ALL (Figs. 3B). In the older population, the prognosis is still poor. However, there is some improvement, both in the context of published data and according to our study. In this series (including patients regardless of treatment received, Fig. 5A), the five-year survival has increased from about 10% to more than 20%. If only patients considered fit to receive chemotherapy are included, the five-year survival has increased to more than 40%. The treatment intensity of older patients with AML has always been controversial.[9] Comorbidities often prevent older patients with acute leukemias from getting aggressive chemotherapy. High-risk cytogenetics portend a lower chance to come into remission. Due to its rarity and the perceived poor prognosis, there are few case series in which the treatment and prognosis of patients with AUL is reported. In a series from pathology files, 24 patients with a median age of 68 years (range 29-86 years) are described.[10] Among the patients who received induction chemotherapy, 14/15 (93.3%) came into remission and 11 went on to receive an allogeneic stem cell transplantation. In a Japanese series, the outcome of 10 patients with AUL who underwent allogeneic transplantation is described.[11] The median age of these patients was 45 years (range 22-63). Six of the 10 patients were transplanted in first complete remission. The one-year survival of the entire group was 37.5%. As far as remission induction is concerned, both myeloid and lymphoid regimens were used in these series.

We believe that with the advent of new treatments, the prognosis of older patients with AUL is not universally poor and can improve. Examples for new treatment approaches in AML are *FLT3*-inhibitors, *BCL-2* inhibitors, *IDH* inhibitors, demethylating agents and treatments targeting minimal residual disease.[12,13] The patient described in the first part of this manuscript is an example that older patients with AUL receiving appropriate treatment can come into and stay in remission.

By definition, AUL is derived from an immature cell type , which is supported by the expression of the stem cell antigen CD34 in our case as in most other acute leukemias.[14,15] Similar to many other types of acute leukemias, AUL is heterogeneous. This becomes apparent from the survival curves (Fig. 3A and B). Younger patients with acute leukemias have less genetic complexity and often respond better to chemotherapy. In addition, younger patients can tolerate chemotherapy better. Interestingly, the cytogenetic profile for AUL, reported in three publications, showed a normal karyotype in three out of 11; seven out of nine; and 14 out of 15 cases, respectively. [10,11,16] Normal cytogenetics is considered standard-risk feature for AML, however, due to the referral bias and the limited sample size, this may not apply to the entire cohort of patients with AUL. Molecular

methods and NGS have added complexity and new insights for the diagnosis and treatment of acute leukemias.[17] In the afore-mentioned case series[10] and a different series from a leukemia reference laboratory[16], *ASXL1*, *SRSF2*, *RUNX1*, *TET2* and *DNMT3A* were mutated in some, but not all cases. This argues for the heterogeneity of AUL, but due to the limited number of cases, no definite conclusions can be drawn. MPAL is another rare type of acute leukemia, and is defined by the co-expression of bona fide myeloid and lymphoid markers. In a recent study of pediatric MPAL, a heterogeneous genotype was described with *ZNF384* rearrangements found in the B-myeloid type and biallelic *WT1* mutations in the T-myeloid type.[18]

How does our patient fit into the molecular and cytogenetic risk categories? If he had AML, with normal cytogenetics, he would be considered intermediate-risk. The mutations of *GATA2*, *NF1* and *BCOR* are occasionally observed in myeloid leukemias, but may or may not add to the known risk profile.[19-21]

Due to the rarity of AUL, there are no clear treatment recommendations. In the pediatric, adolescent and young adult populations, we would favor multi-agent chemotherapy regimens similar to acute lymphoblastic leukemia. This recommendation is similar to MPAL.[22] Due to the rarity of disease and lack of a clear risk stratification system, treatment should be individualized. We believe that patients who come into remission should be considered for allogeneic stem cell transplantation if they have a matched donor and meet other criteria such as organ function and social support. However, certain patients might be cured with only chemotherapy and could avoid stem cell transplantation. Cytogenetics, molecular landscape, response to therapy and minimal residual disease could be considered in the decision-making process. Patients who do not come into remission should be considered for AML-active regimens. For the adult populations, either myeloid or lymphoid regimens might be acceptable. For the frail elderly populations or those with comorbidities that preclude aggressive chemotherapy, a trial of low-dose chemotherapy with hypomethylating agents, venetoclax, low-dose cytarabine or vincristine and steroids could be considered. An alternative is targeted treatment if a molecular target can be identified. In the evolving era of treatment for acute leukemias, more research is warranted to improve outcomes.

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AUTHORSHIP
Contributions: A.Q., R.M., V.G. designed and performed research and analyzed data. C.C., A.M.,M.K., R.A., S.W. and R.R. were involved in the care of patients with acute undifferentiated leukemia and reviewed data. R.M. and A.Q. wrote the manuscript.

Conflict-of-interest disclosure: The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

FIG 1

FIG 1 A

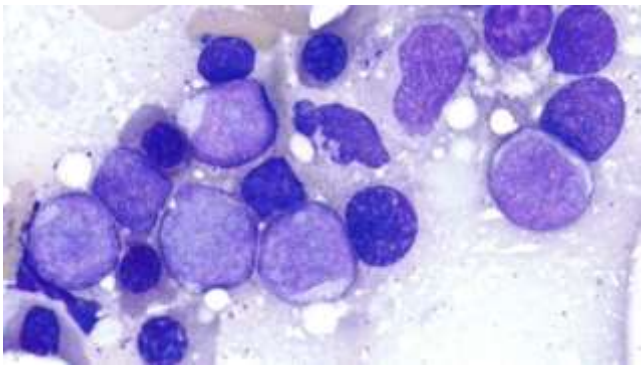

FIG 1 B

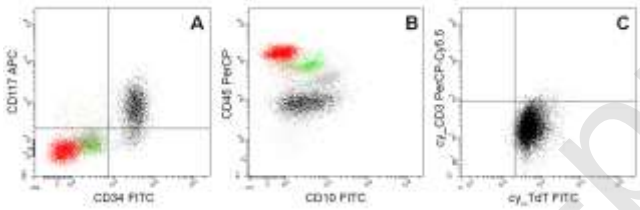

Fig. 1A. Bone marrow aspirate at high power magnification. Medium size blasts with agranular cytoplasm and a high nuclear/cytoplasmic ratio. No Auer rods. The nuclei are oval with small irregular nucleoli B**. Selected surface markers.** (Medium-sized blasts black, lymphocytes red, monocytes green, granulocytes gray) CD34 positive, CD117 positive, CD45 dim, CD10 partially positive, cytoplasmic CD3 negative, cytoplasmic TdT positive.

FIG 2

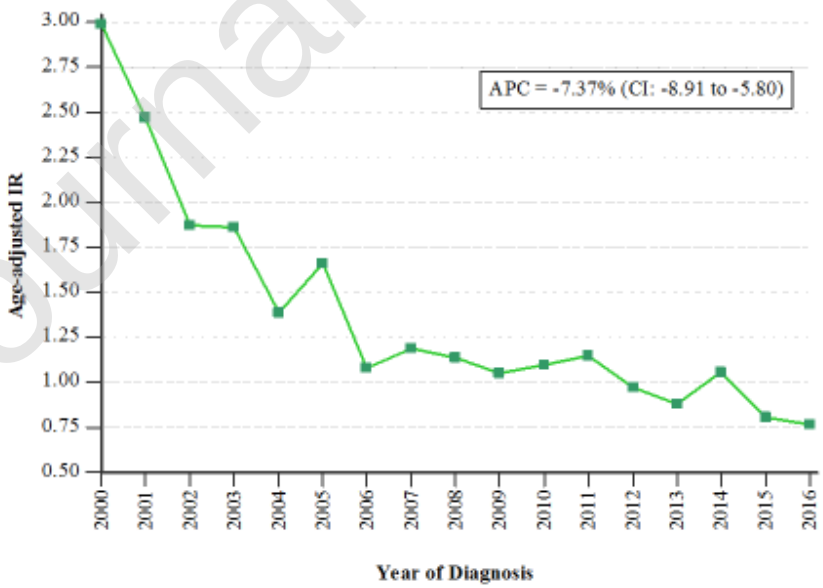

Fig. 2. Incidence Rates of AUL per 1 million person-year, adjusted according to the to the 2000 U.S. standard population. APC: annual percentage change. CI: 95% confidence intervals.

FIG 3

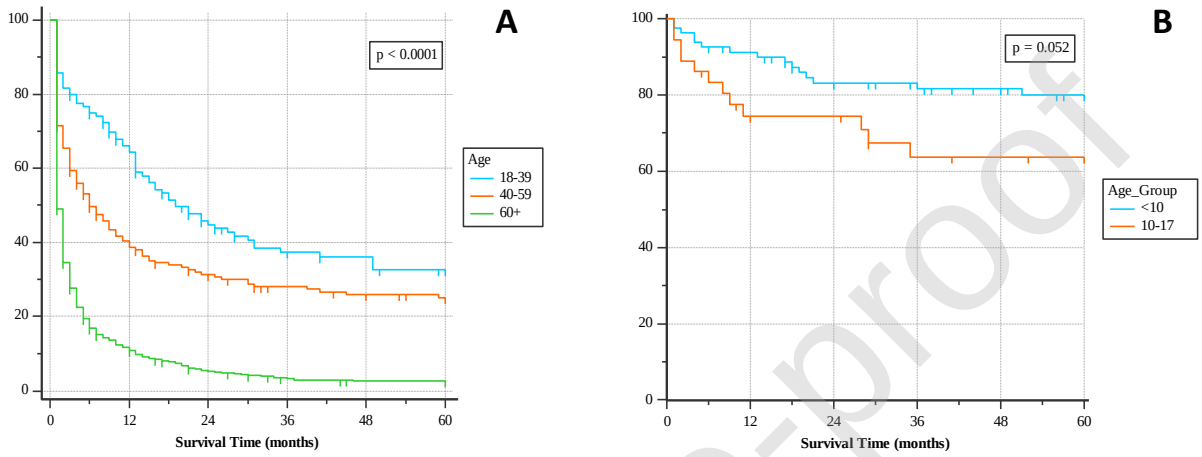

Fig. 3. (A) Survival in different age groups among adult AUL. HRs: 60+/18-39 = 3.13 (CI: 2.66-3.67) and 60+/40-59 = 2.15 (CI: 1.85-2.49). **(B) Survival in different age groups among the pediatric AUL**. HR for the 10-17 age group/<10 is 2.32 (CI: 0.99-5.41). [Y axis survival probability]

FIG 4

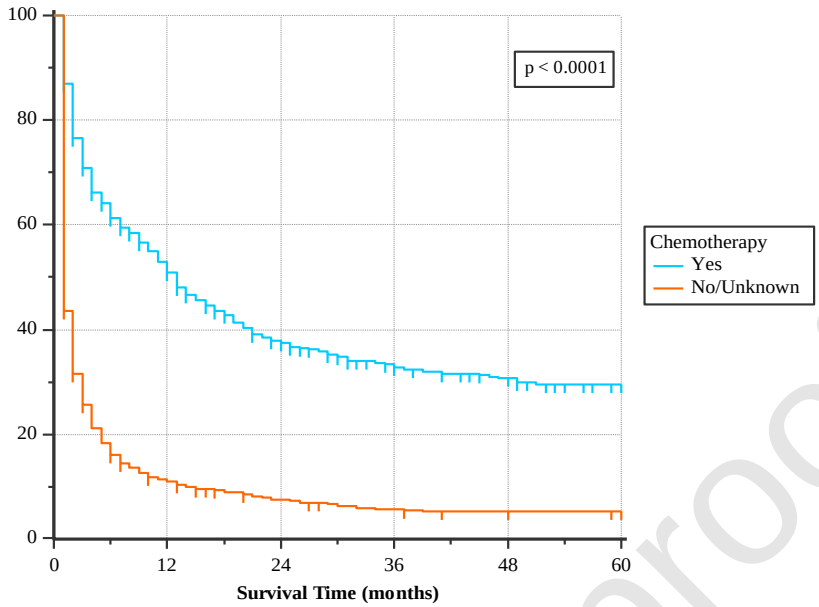

Fig. 4. Survival of AUL patients according to chemotherapy status. HR = "No/Unknown" vs yes = 3.45 (CI: 3.01-3.95). [Y axis survival probability]

FIG 5

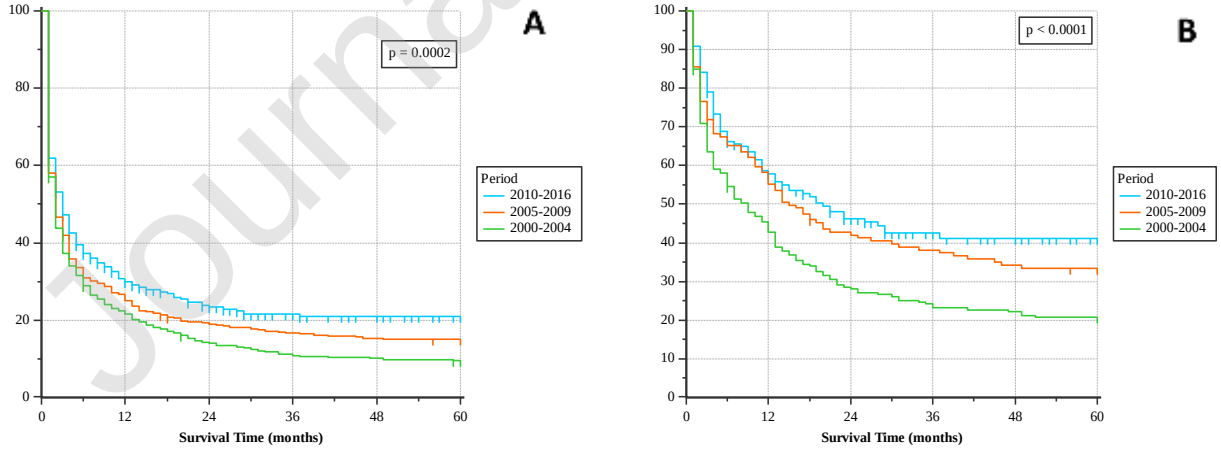

Fig. 5. (A) Survival of AUL patients according to period of diagnosis. HRs: 2000-2004/2010-2016 = 1.29 (CI: 1.13-1.47), 2000-2004/2005-2009 = 1.13 (CI: 0.98-1.29), 2005-2009/2010-2016 = 1.14 (CI: 0.98-1.33). **(B) Survival of AUL patients (having received chemotherapy)**

according to period of diagnosis. HRs: 2000-2004/2010-2016 = 1.63 (CI: 1.27-2.11), 2000-2004/2005-2009 = 1.40 (CI: 1.08-1.83), 2005-2009/2010-2016 = 1.16 (CI: 0.89-1.53). [Y axis survival probability]

FIG 6

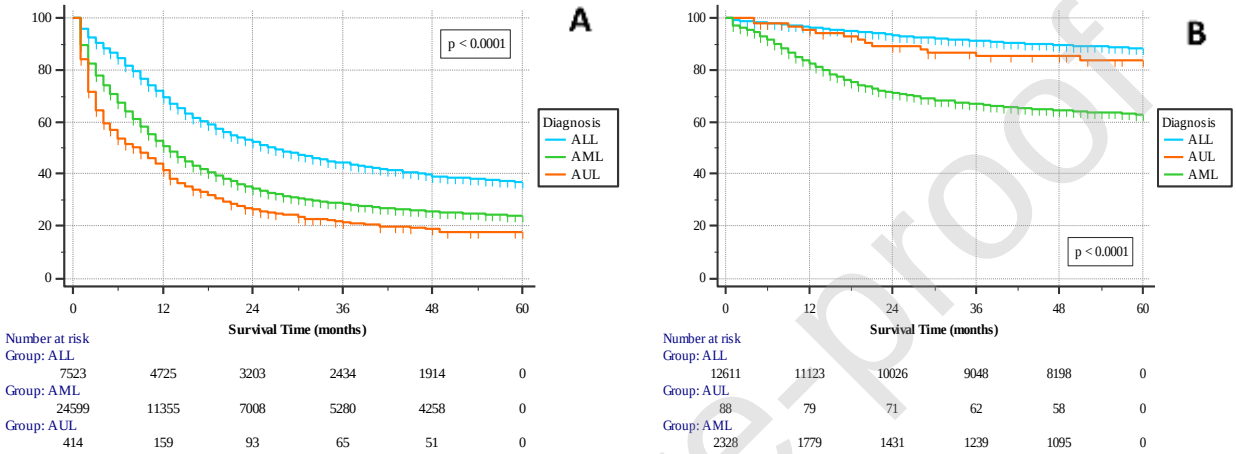

Fig. 6. (A) Survival among the different types of acute leukemia in the adult population who received chemotherapy. HRs = AUL/ALL = 2.07 (CI: 1.81- 2.37), AUL/AML = 1.30 (CI: 1.14-1.49) and AML/ALL = 1.59 (CI: 1.54 to 1.64). **(B) Survival among the different types of acute leukemia in the pediatric population treated with chemotherapy.** HRs = AML/ALL = 3.97 (CI: 3.50-4.5), AML/AUL = 2.74 (CI: 1.56-4.82), AUL/ALL = 1.45 (CI: 0.83-2.52). [Y axis survival probability]

FIG 7

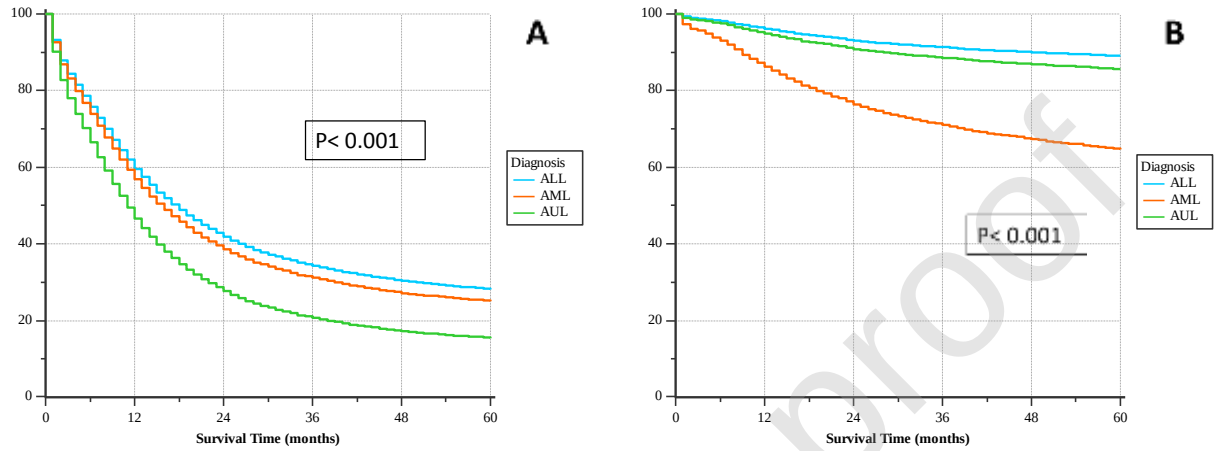

Fig. 7. (A) Adjusted survival among the different types of acute leukemia in the adult subgroup treated with chemotherapy. HRs = AUL/ALL = 1.47 (CI: 1.31-1.65) and AML/ALL = 1.09 (CI: 1.05-1.13). **(B) Adjusted survival among the different types of acute leukemia among children treated with chemotherapy.** HRs: AML/ALL = 3.75 (CI: 3.42-4.10) and AUL/ALL = 1.33 (CI: 0.77-2.30) [Y axis survival probability]

Table 1. Laboratory investigations of the patient performed at time of diagnosis and results of diagnostic studies.

Variable	Reference Range	Day of Admission
White cell count (WBC)	$3.7 – 10.3 \times 10^9$/L	5.59
Hemoglobin	13.7 – 17.5 g/dL	12.9
Platelets	$155 – 369 \times 10^9$/L	117

Differential count	Blasts Neutrophils Monocytes Basophils	**18%** 30% 12% 1 %
LDH	116 – 250 U/L	174
Uric acid	3.7 – 8.0 mg/dL	4.3
Creatinine	0.8 – 1.3 mg/dL	0.74

Bone marrow aspirate	Cellularity 40%, megakaryocytes adequate, granulocytic maturation decreased, infiltration with 36% undifferentiated blasts (Fig.1A)
Surface marker analysis (flow)	No myeloid or lymphoid specific antigens, CD34+, variable CD117, moderate to dim CD45, partial dim CD10, partial dim CD7, cytoplasmic TdT + (Fig 1B)
Cytogenetics (bone marrow aspirate)	Normal male karyotype
FISH panel	Negative for 9p- or IGH rearrangements, negative for t(8;21), t(9;22), t(11q23), t(15;17), inv(16), inv(3), 5q-, t(6;9), 7q-, +8 or 17p-
PCR assays	Negative for *KIT* mutations, *FLT3 ITD* or *TKD* mutations, negative for *NPM1* mutations
97-gene next generation sequencing panel (NGS)	Mutations in *GATA2* (18.9% allele frequency), *NF1* (10.6% AF), variant in *BCOR* (50.6% AF)

Table 2. ICD-O-3 codes included in this study (2000-2016).
Patients with a preceding different malignancy were excluded from survival analysis.

Diagnosis	ICD-O-3 Code	Type of Leukemia	Number of cases
AUL	**9801**	**Acute Undifferentiated Leukemia**	**1444**
ALL	**All ALL Cases**		**21,385**
	9811	B lymphoblastic leukemia/lymphoma, NOS	7100
	9812	B lymphobl leuk/lymph w/t(9;22)(q34;q11.2); BCR-ABL1	378
	9813	B lymphobl leuk/lymph w/t(v;11q23); MLL rearranged	81
	9814	B lymphobl leuk/lymph w/t(12;21)(p13;q22);TEL-AML1	314
	9815	B lymphoblastic leuk/lymph w/hyperdiploidy	356
	9816	B lymphobl leuk/lymph w/hypodiploidy	117
	9817	B lymphobl leuk/lymph w/t(5;14)(q31;q32); IL3-IGH	10
	9818	B lymphobl leuk/lymph w/t(1;19)(q23;p13.3); E2A PBX1	42
	9835	Precursor cell lymphoblastic leukemia, NOS (OBS 2010+)	5463
	9836	Precursor B-cell lymphoblastic leukemia (OBS 2010+)	5846
	9837	T lymphoblastic leukemia/lymphoma	1678
AML	**All AML Cases**		**37,772**
	9840	Acute erythroid leukemia	655
	9861	Acute myeloid leukemia, NOS	21,034
	9865	Acute myeloid leukemia with t(6;9)(p23;q34);DEK-NUP214	50
	9867	Acute myelomonocytic leukemia	3460
	9869	Acute myeloid leuk. inv(3)(q21;q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1	33
	9870	Acute basophilic leukemia	7
	9871	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), CBFB-MYH11	584
	9872	Acute myeloid leukemia with minimal differentiation	1062
	9873	Acute myeloid leukemia without maturation	1625
	9874	Acute myeloid leukemia with maturation	1931
	9891	Acute monoblastic and monocytic leukemia	2687
	9895	Acute myeloid leukemia with myelodysplasia-related changes	2450
	9896	Acute myeloid leukemia, t(8;21)(q22;q22) RUNX1-RUNX1T1	747
	9897	Acute myeloid leukemia with t(9;11)(p22;q23);MLLT3-MLL	323
	9898	Myeloid leukemia associated with Down Syndrome	67
	9910	Acute megakaryoblastic leukemia	361
	9911	Acute myeloid leuk (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1	25
	9930	Myeloid sarcoma	377
	9931	Acute panmyelosis with myelofibrosis	294
All cases			**60,601**

ICD-O: International Classification of Diseases for Oncology; AUL: acute undifferentiated leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia.

Table 3. Age-Adjusted incidence rates (IR) of acute undifferentiated leukemia, according to age and sex, SEER 18, 2000-2016. All IR are age-adjusted to the 2000 U.S. standard population and expressed per 1,000,000 person-years.

Age	Male		Female	
	Count	IR	Count	IR
0-09 y	43	0.43	39	0.41
10-19 y	16	0.15	26	0.26
20-29 y	40	0.38	26	0.26
30-39 y	31	0.31	24	0.24
40-49 y	43	0.41	38	0.37
50-59 y	88	0.98	50	0.53
60-74 y	228	3.25	203	2.45
75+ y	498	16.04	495	9.45
Total	987	1.66	901	1.11

Table 4. Baseline characteristics of all patients with acute leukemia in SEER (2000-2016).

Variable	Type of Leukemia						P value
	AUL		ALL		AML		
	Cases	Percen-tage	Cases	Percen-tage	Cases	Percen-tage	
Median Age	74 years		12 years		65 years		<0.0001
Age Group							<0.0001
0 – 19	122	8%	13,485	63%	2733	7%	
20 – 39	114	8%	2926	14%	3735	10%	
40 – 59	183	13%	2694	13%	8757	23%	
60+	1025	71%	2280	11%	22,547	60%	
Sex							<0.0001
Male	738	51%	12,046	56%	20,661	55%	
Female	706	49%	9339	44%	17,111	45%	
Race							<0.0001
White	1191	82%	17,664	83%	30,883	82%	
Black	147	10%	1573	7%	3330	9%	
Other	99	7%	1957	9%	3400	9%	
Unknown	7	0.5%	191	1%	159	0.4%	
Ethnicity							<0.0001
Non-Hispanic	1239	86%	13,596	64%	32,897	87%	
Hispanic	205	14%	7789	36%	4875	13%	
Period							<0.0001
2000-2004	640	44%	5811	27%	11,099	29%	
2005-2009	396	27%	6251	29%	10,886	29%	
2010-2016	408	28%	9323	44%	15,787	42%	
Chemotherapy							<0.0001
Yes	502	35%	20,134	94%	26,927	71%	
No/Unknown	942	65%	1251	6%	10,845	29%	

Table 5. Multivariate Cox Regression analysis of AUL patients who received chemotherapy.

Covariate	p value	HR	95% CI
Age (60+ vs 40-59)	<0.0001	5.90	3.22 to 10.79
Age (60+ vs 18-39)	<0.0001	7.16	3.93 to 13.04
Age (60+ vs <18)	<0.0001	16.24	9.16 to 28.79
Period (2000-2004 vs 2005-2009)	0.0311	1.39	1.03 to 1.88
Period (2000-2004 vs 2010-2016)	<0.0001	1.73	1.33 to 2.25

Table 6. Multivariate Cox Regression analysis of all acute leukemia patients who received chemotherapy (SEER, 2000-2016).

Covariate	Adult				Pediatric			
	p	HR	Lower CI	Upper CI	p	HR	Lower CI	Upper CI
Age at diagnosis*	<0.0001	1.033	1.032	1.033	<0.0001	1.053	1.045	1.062
Sex								
Female		1				1		
Male	<0.0001	1.11	1.08	1.14	0.12	1.07	0.98	1.17
Race								
White		1				1		
Other	<0.0001	1.12	1.08	1.16	<0.0001	1.44	1.29	1.60
Ethnicity								
Non-Hispanic	<0.0001	1				1		
Hispanic	<0.0001	1.14	1.10	1.19	<0.0001	1.47	1.35	1.64
Period								
2010-2016		1				1		
2005-2009	<0.0001	1.15	1.12	1.20	0.046	1.12	1.00	1.25
2000-2004	<0.0001	1.34	1.30	1.38	<0.0001	1.37	1.23	1.52
Diagnosis								
ALL		1				1		
AML	<0.0001	1.09	1.05	1.13	<0.0001	3.75	3.42	4.10
AUL	<0.0001	1.47	1.31	1.65	0.30	1.33	0.77	2.30

**Age was analyzed as a continuous variable (for each year increase).*
HR: hazard ratio; CI: 95% confidence interval.