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Original Article

Bladder Cancer Mortality Trend in Montenegro: 1990-2021

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Abstract

Background: Bladder cancer accounts for more than 200,000 deaths annually on a global level, with an age-standardized mortality rate of 2.9 per 100,000 individuals. Despite declining global rates, it remains a substantial public health burden. We aimed to analyze the mortality trend of bladder cancer in Montenegro and identify the measures taken to combat this tumor.

Methods: Bladder cancer mortality data in Montenegro from 1990 to 2021 were collected. Mortality rates were age-standardized to the World Standard Population. The joinpoint, linear and Poisson regressions were used to assess bladder cancer mortality trend.

Results: There was a consistent increase in mortality rates due to bladder cancer, with statistical significance for both the overall population and specifically for males, with an average annual percent change (AAPC) of 1.5% (95% CI: 1.5 (0.5-2.9)) and 1.6% (AAPC (95% CI): 1.6 (0.4-3.3)) respectively. Additionally, there was a notable annual increase in the number of bladder cancer cases: average annual increase was 3.4% for the overall population, 3.5% in male and 2.9% in female, with statistical parameters (AAPC (95% CI), *P*-value) for join point regression: 3.4 (2.4-4.8), <0.001; 3.5 (2.3-5.1), 0.003; and 2.9 (1.2-5.1), 0.004, respectively. The majority of bladder cancer deaths occurred in the age groups of 65-74 (35.8%), 75-84 (33.6%), and 55-64 (16.8%).

Conclusion: The ongoing increase in bladder cancer mortality in Montenegro, particularly among men and elderly should encourage policymakers to take action to reverse this unfavorable trend.

Keywords: Bladder cancer; Mortality; Trend; Montenegro

Introduction

Bladder cancer accounted for 229,000 deaths and 4.39 million DALYs in 2019 (1). It is categorized as the 9th and 19th leading cause of cancer-related deaths in males and females worldwide, respectively (2,3) Notably, half of these deaths occur in regions with lower developmental indices, while higher mortality rates are observed in countries with high Human Development Index (HDI). The highest mortality rates are found in Eastern Asia, North America, and Western Europe, especially in the United States, China, Japan, and Germany (4).

Smoking (1,5,6) and elevated fasting plasma glucose (FPG) (1,7,8) have been identified as risk factors for bladder cancer, with tobacco use being regarded as one of the most significant. A meta-analysis of 83 studies revealed that the risk of bladder cancer is 3.5 times higher in current smokers and twice as high in former smokers compared to those who have never smoked (5). Additionally, diabetes or high FPG is associated with a 35% increased risk for bladder cancer (8). Furthermore, substantial evidence links environmental carcinogens to the etiology of bladder cancer (9).

Significant global advancements have been made in screening, diagnosis (10), and treatment (11) of bladder cancer. However, the relatively low incidence and mortality rate of this cancer in the general population, combined with the prevalence of non-fatal cancer cases, pose challenges in developing efficient screening methodologies (1). Although there is no standard screening test for bladder cancer in individuals of average risk it is recommended that screening be conducted in individuals with a history of the tumor or those in high-risk populations using tests for hematuria, urinary cytology, urinary tumor marker tests, and additional cystoscopy examination (12-16).

In Montenegro, screening for bladder cancer is not routinely conducted; however, a diagnostic protocol for hematuria is in place, adhering to the European Association of Urology guidelines. Comprehensive diagnostics and treatment of both localized and metastatic bladder cancer follow current European standards. Urinary biomarkers are not utilized in Montenegro; therefore, diagnostics for hematuria primarily rely on cystoscopy and cytology, complemented by CT urography when necessary. Noteworthy is the use of the IMAGE1 S™ system in detecting superficial carcinomas, especially carcinoma in situ (CIS), during cystoscopy, and the use of bipolar transurethral resection and enucleation of bladder tumors, which allows for better sampling of tumor changes from the bladder (15). In Montenegro, a detailed determination of pathological parameters is also conducted. Their determination is crucial, as these tumors can behave very differently depending on type, grade, and stage. Identifying fewer common subtypes like nested, micropapillary, lymphoepithelioma-like, sarcomatoid, plasmacytoid, and giant cell urothelial carcinoma is also crucial (16). Numerous immunohistochemical markers such as p40, GATA 3, and uroplakin are used for more refined diagnostics (17). The assessment of PD-L1 status is particularly important as a predictive factor (18).

According to the latest global research (1), bladder cancer experienced a downward trend in age-standardized rates from 1990–2019. However, it remains a substantial burden on public health, with an age-standardized mortality rate of 2.9 per 100,000 individuals and an age-standardized DALY rate of 54.2 per 100.000 recorded in 2019. Bladder cancer is more common in older people. With the aging global population, cancer-related deaths have increased dramatically in these populations (1).

There is no data on the most burdened population by bladder cancer mortality and its trend in Montenegro. Assessing patterns and epidemiological trends is crucial for the development of precise prevention strategies, enabling public health policymakers to make evidence-based decisions and manage costs more effectively. Analyzing trends by gender and age helps identify burdened populations and allocate resources to improve diagnosis and treatment, providing the basis for long-term cancer control options (1).

The objective of this study was to analyze the mortality trend of bladder cancer overall, by sex and age, in Montenegro from 1990-2021 using regression techniques and to identify the measures taken in Montenegro to combat this tumor.

Materials and Methods

Data sources

The data concerning bladder cancer mortality in Montenegro from 1990 to 2021 was collected. Bladder cancer was identified using the International Classification of Diseases code 188 from the 9th edition and code C67 from the 10th edition

(19). The primary data source consists of death certificates filled out by physicians who determine the time and cause of death. The data sources until 2009 were from the State Statistical Office (unpublished data until 1999, and for the period 1999-2009 published in the statistical yearbooks of the Institute for Public Health of Montenegro) (20). After 2009, the data source on causes of death is the Institute for Public Health (21). Population data were sourced from the Statistical Office of Montenegro (22). Mortality rates were age-standardized to the World Standard Population (23) for estimating both the overall and gender-specific trends.

Statistical Analyses

We used three methods for trend analyses: Joinpoint, linear, and Poisson regression. For all regression techniques used, the dependent variable was the year, while the independent variable was the mortality rate or death cases. We assessed the trend of bladder cancer mortality at the overall level and by sex and age groups. Joinpoint regression analyses were executed using the Joinpoint Software, ver. 5.0. 2-May, 2023 from the Surveillance Research Program of the US National Cancer Institute (24), while linear and Poisson regressions were executed SPSS 26 (IBM Corp., Armonk, NY, USA). For trend description, we used the Estimated Annual Percentage Change (EAPC) and the Average Annual Percentage Change (AAPC) (24) in joinpoint regression and β regression coefficient in linear and Poisson regression and its 95% confidence interval (CI). As the Joinpoint programme requires certain settings, we used the following: the grid-search method was chosen for the analysis; the minimum number of observations for points from the end of the series to the first joinpoint was established as 3 and between two joinpoints as 4; the number of joinpoints was set between 0 and 4. The permutation test facilitated the selection of the most fitting joinpoint model with an overall significance level of 0.05. Gender differences were assessed using the parallelism test (25).

Results

Between 1990 and 2021 in Montenegro, 847 individuals died from bladder cancer, comprising 74.38% males and 25.62% females (Table 1), making it the 9th most common cause of cancer-related deaths overall (9th in women, 8th in men). The average annual death cases were 26.5 (19.7 males, 6.8 females), with an age-standardized rate of 2.4 (4.1 in males, 1.1 in females). Notably, the mortality rates in males were 3.7 times higher than in females (Table 1).

Joinpoint regression analysis did not identify any points in time where there was a sudden change in the trend for rates (Fig. 1). The data demonstrate a consistent increase in mortality rates due to bladder cancer, with statistical significance (P<0.05) for both the overall population and specifically for males, with an average annual percent change (AAPC) of 1.5% (95% CI: 1.5 (0.5-2.9)) and 1.6% (AAPC (95% CI): 1.6 (0.4-3.3)), respectively (Table 1, Fig. 1).

Due to small numbers or near-zero values of mortality rate years, joinpoint regression could not be conducted for age groups. Results from linear regression indicate an increase in rates for both the general population and when disaggregated by gender, with a pronounced increase observed in older age groups (Table 1).

In addition to the rising mortality rates, there was also a notable annual increase in the number of bladder cancer cases in Montenegro (Fig. 2). The average annual increase was 3.4% for the overall population, with a 3.5% rise observed in male and 2.9% in female, with statistical parameters (AAPC (95% CI), *P*-value) for joinpoint regression being 3.4 (2.4-4.8), <0.001; 3.5 (2.3-5.1), 0.003; and 2.9 (1.2-5.1), 0.004, respectively.

Table 1: Descriptive statistics for bladder cancer deaths cases and mortality rate in Montenegro and results of regression analyses for period 1990-2021

C67	Joinpoint regression for death cases	Joinpoint regression for mortality rate	Linear regression for mortality rate	Poisson regression for death cases	Mortality rate	Death cases	Overall death cases
	AAPC (95%CI)		β (95%CI)	β (95%CI)	Mean ±sd		
Male	3.5* (2.3-5.1)	1.6*(0.4-3.3)	0.079* (0.028-0.129)	0.037* (0.028-0.045)	4.1±1.5	19.7±8.6	630
15-24							1
25-34							0
35-44							4
45-54					1.9±2.4	0.8±0.9	24
55-64	2.1* (0.2-4.5)		0.108(-0.132-0.347)	0.098* (0.056-0.253)	10.5±6.1	3.4±2.0	110
65-74	9.5* (1.5-18.2)		0.759* (0.266-1.252)	0.356* (0.021-0.77)	31.4±14.3	6.9±3.3	221
75-84	4.2*(0.2-8.3)		1499* (0.386-2.612)	0.273* (0.062-0.483)	67.7±31.3	6.5±3.9	209
85+	6.7*(4.2-9.4)		3.790* (0.829-6.752)	0.073* (0.006-0.140)	89.2±82.5	1.9±1.9	61
Female	2.9*(1.2-5.1)	1.2 (-0.5-3.3)	0.016 (-0.004-0.036)	0.034* (0.019-0.049)	1.1±0.5	6.8±3.6	217
15-24							0
25-34							0
35-44							2
45-54							7
55-64	1.8 (-0.7-4.4)		0.074 (-0.018-0.167)	0.035 (-0.012-0.083)	2.7±2.4	1.0±0.8	32
65-74	0.5 (-2-3)		-0.052 (-0.258-0.153)	-0.023 (-0.089-0.136)	9.5±5.2	2.6±1.5	82
75-84	5.4*(3.1-7.7)		0.514* (0.152-0.876)	0.102* (0.017-0.187)	16.2±10.3	2.4±1.7	76
85+	6.4*(4.2-8.6)		1.167* (0.244-2.090)	0.152* (0.069-0.240)	17.4±25.7	0.6±0.8	18
All	3.4*(2.4-4.8)	1.5* (0.5-2.9)	0.044* (0.018-0.069)	0.036* (0.028-0.043)	2.4±0.8	26.5±10.7	847
15-24							1
25-34							0
35-44							6
45-54	(-0.4) (-3.4-2.7)		-0.018 (-0.067-0.031)	-0.004 (-0.054-0.047)	1.3±1.2	1.0±1.0	31
55-64	2.6*(0.5-4.8)		0.096 (-0.025-0.218)	0.136* (0.051-0.322)	6.4±3.2	4.4±2.2	142
65-74	6.0*(1.6-10.6)		0.310* (0.072-0.548)	0.324* (0.101-0.750)	19.2±6.6	9.5±3.8	303
75-84	5.4*(4.0-6.9)		0.979* (0.567-1.390)	0.371* (0.094-0.649)	36.6±13.8	8.9±4.7	285
85+	8.1* (5.8-10.6)		2.189* (0.879-3.500)	0.109* (0.028-0.191)	44.8±38.8	2.5±2.4	79

AAPC-Average annual percentage change; CI-Confidence interval; β-regression coefficient; *indicated that AAPC and β are statistically significantly different from zero at a *P* less than 0.05

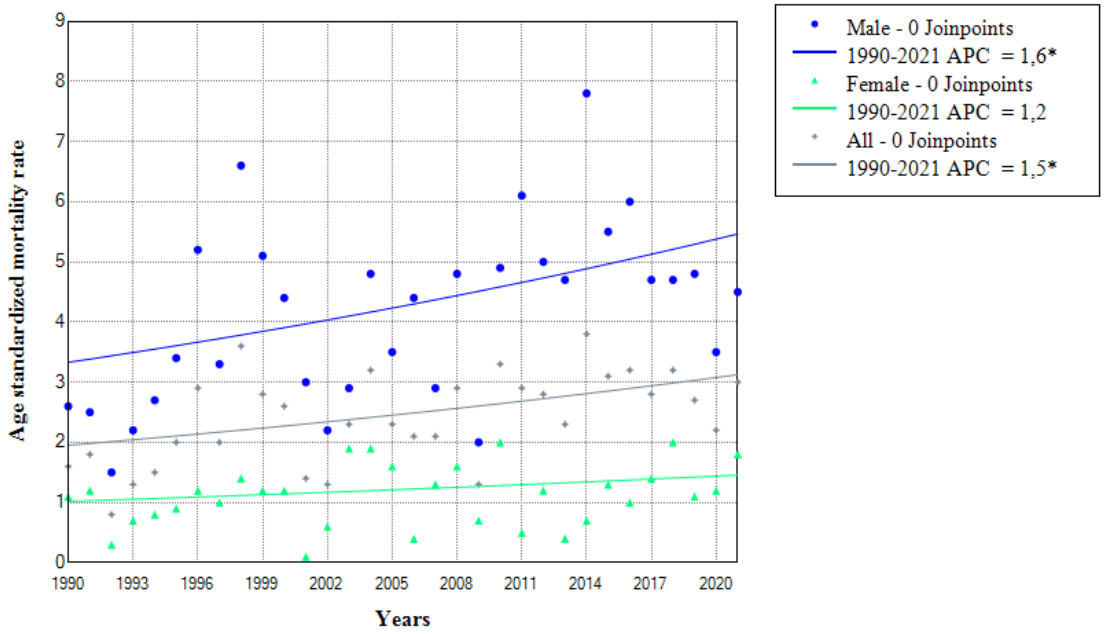

Fig. 1: Joinpoint regression analysis of bladder cancer mortality rate in Montenegro from 1990 to 2021. APC-Annual Percentage Change. *indicated that APC is statistically significantly different from zero at a *P* value less than 0.05

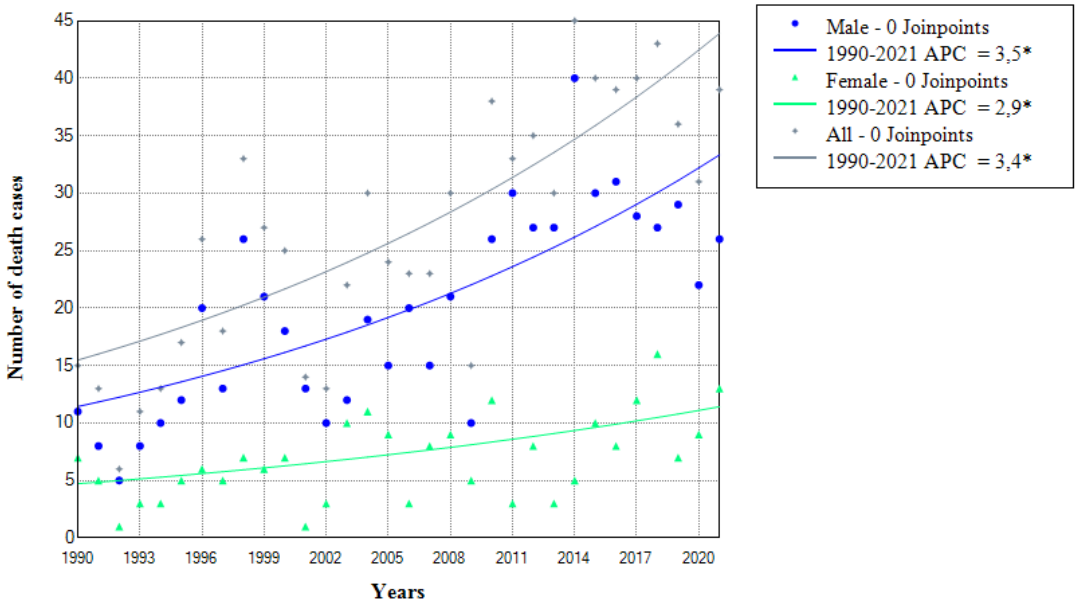

Fig. 2: Joinpoint regression analysis of bladder cancer death cases in Montenegro from 1990 to 2021. APC-Annual Percentage Change. *indicated that APC is statistically significantly different from zero at a *P* less than 0.05

The increase in mortality rates and the number of death cases both overall and by gender are a consequence of increased rates and cases in the older age groups (Table 1). The majority of bladder cancer deaths occurred in the age groups of 65-74 (35.8%), 75-84 (33.6%), and 55-64 (16.8%) (Fig. 3), with the tables also documenting the youngest age at which deaths occurred (Table 1).

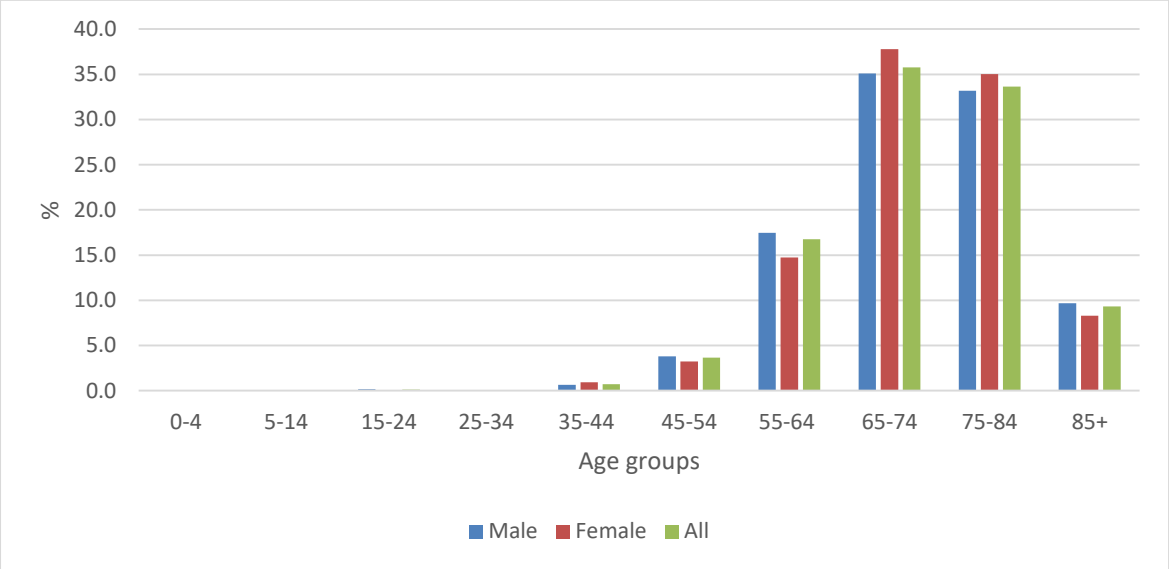

Fig. 3: Distribution of bladder cancer mortality by age groups in Montenegro, 1990-2021

Discussion

This study presents Montenegro's bladder cancer mortality trend from 1990 to 2021. During this period, Montenegro experienced an approximate annual increase of 3.4% in the number of deaths (3.5% for males, 2.9% for females) and mortality rates (1.5% overall, with a 1.6% increase for males and a statistically insignificant increase for females). This trend does not align with the global trend (1,26), where there was a 15.7% reduction in age-standardized mortality over a comparable timeframe (1990-2019), while the number of deaths from bladder cancer increased from 122,000 in 1990 to 229,000 in 2019. The global burden of bladder cancer saw substantial disparities between 1990 and 2019. Western Europe and Eastern Asia accounted for almost half of all bladder cancer deaths. In 2019, the highest age-standardized mortality rates per 100,000 were in Central Europe (5.3), Western Europe (4.8), and North Africa and the Middle East (4.1), with Central Latin America (1.5), the Andean region of Latin America (1.6), and Southeast Asia (1.8) having the lowest rates (1).

Montenegro's average age-standardized rate of 2.4 is about four times lower than the highest rates globally recorded in 2019 in Lebanon (10.4), Monaco (9.4), and more than twice as high as the lowest rates in Palau (1), Albania (1.1) (1).

While a global downward trend in bladder cancer mortality rates has been observed, certain regions and countries have experienced increases (1). For example, mortality rates significantly increased in Central Asia (17.9%), with the largest national increases in Cabo Verde (190.3%), the Northern Mariana Islands (81.8%), and Uzbekistan (64.7%). Conversely, the most significant decreases were recorded in Singapore (−44.9%), Thailand (−42.1%) (1). China has seen a decline in mortality rates for both men (-1.09%) and women (-2.48%) across all age groups over the past few decades (27).

In Montenegro, bladder cancer mortality rates are 3.7 times higher in men. In 2019, global age-

standardized mortality rates were higher among men than women in all age groups (1). Mortality in Montenegro increases with age, consistent with global (1) and country-specific analyses (27,28).

The highest proportion of deaths in Montenegro is in the age groups 65-74 (35.8%), 75-84 (33.6%), and 55-64 (16.8%), with rates peaking in the 85+ age group, while globally, the number of deaths was highest in the age group of 80 to 84 yr in both men and women, and the rates in the 95+ group in both sexes (1). In younger patients (under 40), urothelial bladder cancer tends to be low-grade and thus usually exhibiting slow-growth pattern. Additionally, higher mortality rates in older individuals may be attributed to the less aggressive treatment approaches and the avoidance of radical therapies in this population (29,30).

The increasing trend in bladder cancer mortality in Montenegro cannot be fully explained due to the lack of available data on risk factors contributing to mortality. The disparities in global trends of bladder cancer mortality rates are largely attributed to varying smoking prevalence (1,31). Although Montenegro has somewhat established a tobacco control system (32), partly contributing to the reduction of smoking-associated cancer mortality (33), the possible reason for unfavorable mortality trend could be an increase in smoking prevalence in older age groups (45-54 and 55-64) (34). For instance, global research on risk factors for this cancer suggests the highest contribution of smoking in the age group 55-59 yr with an amount of 43.4% (1).

Our results indicated that the burden of mortality from this cancer is higher in male population, potentially linked to a higher prevalence of smoking among men in Montenegro. The prevalence of current smoking is 36.2% among adult men and 34.5% among women. Slightly more men than women are ex-smokers (17.5% vs. 16.6%). Likewise, slightly more women than men refrained from smoking during their lifetime (48.9% of women vs. 46.3% of men) (34). Globally in 2019, 36.8% of bladder cancer were attributed to smoking, more in men than in women (43.7% via. 15,2%) (1).

Diabetes or high fasting plasma glucose has also been linked to an increased risk of bladder cancer, with a meta-analysis reporting a 35% higher risk (8). High FPG increased by 37.7% globally from 1990 to 2017. Approximately 9.1% of bladder cancer can be attributed to elevated FPG (1). According to 2015 data from the diabetes registry, 12.9% of adults in Montenegro have diabetes. The International Diabetes Federation estimated that in Montenegro, 43.4% of diabetes in the affected population was undiagnosed, equating to 5.6% of undetected cases of adults with diabetes (35).

Further investigation is needed to determine the potential impact of these factors on Montenegro's bladder cancer mortality. Countries reporting an increase in mortality, such as Lithuania (28,36), which is among the highest in Europe for male mortality, attribute the unfavorable trend to insufficient implementation of cancer prevention measures (31).

Montenegro has recently enhanced its focus on cancer surveillance (37-39), yet there remains an absence of specific policies or strategies dedicated to addressing bladder cancer. Globally, there have been significant advancements in the screening, diagnosis (10), and treatment (11) of bladder cancer, with continuous efforts being made to develop new methods for early detection (40,41). One of the key challenges in implementing adequate bladder cancer screening is the lack of level one evidence from randomized studies demonstrating a clear benefit in terms of survival rates or tumor downstaging. Furthermore, no prospective studies show a clear diagnostic benefit of urinary biomarkers in screening. Most newly diagnosed bladder tumors are low-grade and would not be detectable by screening (13).

In Montenegro, bladder cancer detection is based on incidental findings of hematuria in urine or macroscopic hematuria. The diagnostic protocol includes ultrasonography of the urotract, CT urography, and cystoscopy with urinary cytology - the gold standard in bladder tumor diagnosis (14). The role of urinary biomarkers has gained importance due to the low sensitivity of urinary cytology and the desire to shift bladder cancer

diagnostics from invasive (cystoscopy) to non-invasive methods (urinary biomarkers). Biomarkers tested in multicentric studies and widely used in many European and global centers include UroVysion™ (FISH), Nuclear Matrix Protein (NMP)22®, and Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT) (15). These biomarkers have been shown to determine which patients have an increased likelihood of recurrent disease and possible progression (42). Urinary biomarkers are not currently used in Montenegro, but a study on the predictive efficacy of tissue biomarkers in invasive bladder carcinoma is underway, which could lead to earlier detection of high-grade tumors and more effective treatment, ultimately aiming to reduce mortality from this disease.

Countries reporting a decrease in mortality, such as China, attribute the decline to national guidelines improving treatment for patients with this cancer (43), subsequently leading to reduced mortality over recent decade (27).

Strengths, weaknesses, and limitations

This analysis is the first study reporting on bladder cancer mortality in Montenegro, providing information on the trend of mortality from this tumor by total population, gender and age groups, which can serve as the basis for decision-makers in developing future control strategies for vulnerable groups.

We used the best available national data on causes of death, collected annually from death certificates. However, it has several shortcomings. The quality of mortality data in Montenegro has not been studied, raising concerns about the reliability and accuracy of the data, which depends on retrospective data collection. Errors in death certification, medical diagnosis accuracy, and cause of death coding can affect data quality. Different doctors were responsible for coding causes of death before and after 2009, using two classification systems, ICD 9 and ICD 10. Additionally, underreporting of mortality due to underdeveloped infrastructure and tumor reporting mechanisms, common in developing countries, could result in incomplete data.

Conclusion

The increasing bladder cancer mortality in Montenegro underscores the need for in-depth research to uncover the contributing factors. Developing and implementing comprehensive strategies is essential, including establishment of national guidelines focused on the early detection, monitoring, and treatment of individuals diagnosed with bladder cancer. As the highest mortality from this cancer is observed in the older population, these strategies and guidelines should particularly address their needs and challenges. A targeted approach is essential for improving outcomes and potentially reversing the current trend of rising mortality rates associated with bladder cancer in Montenegro.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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