

**TRENDS IN ACUTE LEUKAEMIA INCIDENCE IN ADULTS
IN THE REPUBLIC OF MACEDONIA (1993–2003)
A DESCRIPTIVE EPIDEMIOLOGICAL STUDY**

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Abstract: *Objective:* To analyse trends in incidence rates of acute leukaemia in patients aged 15 and over admitted to hospital. *Design:* A descriptive epidemiological study.

Setting: University teaching hospital, Haematology Clinic, Skopje.

Results: The crude incidence rates of acute leukaemia in adults during this period increased substantially (p for overall trend < 0.001). The lowest crude incidence rates (CIR) were observed in 1996 (CIR = 1.64/100 000; 95% Confidence Interval CI = 1.1–2.4), while the highest were noted in 2003 (CIR = 3.76/100 000; 95% CI = 2.9–4.8). In 1993 the sex ratio of the incidence rates (males to females) was Rate Ratio (RR) = 2.23, while as of 2001 the association between sexes disappeared (RR = 1). The trend in males was not significant ($p = 0.160$), while in females it showed a monotonic increase that was highly significant ($p < 0.001$).

Conclusions: During a short period of time (11 years) we have noted an increase in the incidence rates of acute leukaemia in our population aged 15 years and above. The study suggests that this could be due to increased risk in females, and in adults over 40 years. In addition, according to the census results in 1994 and 2002 the proportion of people aged 65 and above increased by 30.5% implying that this demographic change could account for part of the relative increase in the incidence rates of acute leukaemia. Further analytic studies are needed to address the possible causes of these changes.

What is already known on this topic: The risk of acute leukaemia increases by age and it is higher in males than in females.

What this study adds: The incidence rates are equal between the sexes; the increase in risk of acute leukemia in females could be due to environmental risk factor.

Key words: acute leukaemia; adults; incidence, trends, epidemiology, sex ratio.

Introduction

Acute leukaemia is a life-threatening haematological malignancy. Its prognosis depends on many factors including age, sex and adequate therapy [1, 2]. Acute leukaemia affects both sexes and all ages, but the incidence rates are higher in younger children (0–4 years), the elderly (> 65), and in male compared to female patients [3]. Most epidemiological studies address only the problem of acute leukaemia in children [4]. However there are also a number of other published studies addressing the epidemiology of this disorder in adults [5, 6], as well as the sex differences in the risk of haematological malignancies [7].

Acute leukaemias comprise many different biological subtypes as proposed by the recent WHO classification [8]. Successful classification, however, depends on the availability of sophisticated diagnostic equipment and immunophenotyping, cytogenetics and molecular analysis techniques [9, 10]. For the purpose of this study we included four distinct types of acute leukaemia morphologically and clinically diagnosed and coded by ICD-9 revision at the Haematology Clinic in Skopje. These are: Acute lymphoblastic leukaemia (ALL), Acute myeloblastic leukaemia AML, Acute leukaemia of unknown origin, and myelodysplastic syndrome (RAEBT).

Speculations over the concentration of depleted uranium (DU) used in the ammunition during the 78-day NATO campaign in Yugoslavia in the spring of 1999 increased concern among the general public in the region over the possible negative effects on human health [11]. A series of articles with misleading messages were published in international newspapers on the possible hazardous effects of DU for some cancers, including acute leukaemia [12, 13, 14]. A few studies have addressed this theory in the region [9, 15] but little is known about the possible effects on our population. In the years following the war activities in Yugoslavia, we have registered an increase in the annual number of patients with acute leukaemia in the Republic of Macedonia. We set out to estimate the annual incidence rates of acute leukaemia and the distribution of cases by sex, age, and place of residence over a period of eleven years (1993–2003).

Methods

Our study population consisted of all adult patients aged 15 and above, diagnosed and treated for acute leukaemia at the Haematology Clinic in Skopje

between 1st January 1993 and 31st December 2003. In Macedonia, all patients suspected of acute leukaemia are referred to the Haematology Clinic as the only referral centre. Therefore, we assumed that the results of this study apply to the total adult population aged 15 and over of the Republic of Macedonia.

The patients eligible to be included in the study were citizens of the Republic of Macedonia, aged 15 years and above and diagnosed with acute leukaemia (all types). During this period there were 408 diagnosed cases of acute leukaemia. Of these, 13 were foreigners from neighbouring Kosovo and Albania who were subsequently excluded from further analysis. This left 395 patients eligible for analysis. Each patient diagnosed with a malignant neoplasm at the Haematology Clinic in Skopje, apart from the regular hospital record, is also registered at three places: in a special clinic register for registering malignant neoplasms, in the clinic diary and supplementary, by law, each malignant neoplasm needs to be notified to the City Institute of Health Protection in Skopje using a standardized form (*Registration of malignant neoplasm*) according to the ICD-9 revision.

The clinic register of malignant neoplasms was our primary source for the collection of information on patients. Patients are registered in the clinic register by name, identity number, sex, admission date, place of residence, occupation and the diagnosis. The patients are also registered with the diagnosis by which they were discharged from the hospital. Eight cases were diagnosed and admitted to the hospital in one year, but following remission of the disease they were admitted for further treatment in subsequent years. To avoid the possibility of counting newly-diagnosed patients twice while calculating incidence rates, we set up a rule: to include all patients who were diagnosed for the first time with acute leukaemia, but for validation we considered the last diagnosis by which the patients were discharged from the hospital. To check the reliability of the data registered in the clinic register of malignant neoplasms with those in the hospital records, we randomly selected 25 patients to compare the data. The same data was confirmed in all patients by crosschecking both sources of information.

Statistical Analysis

The first stage of the analysis included description of the study population by sex, age, religion, place of residence, profession and year of diagnosis. We estimated annual cumulative crude and sex-specific incidence rates per 100,000 persons at risk, under the assumption that apart from misdiagnosis, treatment abroad or premature death before possible treatment, all cases of acute leukaemia in Macedonia in adults aged 15 and above were treated at the Haematology Clinic. As numerator we used the number of newly diagnosed cases

of acute leukaemia for each year covered in the analysis, while in the denominator we used the population as it appears in the censuses of 1994 [16] (for years 1993–1998) and 2002 [17] (for years 1999–2003). In addition we age-standardized the incidence rates of the years 1996 and 2003 to the world standard population [18] using the direct method [19]. Finally, we performed a linear trend analysis using the chi square test to determine whether there is a linear increase or decrease that is statistically significant in the annual incidence rates of acute leukaemia overall, and by sex [20].

Results

During the period of eleven years from January 1st 1993 to December 31st 2003 there were 395 patients who were citizens of Macedonia diagnosed and hospitalised for acute leukaemia at the Haematology Clinic in Skopje. Of these, 217 (54.9%) were males, while 178 (45.1%) were females.

As expected, the most frequent type of acute leukaemia was acute myeloblastic leukaemia with 277 cases (70.1%) of the total, then followed acute lymphoblastic leukaemia with 56 cases (14.2%), acute leukaemia of unknown origin with 37 cases (9.4%), and myelodysplastic syndrome (RAEBT) with 25 cases (6.3%) of all the acute leukaemia patients. The great majority of the patients 313 (79.2%) were Christians, while 82 (20.8%) were Muslims. This information, with few exceptions, refers to ethnic Macedonians as Christians and ethnic Macedonian-Albanians as Muslims. The age distribution of the patients ranged from 15 years to 89 for the oldest. The average age of all adult patients diagnosed for the first time with acute leukaemia was 48.9 years, standard deviation of 18.0 years, median 51 and mode of 61 years ($n = 16$). The average age at diagnosis for the males was 48.6, median 52 years, mode of 61 years ($n = 9$), while for the females it was 49.3, median 50.0, mode 43 and 50 years ($n = 8$). The distribution of subtypes of acute leukaemia among selected age groups is shown in Figure 1.

AML was almost equally distributed in all age groups, ALL was more frequent among the young (15–19 years), while the frequency of RAEBT increased with the age of the patients.

We registered 28 towns in Macedonia as places of residence of patients diagnosed with acute leukaemia. Almost half (45.8%) of all acute leukaemia patients reside in three northern towns Skopje ($N = 120$, 30.4%), Tetovo ($N = 34$, 8.6%) and Kumanovo ($N = 27$, 6.8%) where according to the census results of 2002 residents in these three towns number 467,257, 103,205 and 70,841 people respectively or 31.7% of the total population in the country [14]. However, we were not able to control for the different age distributions in these towns since the final results of the census by age groups have not yet been released.

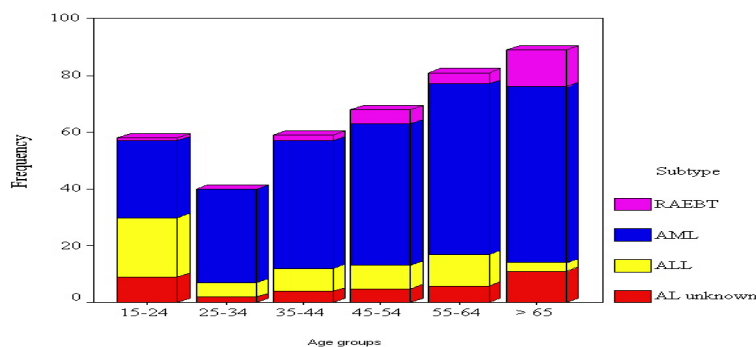


Figure 1 – Frequency distribution of different subtypes of acute leukaemia by age group

Фигура 1 – Дистрибуција на фреквенциите на различни подтипови на акутна леукемија според возрасни групи

In Table 1 we present the frequency, annual crude and sex-specific incidence rates, 95% confidence intervals, male to female rate ratios of acute leukaemia during the period January 1st 1993 to December 31st 2003 in the Republic of Macedonia.

Table 1 – Табела 1

Frequency and incidence rates of acute leukaemia in adults
(15 and over) 1993–2003 in Macedonia
Фреквенција и стапки на инциденца на акутна леукемија кај возрасни
(15 години и повеќе) во Македонија

Year	N	Crude Rates ¹ 95% CI	Rate Ratio	N	Males ² Rates 95% CI	N	Females ³ 95% CI	Rate Ratio M/F 95% CI
1993	32	2.19 (1.5-3.1)	1.33	22	3.03 (2.0-4.0)	10	1.36(0.7-2.4)	2.23 (1.0-4.72)
1994	31	2.12 (1.4-3.0)	1.29	18	2.48 (1.5-3.8)	13	1.76 (1.0-2.9)	1.40 (0.7-2.87)
1995	28	1.92 (1.3-2.8)	1.17	19	2.61 (1.6-4.0)	9	1.22 (0.6-2.2)	2.13 (0.97-4.74)
1996*	24	1.64 (1.1-2.4)	1.0	13	1.79(1.0-3.0)	11	1.49 (0.8-2.6)	1.20 (0.54-2.68)
1997	24	1.64 (1.1-2.4)	1.0	15	2.06 (1.2-3.3)	9	1.22 (0.6-2.2)	1.69 (0.74-3.87)
1998	34	2.32 (1.6-3.2)	1.64	15	2.06 (1.2-3.3)	19	2.57 (1.6-3.9)	0.80 (0.41-1.58)
1999	34	2.13 (1.5-3.0)	1.29	22	2.76 (1.8-4.1)	12	1.50 (0.8-2.5)	1.84 (0.9-3.73)
2000	30	1.88 (1.3-2.7)	1.14	13	1.63 (0.9-2.8)	17	2.12 (1.3-3.3)	0.77 (0.37-1.58)
2001	48	3.00 (2.2-4.0)	1.82	25	3.14 (2.1-4.6)	23	2.87 (1.9-4.2)	1.09 (0.62-1.93)
2002	50	3.13 (2.3-4.1)	1.90	25	3.14 (2.1-4.6)	25	3.12 (2.1-4.5)	1.00 (0.58-1.75)
2003	60	3.76 (2.9-4.8)	2.29	30	3.77 (2.6-5.3)	30	3.74 (2.6-5.3)	1.00 (0.61-1.67)
Total	395			217		178		

* 1996 is the referent year.

1) Crude incidence rates per 100.000 population at risk. The total population of Macedonia aged over 15 according to the census results in 1994 was 1,462,009 citizens, while according to the census of 2002 it was 1,596,267. During this period the population of Macedonia aged over 15 years experienced a relative increase of 9.2%.

2) Male incidence rates. The total male population of Macedonia aged over 15 according to the census in 1994 was 725,442 citizens, while according to the census of 2002 it was 795,749. During this period the male population aged over 15 experienced a relative increase of 9.7%.

3) Female incidence rates. The total female population of Macedonia aged over 15 according to the census in 1994 was 736,567 citizens, while according to the census of 2002 the number was 800,518. During this period the female population experienced a relative increase of 8.6%.

Over the period of eleven years the annual crude incidence rates of acute leukaemia in adults showed variation. In the first years of the analysis the incidence rates were rather stable with a cumulative incidence (I) around 2/100,000 people at risk. The lowest rates were recorded for the years 1996 and 1997 (I = 1.64; 95%CI = 1.1–2.4). In the year 2001 the crude incidence rates rose above 3/100,000 people with a continuous monotonic increase over the next few years to reach the highest rates in 2003, (I = 3.76; 95% CI = 2.9–4.8). The crude incidence rate of 2003 was 2.3 times higher compared to that of the reference year 1996.

With regard to the sex-specific incidence rates of acute leukaemia, over the period of 1993–1999 apart from year 1998 there was a variation in the association between sex and leukaemia rates.

The rate ratio (male/female) in 1993 was 2.3, 95% CI = 1.0–4.7. Over the following years this association weakened, and in the year 2000 there were higher rates in females than in males (RR = 0.77; 95% CI = 0.37–1.58), and finally there was no difference in the last three years of the analysis (RR = 1). We performed a chi square trend analysis to assess changes over time in both series and in each group separately.

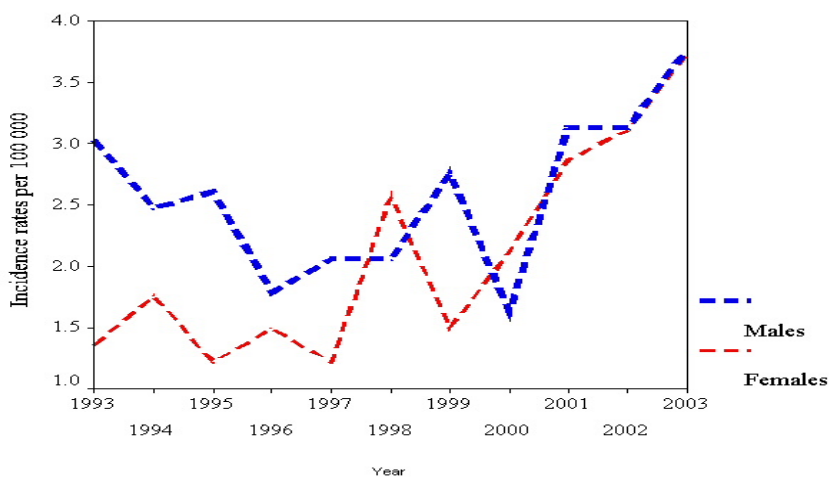


Figure 2 – Sex-specific incidence rates of acute leukaemia in adults in Macedonia (1993–2003)

Фигура 2 – Полово специфични стапки на акутна леукемија кај возрасни во Македонија (1993–2003)

Table 2 – Табела 2

Trend analysis of crude and sex-specific incidence rates (1993–2003)
Тренд анализа на сурови и полого специфични стапки на инциденца (1993–2003)

	χ^2	d.f	p
Total	30.34	10	0.001
Trend	15.91	1	< 0.001
Males	12.87	10	0.231
Trend	1.97	1	0.160
Females	27.64	10	0.002
Trend	19.12	1	< 0.001

χ^2 = chi square;
d.f = degrees of freedom;
p = p value for significance

The overall incidence rate of acute leukaemia shows an increased trend that is highly significant ($p < 0.001$). On the other hand, when broken down by sex the trend is not significant in males ($p = 0.160$), while highly significant in females ($p < 0.001$).

We adjusted the incidence rates for age with the direct method using the world population as a standard. In Table 3, we present age specific rates for 1996 and 2003.

Table 3 – Табела 3

Age-specific incidence rates and number of expected cases of acute leukaemia for the years 1996 and 2003
Возрасно специфични стапки на инциденца и број на очекувани случаи од акутна леукемија за годините 1993 и 2003

1	2	3	4	5	6	7	8	9	10	11	12	13	14
15-19	162.852	165.422	8.36	8.17	2	1	1.23	0.6	8.47	164.820	171.309	2.02	1.03
20-24	153.490	161.945	7.88	8.0	4	2	2.60	1.23	8.22	159.955	166.253	1.62	2.04
25-29	151.339	153.461	7.77	7.58	3	1	1.98	0.65	7.93	154.312	160.387	3.05	1.04
30-34	148.500	148.281	7.63	7.33	2	4	1.34	2.7	7.61	148.085	153.915	1.98	4.15
35-39	145.911	149.837	7.5	7.40	1	4	0.68	2.67	7.15	139.134	144.612	0.94	3.86
40-44	137.304	146.902	7.05	7.26	1	2	0.72	1.36	6.59	128.236	133.285	0.92	1.81
45-49	109.957	142.688	5.65	7.05	1	5	0.90	3.50	6.04	117.534	122.161	1.05	4.27
50-54	99.814	127.760	5.12	6.31	2	7	2.00	5.47	5.37	104.496	108.610	2.08	5.94
55-59	95.913	95.234	4.92	4.70	0	8	0	8.40	4.55	88.539	92.025	0	7.73
60-64	88.948	89.822	4.57	4.44	3	7	3.37	7.80	3.72	72.388	75.238	2.43	5.86
> 65	164.678	214.915	8.46	10.62	5	19	3.03	8.84	8.23	160.150	166.455	4.85	14.71
Total	1,462,009	1,596,267	74.9	78.85	24	60	1.64	3.75		1,437,649	1,494,250	21	51

1) Age groups.

2) Population of Macedonia by age group according to the census in 1994. The total population according to the census in 1994 was 1,945,932.

- 3) Population of Macedonia by age group according to the census in 2002. The total population according to the census in 2002 was 2,022,47 citizens.
- 4, 5) Percentage distribution of the population by age group in 1994 and 2002.
- 6, 7) Number of register cases of acute leukaemia by age group in 1996 and 2003.
- 8, 9) Age-specific incidence rates per 100.000 people at risk in 1996 and 2003.
- 10) Percentage distribution of the world population by age groups.
- 11, 12) Population size by age group that Macedonia would have if it had the same percentage distribution of the population as the world population for the years 1996 and 2003 respectively.
- 13, 14) The number of expected cases of acute leukaemia in Macedonia for the years 1996 and 2003, if it had had the same age distribution of the population as the world population.

According to the census results in 1994 and 2002 there were demographic changes in the population, especially in those aged 65 and above. In 1994, there were 164,678 people aged 65 years and above and this constituted 8.46% of the total population whereas in 2002 there were 214,915 people aged 65 years and above or 10.62% of the total population. The relative increase of the population in this age group between the two censuses is 30.5%.

We can clearly see from the tables that the age-specific incidence rates increased with the age of the patients. However, while in the reference year (1996) the rate ratio of the oldest age group to the youngest was 2.46, in year 2003 it was 14.7.

Discussion

The crude incidence rates of acute leukaemia in adults aged 15 and above over the period from January 1st 1993 to December 31st 2003 shows a trend of linear increase that is statistically highly significant ($p < 0.001$). In the first years of the analysis the incidence rates were higher in males than in females, but in the year 2000 the rates of the females were higher (RR = 0.77), to become equal in the last three years of the analysis (RR = 1.0). The trend of increase is statistically highly significant in females ($p < 0.001$), while not in males ($p = 0.160$). In addition, we considered the fact that women in general survive longer than men and whether the increase in the incidence rates in females is due to a higher proportion of older women patients. However, this was not the case in our study (data not shown).

The risk of acute leukaemia increases with the age of the patients in all years of the analysis. However, while the rate ratio between the oldest group (at higher risk) to the youngest in 1993 was 2.3, in year 2003 the same relationship increased sharply to reach 14.7. This difference appears to be due to the increased risk among the population above 40 years of age in the last three years of the analysis, and as of the decline in the risk of acute leukaemia in the youngest age group at risk (15–19).

According to the census results in 2002, there is a registered increase in the proportion of the older population over 65 of 30.5% relative to the census results of 1994. Bearing in mind the fact that the risk of acute leukaemia is higher in older people, this demographic change can account for part of the absolute increase in the frequency of newly diagnosed patients with acute leukaemia.

On the other hand, the trend analysis showed that the increase is highly significant in females, while this was not the case for males. This raises the question of differential ascertainment of leukaemia cases in females in the early part of the study.

Compared with other countries in the world, the incidence rates of acute leukaemia in Macedonia approach the corresponding rates in the United States [21] and Norway [22]. The age distribution of cases is almost the same, and increases with the age of the patients. AML is equally distributed by sexes and the risk increases by age, while ALL is more frequent among the young (15–19), as expected.

Our results differ from others previously reported in the literature in the sex distribution of this haematological malignancy. While in most of the studies the incidence rates in haematological malignancies are higher in males compared to females [7], in our study the risk of acute leukaemia in the last three years was equally shared in both sexes. Although we have no additional data to explain the cause of these changes, this similarity in the risk of acute leukaemia between sexes in the last three years of the analysis could be due to some unknown environmental risk factor that equally affects health or as of competing risk among males. We cannot exclude the possibility that in the last years of the analysis there were better diagnostic facilities and treatment available at our clinic, which could contribute towards a better ascertainment of new acute leukaemia cases.

Our study has certain limitations. There is no official cancer registry in the Republic of Macedonia, but all of the cases are referred to the central hospital in Skopje. In addition, estimation of the annual incidence rates of acute leukaemia could be influenced by the demographic changes in the population or some irregularities while conducting the census. This could have led to a bias while estimating the population at risk. Due to the small absolute number of acute leukaemia cases and lack of sophisticated diagnostic techniques, we separated only four types of acute leukaemia and were not able to calculate subtype-specific incidence rates. There were incomplete data on the occupation of the patients and we were not able to perform an analysis by occupational exposure of the patients.

The incidence of acute leukaemia in the Republic of Macedonia over the period between 1993 and 2003 increased 2.4 times compared to 1996. This increase is mainly due to the relative increase in the percentage of older popula-

tion over the last eleven years, and the equal distribution of the risk between both sexes as a result of the increased risk in females over 40 years of age. We cannot rule out an environmental contribution to this increase, although exposure to depleted uranium remains highly speculative. This study does not address the causes of the increased incidence rates, but rather describes the size of the problem. Further analytic studies are needed with *a priori* hypotheses to explain the possible causal factors associated with these findings.

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Резиме

ТРЕНД НА СТАПКИТЕ НА ИНЦИДЕНЦА ОД АКУТНА ЛЕУКЕМИЈА КАЈ ВОЗРАСНИ ХОСПИТАЛИЗИРАНИ ПАЦИЕНТИ ВО РЕПУБЛИКА МАКЕДОНИЈА (1993–2003)

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Апстракт: *Цели:* Целта на овој труд е да го анализира трендот на стапките на инциденца од акутна леукемија кај хоспитализирани пациенти на возраст од 15 години и постари.

Дизајн: Спроведовме дескриптивна епидемиолошка студија.

Локација: Клиника за хематологија, Скопје.

Резултати: Грубите стапки на инциденца од акутна леукемија кај возрасните во наведениот период се значително покачени (p за збирниот тренд < 0,001).

Најниската груба стапка на инциденца (CIR) беше забележана во 1996 (CIR = 1,64/100 000); 95% интервал на веродостојност (CI = 1,1–2,4), додека највисоките стапки беа забележани во 2003 (CIR = 3,76/100 000; 95% CI = 2,9–4,8). Во 1993 регистриравме висок сооднос во стапката на инциденца помеѓу половите (мажи во однос на жени) од (RR) = 2,23, додека од 2001 асоцијацијата помеѓу половите исчезнува (RR = 1). Во нашата анализа трендот кај мажите не беше значителен ($p = 0,160$), додека кај жените покажува линеарно покачување кое е статистички значајно ($p < 0,001$).

Заклучоци: За релативно краткиот временски период од 11 години забележавме покачување во стапките на инциденца од акутна леукемија кај нашата популација на возраст над 15 години. Ова истражување укажува дека ова може да биде резултат на покачениот ризик кај женската популација, како и кај возрасните над 40 години. Дополнително, според резултатите од пописот од 1994 и 2002 година, соодносот на луѓе на возраст над 65 години и повеќе е покачен за 30,5% што укажува дека оваа демографска промена може да е резултат на релативното покачување во стапката на инциденца од акутна леукемија. Не треба да ја исклучиме можноста дека нашите наоди се резултат на подобро информиран систем на пријавување и дијагностика на акутната леукемија во Република Македонија. Дополнителни истражувања се потребни за да се проучат можните причини за овие промени.

Клучни зборови: акутна леукемија, возрасни, тренд, инциденца, епидемиологија, полов сооднос.

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