

## DUGOROČNI TREND MORTALITETA OD RAKA BEŠIKE U SRBIJI, 1991-2024: JOINPOINT REGRESIONA ANALIZA

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### SAŽETAK

**Uvod/Cilj:** Rak beške je među glavnim urološkim bolestima. Trendovi mortaliteta od raka beške značajno variraju širom sveta. Ovo istraživanje imalo je za cilj da proceni vremenske trendove smrtnih slučajeva od raka beške u Srbiji.

**Metode:** Ovo je populaciono zasnovana deskriptivna epidemiološka studija. Podaci o mortalitetu od raka beške dobijeni su iz zvanične baze podataka. Direktna standardizacija sa svetskom standardnom populacijom korišćena je za izračunavanje stopa standardizovanih po starosti (ASR) na 100.000 stanovnika. Analiza joinpoint regresije korišćena je za procenu vremenskih trendova u smrtnosti od raka beške, koristeći prosečnu godišnju procentualnu promenu (AAPC) zajedno sa njenim 95% intervalom poverenja (95% CI) u periodu od 1991. do 2024. godine.

**Rezultati:** U periodu od 1991. do 2024. godine, u Srbiji je zabeleženo skoro 20.000 smrtnih slučajeva zbog raka beške (oko 15.000 kod muškaraca i 5.000 kod žena). Prosečna godišnja stopa smrtnosti od raka beške bila je znatno viša kod muškaraca nego kod žena (5,94 prema 3,87 na 100.000, respektivno). Značajno povećanje trenda smrtnosti od raka beške zabeleženo je i kod muškaraca (AAPC = 0,6%; 95% IC = 0,4 do 0,9) i kod žena (AAPC = 1,3%; 95% IC = 1,0 do 1,5). Trendovi kod muškaraca i žena nisu bili paralelni, jer je konačni izabrani model odbacio paralelizam ( $p = 0,008$ ). Značajan porast smrtnosti od raka beške kod žena primećen je u srednjem dobu (starosne grupe od 55 do 69 godina), dok je kod muškaraca izraženiji porast primećen kod starijih osoba (starosne grupe od 70 i više godina).

**Zaključak:** Povećanje smrtnosti od raka beške u Srbiji tokom više od tri decenije ukazuje na potrebu za daljim analitičkim istraživanjem.

**Cljučne reči:** rak beške, mortalitet, trendovi, regresiona analiza spojnih tačaka.

### Uvod

Novije procene GLOBOCAN-a ukazuju da je broj novih slučajeva raka beške u svetu 2022. godine iznosio oko 614.000, što ga čini 9. uzrokom među svim novim slučajevima raka, sa stopom incidencije standardizovanom prema starosti (eng. age-standardized incidence rate - ASIR) od 5,6 (1). Na globalnom nivou, bilo je oko 220.000 smrtnih slučajeva 2022. godine, što čini rak beške 13. uzrokom smrti od raka u svetu kod oba pola, sa stopom smrtnosti standardizovanom prema starosti (eng. age-standardized mortality rate - ASMR) od 1,8. Evropa i Severna Amerika zabeležile su najveće starosno standardizovane stope incidencije

i mortaliteta (ASIR i ASMR), dok su najniže stope zabeležene u Latinskoj Americi i Karibima i Aziji (1). Zemlje sa najvišom stopom incidencije standardizovanom prema starosti za rak beške bile Španija, Grčka i Italija (19,3; 18,1; i 18,1), dok su najveće stope smrtnosti standardizovane prema starosti zabeležene u Egiptu, Francuskoj i Italiji (8,8; 3,4; i 3,1, tim redosledom) (1). U Srbiji su 2022. godine zabeležene stope incidencije standardizovane prema starosti od 23,4 kod muškaraca (što je 4. mesto) i 9,4 kod žena (8. mesto), i stope smrtnosti standardizovane prema starosti od 6,4 kod muškaraca (5. mesto) i 1,8 kod žena (1).

## LONG-TERM TREND OF BLADDER CANCER MORTALITY IN SERBIA, 1991-2024: A JOINPOINT REGRESSION ANALYSIS

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### SUMMARY

**Introduction/Aim:** Bladder cancer is among the main urological diseases. Bladder cancer mortality trends vary significantly worldwide. This research sought to assess temporal trends in deaths due to bladder cancer in Serbia.

**Methods:** This was a population-based descriptive epidemiological study. Bladder cancer mortality data were obtained from an official database. Direct standardization with the World standard population was used to compute the age-standardized rates (ASRs) per 100,000. Joinpoint regression analysis was employed to assess temporal trends in bladder cancer mortality using the average annual percentage change (AAPC) alongside its 95% confidence interval (95% CI) over the 1991-2024 period.

**Results:** During the period 1991-2024, almost 20,000 deaths due to bladder cancer (about 15,000 among men and 5,000 among women) occurred in Serbia. Average annual ASR of mortality from bladder cancer was notably higher among males than females (5.94 versus 3.87 per 100,000, respectively). Significant increases in bladder cancer mortality trends were recorded for both males (AAPC=0.6%; 95% CI=0.4 to 0.9) and females (AAPC=1.3%; 95% CI=1.0 to 1.5). The male and female trends were not parallel, as the final selected model rejected parallelism ( $p = 0.008$ ). A significant increase in bladder cancer mortality in women was recorded in middle age (age groups 55 to 69 years), while in men a more pronounced increase was observed in older people (age groups 70 and older).

**Conclusion:** An increase in bladder cancer mortality during more than three decades in Serbia implies that further analytical research is needed.

**Key words:** bladder cancer, mortality, trends, joinpoint regression analysis

### Introduction

The most recent GLOBOCAN data indicates that the number of new bladder cancer cases in the world in 2022 was around 614 000, ranking as the 9th cause among all new cases of cancer, with an age-standardized incidence rate (ASIR) of 5.6 (1). Globally, in 2022 there were around 220 000 deaths making bladder cancer the 13th cause of death due to cancer globally for both sexes combined, the corresponding age-standardized mortality rate (ASMR) being 1.8. Europe and Northern America had the highest age-standardized incidence and mortality rates, while the lowest were recorded in Latin America

& Caribbean and Asia (1). Countries showing the highest ASIR of bladder cancer were Spain, Greece and Italy (19.3, 18.1 and 18.1, respectively), while the highest ASMR were recorded in Egypt, France and Italy (8.8, 3.4 and 3.1, respectively) (1). In 2022, ASIR of 23.4 in males (ranking 4th) and 9.4 in females (ranking 8th), and ASMR of 6.4 in males (ranking 5th) and 1.8 in females were recorded in Serbia (1).

More than three quarters of newly recorded cases and deaths of bladder cancer occurred in males. Namely, in males, there were around 471 000 new cases in 2022 (ranking as the 6th leading

Više od tri četvrtine novo-zabeleženih slučajeva i smrtnih slučajeva izazvanih rakom bešike dogodilo se kod muškaraca. Naime, kod muškaraca je 2022. godine bilo oko 471.000 novih slučajeva (što ga čini 6. najčešćim uzrokom raka kod muškaraca) sa stopom incidencije koja je standardizovana po starosti od 9,3, i oko 166.000 smrtnih slučajeva (što ga čini 9. najčešćim uzrokom smrti od raka kod muškaraca) sa stopom smrtnosti standardizovanom po starosti od 3,1, dok je kod žena bilo oko 143.000 novih slučajeva sa starosno standardizovanom stopom incidencije (ASIR) od 2,4 i oko 55.000 smrtnih slučajeva (ASMR od 0,8) (1). Istraživanja opterećenja bolestima prema regionima pokazuju značajne razlike, sa najvišom starosno standardizovanom stopom incidencije u Južnoj Evropi, a zatim u Severnoj Evropi, Zapadnoj Evropi, Severnoj Americi i Istočnoj Evropi, kod muškaraca i žena (2). Najviše starosno standardizovane stope incidencije raka bešike kod muškaraca bile su u Španiji, Grčkoj i Italiji (32,4; 32,2; i 30,4, tim redom), a kod žena u Burkini Faso, Holandiji i Danskoj (9,3; 9,2; i 8,6 tim redom) (1). Najviše starosno standardizovane stope smrtnosti kod muškaraca bile su u Egiptu (15,6), Francuskoj (6,2) i Italiji (5,5), a kod žena u Egiptu (3,5), Ujedinjenom Kraljevstvu (1,7) i Nemačkoj (1,5).

Globalne varijacije u trendovima obolevanja od raka bešike u velikoj meri odražavaju promenljivu prevalenciju poznatih faktora rizika za ovo oboljenje. Prema Međunarodnoj agenciji za istraživanje raka (eng. International Agency for Research on Cancer – IARC), nekoliko kancerogenih agenasa sa dovoljnim dokazima za pojavu raka bešike kod ljudi je navedeno, uključujući pušenje duvana, različite vrste profesionalne izloženosti, kontaminaciju vode za piće arsenom, infekciju *Schistosoma haematobium*, određene lekove, korišćenje opijuma (3). Prema novijem sistematskom pregledu (4), drugi relevantni faktori rizika takođe uključuju fizičku aktivnost, gojaznost, dijetetske faktore, socioekonomski status, urolitijazu. Pušenje cigareta se smatra odgovornim za oko 50% slučajeva raka bešike, pri čemu se ovaj rizik povećava sa većim intenzitetom i dužim trajanjem pušenja (5). Pored toga, porodična agregacija raka bešike je dobro opisana u literaturi, sa prijavljenom prevalencijom od 4% do 50% u različitim studijama (4,6). Rizik od raka bešike povećava se sa starošću, pri čemu se nagli porast beleži posle 50. godine (7), što ukazuje da rak bešike može postati značajan problem

javnog zdravlja u starijoj populaciji. Naime, projekcije pokazuju da se očekuje porast broja slučajeva raka bešike od oko 73% na godišnjem nivou do 2040. godine u poređenju sa 2020. godinom, i porast broja smrtnih slučajeva od oko 87% na godišnjem nivou (8).

Ispitivanja trendova incidencije raka bešike u svetu su pokazala da su stope kod muškaraca uglavnom stabilne ili u padu, osim u nekim zemljama Centralne i Istočne Evrope (Bugarska, Poljska, Slovačka i Belorusija), Severne Evrope (Letonija, Estonija, Litvanija, Island) i Južne Evrope (Slovenija, Španija, Hrvatska) (1). Kod žena, trendovi kretanja stopa incidencije pokazali su porast u većem delu sveta, naročito u zemljama Centralne i Istočne Evrope (Bugarska, Slovačka, Poljska, Ruska Federacija, itd.), Južne Evrope (Slovenija, Španija, Hrvatska), i Centralne i Južne Amerike (Ekvador) (1). Razlike u smrtnosti od raka bešike uglavnom odražavaju različit pristup zdravstvenoj zaštiti, rano otkrivanje bolesti i lečenje. Stope smrtnosti pokazale su trend opadanja, naročito u zemljama sa najvišim stepenom razvoja, ali postoje i mesta gde su te stope porasle u prethodnih nekoliko decenija. Kod muškaraca, trend povećanja stopa smrtnosti od raka bešike zabeležen je u zemljama Centralne i Istočne Evrope (Bugarska, Rumunija), Istočne Evrope (Slovenija, Hrvatska), Severne Evrope (Litvanija, Letonija), Centralne i Istočne Azije (Kina) i Centralne i Južne Amerike (Kuba, Brazil, Čile, Meksiko) (1). Kod žena, smrtnost od raka bešike je pokazala trend porasta u Južnoj Evropi (Slovenija, Hrvatska, Španija), Centralnoj i Istočnoj Evropi (Poljska, Mađarska, Bugarska) i Centralnoj i Južnoj Americi (Kuba, Meksiko, Brazil) (1). Otprilike jedna četvrtina slučajeva raka bešike dijagnostikovana je u uznapređevaloj fazi bolesti, sa petogodišnjim stopama preživljavanja koje naglo opadaju u najvišim stadijumima bolesti, i iznose od 5 do 7% (5). Imajući u vidu razlike koje se tiču toga da li su neinvazivni karcinomi uključeni u registre ili ne, a to su karcinomi sa povoljnijim stopama preživljavanja, smatra se da je adekvatnije pratiti kontrolu bolesti procenjivanjem i upoređivanjem stopa smrtnosti raka bešike (1).

Tokom poslednjih nekoliko decenija, Srbija se suočava se brojnim socioekonomskim i političkim izazovima. Imajući u vidu starosnu strukturu stanovništva u Srbiji, jednoj od najstarijih populacija u Evropi, sa statusom srednje razvijene ekonomije i značajnim opterećenjem nezaraznim bolestima,

cancer type in males) with an ASIR of 9.3, and about 166 000 deaths (ranking as the 9th most common cause of death from cancer in males) with an ASMR of 3.1, while in females there were around 143 000 new cases with an ASIR of 2.4 and about 55 000 deaths (ASMR of 0.8) (1). Region-specific burden shows substantial variations, with the highest ASIR observed in Southern Europe, with the subsequent highest rates recorded in Northern Europe, Western Europe, Northern America and Eastern Europe, both for males and females (2). Countries showing the highest ASIR of bladder cancer were Spain, Greece and Italy for males (32.4, 32.2 and 30.4, respectively) and Burkina Faso, the Netherlands and Denmark for females (9.3, 9.2 and 8.6, respectively) (1). The highest ASMR in males were observed in Egypt (15.6), France (6.2) and Italy (5.5), and in females in Egypt (3.5), the United Kingdom (1.7) and Germany (1.5).

Global variations in bladder cancer trends to a great extent correspond to the changing prevalence of known disease risk factors. According to the International Agency for Research on Cancer (IARC) several carcinogenic agents are listed as having sufficient evidence for the occurrence of human bladder cancer, including tobacco smoking, various occupational exposures, drinking water contaminated with arsenic, *Schistosoma haematobium* infection, certain drugs, opium consumption (3). According to recent systematic review (4), other relevant risk factors also include physical activity, obesity, dietary factors, socioeconomic status, urolithiasis. Cigarette smoking is estimated to account for around 50% of all cases of bladder cancer, with risk increasing with higher intensity and longer duration of smoking (5). Additionally, familial aggregation of bladder cancer is well described in literature, with reported prevalence ranging from 4% up to 50% across studies (4, 6). Risk for bladder cancer increases with age, demonstrating a steep increase after the age of 50 (7), indicating that bladder cancer can become a significant public health issue in ageing populations. Namely, projections show that by 2040 the world will experience an increase of around 73% in the annual number of cases of bladder cancer compared to 2020, and an increase of almost 87% in annual number of deaths (8).

Investigations of trends in bladder cancer incidence across the world have shown that rates in males have mostly been stable or decreasing, except in some countries in Central and Eastern Europe (Bulgaria, Poland, Slovakia, Belarus), Northern Europe (Latvia, Estonia, Lithuania, Iceland), Southern Europe (Slovenia, Spain, Croatia) (1). In females, trends in incidence rates have shown an increase in most parts of the world, especially in countries in Central and Eastern Europe (Bulgaria, Slovakia, Poland, Russian Federation, etc.), Southern Europe (e.g. Slovenia, Spain, Croatia) and Central and South America (Ecuador) (1). Disparities in bladder cancer morality most often reflect access to healthcare, early detection and treatment. Mortality rates have shown decreasing trends especially in countries with the highest level of development, but there were locations that experienced and increase over the last decades. In males, an increasing trend in mortality rates from bladder cancer was observed in countries in Central and Eastern Europe (Bulgaria, Romania), Southern Europe (Slovenia, Croatia), Northern Europe (Lithuania, Latvia), Central & Eastern Asia (China) and Central and South America (Cuba, Brazil, Chile, Mexico) (1). In females, mortality due to bladder cancer showed an upward trend in Southern Europe (Slovenia, Croatia, Spain), Central and Eastern Europe (Poland, Hungary, Bulgaria) and Central and South America (Cuba, Mexico, Brazil) (1). About one quarter of bladder cancer cases are detected at an advanced stage, with 5-year survival rates sharply decreasing for the most advanced stages, ranging from about 5-7% (5). Given the differences in whether non-invasive carcinomas are included or not in registries, which are cancers with more favorable survival, it is considered more appropriate to monitor disease control by estimating and comparing rates of bladder cancer mortality (1).

Over the last few decades, Serbia has been facing numerous socioeconomic and political challenges. Given Serbia's aging population, among the oldest in Europe, with a status of an upper-middle economy and a significant burden of non-communicable diseases, it is essential to investigate trends in disease burden in order to inform national cancer control strategies, improve resource allocation and consequently outcomes. This research sought to assess temporal trends in deaths due to bladder cancer in Serbia.

ispitivanje trendova opterećenja bolestima je od ključne važnosti kako bi se unapredile nacionalne strategije za kontrolu kancera, dodeljivanje sredstava i posledično ishodi bolesti. Ovo istraživanje imalo je za cilj da proceni vremenske trendove smrtnih slučajeva od raka bešike u Srbiji.

## Metod

### Izvori podataka

Podaci o smrtnosti od raka bešike (Međunarodna klasifikacija bolesti (MKB) za klasifikaciju smrti, povreda i uzroka smrti MKB-9 kod 188 i MKB-10 kod C67) preuzeti su iz Zavoda za statistiku Srbije (neobjavljeni podaci). U Srbiji su podaci o smrtnosti od 1991. do 1996. godine kodirani prema MKB-9, dok se od 1997. godine statistika smrtnosti obrađuje korišćenjem MKB-10 (9). Svetska zdravstvena organizacija (SZO) definiše osnovni uzrok smrti kao „bolest ili povredu koja je pokrenula niz bolesnih stanja koja su direktno dovela do smrti, ili okolnosti nesrećnog slučaja ili nasilja koje su uzrokovale smrtonosnu povredu“. Prema SZO, zvanični podaci o smrtnosti u Srbiji su srednjeg kvaliteta, sa podacima koji su više od 90% kompletni i sa nejasno definisanim uzrocima koji predstavljaju manje od 10% svih registracija (10). Ovde predstavljeno istraživanje obuhvatilo je celokupnu populaciju Srbije, sa približno 7,6 miliona stanovnika 1991. godine i 6,6 miliona 2024. godine, na osnovu popisa iz 1991. i 2022. godine, pri čemu su procene brojeva stanovništva za sve preostale godine razmatrane u ovoj studiji dobijene od Republičkog zavoda za statistiku Srbije.

### Merenja

Smrtnost od raka bešike je predstavljena sirovim, uzrasno specifičnim i uzrasno standardizovanim stopama na 100.000 osoba. Za izračunavanje je korišćena petogodišnja starosna grupa smrti. Direktna standardizacija sa svetskom standardnom populacijom korišćena je za izračunavanje stopa standardizovanih po starosti (ASR).

### Statistička analiza

Za procenu vremenskih promena u smrtnosti od raka bešike, izvršena je joinpoint regresiona analiza (Softver za Joinpoint regresiju, verzija 4.5.0.1, Program za istraživanje nadzora, Nacionalni institut za rak SAD), kako su opisali Kim i saradnici (11). Ova metoda omogućava otkrivanje tačaka gde se

dešavaju statistički značajne promene u trendovima. Primenjena je Grid Search metoda. Analiza je izvršena sa minimalnim brojem joinpointa (nula, što odgovara pravoj liniji), a zatim je evaluirana usklađenost modela sa maksimalno 5 joinpointa. Značajnost je određena metodom Monte Karlo permutacije, dok je procedura permutacije procenila paralelizam. Godišnje procentualne promene (APC) i prosečne godišnje procentualne promene (AAPC) zajedno sa odgovarajućim intervalima poverenja od 95% (95%CI) izračunate su za smrtnost od raka bešike tokom perioda istraživanja. Rezultati joinpoint analize nisu predstavljeni za muškarce mlađe od 45 godina i žene mlađe od 55 godina, jer je svaka petogodišnja starosna grupa beležila <5 slučajeva raka bešike u bilo kojoj datoj godini. Statistička značajnost je postavljena na  $p < 0,05$ .

### Etička pitanja

Istraživanje je sprovedeno u skladu sa odredbama Helsinške deklaracije i odobreno je od strane Etičke komisije Fakulteta medicinskih nauka Univerziteta u Kragujevcu (No: 01-4801).

## Rezultati

U periodu od 1991. do 2024. godine, u Srbiji je zabeleženo skoro 20.000 smrtnih slučajeva zbog raka bešike (oko 15.000 kod muškaraca i 5.000 kod žena) (Tabela 1). Ukupna prosečna godišnja ASR smrtnosti od raka bešike iznosila je 3,41 na 100.000. Prosečna godišnja ASR smrtnosti od raka bešike bila je znatno viša kod muškaraca nego kod žena (5,94 prema 3,87 na 100.000, tim redosledom).

Tokom celog posmatranog perioda, u Srbiji je detektovano značajno povećanje trenda mortaliteta od raka bešike (AAPC = 0,8%, 95% CI = 0,6 do 1,0) (Slika 1).

Značajno povećanje trendova smrtnosti od raka bešike zabeleženo je i kod muškaraca (AAPC = 0,6%; 95% CI = 0,4 do 0,9) i kod žena (AAPC = 1,3%; 95% CI 1,0 do 1,5) (Slika 2 Tabela 2). Test uporedivosti je pokazao da trendovi kod muškaraca i žena nisu paralelni, jer je konačni izabrani model odbacio paralelizam ( $p = 0,008$ ) (Slika 2).

Stope smrtnosti od raka bešike porasle su sa godinama u oba pola (Tabela 2, Slike 3-4). Trendovi mortaliteta bili su stabilni kod muškaraca u starosnim grupama mlađim od 70 godina, osim neznatnog trenda opadanja zabeleženog u starosnoj grupi 50-54 godina (AAPC = -0,8%, 95% CI = -1,7 do 0,1)

## Methods

### Data source

Bladder cancer mortality data (International Classification of Diseases (ICD) to classify death, injury and cause of death ICD-9 code 188 and ICD-10 code C67) were retrieved from the Statistical Office of Serbia (unpublished data). In Serbia, mortality data from 1991 to 1996 were coded according to ICD-9, while from 1997 onwards, mortality statistics have been processed using ICD-10 (9). The World Health Organization (WHO) defines the underlying cause of death as “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury”. According to WHO, Serbia’s official mortality data are of medium quality, having data that are more than 90% complete and with ill-defined causes representing less than <10% of all registrations (10). Here presented research encompassed Serbia’s entire population with approximately 7.6 million in 1991 and 6.6 million in 2024, based on the 1991 and 2022 censuses, with population figures’ estimates for all remaining years considered in this study obtained from the Statistical Office of the Republic of Serbia.

### Measures

Bladder cancer mortality is presented as crude, age-specific and age-standardized rates per 100,000 persons. The five-year age group of death was used for calculations. Direct standardization with the World standard population was used to compute the age-standardized rates (ASRs).

### Statistical analysis

To assess temporal changes in bladder cancer mortality, joinpoint regression analysis was performed (Joinpoint regression software, Version 4.5.0.1, Surveillance Research Program, U.S. National Cancer Institute), as described by Kim et al. (11). This method allows for detection of points where statistically significant shifts in trends take place. The Grid Search Method was employed. The analysis was performed with minimum joinpoints (zero, corresponding to a straight line), and subsequently evaluated model fit with a maximum of 5 joinpoints. Significance was determined using the Monte Carlo Permutation method, while

permutation procedure assessed parallelism. The annual percentage changes (APC) and average annual percent changes (AAPC) alongside their corresponding 95% confidence intervals (95%CI) were computed for bladder cancer mortality throughout the study period. Joinpoint results are not presented for men under 45 years of age and women under 55 years, due to each quinquennial age group recording <5 bladder cancer cases in any given year. Statistical significance was set at  $p < 0.05$ .

### Ethical considerations

This research complied to the Declaration of Helsinki guidelines and obtained approval from the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac (No: 01-4801).

## Results

During the period 1991-2024, almost 20,000 deaths due to bladder cancer (about 15,000 among men and 5,000 among women) occurred in Serbia (Table 1). The overall average annual ASR for mortality from bladder cancer was 3.41 per 100,000. Average annual ASR of mortality from bladder cancer was notably higher among males than females (5.94 versus 3.87 per 100,000, respectively).

Over the whole observed period, a significant increase in bladder cancer mortality trend in Serbia was detected (AAPC= 0.8%, 95%CI=0.6 to 1.0) (Figure 1).

Significant increases in bladder cancer mortality trends were recorded for both males (AAPC=0.6%; 95%CI=0.4 to 0.9) and females (AAPC=1.3%; 95%CI=1.0 to 1.5) (Figure 2 Table 2). The comparability test indicated that the male and female trends were not parallel, as the final selected model rejected parallelism ( $p = 0.008$ ) (Figure 2).

Mortality rates from bladder cancer rose with advancing age in both sexes (Table 2, Figures 3-4). Mortality trends were stable among men in age groups younger than 70 years, except for a non-significant decreasing trend noted in the 50-54 age group (AAPC=-0.8%, 95%CI=-1.7 to 0.1) (Table 2). A significant trend of increased bladder cancer mortality was observed in men aged 70 years and above. Women aged 55-69 experienced a significant increase in bladder cancer mortality trend, while a stable trend was observed in the

**Tabela 1.** Smrtnost od raka beške kod muškaraca i žena u Srbiji, 1991-2024; broj slučajeva, sirove stope i stopa standardizovana po uzrastu (ASR) na 100.000 (koristeći svetsku standardnu populaciju)

| Godine        | Ukupno        |              |             | Muškarci      |              |             | Žene         |              |             |
|---------------|---------------|--------------|-------------|---------------|--------------|-------------|--------------|--------------|-------------|
|               | Broj          | Sirova stopa | ASR         | Broj          | Sirova stopa | ASR         | Broj         | Sirova stopa | ASR         |
| 1991          | 379           | 4,99         | 2,90        | 283           | 7,62         | 5,02        | 96           | 2,47         | 1,27        |
| 1992          | 383           | 5,04         | 2,88        | 288           | 7,75         | 5,02        | 94           | 2,42         | 1,24        |
| 1993          | 437           | 5,74         | 3,27        | 340           | 9,14         | 5,97        | 97           | 2,49         | 1,23        |
| 1994          | 420           | 5,51         | 3,06        | 326           | 8,75         | 5,51        | 94           | 2,41         | 1,18        |
| 1995          | 410           | 5,37         | 2,93        | 308           | 8,27         | 5,04        | 102          | 2,61         | 1,28        |
| 1996          | 440           | 5,77         | 3,10        | 332           | 8,92         | 5,45        | 108          | 2,77         | 1,27        |
| 1997          | 449           | 5,91         | 3,10        | 343           | 9,25         | 5,51        | 106          | 2,72         | 1,27        |
| 1998          | 444           | 5,87         | 2,99        | 337           | 9,14         | 5,32        | 107          | 2,76         | 1,22        |
| 1999          | 509           | 6,75         | 3,46        | 381           | 10,38        | 6,03        | 128          | 3,31         | 1,50        |
| 2000          | 474           | 6,31         | 3,12        | 341           | 9,33         | 5,21        | 133          | 3,45         | 1,51        |
| 2001          | 497           | 6,62         | 3,19        | 378           | 10,36        | 5,50        | 119          | 3,09         | 1,30        |
| 2002          | 563           | 7,51         | 3,51        | 448           | 12,28        | 6,56        | 115          | 2,98         | 1,16        |
| 2003          | 519           | 6,94         | 3,17        | 386           | 10,61        | 5,52        | 133          | 3,46         | 1,35        |
| 2004          | 527           | 7,06         | 3,19        | 401           | 11,05        | 5,72        | 126          | 3,29         | 1,26        |
| 2005          | 519           | 6,98         | 3,10        | 394           | 10,89        | 5,44        | 125          | 3,27         | 1,30        |
| 2006          | 612           | 8,26         | 3,63        | 470           | 13,04        | 6,54        | 142          | 3,73         | 1,38        |
| 2007          | 620           | 8,40         | 3,61        | 472           | 13,15        | 6,48        | 148          | 3,90         | 1,44        |
| 2008          | 546           | 7,43         | 3,09        | 406           | 11,36        | 5,34        | 140          | 3,71         | 1,40        |
| 2009          | 596           | 8,14         | 3,33        | 444           | 12,47        | 5,70        | 152          | 4,04         | 1,50        |
| 2010          | 569           | 7,80         | 3,21        | 428           | 12,07        | 5,65        | 141          | 3,76         | 1,33        |
| 2011          | 646           | 8,90         | 3,64        | 482           | 13,65        | 6,28        | 164          | 4,40         | 1,59        |
| 2012          | 708           | 9,83         | 3,96        | 550           | 15,69        | 7,16        | 158          | 4,28         | 1,49        |
| 2013          | 641           | 8,95         | 3,51        | 492           | 14,10        | 6,25        | 149          | 4,05         | 1,48        |
| 2014          | 655           | 9,18         | 3,42        | 478           | 13,76        | 5,85        | 177          | 4,84         | 1,55        |
| 2015          | 706           | 9,92         | 3,90        | 546           | 15,76        | 6,94        | 160          | 4,38         | 1,52        |
| 2016          | 687           | 9,73         | 3,68        | 497           | 14,46        | 6,07        | 190          | 5,25         | 1,85        |
| 2017          | 697           | 9,93         | 3,65        | 536           | 15,67        | 6,44        | 161          | 4,47         | 1,52        |
| 2018          | 737           | 10,55        | 3,77        | 557           | 16,37        | 6,52        | 180          | 5,03         | 1,73        |
| 2019          | 776           | 11,17        | 4,07        | 579           | 17,11        | 6,91        | 197          | 5,53         | 1,88        |
| 2020          | 717           | 10,39        | 3,77        | 559           | 16,64        | 6,64        | 158          | 4,46         | 1,55        |
| 2021          | 709           | 10,37        | 3,66        | 522           | 15,69        | 6,14        | 187          | 5,33         | 1,77        |
| 2022          | 712           | 10,68        | 3,82        | 526           | 16,23        | 6,43        | 186          | 5,43         | 1,77        |
| 2023          | 686           | 10,36        | 3,61        | 505           | 15,68        | 6,01        | 181          | 5,32         | 1,76        |
| 2024          | 703           | 10,67        | 3,63        | 489           | 15,26        | 5,77        | 214          | 6,33         | 1,95        |
| <b>Ukupno</b> | <b>19,693</b> | <b>8,03</b>  | <b>3,41</b> | <b>14,824</b> | <b>12,41</b> | <b>5,94</b> | <b>4,868</b> | <b>3,87</b>  | <b>1,46</b> |

(Tabela 2). Značajan trend povećanog mortaliteta od raka beške uočen je kod muškaraca starijih od 70 godina. Žene starosti 55-69 godina doživele su značajan porast trenda smrtnosti od raka beške, dok je stabilan trend zabeležen u starijoj starosnoj grupi (70-84). U najstarijoj starosnoj grupi žena (85

+), zabeležen je izražen trend povećanja smrtnosti od raka beške (AAPC = 3,0%, 95%CI = 1,5 do 4,6).

Dobno specifične stope smrtnosti od raka beške kod muškaraca bile su oko četiri puta veće nego kod žena tokom celog posmatranog perioda (Tabela 2, Slike 3-4).

**Table 1.** Bladder cancer mortality in men and women in Serbia, 1991-2024; number of cases, crude rates and age standardized rate (ASR) per 100,000 (using World standard population)

| Years   | Total  |            |      | Men    |            |      | Women  |            |      |
|---------|--------|------------|------|--------|------------|------|--------|------------|------|
|         | Number | Crude rate | ASR  | Number | Crude rate | ASR  | Number | Crude rate | ASR  |
| 1991    | 379    | 4.99       | 2.90 | 283    | 7.62       | 5.02 | 96     | 2.47       | 1.27 |
| 1992    | 383    | 5.04       | 2.88 | 288    | 7.75       | 5.02 | 94     | 2.42       | 1.24 |
| 1993    | 437    | 5.74       | 3.27 | 340    | 9.14       | 5.97 | 97     | 2.49       | 1.23 |
| 1994    | 420    | 5.51       | 3.06 | 326    | 8.75       | 5.51 | 94     | 2.41       | 1.18 |
| 1995    | 410    | 5.37       | 2.93 | 308    | 8.27       | 5.04 | 102    | 2.61       | 1.28 |
| 1996    | 440    | 5.77       | 3.10 | 332    | 8.92       | 5.45 | 108    | 2.77       | 1.27 |
| 1997    | 449    | 5.91       | 3.10 | 343    | 9.25       | 5.51 | 106    | 2.72       | 1.27 |
| 1998    | 444    | 5.87       | 2.99 | 337    | 9.14       | 5.32 | 107    | 2.76       | 1.22 |
| 1999    | 509    | 6.75       | 3.46 | 381    | 10.38      | 6.03 | 128    | 3.31       | 1.50 |
| 2000    | 474    | 6.31       | 3.12 | 341    | 9.33       | 5.21 | 133    | 3.45       | 1.51 |
| 2001    | 497    | 6.62       | 3.19 | 378    | 10.36      | 5.50 | 119    | 3.09       | 1.30 |
| 2002    | 563    | 7.51       | 3.51 | 448    | 12.28      | 6.56 | 115    | 2.98       | 1.16 |
| 2003    | 519    | 6.94       | 3.17 | 386    | 10.61      | 5.52 | 133    | 3.46       | 1.35 |
| 2004    | 527    | 7.06       | 3.19 | 401    | 11.05      | 5.72 | 126    | 3.29       | 1.26 |
| 2005    | 519    | 6.98       | 3.10 | 394    | 10.89      | 5.44 | 125    | 3.27       | 1.30 |
| 2006    | 612    | 8.26       | 3.63 | 470    | 13.04      | 6.54 | 142    | 3.73       | 1.38 |
| 2007    | 620    | 8.40       | 3.61 | 472    | 13.15      | 6.48 | 148    | 3.90       | 1.44 |
| 2008    | 546    | 7.43       | 3.09 | 406    | 11.36      | 5.34 | 140    | 3.71       | 1.40 |
| 2009    | 596    | 8.14       | 3.33 | 444    | 12.47      | 5.70 | 152    | 4.04       | 1.50 |
| 2010    | 569    | 7.80       | 3.21 | 428    | 12.07      | 5.65 | 141    | 3.76       | 1.33 |
| 2011    | 646    | 8.90       | 3.64 | 482    | 13.65      | 6.28 | 164    | 4.40       | 1.59 |
| 2012    | 708    | 9.83       | 3.96 | 550    | 15.69      | 7.16 | 158    | 4.28       | 1.49 |
| 2013    | 641    | 8.95       | 3.51 | 492    | 14.10      | 6.25 | 149    | 4.05       | 1.48 |
| 2014    | 655    | 9.18       | 3.42 | 478    | 13.76      | 5.85 | 177    | 4.84       | 1.55 |
| 2015    | 706    | 9.92       | 3.90 | 546    | 15.76      | 6.94 | 160    | 4.38       | 1.52 |
| 2016    | 687    | 9.73       | 3.68 | 497    | 14.46      | 6.07 | 190    | 5.25       | 1.85 |
| 2017    | 697    | 9.93       | 3.65 | 536    | 15.67      | 6.44 | 161    | 4.47       | 1.52 |
| 2018    | 737    | 10.55      | 3.77 | 557    | 16.37      | 6.52 | 180    | 5.03       | 1.73 |
| 2019    | 776    | 11.17      | 4.07 | 579    | 17.11      | 6.91 | 197    | 5.53       | 1.88 |
| 2020    | 717    | 10.39      | 3.77 | 559    | 16.64      | 6.64 | 158    | 4.46       | 1.55 |
| 2021    | 709    | 10.37      | 3.66 | 522    | 15.69      | 6.14 | 187    | 5.33       | 1.77 |
| 2022    | 712    | 10.68      | 3.82 | 526    | 16.23      | 6.43 | 186    | 5.43       | 1.77 |
| 2023    | 686    | 10.36      | 3.61 | 505    | 15.68      | 6.01 | 181    | 5.32       | 1.76 |
| 2024    | 703    | 10.67      | 3.63 | 489    | 15.26      | 5.77 | 214    | 6.33       | 1.95 |
| Overall | 19,693 | 8.03       | 3.41 | 14,824 | 12.41      | 5.94 | 4,868  | 3.87       | 1.46 |

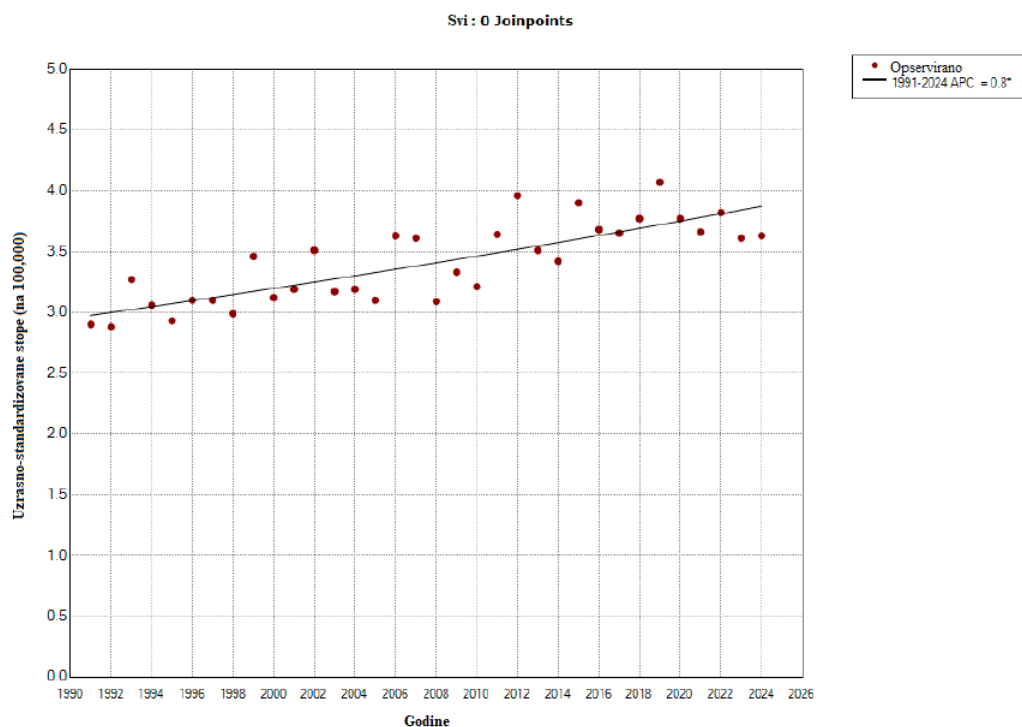
older age group (70-84). In the oldest age group of women (85+), a pronounced increase in bladder cancer mortality trend was recorded (AAPC=3.0%, 95%CI=1.5 to 4.6).

Age-specific mortality rates for bladder cancer in men were approximately fourfold higher than

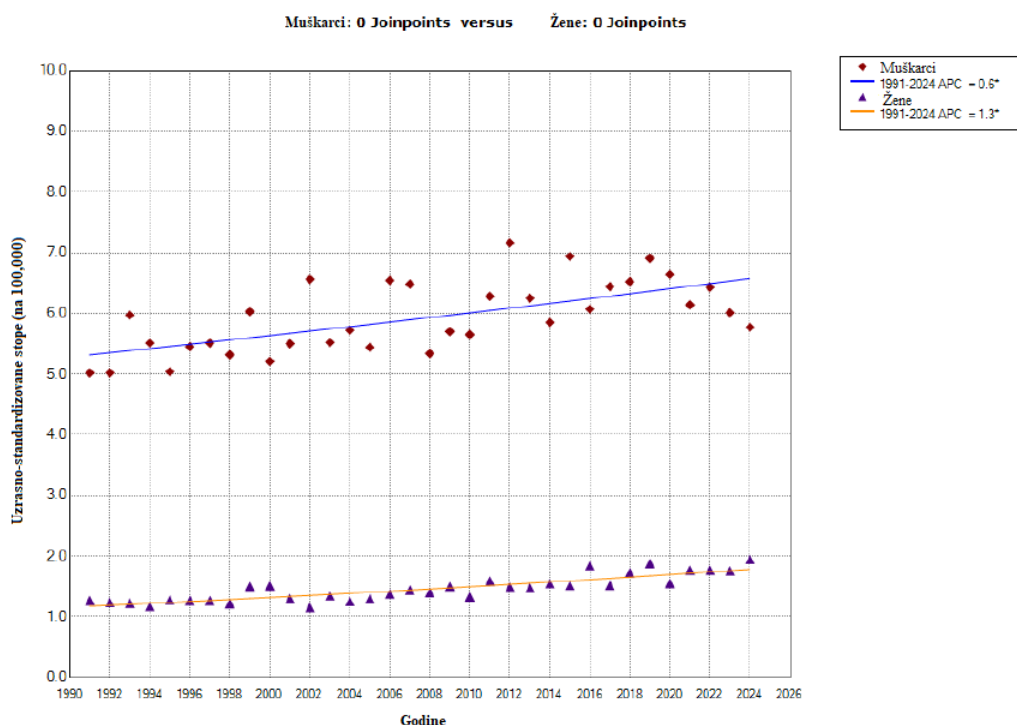
those observed in women during the entire studied period (Table 2, Figures 3-4).

## Discussion

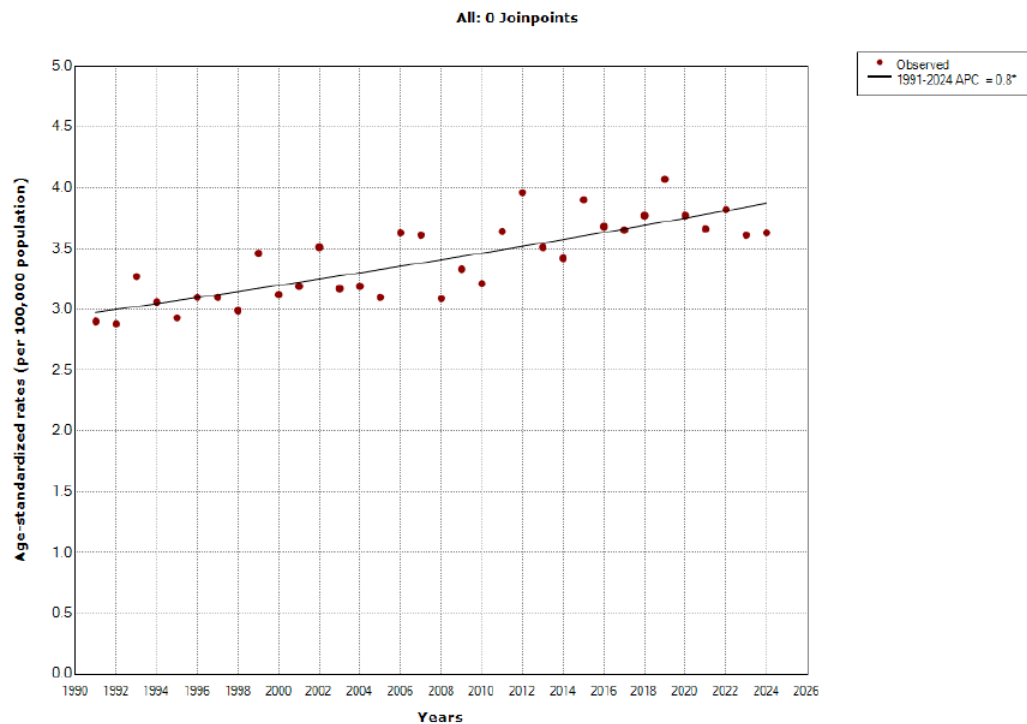
The findings of this research indicate unfavorable long-term patterns in mortality from



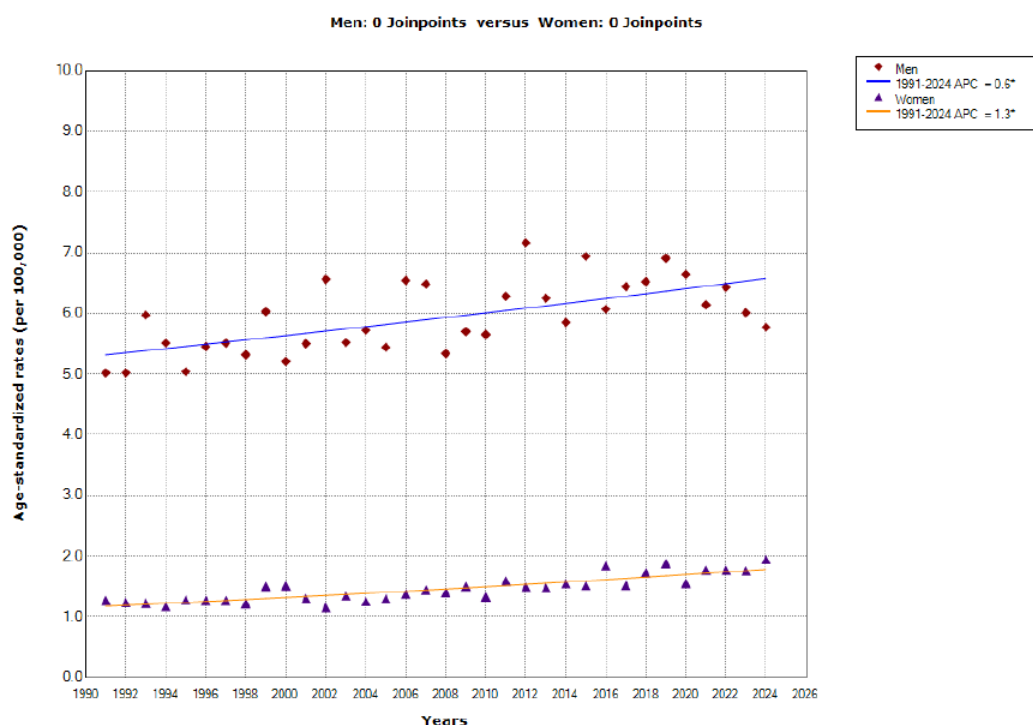
**Figura 1.** Trendovi u stopama mortaliteta od raka bešike standardizovanim po starosti (na 100.000) u Srbiji, 1991-2024; analiza joinpoint regresije. \*Statistički značajan trend ( $P < 0,05$ ). APC = Godišnja procentualna promena.



**Figura 2.** Trendovi u stopama mortaliteta od raka bešike standardizovanim po starosti (na 100.000) kod muškaraca i žena u Srbiji, 1991-2024; analiza joinpoint regresije. \* Statistički značajan trend ( $P < 0,05$ ). APC = Godišnja procentualna promena.



**Figure 1.** Trends in age-standardized rates of bladder cancer mortality (per 100,000) in Serbia, 1991-2024; a joinpoint regression analysis. \*Statistically significant trend ( $P < 0.05$ ). APC = Annual Percentage Change.



**Figure 2.** Trends in age-standardized rates of bladder cancer mortality (per 100,000) in men and women in Serbia, 1991-2024; a joinpoint regression analysis. \*Statistically significant trend ( $P < 0.05$ ). APC = Annual Percentage Change.

Tabela 2. Joinpoint analiza: trendovi\* u stopama smrtnosti od raka beške specifičnim za uzrast i standardizovanim po uzrastu, kod muškaraca i žena u Srbiji, 1991-2024

| Uzrast**    | Muškarci                                   |             |                   |         |                     |                      | Žene                |                      |                   |         |                     |                      |
|-------------|--------------------------------------------|-------------|-------------------|---------|---------------------|----------------------|---------------------|----------------------|-------------------|---------|---------------------|----------------------|
|             | Uzrasno-specifične stope (na 100,000)      |             |                   |         |                     |                      |                     |                      |                   |         |                     |                      |
|             | Godina 1991                                | Godina 2024 | Prosečna godišnja | AAPC*** | Donja granica 95%CI | Gornja granica 95%CI | Godina 1991         | Godina 2024          | Prosečna godišnja | AAPC*** | Donja granica 95%CI | Gornja granica 95%CI |
| 45-49       | 0,49                                       | 1,66        | 1,92              | 0,1     | -1,6                | 1,9                  |                     |                      |                   |         |                     |                      |
| 50-54       | 5,58                                       | 5,34        | 5,71              | -0,8    | -1,7                | 0,1                  |                     |                      |                   |         |                     |                      |
| 55-59       | 11,26                                      | 10,30       | 11,22             | 0,1     | -0,7                | 0,8                  | 1,71                | 5,27                 | 2,79              | 2.7*    | 0.9                 | 4.5                  |
| 60-64       | 20,74                                      | 19,08       | 21,72             | 0,3     | -0,3                | 0,9                  | 2,86                | 9,13                 | 5,11              | 2.7*    | 1.6                 | 3.7                  |
| 65-69       | 30,82                                      | 33,02       | 37,15             | 0,4     | -0,0                | 0,9                  | 8,17                | 7,92                 | 7,96              | 1.3*    | 0.4                 | 2.2                  |
| 70-74       | 41,40                                      | 56,63       | 53,87             | 0,5*    | 0,1                 | 0,8                  | 10,38               | 17,06                | 13,18             | 0.2     | -0.6                | 0.9                  |
| 75-79       | 80,60                                      | 84,99       | 83,48             | 0,8*    | 0,1                 | 1,5                  | 21,45               | 26,88                | 20,22             | 0.4     | -0.3                | 1.1                  |
| 80-84       | 64,95                                      | 87,43       | 106,49            | 1,4*    | 0,7                 | 2,0                  | 28,45               | 31,96                | 27,59             | 0.2     | -0.6                | 0.9                  |
| 85+         | 89,01                                      | 148,26      | 119,35            | 2,4*    | 1,5                 | 3,2                  | 22,14               | 45,29                | 29,12             | 3.0*    | 1.5                 | 4.6                  |
| Svi uzrasti | Uzrasno-standardizovane stope (na 100,000) |             |                   |         |                     |                      |                     |                      |                   |         |                     |                      |
|             | Godina 1991                                | Godina 2024 | Prosečna godišnja | AAPC*** | Donja granica 95%CI | Gornja granica 95%CI | Donja granica 95%CI | Gornja granica 95%CI | Godina 1991       | AAPC*** | Godina 2024         | Prosečna godišnja    |
|             | 5,02                                       | 5,77        | 5,94              | 0,6*    | 0,4                 | 0,9                  | 1,27                | 1,95                 | 1,46              | 1,3*    | 1,0                 | 1,5                  |

\* Statistički značajan trend; \*\* Rezultati Joinpoint-a nisu prikazani za podgrupe starosti <45 godina za mortalitet kod muškaraca i za podgrupe starosti <55 godina za mortalitet kod žena, zbog manje od 5 slučajeva raka beške. \*\*\* za ceo prikazani period AAPC (prosečna godišnja procentualna promena); CI = interval poverenja.

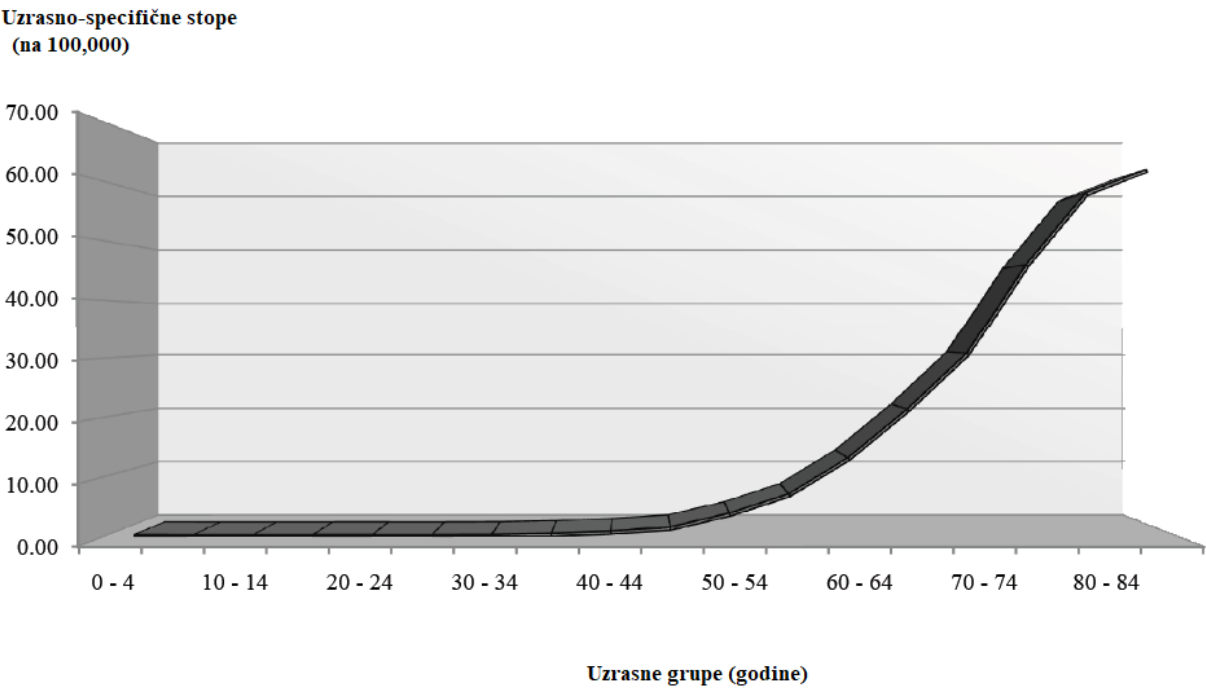
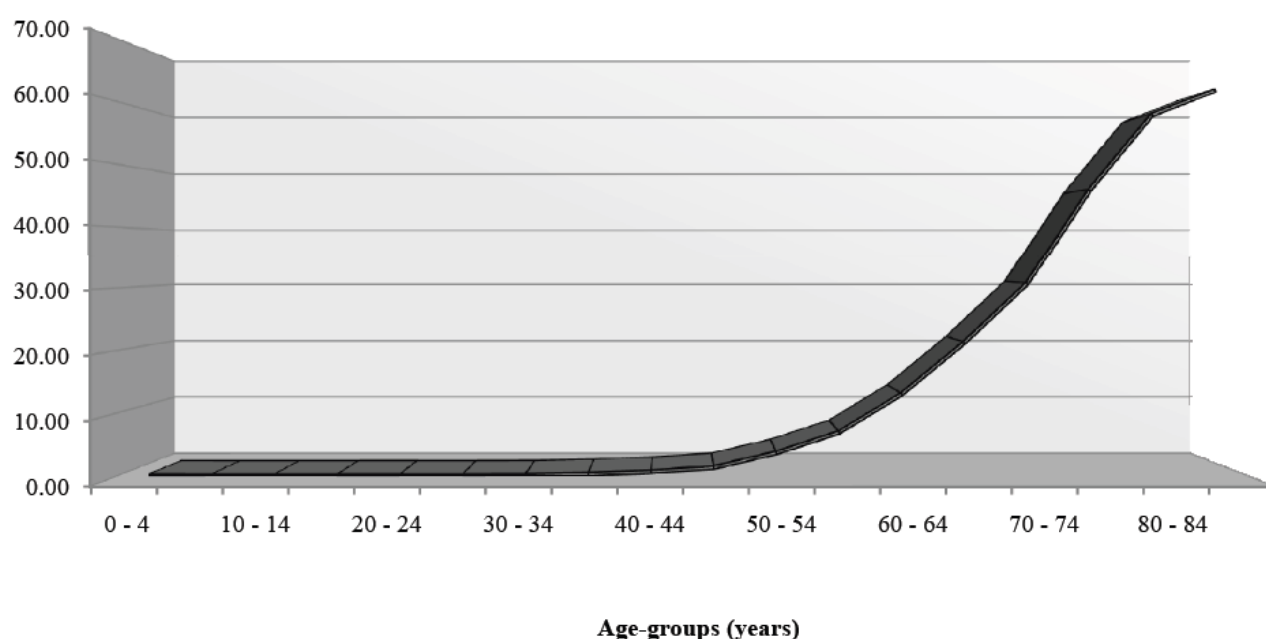


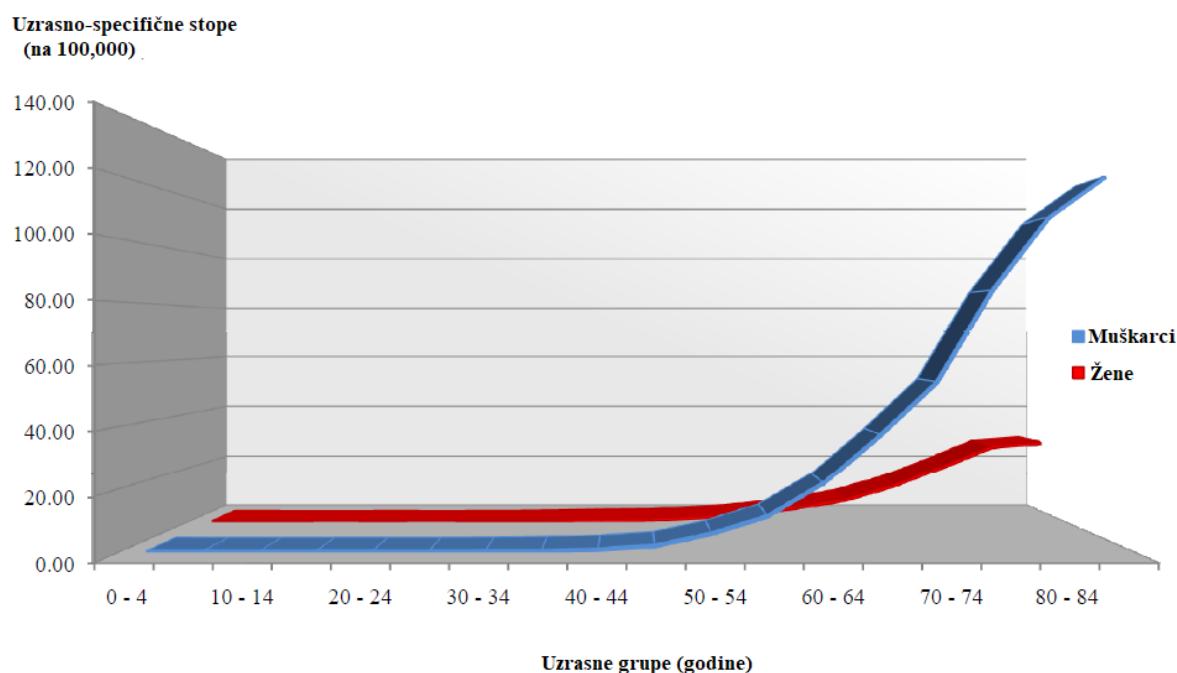
Figura 3. Stope mortaliteta od raka beške po uzrastu za oba pola zajedno u Srbiji, 1991-2024.

**Table 2.** Joinpoint analysis: trends\* in age-specific and age-standardized rates of bladder cancer mortality, in men and women in Serbia, 1991-2024

| Age**    | Men                                  |           |                |         |             |             | Women     |           |                |         |             |                      |
|----------|--------------------------------------|-----------|----------------|---------|-------------|-------------|-----------|-----------|----------------|---------|-------------|----------------------|
|          | Age-specific rates (per 100,000)     |           |                |         |             |             |           |           |                |         |             |                      |
|          | Year 1991                            | Year 2024 | Average annual | AAPC*** | Lower 95%CI | Upper 95%CI | Year 1991 | Year 2024 | Average annual | AAPC*** | Lower 95%CI | Gornja granica 95%CI |
| 45-49    | 0.49                                 | 1.66      | 1.92           | 0.1     | -1.6        | 1.9         |           |           |                |         |             |                      |
| 50-54    | 5.58                                 | 5.34      | 5.71           | -0.8    | -1.7        | 0.1         |           |           |                |         |             |                      |
| 55-59    | 11.26                                | 10.30     | 11.22          | 0.1     | -0.7        | 0.8         | 1.71      | 5.27      | 2.79           | 2.7*    | 0.9         | 4.5                  |
| 60-64    | 20.74                                | 19.08     | 21.72          | 0.3     | -0.3        | 0.9         | 2.86      | 9.13      | 5.11           | 2.7*    | 1.6         | 3.7                  |
| 65-69    | 30.82                                | 33.02     | 37.15          | 0.4     | -0.0        | 0.9         | 8.17      | 7.92      | 7.96           | 1.3*    | 0.4         | 2.2                  |
| 70-74    | 41.40                                | 56.63     | 53.87          | 0.5*    | 0.1         | 0.8         | 10.38     | 17.06     | 13.18          | 0.2     | -0.6        | 0.9                  |
| 75-79    | 80.60                                | 84.99     | 83.48          | 0.8*    | 0.1         | 1.5         | 21.45     | 26.88     | 20.22          | 0.4     | -0.3        | 1.1                  |
| 80-84    | 64.95                                | 87.43     | 106.49         | 1.4*    | 0.7         | 2.0         | 28.45     | 31.96     | 27.59          | 0.2     | -0.6        | 0.9                  |
| 85+      | 89.01                                | 148.26    | 119.35         | 2.4*    | 1.5         | 3.2         | 22.14     | 45.29     | 29.12          | 3.0*    | 1.5         | 4.6                  |
| All ages | Age-standardized rates (per 100,000) |           |                |         |             |             |           |           |                |         |             |                      |
|          | Year 1991                            | Year 2024 | Average annual | AAPC*** | Lower 95%CI | Upper 95%CI | Year 1991 | Year 2024 | Average annual | AAPC*** | Lower 95%CI | Gornja granica 95%CI |
|          | 5.02                                 | 5.77      | 5.94           | 0.6*    | 0.4         | 0.9         | 1.27      | 1.95      | 1.46           | 1.3*    | 1.0         | 1.5                  |

\* Statistically significant trend; \*\* Joinpoint results are not shown for the subgroups aged <45 years for mortality in men and for the subgroups aged <55 years for mortality in women, due to fewer than 5 cases of bladder cancer occurring. \*\*\* for full period presented AAPC (Average Annual Percent Change); CI = Confidence Interval.

**Age-specific rates  
(per 100,000)****Figure 3.** Age-specific mortality rates from bladder cancer in both sexes together in Serbia, 1991-2024



**Figura 4.** Stope mortaliteta od raka beške po uzrastu kod muškaraca i žena u Srbiji, 1991-2024.

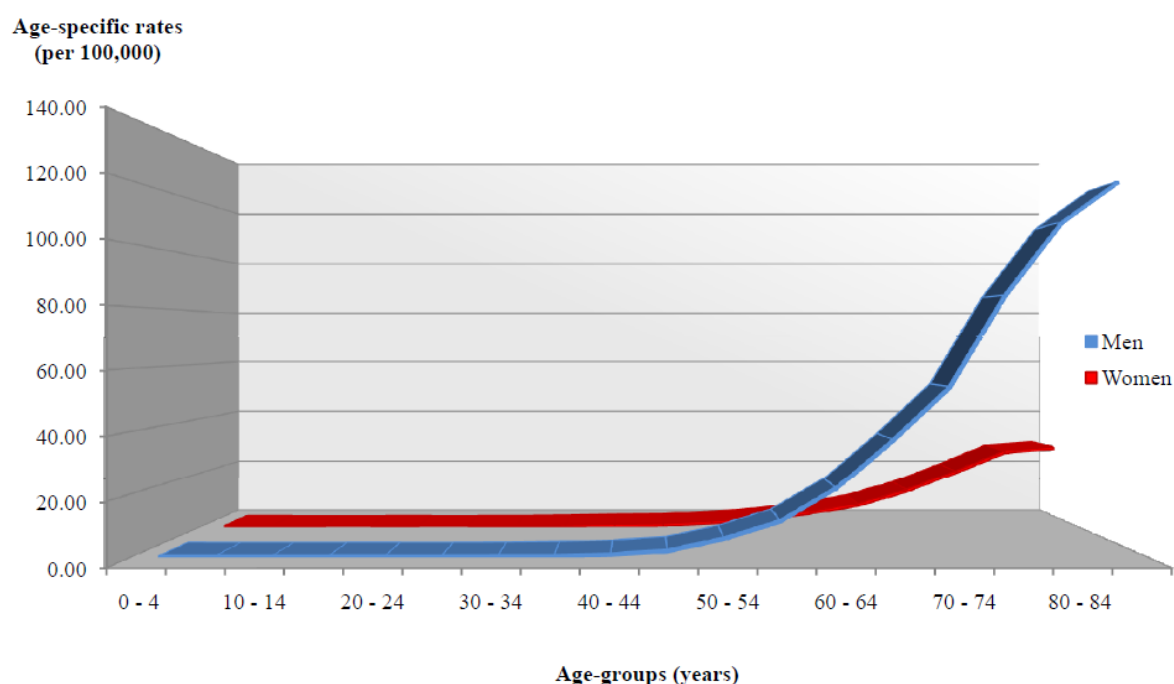
## Diskusija

Rezultati ovog istraživanja ukazuju na nepovoljne dugoročne obrasce u trendovima smrtnosti od raka beške u Srbiji, sa značajnim porastom trenda u oba pola tokom celog posmatranog perioda. Posebno zabrinjava porast trenda smrtnosti od raka beške kod žena srednje životne dobi (starosne grupe od 55 do 69 godina).

Iako su u mnogim razvijenim zemljama zabeleženi opadajući ili stabilni trendovi smrtnosti od raka beške (1), naša studija je pokazala da stope smrtnosti rastu kod oba pola. Slično tome, prethodne analize su pokazale da su stope incidencije raka beške standardizovane po starosti bile u porastu kod muškaraca u periodu 1999-2009, dok su stope smrtnosti standardizovane po starosti bile stabilne ili u porastu kod muškaraca (12). Mogući razlozi za tako nepovoljne trendove mogu biti razlike u prevalenciji faktora rizika. Podaci najnovijeg izveštaja SZO o globalnoj epidemiji korišćenja duvana ukazuju da je prevalencija svakodnevnog pušenja cigareta kod odraslih u Srbiji bila među najvišim zabeleženim na području Evrope 2023. godine i iznosila je 29% (13). Dobno standardizovana prevalencija pušenja duvana (svakodnevno ili povremeno) kod osoba starih 15 godina i više u padu je poslednjih decenija, sa 44,9% 2000. godine na procenjenih 39% 2025. godine, i projektovanih 38,1% 2030. godine (14). Međutim, tokom

ovog perioda samo je prevalencija pušenja kod muškaraca bila u padu (sa 50,8% 2000. godine na 38,9% 2025. godine), dok kod žena skoro da nije bilo promene (sa 39,1% 2000. godine na 39,2% 2025. godine). Naime, pušenje duvana je poznati faktor rizika za rak beške, ali istraživanja pokazuju da utiče i na ishod bolesti (15). U jednoj studiji, koja je obuhvatila pacijente iz Finske i Kanade, pokazano je da je kod pušača bilo lošije preživljavanje nakon lečenja raka beške, ali samo kod muškaraca, dok su žene imale lošije ishode bez obzira na njihov pušački status (16). Postoji pozitivna korelacija dobno standardizovanih stopa smrtnosti i kod muškaraca i kod žena sa stopom pušenja duvana (17).

Otkrivanje raka beške nekada može biti izazovno u okolnostima kada ova dijagnoza nije uzeta u obzir u trenutku kada se pacijenti jave sa simptomima. Najčešći simptom bolesti – hematurija često se javlja kod ponovljenih infekcija urinarnog trakta kod žena i stoga ponekad žene ređe traže lekarsku pomoć (18). Takođe, i kada potraže lekarsku pomoć, žene se ređe podvrgavaju dodatnoj dijagnostici i zbog toga dijagnoza kasni i više od 6 meseci u odnosu na muškarce (19). Ovo je naročito slučaj kod starijih žena koje imaju povećani rizik od bolesti (20). To može dovesti do odlaganja davanja uputa i kašnjenja dijagnoze kod žena, što za posledicu može imati lošije ishode lečenja. U Srbiji



**Figure 4.** Age-specific mortality rates from bladder cancer in men and women in Serbia, 1991-2024

bladder cancer in Serbia, with significant upward trends in both sexes throughout the whole studied period. Notably, the rise in trends of bladder cancer mortality among middle aged women (age groups 55 to 69 years) is particularly worrying.

Despite many developed countries recording a decreasing or stable trends in mortality from bladder cancer (1), our study showed that mortality rates have been increasing in both sexes. Similarly, previous analyses have shown that ASRs of incidence of bladder cancer have been increasing in males over the 1999-2009 period, while the ASRs of mortality were stable or increasing in males (12). Possible reasons for such unfavorable trends could include differences in prevalence of risk factors. Data from the latest WHO report on the global tobacco epidemic indicate that adult daily smoking prevalence in Serbia was among the highest recorded in the European region in 2023 - 29% (13). Age-standardized prevalence of tobacco smoking (current on a daily or non-daily basis) in persons aged 15 and older has been decreasing over the last decades, from 44.9% in 2000 to estimated 39% in 2025, with projected 38.1% in 2030 (14). However, over this period only smoking prevalence in men has experienced a decrease (from 50.8% in 2000 to 38.9% in 2025), while women experienced almost no change (from 39.1% in 2000 to 39.2% in 2025). Namely, tobacco

smoking is an established risk factor for bladder cancer, but research shows that it also has effects on disease outcomes (15). A study that included patients from Finland and Canada showed that smokers had poorer survival following treatment for bladder cancer but only in men, while women had poorer outcomes irrespective of their smoking status (16). There is a positive correlation between the age-standardized mortality rates for both men and women and the rate of tobacco use (17).

Detecting bladder cancer can sometimes be challenging in the circumstances where it is not a considered diagnosis once patients present with symptoms. The most common presenting symptom of the disease – hematuria, is often seen in recurrent infections of the urinary tract in women and as such they are sometimes less likely to seek doctor's care (18). Further on, even when they do seek care women are less likely to undergo additional diagnostics and experience more than a 6-month delay in diagnosis compared to men (19). This is especially the case in older women who have a higher risk for the disease (20). This can lead to delayed referrals and delays in diagnosis in women, which consequently leads to poorer treatment outcomes. So far, Serbia does not have a national guideline for the diagnosis and management of urinary bladder cancer. Establishing these guidelines would likely increase awareness in

do sada ne postoji nacionalni vodič dobre prakse za lečenje i dijagnostiku raka bešike. Takav vodič bi podigao svest lekara opšte prakse u primarnoj zdravstvenoj zaštiti, pomogao da se izdaju uputi na vreme za dodatnu dijagnostiku kod oba pola, i da se poboljša rano otkrivanje bolesti, pravovremeno lečenje i ishodi raka bešike. Podaci pokazuju da bi osnivanje citoskopskog nadzora (21), kao i uvođenje novih modaliteta lečenja (22) mogli da pomognu u smanjivanju smrtnosti od raka bešike.

Nalazi ovog istraživanja su pokazali da je povećanje stopa smrtnosti od raka bešike bilo izraženije kod žena. Prema velikoj meta-analizi skoro 28.000 pacijenata sa rakom bešike, lošiji ishodi preživljavanja bili su kod žena (HR=1,20, 95% CI 1,09-1,32) nakon lečenja metodom radikalne cistektomije u poređenju sa muškarcima (23). Prema istoj studiji, lošije preživljavanje kod žena bilo je čak izraženije u analizi podgrupe koja je bila usmerena na evropsku populaciju (HR=1,34, 95%CI 1,19-1,51). Drugi mogući razlog za lošije ishode mogla bi biti činjenica da se žene često jave na lečenje sa agresivnijim karakteristikama biologije tumora u odnosu na muškarce, kao što je pokazala jedna kohortna studija u Nemačkoj (24). Ove razlike se mogu javiti zbog razlika u ponašanju koje se tiče zdravlja, u traženju i pristupu zdravstvenoj zaštiti (25), kao i zbog hormonskih i sredinskih faktora. Prema najnovijim procenama, broj ljudi za koje se očekuje da će biti pokriveni univerzalnom zdravstvenom zaštitom i osnovnim uslugama opada tokom poslednjih godina u Srbiji (14). Postoje oprečni nalazi u dostupnoj literaturi po pitanju uloge estrogena. Dok s jedne strane, estrogen može da bude protektivni faktor, doprinoseći nižoj incidenciji bolesti, s druge strane, postoje dokazi koji pokazuju da on može doprineti lošijem ishodu tako što potpomaže rast tumora (20). Međutim, i dalje ostaje da se ove hipoteze razjasne.

Lošiji ishodi kod žena se takođe mogu pripisati razlikama koje se tiču patohistologije tumora. Naime, nacionalni podaci iz Ujedinjenog Kraljevstva (25) i Sjedinjenih Američkih Država (26) su pokazali da žene značajno češće imaju karcinome koji nisu urotelni (npr. karcinom skvamoznih ćelija), koji imaju lošiju prognozu. Kada se uzmu u obzir molekularni podtipovi, žene češće imaju mišićni invazivni rak bešike, što je agresivniji oblik bolesti, u odnosu na muškarce (27).

Rak mokraćne bešike se najčešće dijagnostikuje u starijoj populaciji, s obzirom da je sred-

nji uzrast u trenutku dijagnoze oko 70 godina (1,2). Ono što dodatno utiče na ishode lečenja raka bešike u starijoj populaciji jeste prisustvo pridruženih hroničnih bolesti i stanja. Starost doprinosi i verovatnoći nastanka bolesti kao i prognozi bolesti. Studije beleže razlike koje se tiču ishoda lečenja raka bešike, pri čemu neke pokazuju bolje preživljavanje kod mlađih osoba (28), dok neka istraživanja pokazuju suprotno kada su u pitanju prognoza i ishodi između mlađih i starijih pacijenata u zavisnosti od stadijuma bolesti (29). Starija dob u trenutku postavljanja dijagnoze je jak negativni prognostički faktor i za ukupno preživljavanje i za kancer-specifično preživljavanje (28). Četvrtina populacije u Srbiji je bila starija od 65 godina 2023. godine, sa projektovanim rastom u udelu najstarijih starosnih grupa i kod muškaraca i žena do 2050. godine (14). Jedna velika studija Baze podataka o nadzoru, epidemiologiji i krajnjim rezultatima u Americi pokazala je da su u poređenju sa osobama mlađim od 55 godina, oni koji su bili u starosnoj grupi od 55 do 64 godina imali značajno veći rizik od smrtnog ishoda (HR=1,43; 95% CI 1,36-1,50), kao i u starosnoj grupi 65-74 godina (HR=2,29; 95% CI 2,1-2,4) i kod osoba starih 75 godina i više (HR=5,36; 95% CI 5,13-5,59) u periodu 2004-2015 (28). Ova studija je takođe pokazala da je osim ukupnog, kancer-specifični rizik od smrtnog ishoda bio u porastu sa godinama kod pacijenata sa rakom bešike (28). Slični nalazi su zabeleženi za kancer-specifični mortalitet kod pacijenata starih 80 godina i više u poređenju sa onima koji su bili mlađi od 60 godina u slučajevima kancera niskog rizika (HR=7,04,  $p<0,001$ ) i kancera visokog rizika (HR=1,38,  $p<0,001$ ) (29). Stope smrtnosti od raka bešike su se povećale sa starošću i bile su skoro 300 puta veće u starosnoj grupi 80-84 godina u poređenju sa starosnom grupom 35-39 godina u Kini (30). Primećene razlike u ishodima prema uzrastu mogu se pripisati uznapredovanom stadijumu bolesti u trenutku dijagnoze koja je postavljena u kasnijoj dobi, razlikama u pristupu zdravstvenoj zaštiti, i različitim modalitetima lečenja koji nekad obuhvataju manje agresivnije modalitete za starije osobe zbog komorbiditeta i neotpornosti (20).

### Ograničenja studije

Ovo istraživanje podleže određenim ograničenjima. Primarno, uprkos proceni SZO o podacima o registraciji smrtnosti u Srbiji kao srednjeg kvaliteta-

primary care practitioners, help improve timely referrals to additional diagnostics for both sexes, and improve early detection, timely treatment and outcomes of bladder cancer. Evidence shows that establishing cystoscopic surveillance (21) as well as introducing new treatment modalities (22) can help in reducing mortality from bladder cancer.

The results of this research show that women experienced a more pronounced rise in mortality rates of bladder cancer. According to a large meta-analysis of almost 28,000 patients with bladder cancer, females exhibited poorer survival outcomes (HR=1.20, 95% CI 1.09-1.32) after treatment with radical cystectomy compared to males (23). According to the same study, the worse survival in females was even more expressed in the sub-group analysis that concentrated on European population (HR=1.34, 95% CI 1.19-1.51). Another possible reason for worse outcomes could be that females often present for treatment with more aggressive characteristics of tumor biology compared to males, as one cohort study in Germany showed (24). These differences could likely be due to differences in health-related behavior and seeking and access to healthcare (24), as well as due to hormonal and environmental factors. According to the latest estimates, the number of people expected to be covered with universal health coverage and essential services is decreasing over the last years in Serbia (14). There is discrepancy in findings in the available literature regarding the role of estrogen. While estrogen might act as a protective factor, thus contributing to lower incidence of the disease, there has also been evidence that it might contribute to a worse outcome by promoting tumor growth (20). However, these hypotheses still remain to be elucidated.

Worse outcome in women could also be attributed to differences in pathohistology of tumors. Namely, national data from the UK (25) and USA (26) showed that women substantially more often have non-urothelial carcinomas (i.e. more squamous-cell carcinoma) which have poorer prognosis. Looking at molecular subtypes, women more often have muscle invasive type of bladder cancer which is a more aggressive form of disease, compared to men (27).

Bladder cancer is most often diagnosed in the older population, median age in the moment of detection being around 70 years (1, 2). What

additionally affects the outcomes of bladder cancer treatment in the elderly is the presence of concomitant chronic diseases and conditions. Age contributes both to the likelihood of developing bladder cancer and the prognosis of the disease. Studies have noted discrepancies in bladder cancer outcomes, with some showing superior survival in younger persons (28), while some research showed the opposite for prognosis and outcomes between younger and older patients varying with disease stage (29). Older age at diagnosis is a strong negative prognostic factor for both overall survival as well as cancer-specific survival (28). In 2023, a quarter of Serbia's population was over the age of 65, with projected increase in the share of the oldest age groups by 2050 for both males and females (14). A large study of the Surveillance, Epidemiology, and End Results database in America showed that compared to persons under the age of 55, those aged 55-64 had a significantly elevated risk of death of HR=1.43 (95% CI 1.36-1.50), those aged 65-74 HR=2.29 (95% CI 2.1-2.4) and those aged 75 and over – HR=5.36 (95% CI 5.13-5.59) over the 2004-2015 period (28). This study also showed that cancer-specific mortality, as well as the overall, rose with advancing age in patients with bladder cancer (28). Similar findings were noted for cancer-specific mortality in cases 80 years old and above compared to those under the age of 60 in low-risk cancer (HR=7.04,  $p<0.001$ ) and high-risk cancer cases (HR=1.38,  $p<0.001$ ) (29). Bladder cancer mortality rates markedly rose with age, being almost 300-fold higher in the 80-84 compared to 35-39 age-group in China (30). The observed differences in outcomes by age could be attributed to more advanced stage at diagnosis which was made at later age, differences in access to healthcare, and different treatment choices that sometimes comprise less aggressive modalities for older persons due to comorbidities and frailty (20).

### Limitations of this study

This research is subject to certain limitations. Primarily, despite the WHO's judgment of Serbian mortality registration data as medium quality, the accuracy, reliability, completeness, coverage of death certificates for bladder cancer persists a concern. Second, there are no data on the representation of the certain histological types of bladder cancer. Third, in the applied jointpoint

ta, pitanje tačnosti, pouzdanosti, potpunosti i obuhvata potvrda smrti za rak bešike ostaje otvoreno. Drugo, ne postoje podaci o zastupljenosti određenih histoloških tipova raka bešike. Treće, u modelu primenjene joinpoint regresione analize u ovoj studiji, izostavljanje zapažanja za neke godine sa brojem smrtnih slučajeva od raka bešike koji je nula može da pomeri ili utiče na identifikaciju ili lokaciju promena u trendovima, što utiče na analizu (posebno kod žena). Stoga, neki od zapaženih trendova u smrtnosti od raka bešike zahtevaju dalju potvrdu kroz buduće analitičko-epidemiološke studije.

## Zaključak

Tokom prethodne tri decenije, značajan porast trendova smrtnosti od raka bešike je primećen u Srbiji. Stalan porast trendova smrtnosti od raka bešike je zabeležen tokom celog perioda kod oba pola. Posebno zabrinjava trend porasta smrtnosti kod žena srednje starosne dobi (u starosnoj grupi 55-69 godina). Dalja istraživanja raka bešike bi unapredila preventivne napore, naročito za grupe u najvećem riziku.

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## Konflikt interesa

Autor je izjavio da nema konflikta interesa.

## Reference

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2024. Available from: <https://gco.iarc.who.int/today>, accessed [27 September 2025].
2. Elmadani M, Klara S, Mustafa M, Kiptulon EK, Orsolya M. Global Burden of Rare Cancers: Insights from GLOBOCAN 2022 Estimates. *Cancers*. 2025;17(10):1721. doi: 10.3390/cancers17101721
3. Coglian VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst*. 2011;103(24):1827-1839. doi: 10.1093/jnci/djr483
4. Jubber I, Ong S, Bukavina L, Black PC, Compérat E, Kamat AM, et al. Epidemiology of Bladder Cancer in 2023: A Systematic Review of Risk Factors. *Eur Urol*. 2023;84(2):176-190. doi: 10.1016/j.eururo.2023.03.029
5. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. *Med Sci (Basel)*. 2020;8(1):15. doi: 10.3390/medsci8010015
6. Mossanen M, Nassar AH, Stokes SM, Martinez-Chanza N, Kumar V, Nuzzo PV, et al. Incidence of Germline Variants in Familial Bladder Cancer and Among Patients With Cancer Predisposition Syndromes. *Clin Genitourin Cancer*. 2022;20(6):568-574. doi: 10.1016/j.clgc.2022.08.009
7. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al, editors (2021). *Cancer Incidence in Five Continents*, Vol. XI. IARC Scientific Publication No. 166. Lyon: International Agency for Research on Cancer. Available from: <https://publications.iarc.fr/597>.
8. Zhang Y, Rumgay H, Li M, Yu H, Pan H, Ni J. The global landscape of bladder cancer incidence and mortality in 2020 and projections to 2040. *J Glob Health*. 2023;13:04109. doi: 10.7189/jogh.13.04109
9. Statistical Office of the Republic of Serbia. Demographic yearbook in the Republic of Serbia, 1991-2024. Belgrade: Statistical Office of the Republic of Serbia; 2025. Available from: <https://www.stat.gov.rs/en-us/>, accessed [27 September 2025].
10. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005;83:171-177. doi: org/10.1590/S0042-96862005000300009
11. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19:335-351. doi: 10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z
12. Mihajlović J, Pechlivanoglou P, Miladinov-Mikov M, Zivković S, Postma MJ. Cancer incidence and mortality in Serbia 1999-2009. *BMC Cancer*. 2013;13:18. doi: 10.1186/1471-2407-13-18
13. World Health Organization. WHO report on the global tobacco epidemic, 2025: warning about the dangers of tobacco. Geneva, Switzerland: World Health Organization; 2025. Available from: <https://www.who.int/publications/i/item/9789240112063>, accessed [27 September 2025].
14. World Health Organization. World Health Organization 2025 data. Serbia [Country overview]. Geneva, Switzerland: World Health Organization; 2025. Available from: <https://www.who.int/>, accessed [27 September 2025].
15. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. *Eur Urol*. 2016;70(3):458-466. doi: 10.1016/j.eururo.2015.06.042
16. Boström PJ, Alkhateeb S, Trottier G, Athanasopoulos PZ, Mirtti T, Kortekangas H, et al. Sex differences in bladder cancer outcomes among smokers with advanced bladder cancer. *BJU Int*. 2012;109(1):70-76. doi: 10.1111/j.1464-

regression analysis model in this study, omitting observations for some years with the number of bladder cancer deaths that is zero may shift or affect the identification or location of the changes in the trends, which affects the analysis (especially in women). Thus, some of the observed trends in bladder cancer mortality warrant further confirmation through future analytical-epidemiological studies.

## Conclusion

Over the past three decades, significantly increasing trends in mortality from bladder cancer have been observed in Serbia. A continuous upward trend in bladder cancer mortality was recorded throughout the entire period in both sexes. Trends of increased bladder cancer mortality among the middle-aged women (age group 55–69 years) are particularly concerning. Further research into bladder cancer could enhance preventive efforts, especially for groups at greatest risk.

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## Competing interests

The authors declared no competing interests.

## References

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2024. Available from: <https://gco.iarc.who.int/today>, accessed [27 September 2025].
2. Elmadani M, Klara S, Mustafa M, Kiptulon EK, Orsolya M. Global Burden of Rare Cancers: Insights from GLOBOCAN 2022 Estimates. *Cancers*. 2025;17(10):1721. doi: 10.3390/cancers17101721
3. Coglian VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst*. 2011;103(24):1827-1839. doi: 10.1093/jnci/djr483
4. Jubber I, Ong S, Bukavina L, Black PC, Compérat E, Kamat AM, et al. Epidemiology of Bladder Cancer in 2023: A Systematic Review of Risk Factors. *Eur Urol*. 2023;84(2):176-190. doi: 10.1016/j.eururo.2023.03.029
5. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. *Med Sci (Basel)*. 2020;8(1):15. doi: 10.3390/medsci8010015
6. Mossanen M, Nassar AH, Stokes SM, Martinez-Chanza N, Kumar V, Nuzzo PV, et al. Incidence of Germline Variants in Familial Bladder Cancer and Among Patients With Cancer Predisposition Syndromes. *Clin Genitourin Cancer*. 2022;20(6):568-574. doi: 10.1016/j.clgc.2022.08.009
7. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al, editors (2021). *Cancer Incidence in Five Continents*, Vol. XI. IARC Scientific Publication No. 166. Lyon: International Agency for Research on Cancer. Available from: <https://publications.iarc.fr/597>.
8. Zhang Y, Rumgay H, Li M, Yu H, Pan H, Ni J. The global landscape of bladder cancer incidence and mortality in 2020 and projections to 2040. *J Glob Health*. 2023;13:04109. doi: 10.7189/jogh.13.04109
9. Statistical Office of the Republic of Serbia. *Demographic yearbook in the Republic of Serbia, 1991-2024*. Belgrade: Statistical Office of the Republic of Serbia; 2025. Available from: <https://www.stat.gov.rs/en-us/>, accessed [27 September 2025].
10. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005;83:171-177. doi: org/10.1590/S0042-96862005000300009
11. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19:335-351. doi: 10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z
12. Mihajlović J, Pechlivanoglou P, Miladinov-Mikov M, Zivković S, Postma MJ. Cancer incidence and mortality in Serbia 1999-2009. *BMC Cancer*. 2013;13:18. doi: 10.1186/1471-2407-13-18
13. World Health Organization. WHO report on the global tobacco epidemic, 2025: warning about the dangers of tobacco. Geneva, Switzerland: World Health Organization; 2025. Available from: <https://www.who.int/publications/i/item/9789240112063>, accessed [27 September 2025].
14. World Health Organization. World Health Organization 2025 data. Serbia [Country overview]. Geneva, Switzerland: World Health Organization; 2025. Available from: <https://www.who.int/>, accessed [27 September 2025].
15. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. *Eur Urol*. 2016;70(3):458-466. doi: 10.1016/j.eururo.2015.06.042
16. Boström PJ, Alkhateeb S, Trotter G, Athanasopoulos PZ, Mirtti T, Kortekangas H, et al. Sex differences in bladder cancer outcomes among smokers with advanced bladder cancer. *BJU Int*. 2012;109(1):70-76. doi: 10.1111/j.1464-410X.2011.10371.x
17. Teoh JY, Huang J, Ko WY, Lok V, Choi P, Ng CF, et al. Global Trends of Bladder Cancer Incidence and Mortality, and Their Associations with Tobacco Use and Gross Domestic

- 410X.2011.10371.x
17. Teoh JY, Huang J, Ko WY, Lok V, Choi P, Ng CF, et al. Global Trends of Bladder Cancer Incidence and Mortality, and Their Associations with Tobacco Use and Gross Domestic Product Per Capita. *Eur Urol*. 2020;78(6):893-906. doi: 10.1016/j.eururo.2020.09.006
  18. Burge F, Kockelbergh R. Closing the Gender Gap: Can We Improve Bladder Cancer Survival in Women? - A Systematic Review of Diagnosis, Treatment and Outcomes. *Urol Int*. 2016;97(4):373-379. doi: 10.1159/000449256
  19. Cohn JA, Vekhter B, Lyttle C, Steinberg GD, Large MC. Sex disparities in diagnosis of bladder cancer after initial presentation with hematuria: a nationwide claims-based investigation. *Cancer*. 2014;120(4):555-561. doi: 10.1002/cncr.28416
  20. Toren P, Wilkins A, Patel K, Burley A, Gris T, Kockelbergh R, et al. The sex gap in bladder cancer survival - a missing link in bladder cancer care? *Nat Rev Urol*. 2024;21(3):181-192. doi: 10.1038/s41585-023-00806-2
  21. Zlatev DV, Altobelli E, Liao JC. Advances in imaging technologies in the evaluation of high-grade bladder cancer. *Urol Clin North Am*. 2015;42(2):147-157, vii. doi: 10.1016/j.ucl.2015.01.001
  22. Godlewski D, Czech S, Szpara J, Bartusik-Aebischer D, Aebischer D. A Narrative Review of Current Advances and Future Changes Regarding Bladder Cancer Treatment. *Uro*. 2025;5(2):11. doi: 10.3390/uro5020011
  23. Liu S, Yang T, Na R, Hu M, Zhang L, Fu Y, et al. The impact of female gender on bladder cancer-specific death risk after radical cystectomy: a meta-analysis of 27,912 patients. *Int Urol Nephrol*. 2015;47(6):951-958. doi: 10.1007/s11255-015-0980-6
  24. Soave A, Dahlem R, Hansen J, Weisbach L, Minner S, Engel O, et al. Gender-specific outcomes of bladder cancer patients: a stage-specific analysis in a contemporary, homogenous radical cystectomy cohort. *Eur J Surg Oncol*. 2015;41(3):368-377. doi: 10.1016/j.ejso.2014.03.003
  25. Ball KS, Hounsborne L, Verne J, Kockelbergh R. Non-transitional cell carcinoma only partly explains adverse survival outcomes in females with T1-T4 bladder cancer: A summary of UK epidemiological data. *Journal of Clinical Urology*. 2017;10(1\_suppl):14-18. doi:10.1177/2051415816679529
  26. Krimphove MJ, Szymaniak J, Marchese M, Tully KH, D'Andrea D, Mossanen M, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. *Eur Urol Focus*. 2021;7(1):124-131. doi: 10.1016/j.euf.2019.06.001
  27. de Jong JJ, Boormans JL, van Rhijn BWG, Seiler R, Boorjian SA, Konety B, et al. Distribution of Molecular Subtypes in Muscle-invasive Bladder Cancer Is Driven by Sex-specific Differences. *Eur Urol Oncol*. 2020;3(4):420-423. doi: 10.1016/j.euo.2020.02.010
  28. Lin W, Pan X, Zhang C, Ye B, Song J. Impact of Age at Diagnosis of Bladder Cancer on Survival: A Surveillance, Epidemiology, and End Results-Based Study 2004-2015. *Cancer Control*. 2023;30:10732748231152322. doi: 10.1177/10732748231152322
  29. Luzzago S, Knipper S, Palumbo C, Rosiello G, Pecoraro A, Deuker M, et al. Effect of Age on Cancer-specific Mortality in Patients With Urothelial Carcinoma of the Urinary Bladder: A Population-based Competing-risks Analysis Across Disease Stages. *Am J Clin Oncol*. 2020;43(12):880-888. doi: 10.1097/COC.0000000000000766
  30. Yang Y, Cheng Z, Jia X, Shi N, Xia Z, Zhang W, et al. Mortality trends of bladder cancer in China from 1991 to 2015: an age-period-cohort analysis. *Cancer Manag Res*. 2019;11:3043-3051. doi: 10.2147/CMAR.S189220



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- Product Per Capita. *Eur Urol.* 2020;78(6):893-906. doi: 10.1016/j.eururo.2020.09.006
18. Burge F, Kockelbergh R. Closing the Gender Gap: Can We Improve Bladder Cancer Survival in Women? - A Systematic Review of Diagnosis, Treatment and Outcomes. *Urol Int.* 2016;97(4):373-379. doi: 10.1159/000449256
  19. Cohn JA, Vekhter B, Lyttle C, Steinberg GD, Large MC. Sex disparities in diagnosis of bladder cancer after initial presentation with hematuria: a nationwide claims-based investigation. *Cancer.* 2014;120(4):555-561. doi: 10.1002/cncr.28416
  20. Toren P, Wilkins A, Patel K, Burley A, Gris T, Kockelbergh R, et al. The sex gap in bladder cancer survival - a missing link in bladder cancer care? *Nat Rev Urol.* 2024;21(3):181-192. doi: 10.1038/s41585-023-00806-2
  21. Zlatev DV, Altobelli E, Liao JC. Advances in imaging technologies in the evaluation of high-grade bladder cancer. *Urol Clin North Am.* 2015;42(2):147-157, vii. doi: 10.1016/j.ucl.2015.01.001
  22. Godlewski D, Czech S, Szpara J, Bartusik-Aebischer D, Aebischer D. A Narrative Review of Current Advances and Future Changes Regarding Bladder Cancer Treatment. *Uro.* 2025;5(2):11. doi: 10.3390/uro5020011
  23. Liu S, Yang T, Na R, Hu M, Zhang L, Fu Y, et al. The impact of female gender on bladder cancer-specific death risk after radical cystectomy: a meta-analysis of 27,912 patients. *Int Urol Nephrol.* 2015;47(6):951-958. doi: 10.1007/s11255-015-0980-6
  24. Soave A, Dahlem R, Hansen J, Weisbach L, Minner S, Engel O, et al. Gender-specific outcomes of bladder cancer patients: a stage-specific analysis in a contemporary, homogenous radical cystectomy cohort. *Eur J Surg Oncol.* 2015;41(3):368-377. doi: 10.1016/j.ejso.2014.03.003
  25. Ball KS, Hounsoms L, Verne J, Kockelbergh R. Non-transitional cell carcinoma only partly explains adverse survival outcomes in females with T1–T4 bladder cancer: A summary of UK epidemiological data. *Journal of Clinical Urology.* 2017;10(1\_suppl):14-18. doi:10.1177/2051415816679529
  26. Krimphove MJ, Szymaniak J, Marchese M, Tully KH, D'Andrea D, Mossanen M, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. *Eur Urol Focus.* 2021;7(1):124-131. doi: 10.1016/j.euf.2019.06.001
  27. de Jong JJ, Boormans JL, van Rhijn BWG, Seiler R, Boorjian SA, Konety B, et al. Distribution of Molecular Subtypes in Muscle-invasive Bladder Cancer Is Driven by Sex-specific Differences. *Eur Urol Oncol.* 2020;3(4):420-423. doi: 10.1016/j.euo.2020.02.010
  28. Lin W, Pan X, Zhang C, Ye B, Song J. Impact of Age at Diagnosis of Bladder Cancer on Survival: A Surveillance, Epidemiology, and End Results-Based Study 2004-2015. *Cancer Control.* 2023;30:10732748231152322. doi: 10.1177/10732748231152322
  29. Luzzago S, Knipper S, Palumbo C, Rosiello G, Pecoraro A, Deuker M, et al. Effect of Age on Cancer-specific Mortality in Patients With Urothelial Carcinoma of the Urinary Bladder: A Population-based Competing-risks Analysis Across Disease Stages. *Am J Clin Oncol.* 2020;43(12):880-888. doi: 10.1097/COC.0000000000000766
  30. Yang Y, Cheng Z, Jia X, Shi N, Xia Z, Zhang W, et al. Mortality trends of bladder cancer in China from 1991 to 2015: an age-period-cohort analysis. *Cancer Manag Res.* 2019;11:3043-3051. doi: 10.2147/CMAR.S189220



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