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Malignant Lymphatic and Hematopoietic Neoplasms Mortality in Serbia, 1991–2010: A Joinpoint Regression Analysis

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Abstract

Background: Limited data on mortality from malignant lymphatic and hematopoietic neoplasms have been published for Serbia.

Methods: The study covered population of Serbia during the 1991–2010 period. Mortality trends were assessed using the joinpoint regression analysis.

Results: Trend for overall death rates from malignant lymphoid and haematopoietic neoplasms significantly decreased: by −2.16% per year from 1991 through 1998, and then significantly increased by +2.20% per year for the 1998–2010 period. The growth during the entire period was on average +0.8% per year (95% CI 0.3 to 1.3). Mortality was higher among males than among females in all age groups. According to the comparability test, mortality trends from malignant lymphoid and haematopoietic neoplasms in men and women were parallel (final selected model failed to reject parallelism, $P = 0.232$). Among younger Serbian population (0–44 years old) in both sexes: trends significantly declined in males for the entire period, while in females 15–44 years of age mortality rates significantly declined only from 2003 onwards. Mortality trend significantly increased in elderly in both genders (by +1.7% in males and +1.5% in females in the 60–69 age group, and +3.8% in males and +3.6% in females in the 70+ age group). According to the comparability test, mortality trend for Hodgkin's lymphoma differed significantly from mortality trends for all other types of malignant lymphoid and haematopoietic neoplasms ($P<0.05$).

Conclusion: Unfavourable mortality trend in Serbia requires targeted intervention for risk factors control, early diagnosis and modern therapy.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. Data are owned by the Statistical Office of the Republic of Serbia. Data may be obtained from the Statistical Office of the Republic of Serbia (http://webrzs.stat.gov.rs/) by contacting Statistical Office of the Republic of Serbia, Belgrade, 5 Milana Rakica St. Phone: +381 11 2412 922. Fax: +381 11 2411 260. Dissemination and Public Relations Division, +381 11 2401-284, stat@stat.gov.rs.

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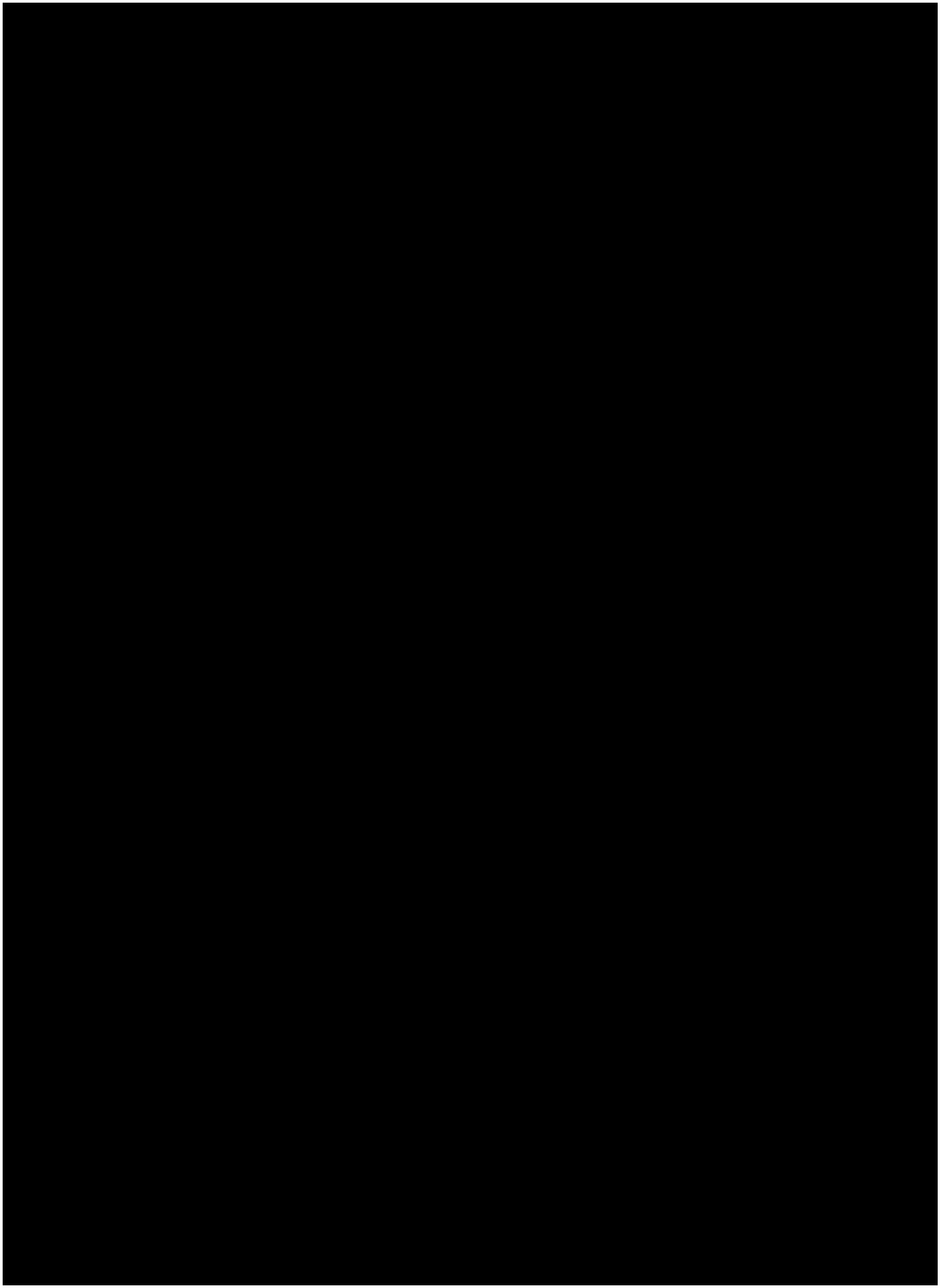
Introduction

Malignant lymphoid and haematopoietic neoplasms (MLHN) are a heterogeneous group of diseases, with different incidence, mortality and survival pattern, with multifactorial etiologies, and without successful prevention or screening strategies [1–5]. Based on GLOBOCAN 2008 estimates [6], MLHN cause more than 550,000 deaths per year (accounting for 7.3% of all cancer deaths). Leukemia, with an estimated 257,000 deaths, accounts for 3.4% of all cancer deaths, followed by non-Hodgkin lymphoma (191,599 deaths, 2.5%), multiple myeloma (72453 deaths, 1.0%), and Hodgkin lymphoma (29902 deaths, 0.4%). Almost a half of the deaths from MLHN were registered in Asia in 2008 [6].

During the 1970–2009 period, mortality from leukemia steadily declined in developed countries (in most European countries, the United States of America, Japan) in children and young adults, but decline was not observed at the age of 70 or more [7]. Mortality from non-Hodgkin lymphoma was on the rise until mid-1990s, and started to level off or decline in the following decade in both genders in the European Union, Japan, Australia, however the rates were still increasing in Eastern Europe [8,9]. Mortality from Hodgkin lymphoma has been decreasing in developed countries in the recent decade (for example, in the United States of America by −2.2% per year for both genders in all races, in Italy by −3.5% per year among men and −3.4% per year among women) [10–13]. The highest multiple myeloma mortality rates were reported in developed countries in 2008 [1,6]. In the European Union, multiple myeloma mortality tended to increase throughout the 1970–2003 period for both genders [14].



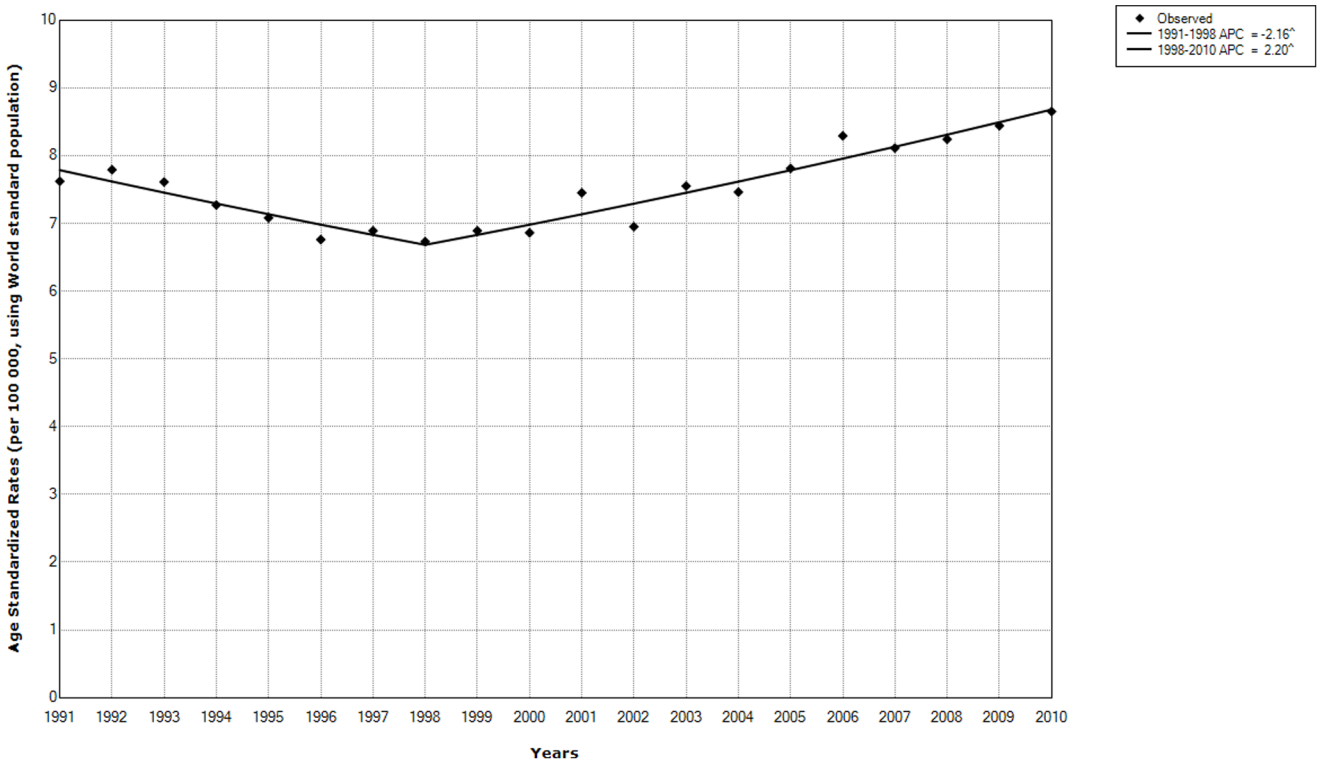


Figure 1. Malignant lymphatic and hematopoietic neoplasms (according to ICD-10: codes C 81–96). Age-standardized mortality rates, per 100 000 inhabitants, using World standard population (marked with diamonds). Based on the results of joinpoint regression analysis, one corresponding joinpoint and two trends (marked with two lines) had been identified for the overall mortality trend in Serbia 1991–2010. Annual Percentage Changes (APC) are given. * $p<0.05$.
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then significantly decreased by −9.3% (95% CI −13.3 to −5.1) per year from 1993 to 1999. Afterwards, the trend increased by + 12.2% (95% CI −8.2 to 37.2) per year from 1999 to 2002, than significantly decreased by −3.4% (95% CI −5.5 to −1.2) from 2002 onwards. Since 1991, non-Hodgkin's lymphoma mortality rates have significantly increased among Serbian population by + 2.7% per year (95% CI 1.9 to 3.5). Multiple myeloma's mortality significantly increased by +2.5% (95%CI 1.8 to 3.3) per year during the entire period. Leukemia's death rates were stable throughout the period (AAPC = +0.2%, 95% CI −0.4 to 0.8). Lymphoid leukemia's death rates non-significantly declined throughout the period, AAPC was −0.4% (95%CI −1.1 to 0.2). Myeloid leukemia's mortality rates were significantly increased by +1.7% (95% CI 0.5 to 2.9) per year.

The age-specific mortality rates for all types of MLHN grew with age (Table 3). Statistically significant increased mortality trends for non-Hodgkin's lymphoma, multiple myeloma, lymphoid leukemia and myeloid leukemia were observed in the entire study period among persons aged 70 years and over, while increased mortality trends for Hodgkin's lymphoma and all leukemia were not significant. Death rates from non-Hodgkin's lymphoma, multiple myeloma and myeloid leukemia were significantly increased in persons 45–69 years old, but the decreasing mortality trends for Hodgkin's lymphoma and lymphoid leukemia are encouraging. Statistically significant downward trend for mortality from myeloid leukemia was recorded in the age group 15–44 years.

Discussion

This study describes temporal trends of mortality from MLHN in Serbia in the last two decades. The main finding of this study is the significant increase of overall mortality from MLHN in Serbia. A rise in mortality rates started in 1998, and was identified in both genders. The increasing trend was more pronounced in the elderly. Significant decrease of mortality in younger age groups in both genders could be promising. The overall increase in mortality is mostly attributable to rise in non-Hodgkin's lymphoma, multiple myeloma and myeloid leukemia.

Most of the developed countries showed a similar increase in mortality from non-Hodgkin's lymphoma in both genders since 1960 (United States of America, United Kingdom, Netherlands, Switzerland, Norway, Sweden, Japan, France, Finland, Canada, Australia), but the rates decreased from 1995 onwards [6,10]. Also, data for the 27 European Union member states showed that mortality from non-Hodgkin's lymphoma peaked in the late 1990s and declined thereafter in both genders (by −1.3% per year in men and −2.1% per year in women) [14]. The rates were, however, still increasing in eastern European countries (in the Russian Federation in both genders, in women in Romania, Latvia and Slovakia) [8]. Serbia is among the countries with the lowest mortality rates from non-Hodgkin's lymphoma in the world, but mortality continually increased by +2.7% per year (95% CI 1.9 to 3.5%) during the 1990–2010 period.

The temporal trends in mortality from non-Hodgkin's lymphoma, in addition to changes in incidence or classification of disease, likely reflect improvements of treatment and survival. The incidence of non-Hodgkin's lymphoma has been rising in many

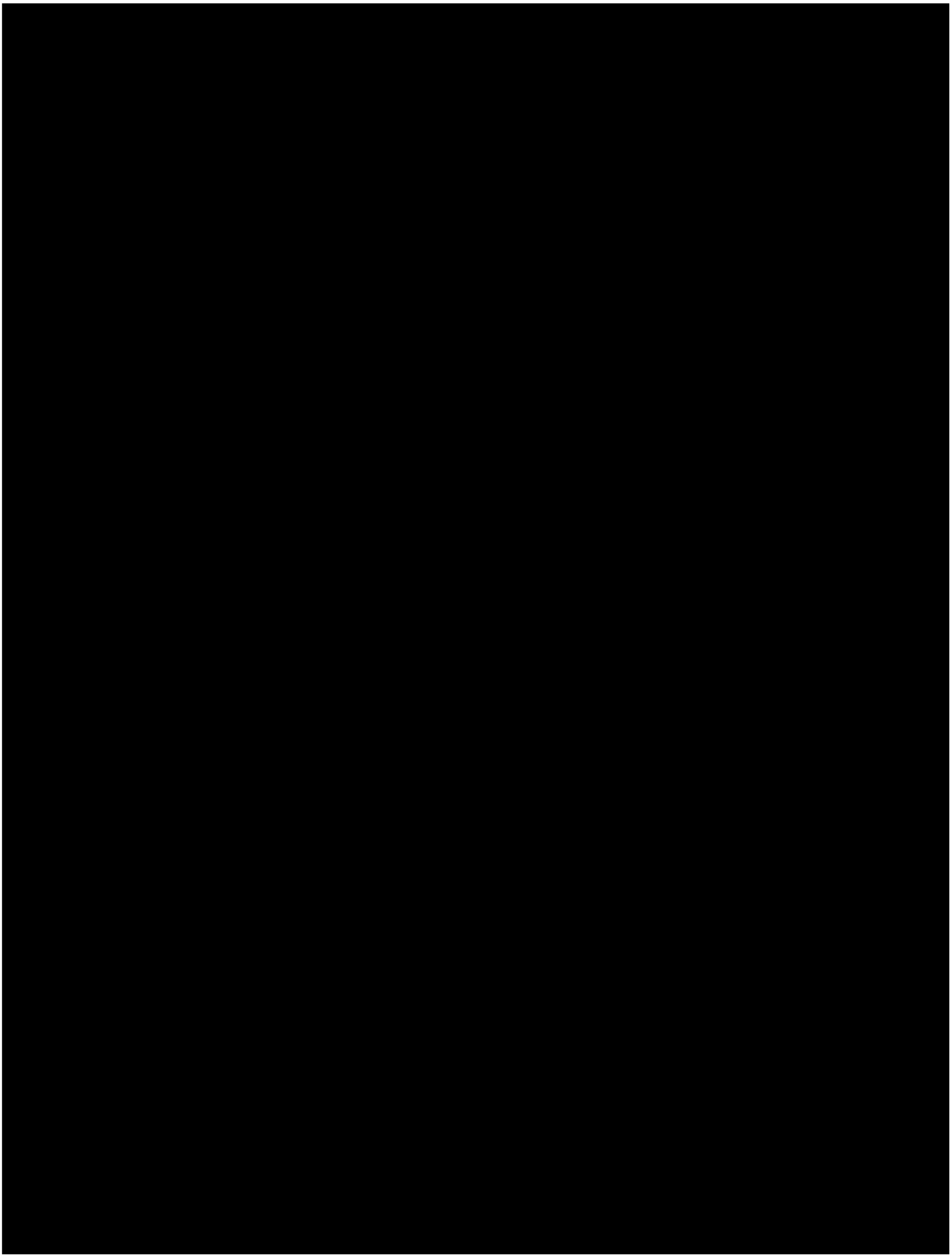

Table 2. Joinpoint regression analysis of malignant lymphatic and hematopoietic neoplasms mortality in Serbia, excluding the Autonomous Province of Kosovo and Metohia, by sex and age, in 1991–2010 period.

Age	Average age-specific rates (per 100 000)	AAPC[†]	95%CI[‡]
Male			
0–14	1.65	−4.6*	−6.4 to −2.7
15–44	4.04	−1.6*	−2.7 to −0.4
45–59	15.19	+0.8[§]	−0.3 to 1.9
60–69	37.47	+1.7*,**	0.8 to 2.6
70+	55.20	+3.8*	2.8 to 4.9
All males		+0.8*,[††]	0.1–1.4
Female			
0–14	0.93	−7.0*	−11.0 to −2.7
15–44	2.84	−0.8[‡‡]	−1.8 to 0.3
45–59	10.03	+0.7	−0.1 to 1.6
60–69	23.69	+1.5*	0.6 to 2.4
70+	34.19	+3.6*,[§§]	2.4 to 4.8
All females		+0.8*,[†‡]	0.3–1.4

* Joinpoint is significantly different from zero at alpha = 0.05;
[†] Average Annual Percent Change;
[‡] CI − Confidence Interval.
[§] Two joinpoints, for trend in 45–59 years old males: Trend 1 (1991–1993): annual percent change (APC) (95% CI) = +17.0 (−6.3 to 46.1); Trend 2 (1993–1998): APC (95% CI) = −7.2* (−13.5 to −0.4); Trend 3 (1998–2010): (APC) (95% CI) = +3.2* (1.9 to 4.6).
** One joinpoint, for trend in 60–69 years old males: Trend 1 (1991–1997): (APC) (95% CI) = −3.5* (−6.7 to −0.2); Trend 2 (1997–2010): APC (95% CI) = +3.5* (2.5 to 4.6).
[††] One joinpoint, for trend in all males: Trend 1 (1991–1998): (APC) (95% CI) = −2.7* (−4.0 to −1.4); Trend 2 (1998–2010): APC (95% CI) = +2.4* (1.8 to 3.1).
[‡‡] Three joinpoints, for trend in 15–44 years old females: Trend 1 (1991–1994): annual percent change (APC) (95% CI) = +4.8 (−8.5 to 20.0); Trend 2 (1994–1999): APC (95% CI) = −8.1 (−15.6 to 0.1); Trend 3 (1999–2003): (APC) (95% CI) = +10.1 (−3.8 to 26.0); Trend 4 (2003–2010): (APC) (95% CI) = −4.3* (−7.7 to −0.8).
[§§] One joinpoint, for trend in 70+ years old females: Trend 1 (1991–1993): (APC) (95% CI) = −16.8 (−40.3 to 16.0); Trend 2 (1993–2010): APC (95% CI) = +4.6* (3.4 to 5.8).
[†‡] One joinpoint, for trend in all females: Trend 1 (1991–1998): (APC) (95% CI) = −1.3 (−3.3 to 0.8); Trend 2 (1998–2010): APC (95% CI) = +1.8* (0.9 to 2.8).
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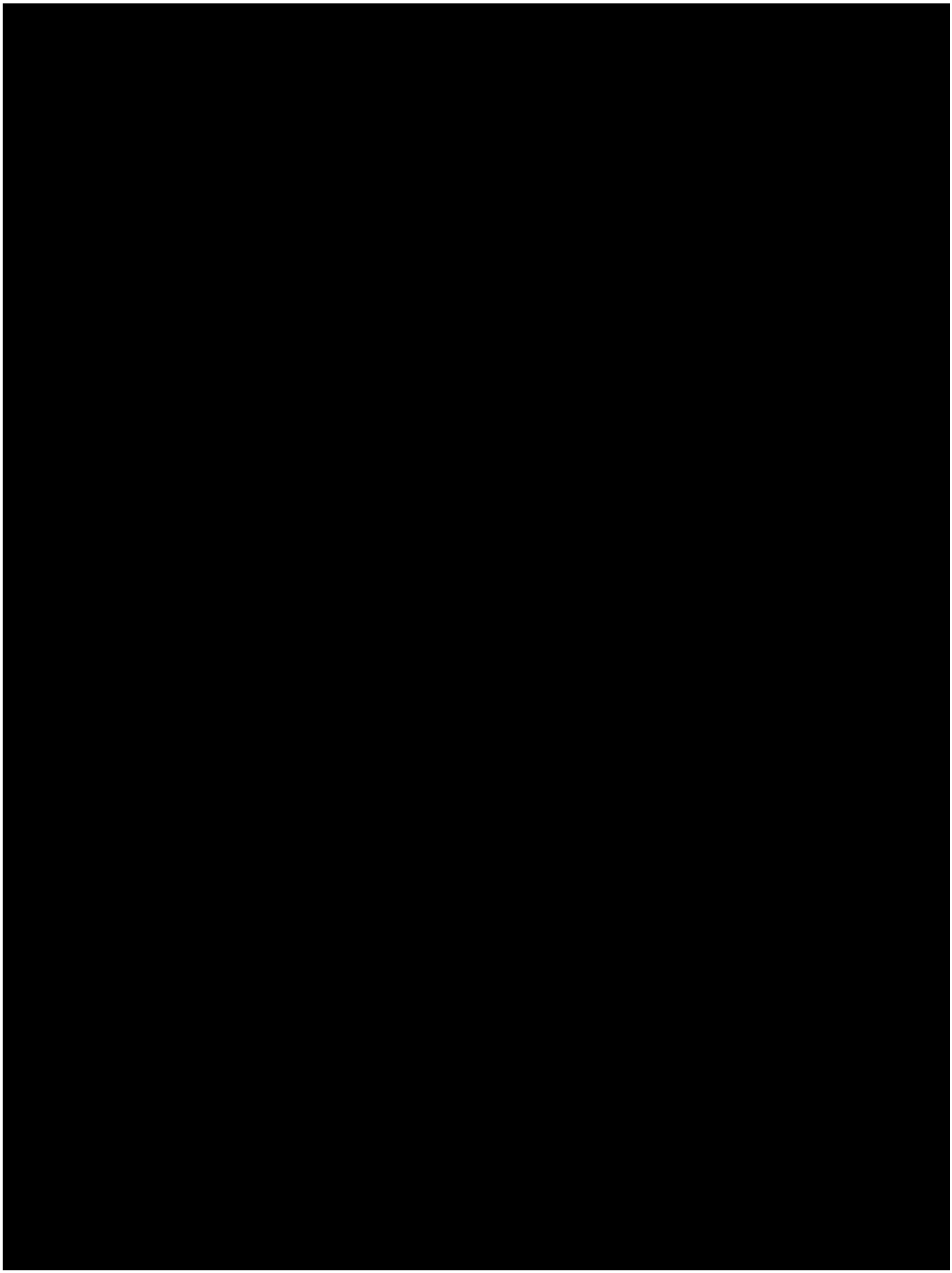
have been stable over the last 10 years in white and Hispanic, but significantly increased in black and at Asian/Pacific Islander populations in the USA[10,22]. In developed countries, the favorable patterns for Hodgkin's lymphoma death rates in more recent years are being linked with advancements in treatment with a consequently better survival [10,23]. In one university hospital in Serbia, the overall survival rate was 76% [41]. The observed patterns of the increased rates of deaths during the 1991–1993 and 1999–2002 periods might have been the consequence of decresead availability of advanced treatment modalities in Serbia in those years [37]. The Yugoslav wars, the United Nations Security Council economic embargo against Serbia and Montenegro between 1992 and 1995, the NATO bombing of Yugoslavia in 1999, which resulted in deterioration of health care in Serbia, had a distinctly adverse effect on mortality from malignant neoplasms.

In a survey of cancer mortality in the European Union, Bosetti et al [14] observed steady increase in mortality from multiple myeloma until 1990s, but with tendency to level off in recent years. In the recent decline in mortality from multiple myeloma, improved treatment may have an important role [42,43]. Serbia (with rate 1.1 per 100,000) was among the countries with intermediate rates, wherein mortality continuously increased since 1991, by +2.5% per year. The suspected risk factors for multiple myeloma include ionizing radiation, occupational exposures, chemicals, obesity, alcohol, and tobacco [44–46]. The multiple myeloma percentage (7.79%) in the group of patients belonging to clean-up workers in study in Chernobyl in the 1996–2005 period turned out to be twice as much as in patients in general population (4.0%) [44]. In a case-control study in Belgrade, it was found that factors associated with the occurrence of multiple myeloma were smoking and rheumatoid arthritis in personal history, while consumption of vegetables had a protective role [45]. According to the National Health Survey data for 2006, 3.4% of the adult population of Serbia drank alcohol on a daily basis, which is an increase of 0.1% in comparison with 2000 (3.3%) [47]. Serbia has joined World Health Organization Convention on Tobacco Control in 2006, and real effect on reduction in the tobacco smoking is expected in the near future.

Mortality from leukemia steadily declined in most European countries, the United States and Japan, in both genders aged 0–69, over the 1970–2009 period [7]. Survival from leukaemia is very poor in the elderly [10,23]. The favorable trends for mortality from leukemia are associated with diagnosis and/or treatment improvements and better survival in developed countries [23,48]. However, deaths rates for leukemia have increased in Serbia since 1998. Our data indicated that significant increase in leukemia mortality coincides with the steeply increased mortality rates for myeloid leukemia since 1999. Data about leukemia incidence and survival rate in Serbia are very scanty. There is no single known cause for leukemia. The risk factors for leukemia are chromosomal abnormalities, ionizing radiation, occupational exposure to benzene, hair dyes, viruses, diet [27,29,44,46,49,50]. The International Agency for Research on Cancer expert working group confirmed the association between tobacco smoking and myeloid leukemia [51]. The tobacco exposure in Serbia is high. In 2000, 48% of men and 38% of women in Serbia were smokers [47]. One case control study suggested that MTHFR 677 gene variants have no significant influence on the susceptibility to chronic myeloid leukemia in the Serbian population [52]. An earlier case control study has shown that working in a hazardous industry, hair dye



for health care per capita are much lower than in well-developed countries, and therefore the availability of treatment has not always been gratifying in the past.

Strengths and limitations of the study

The present study is the only study that has reported data on the mortality trends from MLHN in Serbia in the last two decades. This study highlights the necessity for widespread adoption of the contemporary treatment for MLHN in Serbia, which may lead to improved outcomes and the avoidance of a substantial number of deaths. Also, this study provides a basis for comparison across regions. These trends are crucial not only for monitoring of the epidemiological situation regarding MLHN, but also for evaluation of various preventive and therapeutic measures.

The question about the validity of causes of death reported in national statistics was a limitation. World Health Organization assessed data quality and confirmed that Serbia has comprehensive death registration systems and judged that cause-of-death data were of moderate quality: the proportion of cases with uncertain death cause was <10% [40]. Advantages of mortality statistics data in Serbia are national coverage and the consistent quality. Registration data was 100% complete for the population of Serbia, with death registration coverage of 97% [40]. Based on the World Health Organization's latest estimates, data for the most recent years concerning percentages of ill-defined causes of deaths and ill-defined cancer deaths in Serbia suggest further improvement in the quality of mortality data (4.4 and 3.8, respectively) [59]. The proportion of cases with uncertain death cause (revision 9 codes 780–799 and revision 10 codes R00–R99) in the observed period was on an average 6.8%, with a non-significant decreasing trend ($P = 0.137$), so that a significant increase in mortality from MLHN could hardly be attributed only to the improvement of the quality of mortality statistics in Serbia. Although the increased mortality trends from the MLHN (in overall and by types: non-Hodgkin's lymphoma, multiple myeloma and myeloid leukemia) are real, a limitation of this study could be related to the potential impact of the cases which were registered as Lymphoma or Leukemia not otherwise specified (NOS). So far, the number of deaths for the particular lymphoma and leukemia subtypes in Serbia was not available. Namely, the Statistical Office of the Republic of Serbia plans to control the fourth characters in the database of deceased starting from 2015, according to Eurostat recommendations. It is important to continue efforts to assess and improve the quality of the mortality statistics. Although changes and improvements in the classification and coding of lymphomas and leukemia may have had some influence on the mortality trends, the reasons for the observed increased mortality are still insufficiently understood.

Absence of reliable data on incidence of MLHN, therapy and survival in Serbia during the observed period was the study's limitation. Serbia experienced substantial social and economic changes during the studied period, which could affect distribution of risk factors and the quality of medical care. The lack of data on changes in risk factors for MLHN in Serbia made it impossible to adjust mortality rates for these factors and to directly examine their impact on changes in the rates.

This study could be an important resource for epidemiological and other types of studies in the future.

Author Contributions

Conceived and designed the experiments: MI. Performed the experiments: MI II. Analyzed the data: MI II. Contributed reagents/materials/analysis tools: MI II. Wrote the paper: MI II.

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