

Epidemiology of de novo Acute Myeloid Leukemia in Kuwait per the 2016 WHO Classification

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Highlights of the Study

- An understanding of the prevalence and incidence of acute myeloid leukemia (AML) in Kuwait is lacking.
- This retrospective study investigated AML incidence and patient demographics in Kuwait from 2014 to 2020.
- We found an increased incidence of AML over this period, with improved survival seen in younger patients under 55 years.

Keywords

Acute myeloid leukemia · Epidemiology · Incidence · Kuwait

Abstract

Objective: Acute myeloid leukemia (AML) is a hematological malignancy that arises from the clonal proliferation of immature myeloid cells. Although the number of AML cases has dramatically increased worldwide, information on its prevalence and incidence in Kuwait is lacking. This study reports the incidence of AML and patient demographics in the country from 2014 to 2020, based on the 2016 WHO classification of AML. **Subjects and Methods:** Data on patients with AML, including acute promyelocytic leukemia (APL), were collected from a clinical cohort with 281 cases analyzed in

this study. **Results:** The overall median age of the population was 47 years with a 1.1:1 male-to-female ratio. Over the study period, the incidence of AML demonstrated a general increasing trend, with the highest and lowest overall incidence occurring in 2018 and 2015, respectively. The frequency of APL in our cohort was 8.9%. Regarding the 2017 European LeukemiaNet (ELN) risk stratification of patients with AML, 37%, 46%, and 17% of patients had a favorable, intermediate, and adverse risk, respectively. A total of 57% of cases achieved complete remission post-induction, and the median overall survival was 37 months. **Conclusion:** Our study may help predict the future trends of AML in Kuwait to help improve clinical management and patient outcomes.

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Introduction

Acute myeloid leukemia (AML) is a malignant disorder of the bone marrow (BM) characterized by clonal expansion and differentiation arrest of myeloid progenitor cells. It is the second most common type of leukemia diagnosed in adults and children, with most cases occurring in adults. AML makes up approximately 31% of all cases of adult leukemia [1]. Acute promyelocytic leukemia (APL) is a rare subtype that accounts for 10%–15% of adult AML [2].

The prognosis of AML depends on multiple pretreatment factors, such as age and cytogenetic profile upon diagnosis, and certain posttreatment factors, such as response to induction and, more recently, measurable residual disease. Older age at AML diagnosis is associated with greater prevalence of comorbidity and inferior performance status, both of which increase the risk of toxicity and death with intensive induction therapy [3]. The prevalence of AML has increased with improved mortality rates over the last 30 years due to the development of new antileukemia drugs and better management of chemotherapy complications [4]. However, the prognosis of AML remains poor with a 5-year overall survival (OS) of 28.3% [5]. Furthermore, although the OS is 40%–50% in patients younger than 50 years of age with de novo AML, the OS for older patients is only 5%–10% [6].

Several studies have reported a marked increase in the global number of leukemia cases, and leukemia was ranked 13th among cancers worldwide. Moreover, a Gulf Cooperation Council report on cancer ranked leukemia as the 4th most common cancer in the Gulf region [7]. In 2017, the Saudi Cancer Registry reported that leukemia was ranked 5th among cancers in both genders of all ages in the Saudi population, reporting an overall prevalence of 7.6% in males and 4.4% in females [8]. The population of Kuwait is generally young; the percentage of the aged population 65 years and over is 2.83% of the total population [9]. The epidemiology of AML in Kuwait was initially described in 1994 based on the French-American-British classification [10].

As the prognosis and prevalence of AML in Kuwait based on the 2016 WHO classification of AML is unknown, we conducted a retrospective study using a population-based registry to achieve the following objectives: (i) to describe a cohort of patients with AML in terms of demographic characteristics, risk stratification, and treatment history; (ii) to compare patient demographics between APL and non-APL cases; (iii) to characterize the

Table 1. Demographic features and clinical characteristics of 281 AML cases

Characteristic	n (%)
Median age in years (IQR)	47 (27–60)
Gender	
Male	148 (53.0)
Female	133 (47.0)
Nationality	
Kuwaiti	106 (37.7)
Non-Kuwaiti	175 (62.3)
Diagnosis	
APL	25 (8.9)
Non-APL	256 (91.1)
ELN-2017 risk group	
Favorable	104 (37.0)
Intermediate	130 (46.0)
Adverse	47 (17.0)
Blood profile	
Median WBC (IQR), $\times 10^9/L$	11 (46)
Median Hb (IQR), g/L	81 (20)
Median Plt (IQR), $\times 10^9/L$	44 (56)
Treatment intensity [†]	
Intense	210 (75.0)
Low-intensity	28 (10.0)
BMT	46 (15.6)
Induction outcome [†]	
Complete remission	159 (57.0)
Refractory	22 (8.0)
Death	63 (22.0)

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ELN, European LeukemiaNet; Hb, hemoglobin; IQR, interquartile range; Plt, platelet; WBC, white blood cell. [†] The total number does not add up to 281, owing to missing data due to loss to follow-up or patients being unfit for treatment.

incidence of AML in Kuwait; and (iv) to identify factors associated with survival among patients with AML based on the revised 2016 WHO classification.

Subjects and Methods

Data Collection

The work described was conducted in accordance with the Declaration of Helsinki of the World Medical Association. Data on AML and patient characteristics were collected from a clinical cohort. Patient data for the clinical cohort were extracted from the electronic medical record database of participating hospitals. Patients were eligible for inclusion in the study if they were diagnosed with AML (including APL) and received care from a hematologist/oncologist at the Kuwait Cancer Center from January 1st 2014, to December 31st 2020. Data on demographic characteristics, risk factors, and cancer-related factors were collected for 281 patients

Table 2. Comparison between the clinical characteristics of patients with APL and non-APL

Characteristic	APL (<i>n</i> = 25)	Non-APL (<i>n</i> = 256)	<i>p</i> value
Sex, <i>n</i> (%)			
Male	12 (48.0)	136 (53.0)	0.6 [†]
Female	13 (52.0)	120 (47.0)	
Blood profile			
Median WBC (IQR), ×10 ⁹ /L	3 (2, 13)	12 (3, 49)	0.002 [‡]
Median Hb (IQR), g/L	80 (67–88)	82 (73–94)	0.3 [‡]
Median Plt (IQR), ×10 ⁹ /L	19 (11–33)	45 (26–88)	<0.001 [‡]

APL, acute promyelocytic leukemia; Hb, hemoglobin; IQR, interquartile range; Plt, platelet; WBC, white blood cell. [†]The *p* value was generated using Pearson's χ^2 test. [‡]The *p* value was generated using *t*-test.

at diagnosis, who were then further categorized as favorable or unfavorable, which includes categorizations of intermediate and adverse, according to the European LeukemiaNet (ELN) 2017 guidelines [11].

Statistical Analysis

Demographic characteristics were described for the complete sample set (*n* = 281). The characteristics of patients with APL or non-APL were compared using Pearson's χ^2 test and *t* test. To estimate the incidence of AML per 100,000 in the population of Kuwait, data from the Public Authority of Civil Information (PACI) were used for total population size along with AML frequency according to the year [12]. To investigate the OS of patients, Kaplan-Meier survival curves were constructed, and the OS was defined as the time interval between the date of diagnosis and date of death or date of the last follow-up visit. The OS curves were correlated with specific prognostic factors reported in the literature, including genetic subtype (CBF-AML, AML-NPM1, PML-RARA, and other subtypes), age at diagnosis, and 2017 ELN risk group. A comparison of different survival curves was performed using the log-rank test. A *p* value <0.05 was considered statistically significant. Statistical analyses were conducted using R version 2.7 (RStudio, Boston, MA, USA).

Results

Table 1 shows the demographic and clinical features of the 281 participating patients at diagnosis. The overall median age at diagnosis of our cohort was 47 years. Our cohort consisted of 148 (53%) males and 133 (47%) females, exhibiting a male-to-female ratio of 1.1:1. The analysis also revealed that ABL-RARA APL accounted for 8.9% of all cases of AML. Additionally, patients in our study cohort were stratified into the ELN risk categories as follows: 104 (37%), 130 (46%), and 47 (17%) as favorable, intermediate, and adverse risk, respectively. The laboratory parameters at presentation were also documented as follows: median white blood cell (WBC) count

of $11 \times 10^9/L$, hemoglobin concentration of 81 g/L, and platelet count of $44 \times 10^9/L$.

With regard to treatment of AML, the DA10 standard protocol with 3 days of anthracycline and 7 days of cytarabine as an induction treatment was the most common protocol used to treat 169 (60%) fit non-APL cases with AML. All patients with APL were treated with ATRA-based therapy. Twenty (7%) unfit patients were treated with azacytidine-based therapy. Other protocols were also used (fludarabine-based). Regarding postinduction treatment outcome, 159 (57%) patients achieved complete remission (CR) after the first round, whereas 22 (8%) cases had primary refractory disease and 63 (22%) cases died during induction treatment or shortly after (Table 1). Patients who died were mostly frail cases unfit to receive chemotherapy.

We also compared the clinical characteristics of APL (*n* = 25) and non-APL (*n* = 256) patient groups in our cohort (Table 2). We found that the male-to-female ratio in the APL and non-APL subgroup was 1:1.08 versus 1.1:1, respectively, which was not statistically significant. In contrast, we found a statistically significant difference between the two groups in terms of median WBC and platelet count at presentation.

Figure 1 illustrates that the AML incidence in Kuwait ranged from 0.55 to 1.1 per 100,000 persons from 2014 to 2020. Among the population of Kuwait, the highest overall incidence (1.1 per 100,000) was observed in 2018, whereas the lowest overall incidence (0.55 per 100,000) was reported in 2015. We also determined the gender-adjusted incidence and found that the female-adjusted annual incidence range from 0.49 to 1.6, while the male-adjusted annual incidence range from 0.5 to 1.1 per 100,000 population (Fig. 1). Additionally, our analysis revealed that most cases of AML were patients 60 years of age or older.

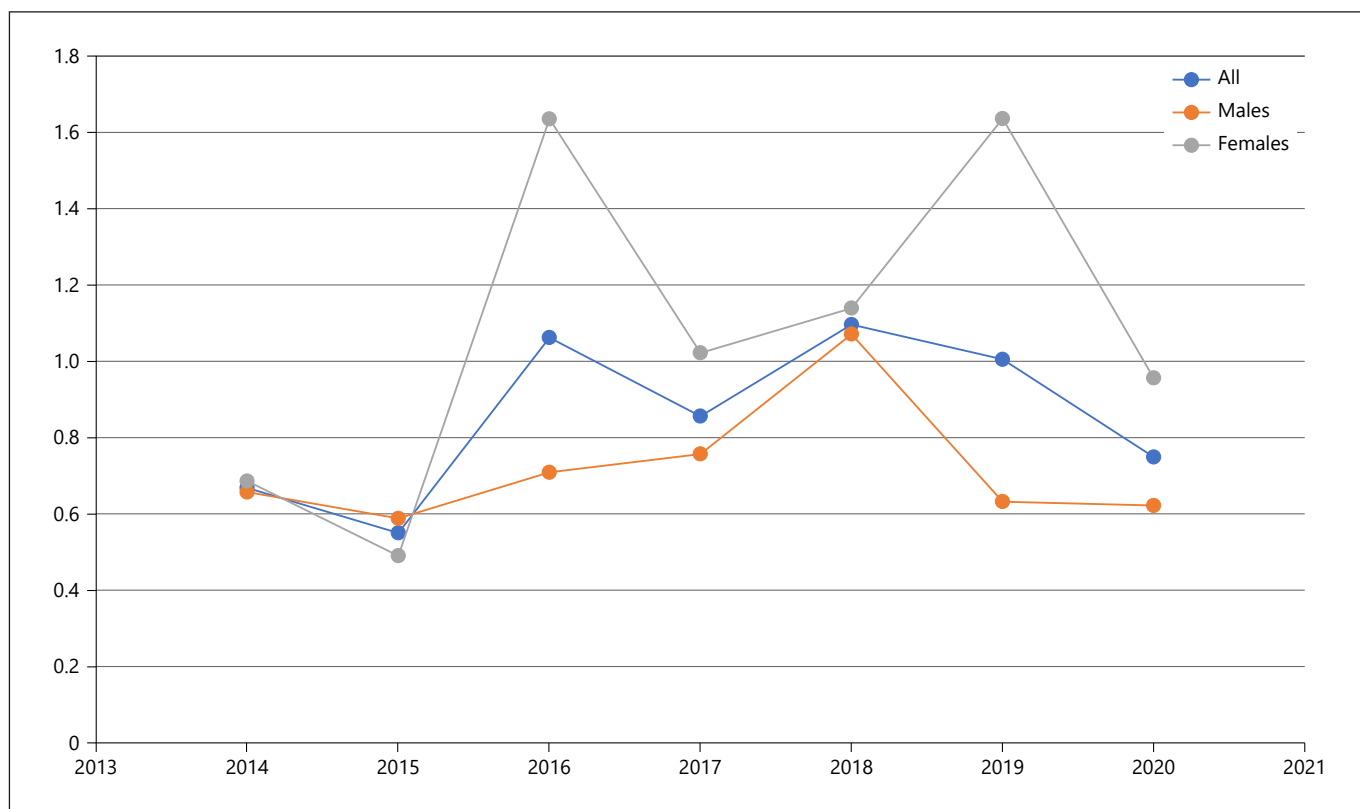


Fig. 1. The crude and gender-adjusted incidence of AML per 100,000 from 2014 to 2020 among the population of Kuwait based on data obtained from the Public Authority of Civil Information, Kuwait.

During the study period, 281 patients were followed up for 5 years. The median OS was 37 months. A comparison was performed among the three most important genetic subtypes in our cohort, namely, CBF-AML, AML-NPM1, and PML-RARA (Fig. 2). Other subtypes were pooled as “Other” to simplify the statistical analysis. We determined that the 12-month OS with 95% confidence interval (95% CI) for CBF-AML was 85% (95% CI: 75–97), AML-NPM1 was 48% (95% CI: 33–68), PML-RARA was 80% (95% CI: 65–97), and “Other” was 66% (95% CI: 58–75). Furthermore, the 24-month OS for CBF-AML was 77% (95% CI: 64–93), AML-NPM1 was 35% (95% CI: 21–58), PML-RARA was 80% (95% CI: 65–97), and “Other” was 57% (95% CI: 48–67) as shown in Figure 2. These findings show a remarkable improvement in the OS of patients with APL compared to non-APL cases. We found that younger patients fared better than those 55 years of age or older.

Next, we evaluated the OS based on ELN risk stratification and found that patients in the favorable risk group fared better than those in the intermediate-risk group.

Moreover, patients in the adverse risk category fared the worst. Furthermore, we found that patients in the favorable risk group and those who received intense chemotherapy fared better in leukemia-free survival multivariable analysis (Fig. 3). Multivariate analysis also showed that younger patients in the favorable risk group and lower WBC exhibited better OS (Fig. 3). As shown in Figure 4, cases positive for FLT3-ITD mutation (FLT3+) fared worse in terms of OS compared to NPM1-mutated (NPM1+) cases that behaved similarly to unmutated cases of AML. The number of patients who underwent allogeneic BM transplantation was only 46 (15.6%).

Discussion

AML is a common malignancy among adults, with an estimated 21,450 newly diagnosed cases and 10,920 deaths in the USA annually [6]. To our knowledge, this is the first study to report the trends of AML incidence in Kuwait, comparing our findings with those of Western countries

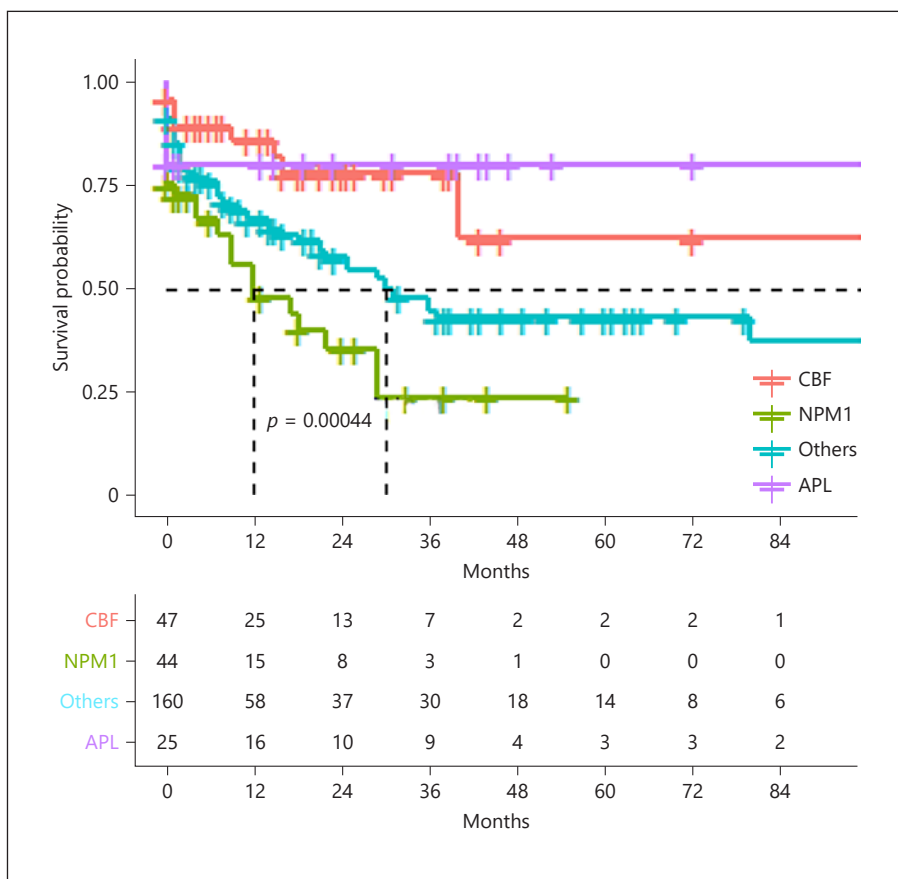


Fig. 2. Median OS according to the genetic subtypes of CBF-AML, AML-NPM1, and PML-RARA. Other subtypes were collapsed into a single category called “Others.”

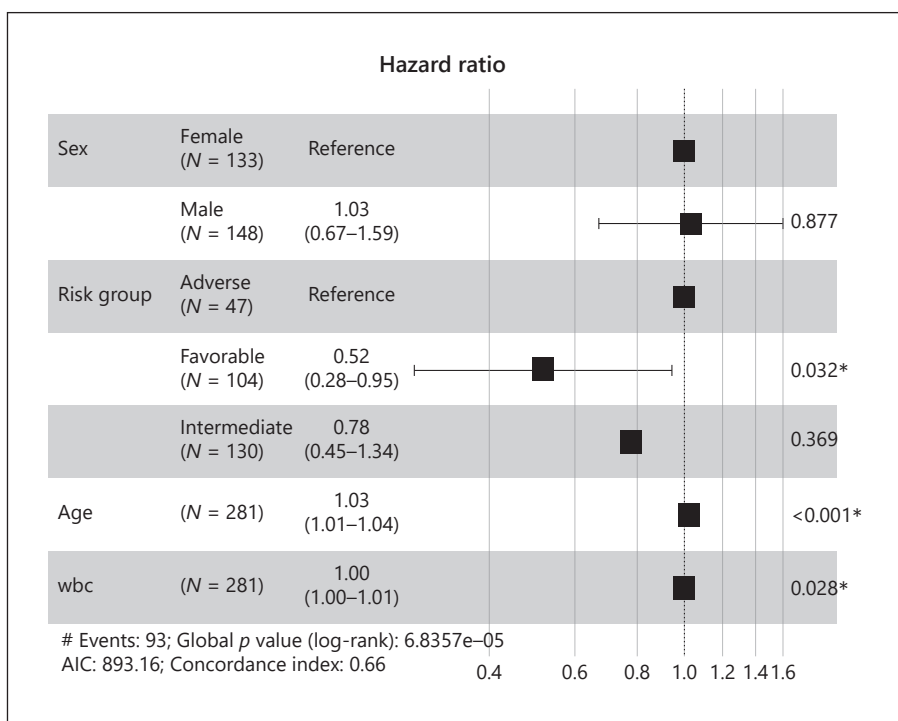


Fig. 3. Multivariate analysis of LFS in the study cohort. * indicates statistical significance. WBC, white blood cells; LFS, leukemia-free survival.

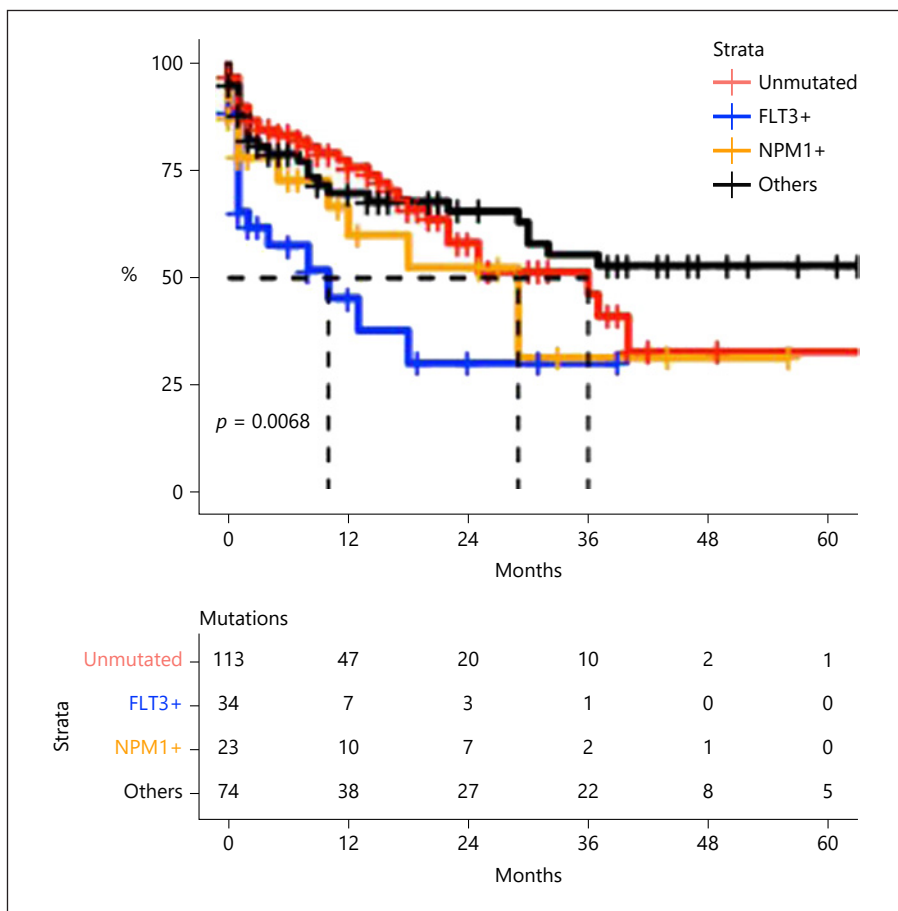


Fig. 4. OS of AML cases according to mutational profile. AML, acute myeloid leukemia; FLT3+, mutation in FMS-like tyrosine kinase 3; NPM1+, mutation in nucleophosmin-1.

and the Middle East. In this retrospective study, we identified 281 cases of AML over a period of 7 years from 2014 to 2020. AML is primarily a disease of older adults; however, we observed a relatively young median age at diagnosis of 47 years in our cohort. This observation likely reflects the young nature of the population of Kuwait. For contrast, in the USA, analysis of Surveillance, Epidemiology, and End Results (SEER) data of AML from 2011 to 2016 showed a median age at AML diagnosis of 68 years [6, 13], and in the UK, the reported median age at diagnosis was 63 years [14]. Interestingly, a recent study of the Western Region of Saudi Arabia reported a median age at diagnosis of 42 years, which was even lower than our cohort [15].

Evidence from population-based studies has shown that males are more likely to develop AML during their lifetime. Our study showed a marginal male predominance with a sex ratio of 1.1:1, matching the distributions reported in most countries. Studies from the USA and the UK reported that males were 1.2–1.6 times more likely to

develop AML than females. Based on SEER data analysis, males are 1.6 times more likely to be diagnosed with AML than females, with an age-adjusted incidence of 5.42 and 3.47 per 100,000 person-years in males and females, respectively [6, 14]. Studies from Saudi Arabia also reported higher frequencies of cases among males than females [15]. These observations indicate that as the population ages, the incidence of AML will also increase; accordingly, associated health care requirements and costs will change with time [9, 16].

The overall incidence of AML in Kuwait ranged from 0.55 to 1.1 per 100,000 persons over the 7-year study period, with the highest incidence being in 2016 and the lowest in 2015. In comparison, the SEER-reported age-adjusted AML incidence was 3.43 per 100,000 per year but has increased over time, with an annual incidence from 2010 and onward consistently higher than 4.2 per 100,000 per year [6]. In 2016, the age-adjusted incidence of AML, including APL, in SEER was 4.3 per 100,000 person-years [6]. The estimated age-adjusted AML inci-

dence in the UK, Canada, and Australia mirrors that of the USA population [6, 17].

In our cohort, 159 (57%) patients achieved CR at the end of induction. Historically, half of patients with AML over 60 years of age receive intensive induction therapy worldwide [18]; however, the response rate to intensive induction differs between patients older than 60 compared to younger, with CR rates of 40%–60% versus 60%–85%, respectively [19]. Clinical presentation of AML at diagnosis was characterized by severe thrombocytopenia and anemia. In our cohort, we found that the median WBC count was $11 \times 10^9/L$, hemoglobin concentration of 81 g/L, and platelet count of $44 \times 10^9/L$. Patients with CBF-AML as well as PML-RARA had longer survival with a plateau in survival curves. We also found that patients with AML over the age of 55 years had shorter OS compared to younger patients. Patients in the ELN intermediate and adverse risk categories showed progressively worse OS compared to the favorable risk group, a finding which is comparable to other published studies [15].

In this analysis, we found that the frequency of patients with APL versus non-APL was 8.9% and 91.1%, respectively. The proportion of cases with APL is consistently higher in countries from Latin America (Brazil: 28.2%, Mexico: 20%, Venezuela: 27.8%, and Peru: 22%) compared with 10% in Northern European countries (UK and Scandinavia) [20]. An evaluation of four clinical trials involving patients with low-risk APL, which is defined as a WBC count less than $10 \times 10^9/L$, from 2010 to 2014 showed that the OS rates ranged from as low as 86% after 3 years to as high as 99% after 4 years [21, 22]. In contrast, the evaluation of three clinical trials from 2015 to 2017 involving patients with high-risk APL, which is defined as a WBC count greater than $10 \times 10^9/L$, showed OS rates ranging from a high of 88% after 3 years to a low of 86% after 5 years [23]. The probability of relapse is significantly higher in the high-risk subset of patients undergoing treatment for APL; approximately 10%–20% of patients with APL relapse regardless of risk stratification [24]. The CBF-AML subtype is associated with a favorable prognosis; however, 40%–50% cannot be cured by multi-combination chemotherapy [11]. A recent study found that novel recurrent mutations in specific genes are important predictors of survival in this type of AML [25], but these mutations were not tested in our study.

In the USA, the estimated median OS of AML was 8.5 months in 2016, and the 2- and 5-year OS was 32.0% and 24.0%, respectively [6, 26]. According to 2011–2016 SEER data, the mortality rate of AML was 2.8 per 100,000 person-years [26]. Most patients with AML diagnosed at 65

years of age or older will die within 1 year from diagnosis, particularly those aged between 75 and 84 years [26]. The median OS of our AML cohort fared better than that reported previously simply because the majority of our cases were less than 55 years old.

In our cohort, AML cases that tested positive for NPM1 mutation (NPM1+) accounted for 15.7% of the total sample. The literature describes the prevalence of NPM1+ AML cases within the range of 20%–30% of total AML cases. The driver mutation NPM1 is a 4-bp insertion in exon 12 of *NPM1*. Cases of AML that test positive for this mutation have a heterogeneous outcome, which is mostly related to the occurrence of other mutations. These associated mutations include those found in the *FLT3*, *DNMT3A*, *IDH1*, *IDH2*, and *TET2* genes, among others [27–30]. These complex genetic interactions may enhance or limit the prognostic value of NPM1-mutated cases of AML. We are currently planning to examine the impact of these mutations on our local cohort.

Our study has a few limitations, such as its retrospective design. The lack of clinical data in several cases due to loss of follow-up is another limitation. The fact that we lack a local BM donor registry led to low utilization of allogeneic BM transplantation services. Furthermore, many expatriates living in Kuwait do not have a local donor available immediately. This study also lacks next-generation sequencing data on certain subtypes of AML to aid in the explanation of variability in treatment outcomes.

Conclusion

AML is a rare hematological malignancy in Kuwait, and its incidence shows an increasing trend from 2014 to 2020. Patients with PML-RARA APL and almost half of those with CBF-AML demonstrated prolonged survival, whereas patients 55 years of age and older showed limited survival. Moreover, improved survival is seen in younger patients with a favorable risk and lower WBC count, as well as in those receiving intense chemotherapy. The establishment of a BM donor registry may improve the outcome of eligible AML cases.

Acknowledgment

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Statement of Ethics

The work described in this retrospective study was conducted in accordance with the Declaration of Helsinki of the World Medical Association.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Salem H. Alshemmari, Mazyad Almazyad, and Mohan Ram: conception and design. Salem H. Alshemmari: development of methodology. Salem H. Alshemmari, Mohan Ram, Liby Mariama John, and Ahmed Alhurairi: patient data acquisition. Salem H. Alshemmari and Mazyad Almazyad: analysis and interpretation of data. All the authors were involved in the writing, review, and/or revision of the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

Our research data are not available for sharing.

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