RESEARCH ARTICLE

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Incidence and Risk Factors of Acute Leukemias in Armenia: A Population-Based Study

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Abstract

Objective: Leukemia represents a serious public health concern as the incidence is increasing worldwide. In this study we aimed to describe the epidemiological profile of acute lymphoblastic (ALL) and myeloid (AML) leukemia, identify disease clusters and find association with possible risk factors. **Methods:** Data on leukemia cases were provided by the National Institute of Health of the Republic of Armenia for the period of 2012-2018. Age-standardized incidence rate was calculated using Segi World Population. SaTScan purely spatial analysis was applied to find leukemia clusters. To find association between leukemia and agricultural and mining activities and demographic data Poisson regression model was used. **Results:** During the studied period 259 new cases of ALL and 478 AML were recorded. The age-standardized incidence rate was 1.5 and 1.9 per 100,000 inhabitants with male to female ratio of 0.97 and 1.1 for ALL and AML, respectively. No significant changes in ALL or AML incidence trends were found. For ALL significant cluster encompassing Shirak, Lori, Tavush and Armavir provinces of Armenia was identified, while Kotayk and Ararat was provinces with the highest incidence of AML. We found significant positive association of ALL with crop density, while no elevated risk estimates were found between AML and exposure variables. **Conclusion:** Altogether, our results suggested that acute leukemias incidence in Armenia follows the pattern described for developing countries.

Keywords: AML- ALL- epidemiology- risk factors- Armenia

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Introduction

Leukemia is a heterogeneous group of haematological neoplasms, characterized by the malignant transformation of hematopoietic stem cells. It is estimated to have the 11th highest incidence among all cancers worldwide, which makes leukemia a public health concern (Forman et al., 2014). Among leukemia types, acute leukemias are the most frequent and fast developing forms, with acute lymphoblastic leukemia (ALL) occurring primarily in children, while acute myeloid leukemia (AML) predominantly affects adults. ALL accounts for about 80% of all pediatric leukemias with a peak incidence in age group <15 years old and a second peak after 50 years of age (Paul et al., 2016; Terwilliger and Abdul-Hay 2017). Contrary, AML accounts for about 25% of all leukemias among adults with median age of diagnosis 65 years (Deschler and Lübbert, 2006). Worldwide, the highest incidence rates of leukemia has been registered in Australia, USA and Western Europe, whereas the lowest rates are found in developing countries (Abboud et al., 2014; Miranda-Filho et al., 2018).

Though the etiology of acute leukemias remains elusive, a number of risk factors has been suggested, including life style, habits and a variety of occupational and environmental exposures. Growing epidemiological studies have reported increased incidence of AML and ALL among farmers and in intense agricultural areas, indicating positive association between pesticides exposure and risk of leukemia (Viel and Richardson, 1991; Turner et al., 2010; Jones et al., 2014; Bailey et al., 2015). In terms of industrial activities, employment in metal production and processing has been associated with increased occurrence of this malignancy (Ahn et al., 2006). Increased risk of leukemia has been reported among metal miners (Sodhi-Berry et al., 2017). Moreover, increased

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mortality rate of leukaemia patients were observed in the vicinity of metal foundries (Fernández-Navarro et al., 2012).

In the absence of national cancer registry, epidemiological studies evaluating the general patterns of overall incidence of leukemia in Armenia are very limited. Previous studies concentrated either on young or adults groups. Consequently, in the study by Poghosyan (2015), which includes patients admitted to one single institution the prevalence of AML were evaluated among adults (>18 years) in the period of 2010 to 2014. During these 5 years period no increase in incidences was found, and 73% of patients were reported to be under 60 year old. In another report the incidence rates of ALL and AML were analyzed among children aged 0-19 for 13 years period (Krmoyan et al., 2019).

Taking into account that accurate estimation of epidemiological situation can add to further health-care resource planning and appropriate allocation, in the present study we aimed to describe epidemiological pattern and spatial distribution of AML and ALL in Armenia and identified possible demographic and environmental risk factors in terms of agricultural and mining activities.

Materials and Methods

Data source

Incidence data for the seven-year period (from 2012 January 1 to 2018 December 31) were provided by the National Institute of Health of the Republic of Armenia, which collects all new cancer cases from all hospitals and outpatient clinics across the country. Leukemia cases were classified according to the International classification of diseases (ICD) 10th version into ALL (C91.0) and AML (C92.0, C93.0, C94.0, C95.0). Incidence data were stratified by age and gender for the whole country and for each province. Population census data from 2011 were obtained from the Statistical Committee of the Republic of Armenia (2011).

Data on the total area of provinces and harvested land by province came from the State Committee of Real Estate Cadastre of the Republic of Armenia (2019). Data on harvested land in hectares were for 2012-2018 period and averaged values were used in further analysis.

Data on metal mines per province was available for the period of 2016-2017 and was obtained from the Extractive Industries Transparency Initiative report (2019). In total, 28 mines, including copper, molybdenum, gold and multimetal are exploited in Armenia.

Descriptive study and time trends evaluation

For our analysis we grouped age at diagnosis into 8, 10-year age categories with category 1 being those aged 0-9 years and category 8 representing those aged 70 years and above. The merging of age cohorts was done to obtain more stable data and as a result reduced probability of statistical errors.

Crude incidence rates were calculated by age groups and sex. Age-standardized rates (ASIR) were calculated by direct standardization method, using the World Standard Population (Bray and Ferlay, 2014). All rates were expressed per 100,000 person-years.

To investigate time trends in incidence of ALL and AML joint point regression analysis were conducted using the Joinpoint Regression Software (version 4.7.0.0), developed by the United States National Cancer Institute (National Cancer Institute, Bethesda, Maryland, USA). This method models time trends using several continuous line segments, joined at ‘joinpoints’, representing the timing (i.e. year). This method allows to identify the calendar year in which a significant variation in trends has occurred (the “joinpoints”). The analysis starts with 0 joinpoint (representing a straight line) and tests for model fit with a user defined number of jointpoints. This iterative procedure estimates whether models of increasing complexity provide a significantly better goodness-of-fit than simpler models. Thus, it selects the best-fitting points where significant increase or decrease of rates occurred. Monte Carlo permutation method is used to test the significance. In addition, annual percent change (APC) for each line segment is estimated, allowing comparison of trends over a specified time interval.

For the analysis the natural logarithm of the age-standardized leukemia incidence rates were used as the response variable and the independent variable was the diagnosis year from 2012 to 2018, stratified by age and gender.

Spatial distribution

To identify leukemia incidence clusters SaTScan statistical software (version 9.6) was used (Kulldorff, 1997). The analysis requires that the geographic information for each province be represented by form of a centroid. To obtain the geographical centroid of each province and to create maps with information on the cancer clusters, the geographical information system MapWindow version5 (GeoSpatial Software Lab, Aidaho, USA) was utilized. Purely spatial analysis were conducted, using the Poisson probability model and constrained to clusters no larger than 50% of the population at risk. Elliptical window were used and age and gender adjustment were done directly in SaTScan. This method tests the null hypothesis that the age and gender adjusted risk of cancer incidence is the same across the country. P values obtained through Monte Carlo hypothesis testing using 999 replications and relative risk values were assigned to provinces.

Statistical analysis

The percent harvested area for each province was derived by dividing total land used for crop production by total land for that province. The percent cropland was categorized using the lower and upper quartiles rounded to the nearest 5% as cutoffs. For evaluation of risk associated with mining activity, provinces was classified as ‘exposed’ if mines were present in that area, regardless of the number of mines and exposed provinces were compared with ones that had no mines.

Poisson regression analysis was used to estimate incidence rate ratios (IRR) with 95% confidence intervals (CI) and to find associations between ALL/AML and demographic and environmental risk factors. Analysis was carried out using SPSS version 19 (IBM Corp., Armonk, NY, USA).

Results

Descriptive study and time trends evaluation

A total of 737 cases of acute leukemia were registered between 2012 and 2018, out of which 259 were ALL and 478 AML (Table 1). On average 37 ALL and 68 AML new cases were recorded annually. In the studied time period, the average age-standardized incidence rates for ALL were 1.6 among males (95% CI: 1.3-1.8), 1.4 among women (95% CI:1.02-1.8) and 1.5 (95% CI:1.3-1.7) in the total population with male to female ration of 0.97. In respect to AML, the age-standardized incidence rates were 2.3 (95% CI: 1.7-2.9), 1.6 (95% CI:1.3-1.9) and 1.9 (95% CI:1.5-2.3) among males, females and whole population, respectively. The overall male to female ratio was 1.1.

ALL and AML incidence rates stratified by gender and age cohorts are summarized in Figure 1 and Supplementary Table S1 and S2. Unsurprisingly, ALL is most common in early childhood as compare to other age groups. Respectively, the highest incidence rates are observed in 0-9 year age group, with sharp decrease for both genders occurring after the age of 9. In AML incidence rates remained low in childhood and early adulthood with increases for both sexes after the age of 39. For women, the growth is gradual, while for males, sharp increase in incidence is observed in 60-69 year age cohort, resulting in the greatest discrepancy between sexes in this age group.

In order to describe the occurrence of significant changes in incidence rate trends over time, a joinpoint regression model was used. For ALL the highest age-standardized rate was recorded in 2016 among males (2.13), while for women in 2012 (2.22) (Figure 2a). No major changes in incidence occurred during the studied period of time. However, a downward trend could be noted in females (annually -5.3%, 95% CI:-17.4-8.6), though not statistically significant. Similarly, the incidence rate of AML remained stable over the 7-year period for both genders (Figure 2b). The highest rate for males occurred in 2015 (3.24), while among females in 2014 and 2015 (2.09 and 2.11, respectively).

Spatial distribution

The SaTScan purely spatial analysis was applied to identify leukemia clusters in Armenia. For ALL one significant cluster was revealed, which encompasses Shirak, Lori, Tavush and Armavir provinces of Armenia (Figure 3a). After adjusting for age and sex, there were 99 observed cases and 74.57 expected cases in these provinces, with a relative risk of 1.53 ($p<0.05$), implying that there is a statistically significant 53% increased risk of ALL compared with the whole country.

Similarly, for AML one significant cluster, which includes Kotayk and Ararat provinces was identified (Figure 3b), with the observed and expected cases as 102 and 76.72, respectively and relative risk of 1.42 ($p<0.05$). This suggested that there is 42% increase in the rate of AML in Kotayk and Ararat relative to the rest of the country.

Statistical analysis

Associations between leukemia and demographic and exposure variables are shown in Table 2. We found statistically significant positive association between ALL and youngest and older age groups (IRR=2.4, % 95CI:1.5-3.8, $p<0.001$ for 0-9 age group and IRR=1.9, %CI: 1.1-3.3, $p<0.001$ for 60-69, respectively) and negative association

Table 1. Incidence Features of Acute Lymphoblastic (ALL) and Acute Myeloid (AML) Leukemia in Armenia for the Period 2012-2018

	ALL average (CI[a])	AML average (CI[a])
Total N of cases	259	478
Crude incidence total	1.3 (1.1-1.5)	2.4 (1.9-2.8)
ASIR[b] total	1.5 (1.3-1.7)	1.9 (1.5-2.3)
Crude incidence males	1.4 (1.2-1.6)	2.6 (2.1-3.2)
ASIR males	1.6 (1.3-1.8)	2.3 (1.7-2.9)
Crude incidence females	1.22(0.9-1.6)	2.2(1.6-2.7)
ASIR[b] females	1.4 (1.02-1.8)	1.6 (1.3-1.9)
Male/Female	0.97	1.1

[a]CI, confidence interval; [b]ASIR, Age-standardized incidence rate per 100,000 person-years

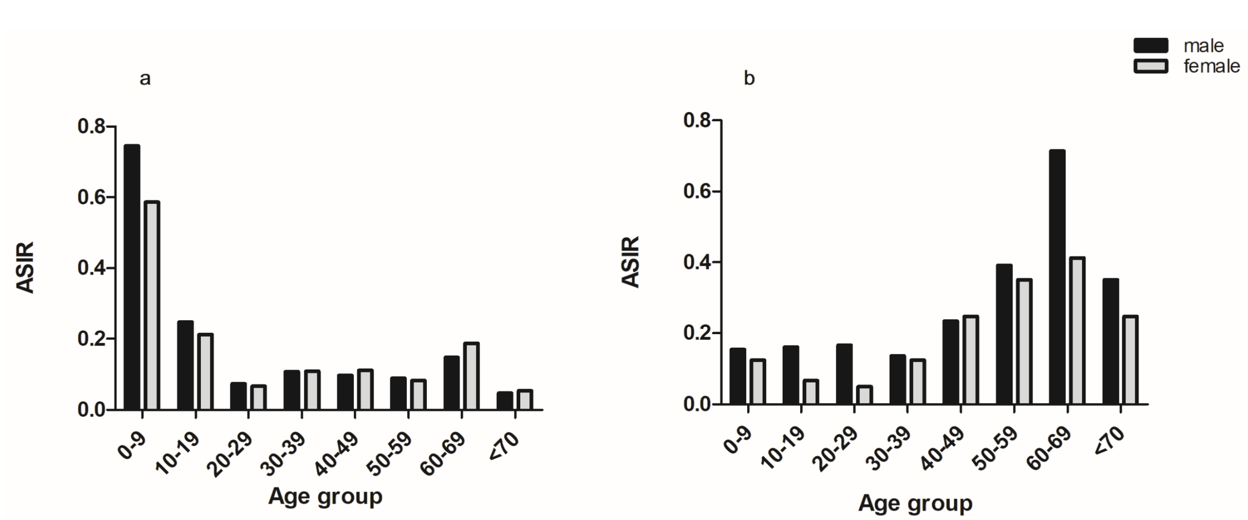

Figure 1. Age and Gender-Categorized Age-Standardized Incidence Rates of Acute Lymphoblastic (a) and acute myeloid leukaemia (b) in Armenia (2012-2018)

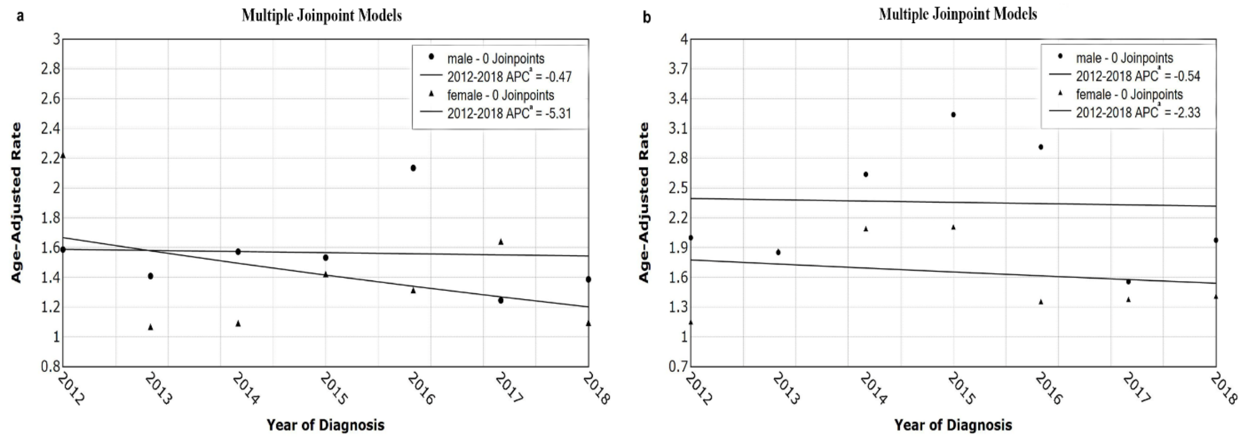

Figure 2. Age-Standardized Incidence Rate Trend Over Time for Acute Lymphoblastic Leukemia (ALL) (a) and acute myeloid leukemia (ALL) (b) in Armenia for the period 2012- 2018

with 20-29 group (IRR=0.3, %95CI:0.2-0.6, p<0.001). Increased risk for ALL was found to be associated with high density of cropland (IRR=1.4, %95=1.1-1.9, p<0.05), while no association was seen for mining activity (IRR = 0.8, % 95CI:0.6-1.1, p>0.05).

We found strong negative association between AML and all age groups below 60 years. Males were at 1.4 higher risk for developing AML (IRR= 1.4 %95 CI: 1.2-1.7, p<0.001) than females. At the same time, no association between risk of AML and exposure variables were found.

Discussion

To the best of our knowledge this is the first study which provides epidemiological profile of acute leukemias incidence in Armenia. Contrary to previous studies that were limited either to youth population or omit an age-standardized rate, here we included all age groups (Poghosyan, 2015; Krmoyan et al., 2019; Hakobyan, 2003). In total, age-standardized incidence rate for both leukemia types were low (1.5 for ALL and 1.9 for AML) as compared to developed countries, however these rates are similar to ones reported for developing countries (Miranda-Filho et al., 2018). Previously, it has been suggested, that low numbers of leukemia in developing countries at least partly can be attributed to the misdiagnosis or unreported cases (Ferman et al., 2013; Abboud et al., 2014). It is worth mentioning that in the absence of population-based cancer registry data used in our study derived from the hospital-based one. The National Institute of Health of the Republic of Armenia compiles data on cancer cases diagnosed in all hospitals and outpatient clinics across all regions of Armenia. However, hospital-based dataset can be biased as it partly depends on the expertise and the facilities at a particular hospital (Bray F et al., 2014). Moreover, there is a complete lack of hematologists in the provinces

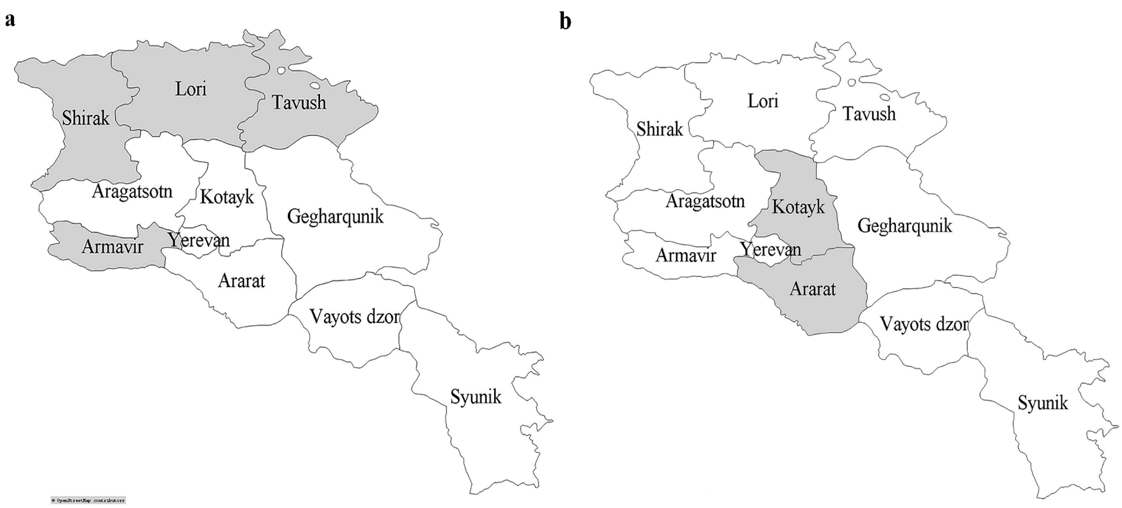

Figure 3. Purely Spatial Analysis of Acute Lymphoblastic Leukemia (a) and acute myeloid leukemia (b) for the period 2012-2018. Clustering representation of SaTScan purely spatial analysis is illustrated utilizing centroid data with age and sex, as covariates. Significant cluster is grey shaded. SaTScan computed results include: (a) population 819970, observed cases=99, expected cases=74.57, relative risk=1.53, p<0.05; (b) population 492204, observed cases=102, expected cases=76.72, relative risk=1.42, p<0.05

Table 2. Incidence Rate Ratios (IRR) and 95% Confidence Intervals (CI) of Acute Lymphoblastic (ALL) and Acute Myeloid (AML) Leukemia in Armenia for the Period 2012-2018

Category	ALL IRR (%95CI)	AML IRR (%95CI
Age group		
0-9	2.4 (1.5-3.8) **	0.1 (0.06-0.2) **
10-19	0.9 (0.6-1.7)	0.1 (0.06-0.14) **
20-29	0.3 (0.2-0.6) **	0.1 (0.05-0.12) **
30-39	0.7 (0.4-1.3)	0.1 (0.09-0.21) **
40-49	0.7 (0.4-1.2)	0.3 (0.2-0.4) **
50-59	0.7 (0.4-1.3)	0.5 (0.4-0.7)**
60-69	1.9 (1.1-3.3) **	1.1 (0.8-1.4)
<70	#	#
Gender		
Male	1.1 (0.8-1.3)	1.4 (1.2-1.7) **
Female	#	#
Percent cropland		
≤5	#	#
5-13	1.1 (0.7-1.7)	1.1 (0.8-1.5)
≥13	1.4 (1.1-1.9)*	1 (0.8-1.3)
Mining activity		
Exposed	0.8 (0.6-1.1)	0.9 (0.8-1.2)
Unexposed	#	#

#, reference group; *, p<0.05, **p<0.05

of Armenia (Andreasyan D et al., 2020). Altogether the mentioned issues can provide a biased profile of cancer incidence.

Our results demonstrated stable trends of the age-standardized ALL and AML incidence rates both in males and females during the observed seven-year period. However, these results should be interpreted with caution as seven-year period is quiet short to make comprehensive conclusion. In overall, Iincidence trends vary across the world, demonstrating diverse pattern. According to the US National Institute of Health (2020), ALL cases have been rising on average 0.6% annually during 2007-2017, while increase in incidence of AML was 1.5 % for the same time period. Over the last decade, in UK stable trends of ALL were registered, while AML incidence rates have increased by 7% between 2005-2007 and 2015-2017 (Cancer Research UK, 2020). In neighboring to Armenia Iran, decreasing trends for both ALL and AML were recorded during 2003-2008 (Koohi et al., 2015).

Age distribution of ALL was found to follow bimodal pattern, with the highest incidence rates observed in children and a second increase in the age group of 60-69 years. This finding corroborates with other studies, which describe it as the most common epidemiological pattern of ALL (Miranda-Filho et al., 2018). As expected, AML cases were clustered more during later adulthood. A gradual increase by age with the incidence peak at age cohort of 60-69 years and decrease in <70 group was shown. In overall, this follows the pattern observed worldwide, where unimodal form, with rates rising with increasing age is described (Miranda-Filho et al., 2018). However, in developed countries the incidence peak after 75 years has been reported. Consequently, in Canada and UK the incidence rates for both genders peaked after 80 years (Bhayat et al., 2009; Shysh et al., 2018). The relatively younger occurrence observed in our study can be ascribed to age characteristics of Armenian population.

In general, for all types of hematological malignancies, including ALL and AML male predominance is reported, which may have genetic and physiological basis (Dorak and Karpuzoglu, 2012). In our study some increased incidence of AML as compared to females was found, with male to female ratio of 1.1. However, incidence rate of ALL did not show inclination for any gender (ratio of 0.97).

We identified significant clusters of ALL and AML incidence by utilizing SaTScan software, which is reliable in the assessment of cancer clusters (Kulldorff et al., 1997). The identified cluster for ALL encompassed Shirak, Lori, Tavush and Armavir provinces of Armenia, while AML occurred the most in Kotayk and Ararat provinces.

We aimed to identify possible risk factors associated with the higher incidence of leukemia in clustered provinces by taking into account the fact that agriculture and mining are the main types of economic activities in Armenia and association of certain types of leukemia with pesticide use and living in proximity of mines has been reported previously. In our study, percentage of cropland was used as a surrogate of exposure to pesticides. We found positive association between the risk of ALL and density of cropland, while no link was found for AML. In contrast to our result, Booth (2015) found no association of ALL and cropland density, however they reported statistically significant exposure-response relationships for certain types of crops. In another study, significantly elevated risk estimates were found for AML and high harvested areas, as well as types of crops (Carozza et al., 2008). This inconsistency with our results may arise from variation in age groups studied. The aforementioned studies investigated relationships of exposure variables and children cancers, while we included all age groups. On the other hand, in the absence of appropriate data, we were not able to study associations between leukemia and types of crops harvested in Armenia.

One major drawback of our study is low number of cases, however since incidence data used for analysis is collected from all hospitals and outpatient clinics across Armenia we believe that it is representative for the country. Another limitation is that we did not take into account potential risk factors such as socioeconomic status and individual level exposures, i.e. smoking. Furthermore, though exposure measurements used in our study are valid methods, they still suffer from the lack of precision and specificity. Further studies incorporating individual-level data are necessary.

In summary, this study is the first to describe the epidemiological profile of acute leukemias in Armenia. In overall, the incidence pattern follows the one described for developing countries. We stress out the importance of blood surveillance in particular regions of the country. Altogether, the obtained results suggest that further carefully planned studies with emphasize on pesticides usage is required to assess risk factors associated with leukemia incidence in Armenia.

Author Contribution Statement

LK and NB analyzed and interpreted the data. DA and YH were involved in data collection and analysis. EB performed an in-depth literature search. LK, NB, EB, RA and HS were involved in manuscript writing and editing. All authors read and approved the final version of the manuscript.

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Approval by Scientific Body

This work was not approved by any Scientific Body and it is not a part of an approved student thesis.

Ethics approval

The study was approved by the Ethics Committee of the Institute of Molecular Biology of the NAS RA (IRB IORG0003427).

Availability of data

Data minimally required to replicate the outcomes of the study is available upon reasonable request.

Conflicts of interest

The authors declare no potential conflicts of interest.

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