

## A JOINPOINT REGRESSION ANALYSIS OF LONG-TERM TRENDS IN LEUKEMIA INCIDENCE AND MORTALITY IN CENTRAL SERBIA AND NIŠAVA DISTRICT (1999-2014)

Marija Andjelković-Apostolović<sup>1,2</sup>, Aleksandra Ignjatović<sup>1,2</sup>, Miodrag Stojanović<sup>1,2</sup>, Zoran Milošević<sup>1,2</sup>, Branislav Apostolović<sup>3</sup>, Marija Topalović<sup>1</sup>, Dušan Simić<sup>4</sup>

Leukemia contributes 2.3% to the overall cancer incidence in Serbia and 2.9% in the total mortality, while the estimated incidence and mortality rate for males and females were 8.7 and 6.3 ‰, respectively and occupies 13th place among both sexes in Central Serbia.

The objective of our study was to examine the time trends of leukemia in Central Serbia, with a focus on Nišava district, from 1999-2014, using a Joinpoint regression analysis and compare them with the trend in other populations, and identify possible changes.

The standardised incidence and mortality were obtained from the Serbian Cancer Registry of Central Serbia. Time trends for incidence and mortality of leukemia were assessed using the annual percent change, estimated through Joinpoint regression analysis (age period cohort models – APC) using the Joinpoint Regression Software.

Our results demonstrate a stable trend of the age-adjusted leukemia incidence rate both in males and females in Central Serbia during the observed 1999-2014 period. However, statistically significant decreasing trend of leukemia incidence rate was found in men from Nišava district, while non-significant slightly increasing pattern was present in women. Joinpoint analysis in our research demonstrated favorable mortality declines until the 2002, and then stable trend in Central Serbia in both sexes to the end of the observed period. Conversely, mortality among males in Nišava district shows a positive trend, but not statistically significant.

The results of the study suggest that leukemia profile in Central Serbia was stable during the study period. It is particularly interesting that incidence is decreasing among male population from Nišava district.

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**Key words:** Leukaemia, Central Serbia, Nišava region, Joinpoint regression analysis

<sup>1</sup>University of Niš, Faculty of medicine, Department for medical statistics, Niš, Serbia

<sup>2</sup>Public Health Institute Niš, Niš, Serbia

<sup>3</sup>Clinical Hospital Center Zemun, Zemun, Serbia

<sup>4</sup>Primary Health Care Center Niš, Niš, Serbia

Contact: Marija Andjelković-Apostolović  
Knjaževačka ulica 173/23, 18000 Niš, Srbija  
E-mail: drmari84@gmail.com

### Introduction

According to the International Agency for Research on Cancer (GLOBOCAN 2012), leukemia contributes 2.3% to the overall cancer incidence in Serbia and 2.9% in the total mortality, while estimated incidence and mortality rate for males and females were 8.7 and 6.3 ‰, respectively (1). Among all cancers in Serbia, leukemia occupies 13<sup>th</sup> place among both sexes.

This evidence is based on research conducted at Los Alamos National Laboratory, studies of nuclear workers at other sites, and others exposed to ionising radiation (2, 3). Occupational exposure to benzene and other solvents is one of the most consistently observed risk factors for myeloid malignancy usually used in manufacture of organic chemicals and chemical intermediates (4, 5). Previous cancer treatment regimens with known cytotoxic agents that have leukemogenic potential, although other factors, such as the intensity of treatment and use of growth factors, also may have played a role in leukemia occurrence (6). Besides different environmental exposures, cigarette smoking also directly affects the central and peripheral hematopoietic system and decreases the number of circulating CD34+ progenitor cells in healthy individuals leading to leukemia (7, 8). Likewise, other factors as genetic disorders (9) and socio economic status (10, 11) are confirmed as risk factors for leukemia incidence. Encouraging news in recent decades is that a significant improvement has been set up in the diagnosis and treatment of leukemia.

The objective of our study was to examine the time trends of leukemia in Central Serbia, with a focus on Nišava district, from 1999-2014, using a Joinpoint regression analysis and compare them with trend in other populations, and identify possible changes.

## Patients and methods

### Data sources

Standardised incidence and mortality for the period 1999-2014 were obtained from the Serbian Cancer Registry of Central Serbia. The Registry, founded in 1985, covers the population of Central Serbia (approximately 5.2 million persons according to the Census of 2011). This Cancer Registry has been collecting data since 1996 when it was reorganised by the Agency for Research on Cancer – IACR, and the European Network of Cancer Registries – ENCR. According to the International Classification of Diseases Tenth Revision (ICD-10) and the Third Edition of International Classification of Diseases for Oncology, leukemia is defined as ICD-10 codes C91-C95 (12).

Time trends for incidence and mortality of leukemia were assessed using the annual percent change, estimated through Joinpoint regression analysis (age period cohort models – APC) using the Joinpoint Regression Software. This software has been developed by the United States National Cancer Institute for the analysis of data from the Surveillance Epidemiology and End Results Program (SEER). This method covers changes in data trends by connecting several different line segments on a log scale at “joinpoints”. The analysis starts with the minimum number of joinpoints (i.e., 0 joinpoint, representing a straight line) and tests for model fit with a maximum of 4 joinpoints. Monte Carlo permutation method is used to test the significance. Additionally, an annual percent change (APC) for each line segment is estimated. The APC is used to determine whether a difference exists from the null hypothesis of no change (0%). In the final model, each joinpoint shows a statistically significant change in trends (increase or decrease) and each of those patterns is described by an APC. In the case of non-statistically significant trends ( $p > 0.05$ ), we used the term “stable”.

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## Results

In the period from 1999 to 2014, the total number of new leukaemia cases in Central Serbia was 7035, among which 523 (7,4%) cases were in Nišava district. Leukemia was diagnosed in 4158 males and 2877 females (male-to-female ratio 1.5:1) in Central Serbia, while in Nišava district the male:female ratio was 1.8:1 (337 males, 186 females).

The total number of fatal cases was 5922 (3383 males and 2539 females died of leukemia with a male to female ratio 1.3:1). In Nišava district the total number of deaths was 336, of which 218 were males and 118 were females (ratio 1.8:1).

**Table 1.** Age-standardized incidence of leukaemia in Serbia and Nišava district in the period from 1999 to 2014.

year	Serbia				Nišava district			
	male		female		male		female	
	No of cases	ASR	No of cases	ASR	No of cases	ASR	No of cases	ASR
1999.	222	6	160	4.2	9	3.3	10	2.6
2000.	233	7.1	153	3.2	26	26	12	2.9
2001.	269	7.5	196	4.8	29	10.6	12	3.3
2002.	276	7.7	212	5.5	25	9.7	13	3
2003.	306	14	207	5.5	21	8.1	8	2.6
2004.	258	7	187	2.3	20	9.5	14	5.5
2005.	256	6.7	191	4.8	17	4.3	14	5
2006.	225	6.2	165	4	19	7	15	3.9
2007.	315	7.7	210	4.5	20	6.4	15	3.3
2008.	211	5	117	2.7	30	8.5	8	2.8
2009.	233	6.4	148	3.6	22	9.3	16	9.4
2010.	260	6.9	148	3.7	19	6.1	/	/
2011.	322	8.4	239	5.8	18	7.5	12	4.4
2012.	207	5.3	158	4	22	6.1	15	5.6
2013.	280	6.7	182	4.6	25	6.2	14	3.5
2014.	285	7.3	204	4.7	15	4.1	8	3.2

\* ASR age-standardised rate per 100 000 (using standard world population)

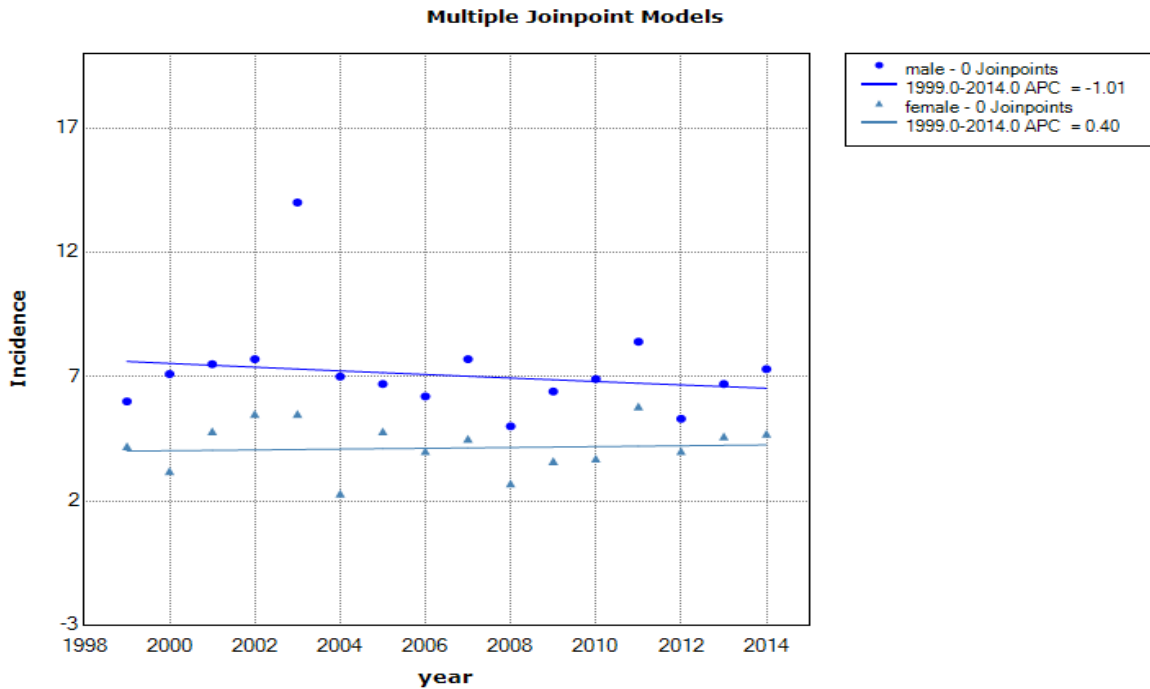
Table 1 shows the age-standardised incidence rates (per 100 000 population) of leukemia in male

and female population of Central Serbia and Nišava district for the period 1999-2014. For the whole

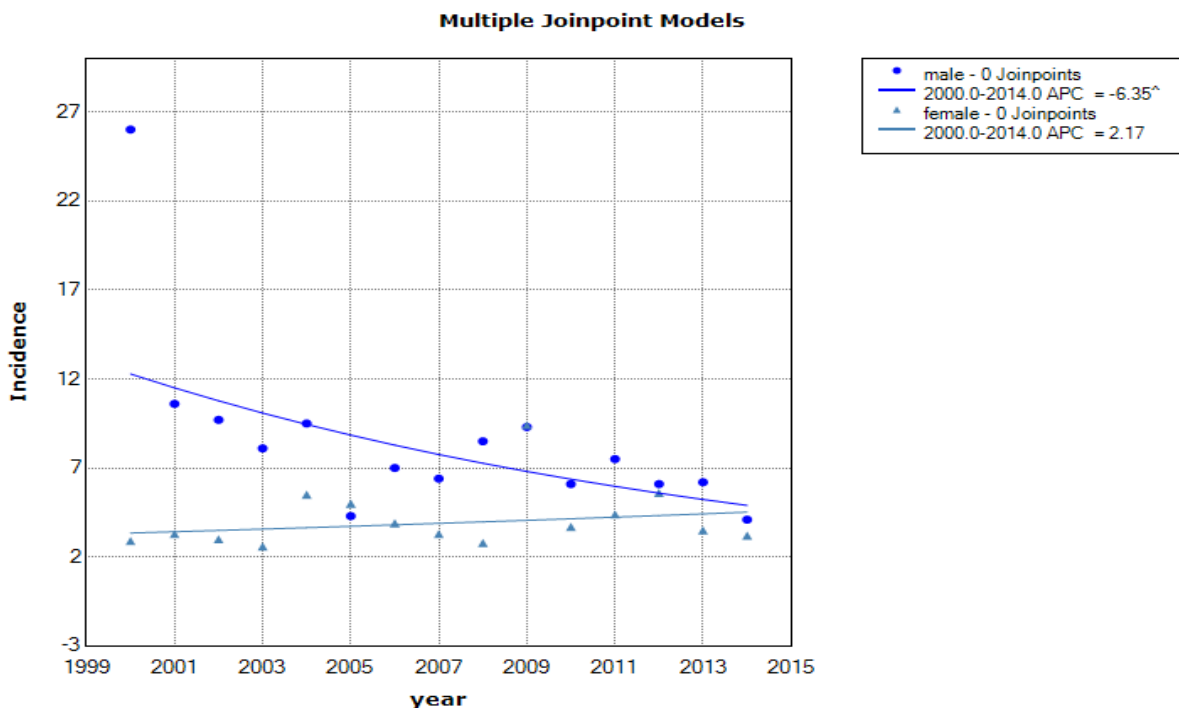
analysed period the average age-standardised incidence for men was 7.24 and for females 4.24 in Central Serbia, and situation with Nišava district is as follows: 8.29 for men and 4.07 for women. The highest age-standardised incidence in Central Serbia in males was in 2003, in females in 2011, and the

lowest values of those rates were in 2008 (1, 2.7 respectively).

The findings from the Joinpoint analysis for leukemia incidence in Central Serbia and Nišava district are shown in Graphs 1 and 2.



**Graph 1.** Incidence trend of leukemia in Central Serbia in the period 1999-2014.



**Graph 2.** Incidence trend of leukemia in Nišava district in the period 1999-2014.

Table 2 reports the distribution of age-standardised mortality leukemia cases by gender in Central Serbia and Nišava district from 1999 to 2014. (per 100 000 population). The average age-standardised mortality for men was 4.90 and for females 3.38 in Central Serbia, while in Nišava district it was: 4.12 for men and 1.87 for women, twice less compared to the women in Central Serbia. In Central

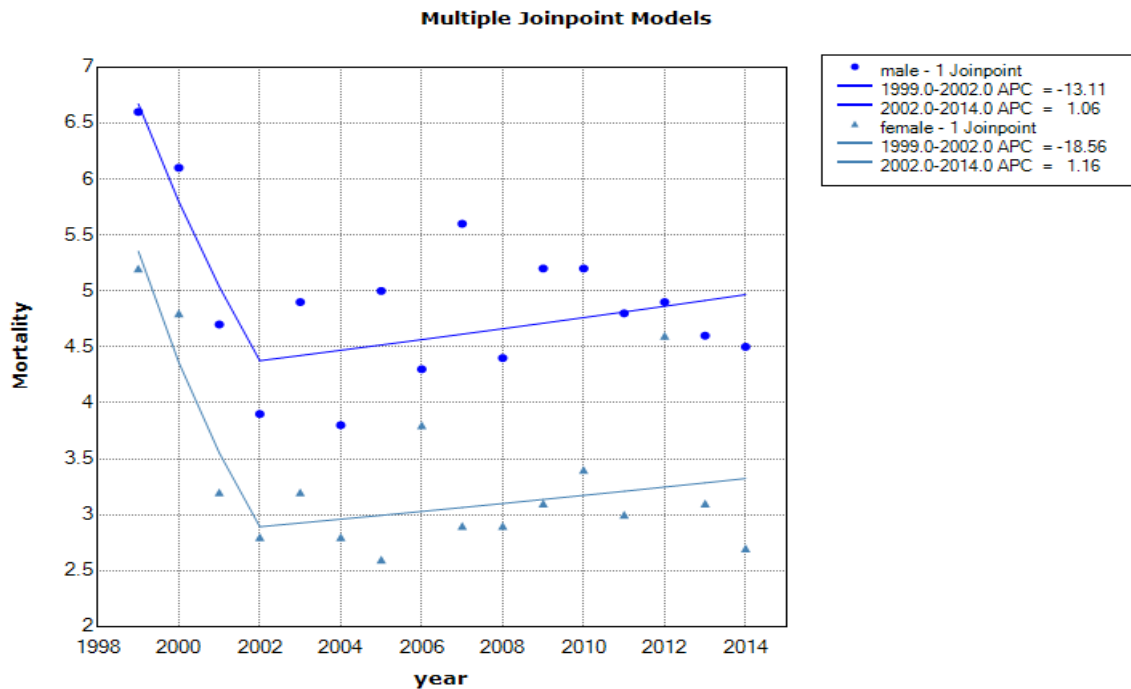
Serbia, ASR of the mortality rate for both sexes was the highest in 1999 (6.6, 5.2, respectively). In Nišava district we did not find available data for 1999 and 2000, as well as for females in 2012-2014.

The results from the Joinpoint analysis for leukemia age-standardised mortality in Central Serbia and Nišava district are presented in Graphs 3 and 4.

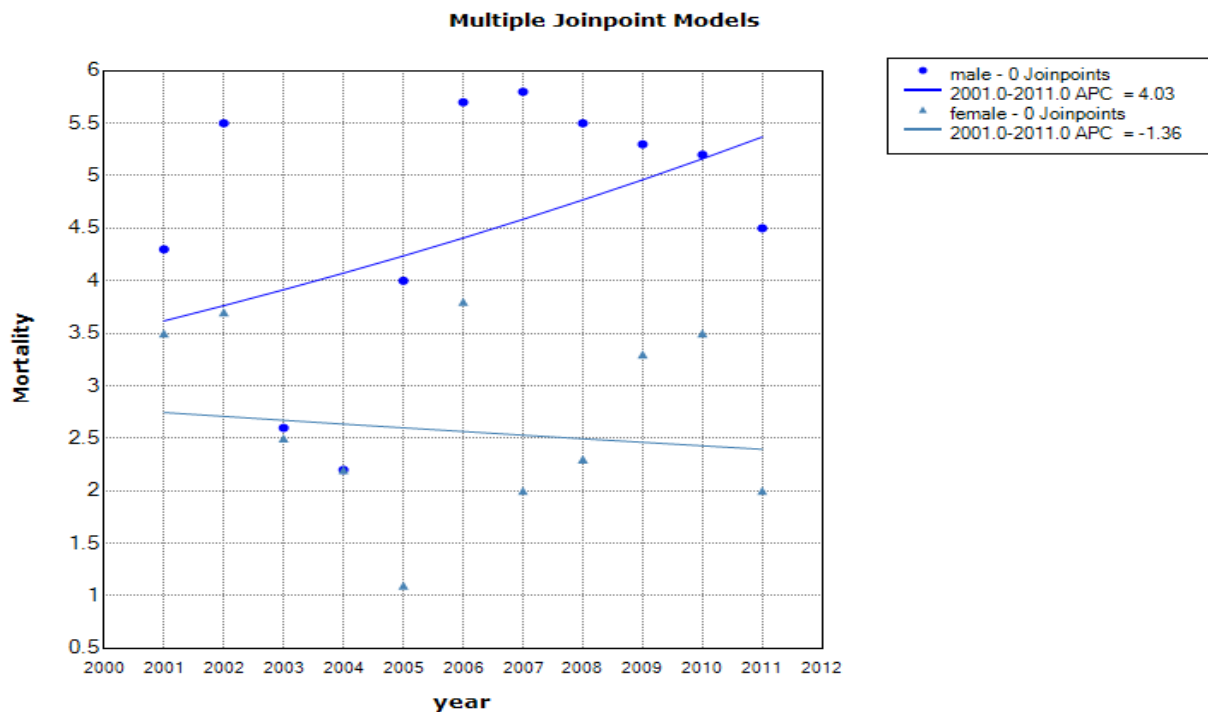
**Table 2.** Age adjusted mortality of leukemia in Serbia and Nišava district in the period from 1999 to 2014.

year	Serbia				Nišava district			
	male		female		male		female	
	No of cases	ASR	No of cases	ASR	No of cases	ASR	No of cases	ASR
1999.	181	6.6	148	5.2	/	0	/	0
2000.	166	6.1	135	4.8	/	0	/	0
2001.	195	4.7	156	3.2	15	4.3	10	3.5
2002.	167	3.9	144	2.8	13	5.5	14	3.7
2003.	203	4.9	141	3.2	9	2.6	8	2.5
2004.	167	3.8	140	2.8	6	2.2	8	2.2
2005.	215	5	130	2.6	14	4	6	1.1
2006.	205	4.3	181	3.8	19	5.7	16	3.8
2007.	247	5.6	166	2.9	19	5.8	9	2
2008.	216	4.4	162	2.9	14	5.5	10	2.3
2009.	233	5.2	179	3.1	17	5.3	14	3.3
2010.	252	5.2	189	3.4	19	5.2	14	3.5
2011.	230	4.8	170	3	16	4.5	9	2
2012.	232	4.9	173	4.6	15	3.6	/	0
2013.	241	4.6	162	3.1	22	6.3	/	0
2014.	233	4.5	163	2.7	20	5.4	/	0

\*\* ASR - age-standardised rate per 100 000 (using standard world population)



**Graph 3.** Mortality trend of leukemia in Central Serbia in the period 1999-2014.



**Graph 4.** Mortality trend of leukemia in Nišava district in the period 1999-2014.

## Discussion

According to our knowledge, this study offers the first nationwide analysis of leukemia incidence and mortality trends over time using cancer registration in Serbia. The use of Joinpoint analysis has allowed statistical testing of trends in incidence and mortality rates for leukemia, detecting some significant changes. Therefore, Joinpoint analysis provides a much clearer picture of what is happening during a particular period in specific terms (identifying the years in which significant changes in trends occurred) than a single summary trend statistic (13).

According to the GLOBOCAN estimates for the year 2012, the age-standardised incidence rate of leukemia in Serbia was 8.6/100 000 in men and 5.7/100 000 in women, which refers Serbia to the 18<sup>th</sup> place in Europe. The highest incidence was recorded in Australia and New Zealand and the lowest in Middle and Western Africa (1). The standardized mortality rate in Serbian men is similar to the European average of 8.5/100 000, while the incidence rate in women is slightly higher than the European average of 5.4/100 000. The Northern Europe has the lowest rate in both sexes. The age-standardised mortality in Serbian men was 2.9/100 000, which is slightly less than average European mortality rate (3.1/100 000). The mortality rate in women in Serbia was 2.9/100 000, also marginally less compared to the European average (3.2/100 000).

Our results demonstrate a stable trend of the age-adjusted leukemia incidence rate both in males and females in Central Serbia during the observed 1999-2014 period. However, statistically significant decreasing trend of leukemia incidence rate was

found in men from Nišava district with APC -6.3% (-10.3 - -2.2;  $p=0,005$ ), while non-significant slightly increasing pattern was present in women. Leukemia incidence profile in Nišava district is consistent with The United Kingdom findings (14). Several studies showed continued declines in incidence trends, similar to our results (15, 16). In addition to the various risk factors included in the etiology of leukemias, it is hard to hypothesise possible reasons for the observed incidence trends. In addition to specific changes of incidence, they might be caused by changes of diagnostic procedures or increased surveillance due to screening programs, as well as changes of classification or reassignment of one diagnostic entity to the other. Generally speaking, the average incidence rate was higher in men compared to women, both in Central Serbia and Nišava region. It is observed that Nišava region has higher average age-standardised incidence in men in comparison to the rest of Central Serbia (7.24: 8.29 per 100 000) but without statistical significance ( $p = 0.4$ ).

The incidence of childhood leukemia in the world is increasing. The reason for this should be sought in ionising radiation to which children are more prone. Considering Serbia was bombarded and exposed to ionizing radiation during 1999, from the given incidence trend we can conclude that radiation, at least, has not yet been reflected in the incidence pattern.

Malvezzi and associates review appropriate leukemia mortality trends in all countries of the EU as a whole, giving predicted rates for 2016 between 4 (Spain and UK) and 5/100 000 (Poland and Italy) (17). Joinpoint analysis in our research demonstrated favorable mortality declines until the 2002, and

then stabile trend in Central Serbia in both sexes to the end of the observed period. Conversely, mortality among males in Nišava district shows a positive trend, but not statistically significant. Mortality trends represent the reflection of improvements of performance status of patients at diagnosis, treatment and improved supportive care. The results of decreased mortality rates are coherent with previously published data (18, 19). In recent decades we have witnessed several major novelties in the treatment of leukemia, such as the initiation of an allogeneic hematopoietic stem cell transplantation (usually limited to patients younger than 65 years) and the recent introduction of tyrosine kinase imatinib inhibitor (20) and monoclonal antibodies (rituximab)(21). Leukemia survival is more noticeable in younger patients in whom improvements are better due to more adequate diagnosis, management and therapy treatment (22).

### Limitations of the study

Some possible limitations should be taken into account. Our research is a registry based study, therefore, possible incomplete data collection is pro-

bable. The World Health Organization labeled the quality of data related to the cause of death in Serbia as moderate (23). Also, GLOBOCAN 2012 categorized data from Serbia as B2 (high quality regional data for incidence and medium quality for complete vital registration for the mortality rates) (24). Furthermore, inability to distinguish between age specific groups of leukemia incidence and mortality, as well as histological types of leukemia and variations in leukemia classifications should be considered.

### Conclusion

The results of the study suggest that leukemia profile in Central Serbia was stabile during the study period. It is particularly interesting that incidence is decreasing among males from Nišava district. Mortality in the investigated period is declining by 2002 in Central Serbia, followed by mild increase to the end of the observed period. The only exception presents the mortality among males from Nišava district, which is rising but without statistically significance.

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## JOINPOINT REGRESIONA ANALIZA TRENDA INCIDENCIJE I MORTALITETA LEUKEMIJE U CENTRALNOJ SRBIJI I NIŠAVSKOM REGIONU U PERIODU 1999-2014. GODINE

Marija Anđelković-Apostolović<sup>1,2</sup>, Aleksandra Ignjatović<sup>1,2</sup>, Miodrag Stojanović<sup>1,2</sup>, Zoran Milošević<sup>1,2</sup>, Branislav Apostolović<sup>3</sup>, Marija Topalović<sup>1</sup>, Dušan Simić<sup>4</sup>

<sup>1</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za medicinsku statistiku, Niš, Srbija

<sup>2</sup>Institut za javno zdravlje, Niš, Srbija

<sup>3</sup>Kliničko-bolnički centar Zemun, Zemun, Srbija

<sup>4</sup>Dom zdravlja Niš, Niš, Srbija

Kontakt: Marija Anđelković Apostolović  
Knjaževačka ulica 173/23, 18000 Niš, Srbija  
E-mail: drmari84@gmail.com

Leukemije su zastupljene sa 2,3% u ukupnoj učestalosti karcinoma u Srbiji i 2,9% u ukupnom mortalitetu, dok su incidencija i mortalitet za oba pola iznosili 8,7 i 6,3 ‰, na osnovu čega ih svrstavamo na 13. mesto među svim karcinomima registrovanim u Centralnoj Srbiji.

Cilj rada bio je da se utvrdi vremenski trend leukemija u Centralnoj Srbiji, sa posebnim osvrtom na Nišavski okrug, u periodu 1999-2014. godine, koristeći Joinpoint regresionu analizu, i uporediti ih sa trendom u drugim populacijama i identifikovati karakteristične promene.

Standardizovane stope incidencije i mortaliteta uzete su iz Registara za rak Centralne Srbije. Trend stope incidencije i mortaliteta je određivan Joinpoint analizom upotrebom Joinpoint Regresioni softvera.

Rezultati ukazuju na stabilan trend incidencije prilagođene za godine među oba pola u Centralnoj Srbiji za ispitivani period. Međutim, utvrđeno je statistički značajno smanjenje incidencije među muškarcima Nišavskog regiona, dok je među ženama iz istog regiona uočen blagi porast trenda, ali bez statističke značajnosti. Joinpoint analiza je u našem istraživanju pokazala pad trenda mortaliteta do 2002. godine, a potom stabilan trend za oba pola u Centralnoj Srbiji do kraja ispitivanog perioda. Suprotno tome, trend mortaliteta među muškarcima iz Nišavskog okruga je rastao, ali bez statističke značajnosti.

Rezultati studije ukazuju da je profil leukemije u Centralnoj Srbiji stabilan tokom perioda istraživanja. Posebno je interesantan pad incidencije kod muškaraca iz Nišavskog okruga.

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**Ključne reči:** leukemija, Centralna Srbija, Nišavski region, Joinpoint regresiona analiza