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Impact of insurance status and distance from residence to treatment center on the outcomes of patients diagnosed with acute myeloid leukemia

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Purpose: Numerous factors may affect the survival outcomes of patients with acute myeloid leukemia (AML), mainly disease-related and treatment-related factors. The impact of other factors, such as the insurance status and the distance to healthcare facilities, are still unclear and may differ between different healthcare systems. We investigated the effects of insurance status and distance to the treatment center on the survival of AML patients.

Materials and methods: This is a single-center, observational, retrospective study of patients diagnosed with AML (2015–2020) and treated at the American University of Beirut Medical Center in Lebanon. Data regarding patient baseline characteristics, disease-related factors, insurance status, and area of residence were collected. Multivariate Cox regression analysis was used to identify main independent predictors of overall survival (OS).

Results: We identified 142 AML patients with a median age of 52 years (range 18–86). Of them, 91 (64%) were males, 77 (54%) had ELN intermediate risk, and 88 (62%) patients received intensive chemotherapy. After a median follow-up of 22.4 months, the median RFS and OS were 37.4 months and not reached, respectively. A Cox regression model for OS was done using the following variables: age, gender, body mass index, comorbidities, smoking status, insurance status, distance from the center, ELN classification, treatment used, and allotransplant. A higher risk of death was seen among the uninsured patients and those living beyond 40 km from the treatment center compared with fully insured patients and those living in proximity to the center (hazard ratio [HR]: 3.65; 95% CI [1.79, 7.45], p-value <0.0001; HR: 4.38; 95% CI [1.75, 10.95], p-value 0.002, respectively).

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Conclusions: The outcome of patients with AML does not depend only on disease-related factors, as the insurance status and the distance from the area of residence to the treatment center were found to be independent predictors of survival in AML patients.

KEYWORDS

acute myeloid leukemia (AML), insurance status, distance, treatment center, survival

Introduction

Acute myeloid leukemia (AML) is a group of hematologic neoplasms with malignant clonal expansion of myeloid stem cells accounting for around 35% of all leukemias (1, 2). Recent advancements in treatment options and the use of targeted therapies have improved the outcomes of patients diagnosed with AML. The 5-year relative survival in the US has improved from 6.4% in 1975 to 30.5% during the period of 2012 to 2018, as per SEER data analysis (2). In a single center study from Lebanon, until 2017, the 3-year overall survival (OS) was 53% and the 3-year leukemia-free survival (LFS) for patients achieving complete remission was 54% (3).

The OS of patients diagnosed with AML depends on many well-described risk factors; age, performance status, cytogenetics, molecular subtype, the type of treatment received, and socioeconomic factors are predictor factors of survival (4, 5). Access to treatment centers may be affected by insurance status and distance traveled, hence influencing the prognosis of patients diagnosed with AML. Although many studies showed a positive correlation between poor survival and lack of insurance and/or increased distance traveled (6, 7), others reported no correlation (6, 8–10).

In Lebanon, universal healthcare services are not available, leading to many inequities in access to healthcare, the ability to pay for it, and sometimes in health outcomes (11). Lebanon encompasses a small area of land of 10,452 square kilometers along the Mediterranean Sea with a population of 6.8 million and the largest per capita population of refugees in the world (12). Lebanon has both public and private healthcare insurances. More than half of the population is uninsured. The uninsured can benefit from medical care covered by the Ministry of Public Health (MoPH), but this would be in public hospitals or private ones with a predetermined payment ceiling.

In this paper, we used a database from the American University of Beirut Medical Center (AUBMC), a main non-profit private tertiary referral medical center for reviewing all cases treated for AML. Our center is located in Beirut, the capital of Lebanon. After controlling for potential confounding factors, we assessed the impact of healthcare insurance and distance traveled to the treatment center on the survival of patients newly diagnosed with AML. To the best of our knowledge, this paper is the first in Lebanon and the region to assess for potential disparities in the management of patients with AML.

Materials and methods

Patients and study characteristics

All consecutive adult patients (≥18 years of age) newly diagnosed with AML who received treatment at the AUBMC between January 2015 and January 2020 were eligible for our study. We included cases of acute promyelocytic leukemia (APL). We excluded patients with an AML diagnosis on their charts with no further information about their disease and those who visited for a second opinion and then were lost to follow-up. The study was approved by the American University of Beirut (AUB) institutional review board, and in accordance with the declaration of Helsinki. A waiver of informed consent was granted for this chart review study.

Patients who were candidates for intensive chemotherapy received anthracyclines-based therapy for induction followed by intermediate dose of continuous cytarabine for consolidation and/or allogeneic hematopoietic cell transplant (allo-HCT). Others received hypomethylating agents, low-dose chemotherapy, or supportive care. Patients with APL received retinoic acid and arsenic trioxide. Allo-HCT was considered for patients with adverse-risk disease, selected patients with intermediate-risk disease based on the 2017 European Leukemia Net (ELN) classification (13), and relapsed/refractory AML.

This study used a database from the electronic medical record system (EMR). Our EMR contains baseline demographics, pathological and clinical data on patients diagnosed with AML. An extensive retrospective chart review was performed to collect information on age at diagnosis, gender, comorbidities at presentation, smoking status, body mass index (BMI), cytogenetic/molecular abnormalities, insurance source at diagnosis, distance to the treatment center, information on treatment administration, and allo-HCT.

Hospitalizations, clinic follow-ups, and disease evaluations were also gathered from the charts of our patients. Patients were classified into three insurance groups: fully insured, publicly insured and uninsured, and two distance groups from our hospital: <40 kilometers (km) or ≥ 40 km. Distance was estimated based on the straight- line driving distance between patients' most recent residence and our tertiary center. We used the last address on patients' charts, which corresponds to patients' address at last encounter. Forty kilometers was chosen being close to the mean distance traveled by all patients. Comorbidities were defined by the presence at diagnosis of one or more chronic health conditions different by etiology from the primary disease (14).

Treatment outcomes

The primary endpoints of this study included 2-year OS and 2–year relapse-free survival (RFS). We calculated response outcomes as per the definition of the International medical group (15). OS was defined as the time that begins at diagnosis and up to the time of the last follow-up or death. RFS was calculated from the date of attaining the leukemia-free state to the date of relapse or death, whichever occurs first.

Statistical methods

Percentages and frequencies were calculated for all the variables. Kaplan-Meier curves were used to estimate OS and RFS, the log-rank was used to check for significant differences between the studied groups. We used the Cox-regression analysis for survival estimates after adjusting for possible confounding factors, using the following: age, gender, body mass index, presence of comorbidities, smoking status, insurance status, distance from the center, ELN classification, and treatment used. We reported odds ratio (OR) and hazard ratio (HR) with 95% confidence intervals (CI). A p-value <0.05 was used to indicate statistical significance. All statistical analysis was performed using the SPSS v.25.0 statistical packages.

Results

Patients' characteristics

Two hundred eighteen patient charts were screened. A total of 142 patients (64% males) were included in our study based on the eligibility criteria. Their baseline characteristics are summarized in Table 1. The median age at diagnosis was 52 years (range, 18-86

TABLE 1 Baseline characteristics.

		Median (range); N(%)
Age, years		52 (18-86)
Gender	Male	91(64%)
	Female	51 (36%)
Comorbidities	Absent	104 (73%)
	Present	38 (27%)
Smoking status	Never smoker	93 (65%)
	Current smoker	19 (13%)
	Ex-smoker	30 (22%)
BMI, Kg/m^2		26.5 (16-42)
Insurance status	Fully Insured	65 (46%)
	Publicly insured	36 (25%)
	Uninsured	41 (29%)
Distance from treatment center	< 40km	57 (40%)
	≥ 40km	85 (60%)
ELN 2017 risk score	Favorable	38 (27%)
	Intermediate	77 (54%)
	Adverse	23 (16%)
	NA	4 (3%)
Chemotherapy received	Intensive chemotherapy	88 (62%)
	Hypomethylating agents	25 (18%)
	Low dose chemotherapy	2 (1%)
	Supportive care	1 (1%)
	ATRA/Arsenic	21 (15%)
	NA	5 (3%)
Allogeneic hematopoietic cell transplantation	Yes	66 (46%)
	No	76 (54%)

BMI, body mass index; ELN, European LeukemiaNet; NA, Not available.

years). The majority of patients are non-smokers (n=93, 65%) with no previous comorbidities (n=104, 73%). Most of patients were fully insured (n=65, 46%), a quarter were publicly insured (n=36, 25%) and almost a quarter were uninsured (n=41, 29%). The median BMI range was 26.5 Kg/m^2 (16-42).

Forty percent (n=57) of our population had a distance to treatment center less than 40 Km. Thirty-eight (27%) patients had a favorable risk as per ELN 2017 classification, 77 (54%) had an intermediate-risk, and 23 (16%) patients had an adverse-risk. Seven patients had core binding factor (CBF) molecular aberrations on molecular studies. Fifty-three subjects had normal cytogenetic and molecular data, 12 subjects had *NPM1* mutations, 10 subjects had *FLT3* mutation and 14 had concomitant *FLT3* and *NPM1* mutations. Only 1 patient had *CEBPA* biallelic mutation. Among all patients, 21 had translocation between chromosome 15 and 17 [t (15, 16)], 10 had complex karyotype and 7 had inversion of chromosome 16 [inv (17)]. One subject had *NPM1* mutation with complex karyotype, one had *FLT3* mutation with complex karyotype and one had both *CEBPA* with *cKit* mutation. Eight had other derangements and 3 had incomplete cytogenetic and molecular data.

Eighty-eight (62%) patients received intensive chemotherapy, 25 (18%) received hypomethylating agents, 21 (15%) received retinoic acid and arsenic trioxide, with only two patients (1%) receiving low dose chemotherapy and one patient (1%) was managed with supportive care. Five (3%) patients were lost to follow-up and did not receive treatment at our center, thus not included in the final analysis. Sixty-six (46%) patients received an allo-HCT in first remission.

Patient outcomes

With a median follow-up of 22.4 months (range; 0-76 months), survival outcomes were estimated using the Kaplan-Meier curves. The mean OS was 52 months [46.1- 58] (median non reachable) and the RFS was 39.6 months [33.5- 45.7] with a median RFS of 37.4 months (Figure 1). The rate of complete remission (CR) was 70% (100 of 142 cases). Out of 41 patients where cause of death was recorded, 80.5% died from septic shock.

Effect of insurance status and distance on survival outcomes

Figure 2 presents the Kaplan-Meier curves for each of the 4 permutations of risk factors: (A) living at less than 40 km of treatment center and being uninsured, (B) living at 40 km or more and being uninsured, (C) living at less than 40 km and being insured, and (D) living at 40 km or more and being insured.

Multivariate Cox analysis of OS was used to adjust for potential confounding factors and showed that patients who are uninsured and those living beyond 40 km of the treatment center have worse OS than others who are fully insured and living in proximity to the specialized treatment facility. Results are statistically significant with P values of <0.0001 and 0.001, respectively (Table 2). Similarly, better OS was seen with subjects who received intensive chemotherapy (p-value= 0.08)

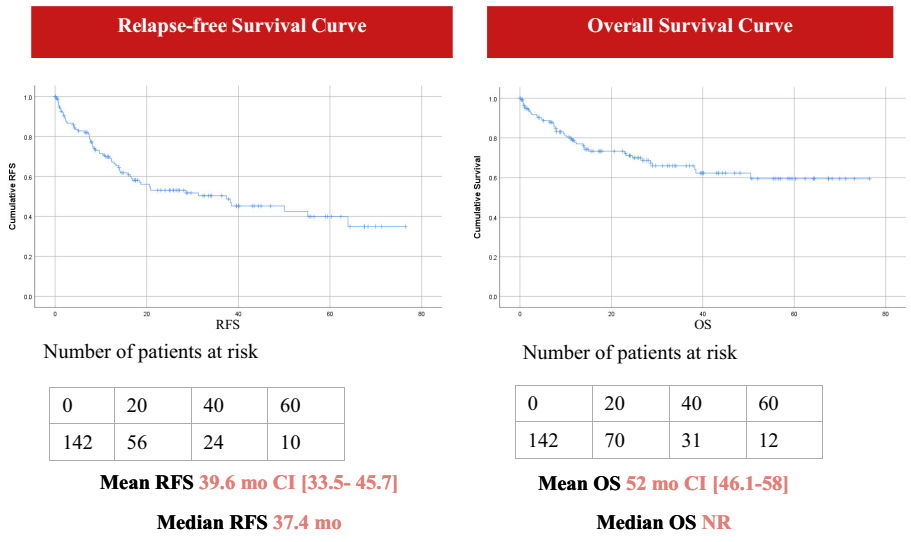

FIGURE 1
Relapse-free Survival and Overall Survival of all our population.

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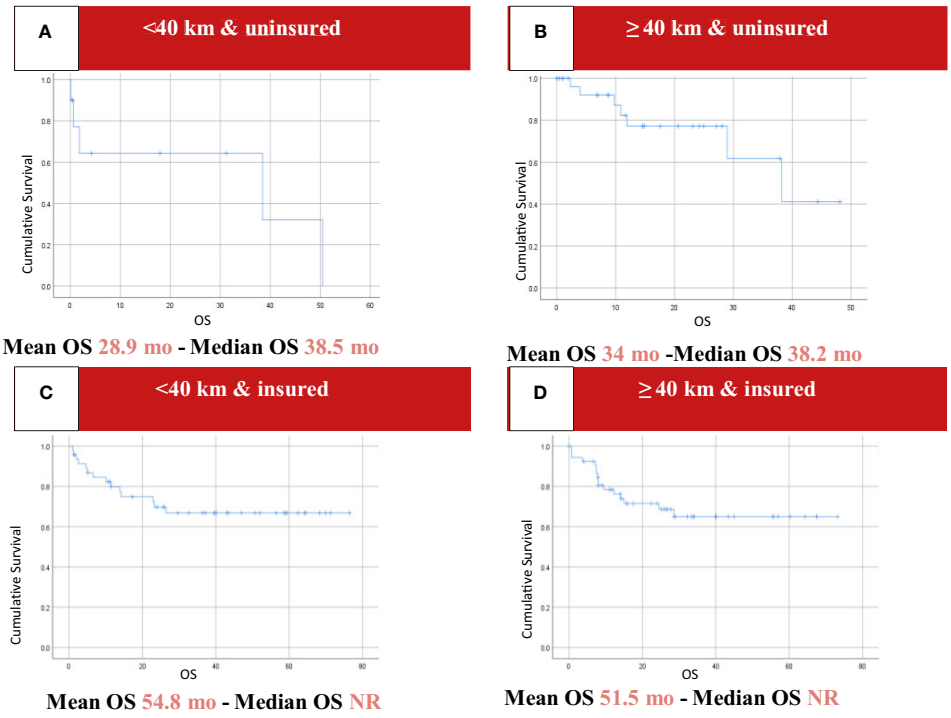

FIGURE 2
Overall Survival according to the four permutations of risk factors. **(A)** <40 km and uninsured **(B)** ≥ 40 km and uninsured **(C)** <40 km and insured **(D)** ≥ 40 km and insured.

and those who received allogenic stem cell transplant (p-value <0.0001).

There was no difference in the incidence of death by septic shock between patients living within 40 Km of treatment center and others living beyond this distance (P= 0.73). Similarly, there was no difference in the percentage of deaths in complete remission between the two groups (P= 1).

All patients with APL survived. Thus, the impact of distance traveled on OS in patients with APL cannot be assessed.

Discussion

This study represents a cohort of patients diagnosed with AML from one of the largest hospitals in Lebanon. We hypothesized that patients without insurance coverage and those living farther away from treatment center would have worse survival estimates. To our knowledge, this study is the first in Lebanon to assess for potential disparities in access to healthcare of AML patients. After adjusting for confounding risk factors, the Cox regression analysis of OS showed

TABLE 2 Multivariable Cox analysis of overall survival (OS).

Variable	HR	95% CI	p-Value
Distance for center >40km	2.22	1.36-3.60	0.001
Body mass index	0.94	0.89-1.00	0.012
Presence of comorbidities	0.38	0.19-0.80	0.010
Insurance status			
Fully insured			0.001
Publicly insured	1.20	0.70 – 2.03	0.550
Uninsured	2.80	1.61-4.83	0.0001
Treatment received			
Intensive Chemotherapy			0.08
Hypomethylating agent	2.85	1.18-6.90	0.021
Low dose chemotherapy	3.13	0.62-15.90	0.167
Allogenic Stem cell transplantation	0.31	0.18-0.55	0.0001

HR, hazard ratio; CI, confidence interval.

that fully insured patients had better OS rates compared to uninsured. Similarly, patients living in proximity to our treatment center had better OS compared to those living farther away.

Ten studies concerning the impact of insurance status on survival outcomes of patients with AML have been identified (6). Our results are consistent with seven of the reported studies. A recent study by Colton et al. (17) investigated the Surveillance, Epidemiologic, and End Results database (SEER) and showed that insurance status was a predictor of death in age groups 15-10 and 25-29, favoring private insurance. Another study by Pulte et al. (16) used the SEER database too and demonstrated lower survival expectations for patients, of all ages, who are uninsured or covered with Medicaid compared to patients with other insurances. Despite the strengths of this study with large sample size, information about prognostic factors like the presence of comorbidities and cytogenetic/molecular derangements did not exist. Master et al. (18) described insurance disparities in more than 60,000 with AML using the National Cancer Data Base (NCDB). They found that uninsured patients with AML had worse outcomes than Medicaid patients, who had worse survival compared to private insurance. Other smaller studies showed similar results. A study of patients from the Virginia Cancer Registry described lower rates of receiving chemotherapy and SCT, as well as lower survival for uninsured patients compared to those with private insurance (19). Ortiz-Ortiz et al. demonstrated disparities related to insurance type in Puerto Rico in 516 cases with leukemia including 159 patients with AML, however, this report did not take into consideration other possible confounding factors (20). Borate et al. (21) utilized the SEER database for 5,541 patients aged between 19 and 64 years and found by multivariate analysis a Hazard ratio (HR) of death of 1.24 for patients with Medicaid coverage compared with private insurance.

There are many differences between the healthcare system in the US and Lebanon. However, similarities reside in the absence of a universal healthcare system. In Lebanon, healthcare coverage is provided by public and private healthcare insurances and almost 50% of the population has no formal healthcare insurance. Our findings are consistent with the mentioned studies for worse survival with lack of insurance.

Selby et al. (22) determined better survival after day 100 of receipt of allo-HCT in patients with a better-insured group. Our study did not show a separate analysis for follow-up after allo-HCT by insurance type because of our small sample size. However, we included allo-HCT in the Cox regression analysis, and the results were statistically significant. Contrary to our study, three small studies, with 2 of them from a single-institution database and one from the New York and California cancer registries, did not show any correlation between insurance type and survival (23–25).

Regarding the effect of distance from the treatment center on the survival of AML patients, the review of the literature revealed two prior studies in the US supporting our results (7, 26). One of the studies analyzed a large allo-HCT cohort from DF/BWCC and showed an apparent worse OS with increased driving distance, one year from transplant. This effect was shown to be independent of other modifiable factors and more prominent on non-relapse mortality (26). The other study from Oklahoma University reported lower rates of complete remission with increased distance. It also showed decreased OS with longer distances; however, this result was not statistically significant (7). In contrast, five other studies from the US, one from Denmark and one from Oman reported a negative association or no effect of distance on survival (8–10, 27–30). Khera et al. (29) evaluated the association between distance and overall mortality in 2849 allo-HCT patients. An association was found in non-myeloablative HCT, however, results did not reach statistical significance. Banerjee et al. (30) evaluated distress and physical function in 1136 patients 2 to 10 years post-transplant, and found no impact of driving distance. Similarly, a single center study from Oman did not show correlation between distance travelled and OS of patients who underwent allo-HCT (28). In a single-center study, Medeiros et al. (8) showed that living within 20 miles of cancer center was associated with worse OS, however, after adjusting for confounding factors, distance lost its impact on survival outcomes. A database study from Nebraska Medical Center demonstrated no effect of travel distance on OS with a non-statistically significant increased mortality in patients living > 100 miles compared to those living <25 miles from the treatment center (31). Rodriguez et al. (27) reported that distance to the cancer center had no impact on OS in those receiving remission induction therapy for AML. Similarly, a Danish study, where healthcare services are universal, showed a lack of association between distance traveled and curative-intent therapy, treatment response, and survival in AML (9).

Many potential explanations exist for the difference between our results and those reported in the literature. First of all, the Lebanese healthcare context is different from healthcare settings in the US or Denmark. In Lebanon, most of the academic tertiary referral centers are located in Beirut, the capital of Lebanon. Previous studies have shown that management of AML at academic or large-volume centers is associated with better survival outcomes (32–35). The reason behind this observation is multifactorial and might be related to earlier diagnosis, decrease time to initiation of chemotherapy, prompt management of emergencies, availability of transplant services, and clinical trials occurring in academic centers (34, 36). Thus, centralization of academic centers in Lebanon leading to increased travel distance for patients living in suburban or rural areas, explains the difficulty in access to resources for the management of AML emergencies and treatment-related complications. Second, traveling longer distances may not appear as a prognostic factor for OS in the reported studies (27, 31) because of potential confounders. In fact, patients in the US traveling to treatment centers have better performance status, educational and financial situation, and compliance to treatment (10, 27, 37, 38).

Compared with prior studies, our study is novel because it shows data from a cohort of patients diagnosed in Lebanon and simultaneously studies the effect of biological and health system factors. We have demonstrated that survival in AML patients was

significantly higher in patients with better healthcare coverage and living close to the treatment center.

Our study has several limitations. First, since our study is retrospective, data on known prognostic factors including functional status, socio-economic level, and cytogenetics were unavailable or incomplete. Therefore, we cannot confirm that patients in each group had an equivalent disease. Second, our cohort size is small relatively from a single tertiary center. However, we think our results are representative of Lebanon, given that we included all patients with AML diagnosed at one of the largest hospitals in Lebanon over five years. Third, some of our patients are medical tourists and may return to their home countries after treatment. Thus, their deaths may not be recorded. Given that most medical tourists are uninsured, the effect of insurance status on survival may be underestimated. Fourth, our recorded insurance status is assessed at diagnosis. However, insurance status can change during the course of the disease, and people may lose their insurance. This may cause an underestimation of the effect of insurance.

Conclusion

In summary, our report detected the presence of health disparities in Lebanon according to insurance and geography. Disparities came as a consequence of a weak, privatized, and centralized healthcare system. With Lebanon sinking into one of the most severe global economic crises, we expect worse healthcare disparities affecting the socially disadvantaged groups. A true paradigm shift is urgently needed in policy making to ensure equity in access and utilization of healthcare services.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by American University of Beirut (AUB) institutional review board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MM and LM collected the data, reviewed the literature, and drafted the manuscript. MC performed statistical analysis. NM, JC, AB and IA reviewed and edited the final draft. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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