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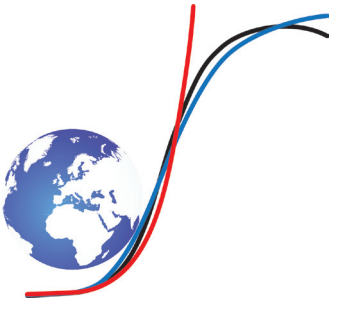

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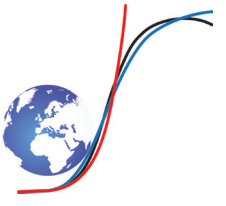

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ESTIMATING ALL-CAUSE EXCESS MORTALITY DURING COVID-19 PANDEMIC IN SERBIA, 2020-2022

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Abstract: Early reports indicated that Serbia was among the best-performing European countries in dealing with COVID-19 health issues based on relatively small COVID-19 mortality. This success can be partly attributed to the government's rapid response and implementation of restrictive measures to curb the spread of the virus. It can also be noted that the high level of solidarity among citizens contributed to the effective containment of the pandemic, with many adhering to experts' prescribed measures and recommendations. Serbia has become an example of good practice in the fight against COVID-19, resulting in positive assessments by international organizations and experts. However, Mortality from the virus alone is insufficient to describe the pandemic's health effects, unlike excess mortality from all causes. This paper aims to estimate excess mortality in Serbia during 2020-2022 and to compare estimated mortality with the reported COVID-19 deaths. Excess was calculated using a negative binomial regression with historical 2015-2019 data. Estimation provides a *P-score* as a percentage difference between the reported and expected number of deaths. Mortality excess in Serbia was 15,437 in 2020 and 35,836 in 2021, with 224 and 524 per 100,000 population rates and *P-scores* of 15% and 36%, respectively. Three prominent waves of excess were observed: the winter of 2020 and the spring and last quarter of 2021. The highest monthly excess was noticed in December 2020, with a rate of 113 per 100,000 and a *P-score* of 84%. The ratios of reported COVID-19 deaths to calculated excess mortality were 20% in 2020 and 27% in 2021. The excess mortality dramatically increases with age. Serbia faced high levels of mortality excess in 2020 and 2021, particularly among older people. During 2022, there was a decrease in mortality trends compared to pandemic years. That year 109,203 died with a rate of 1,639 per 100,000. The excess in 2022 was 7733 (116 per 100,000) with a *P-score* of 8%.

Keywords: SARS-CoV-2, Excess deaths, All-cause mortality, Negative binomial regression

INTRODUCTION

The first COVID-19 case was detected in Serbia on March 6, 2020 (Lazić, Lazić & Kolarić, 2020). After that, the virus spread throughout the country in several "waves" of infection. Following the recommendations of the national crisis headquarters, the Serbian government introduced various anti-epidemic measures, including a state of emergency, lockdowns, travel restrictions, and a mass population vaccination campaign from the end of 2020 onwards. However, it was not easy to monitor the intensity of the spread of the virus. The virus spread data in Serbia were scarce without further division by sex, age, or region. Naturally, there was no documented evidence of associated diseases or risk factors among the infected. Assessing the true impact of COVID-19 using such data was very difficult. According to national data, the health effects of COVID-19 in Serbia were relatively lesser than in neighboring countries and Europe in general. Early data indicated that Serbia was one of the best-performing European countries in crisis management (Karlinsky & Kobak, 2021; Villani et al., 2020). However, questions began to appear as early as 2020 in the media and scientific literature about the accuracy of the official data and its reliability in estimating the burden of disease associated with COVID-19 in Serbia (Galjak & Marinkovic 2023). This debate underscores the importance of accurate and reliable data for evaluating the consequences on the population's health, which this study aims to provide. Accurate COVID-19 mortality assessment requires a stable definition applicable to the entire country's level and the widespread availability of high-quality laboratory tests. However, the mortality from COVID-19 alone does not fully represent the total impact of the pandemic. Deaths from other causes not directly related to COVID-19 also increased during the pandemic due to strain on the health system and all restrictive measures. Therefore, a comprehensive analysis of excess mortality (EM) must include these deaths also (Joffe 2021). EM refers to deaths exceeding the expected number under "normal" conditions in the absence of an emergency. EM incorporates all cases of death directly and indirectly related to COVID-19 (Beaney et al. 2020). Its advantage is that it does not require special tests but uses the existing infrastructure of routine statistics. Therefore, this indicator has become a gold standard for measuring the societal impacts of COVID-19.

This study aims to estimate EM in Serbia from January 1, 2020, to December 31, 2022. The first two years can be characterized as pandemic years. While 2022 was taken to see how persistent the trends from 2020-2021 were. Estimations are based on available mathematical models to compare the historical data with data from an observed two-year period and to compare EM with the reported COVID-related deaths. The study was

inspired by an earlier paper from Wyper and colleagues in the first months of the pandemic (Wyper et al., 2020). They classified Serbia among the top European countries in terms of population vulnerability to COVID-19. Their claim was based on a significant proportion of the elderly, as well as low spending on health in absolute values (Eurostat, 2023). This study tests their original hypothesis by deriving estimations for EMs related to gender, age, and administrative regions in Serbia. It sheds light on the reality of the Serbian experience during the most extreme pandemic periods. The second goal is to show the importance of monitoring total mortality in evaluating health emergencies.

METHODS

Data source

For the study, we obtained publicly available data on the number of deaths by gender at the national and regional levels from the Statistical Office of the Republic of Serbia website. The analyzed age groups included 0-14, 15-44, 45-64, 65-74, 75-84, 85+, and unknown age (Statistical Office of the Republic of Serbia, 2023b). The period for comparison was 2015-2019, for which data on the number of deaths by month and gender were collected. All the data were entered into an empty *.xlsx template file created by the World Health Organization (WHO) Western Pacific Regional Office (Mengjuan et al., 2022). The data on the estimated population size in the middle of the observed year were used to calculate rates per 100,000 population. The Statistical Office provides this data regularly. Data on reported deaths from COVID-19 were retrieved on September 18, 2023, from the WHO dashboard (World Health Organization, 2023b). WHO collects official data from individual countries and presents it transparently, making it easy to download and further analyze.

Definition of terms

All-cause mortality (ACM) is the total number of deaths from all causes. EM represents the difference between the actual number of all-cause deaths recorded during 2020-2022 and the expected number of deaths in the same period (Msemburi et al., 2023). Expected mortality is the estimated number of persons who would die if previous historical mortality trends continued during the observed period. Estimation was calculated using a negative binomial regression (NBR) model and historical data from the pre-pandemic years 2015-2019. NBR is a statistical method for rare events similar to the Poisson distribution but accounts for over dispersion (Hilbe, 2011). NBR is a flexible method and can consider variability, making it advantageous over

other methods, particularly in mortality analysis. Additional information on NBR and the mathematical model behind the estimation can be found online (Mengjuan et al., 2022; Wegman & Wright, 1983). One of the key outputs of NBR is the *P-score*. This score, expressed as a percentage, is the ratio of excess to expected mortality. The score also reflects the relationship between reported COVID-19 deaths and EM, indicating the percentage of excess associated with reported death cases from the COVID-19 virus.

Statistical tool

The WHO Western Pacific office developed the comprehensive ACM online calculator in collaboration with the Department of Statistics at the University of California, Los Angeles (UCLA) (Mengjuan et al., 2022). This online calculator provides a spreadsheet output with the *P-scores*, the expected and excess number of deaths with 95% confidence intervals. Additional tools for this analysis include Microsoft Office Excel 365 and the tidy verse collection of packages in R (Wickham et al., 2019).

RESULTS

Total mortality

In 2020, a total of 116,850 people died in Serbia, with a crude mortality rate of 1694 per 100,000. In 2021, the number of deaths increased to 136,622, resulting in a crude mortality rate of 1999 per 100,000. The highest reported monthly mortality in Serbia in 2020 was in December at 248 per 100,000, while the lowest observed rate was in September at 111 per 100,000. In 2021, the highest monthly mortality occurred in October at 229 per 100,000, with the lowest rate recorded in August at 123 per 100,000. The number of deaths in 2022 was 109,203 with a rate of 1,639 per 100,000. The highest rate was in February of that year at 194, and the lowest in June at 108 per 100,000

The total reported mortality in Serbia was higher than expected in several months. In 2020, this occurred in July, November, and December; in 2021, it was the case from January to June and September to December. The expected mortality was exceeded in 13 out of 24 observed months of 2020 and 2021 (Figure 1). The trend of excess deaths from 2021 carried over into the first two months of 2022. However, the number of registered deaths was within expected limits from March onwards.

In 2020, the total EM using the NBR method was 15,437 (224 per 100,000 population) with a *P-score* of 15%. The highest EM was recorded in December, with a rate of 113 per 100,000 population and a *P-score* of 84%. In 2021, the total EM was 35,836 (524 per 100,000 population), with

a *P-score* of 36%. The highest EM was recorded in October, with a 109 per 100,000 population and a *P-score* of 91%. The EM in 2022 was just 7733 (116 per 100,000) resulted in a *P-score* of 8%. The highest was in February with a *P-score* of 43%, and the lowest in December with a *P-score* of -10%. Apart from December, negative *P-score* were also observed during April, May, June and November of that year.

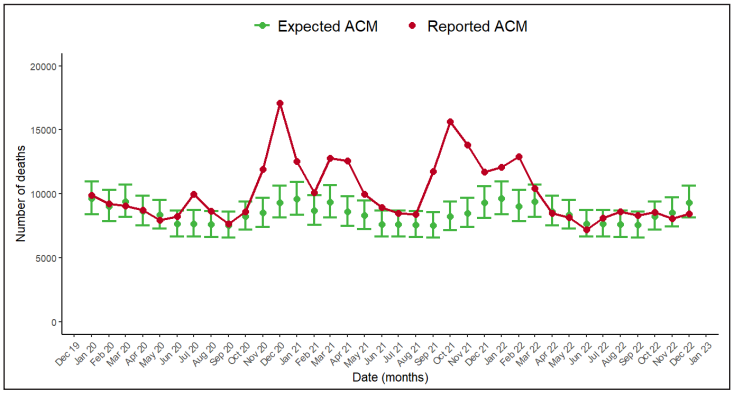

Figure 1. Expected all-cause mortality based on the negative binomial regression with a 95% confidence interval and reported all-cause mortality per month from January 2020 to December 2022 in Serbia.

In 2020, 3163 people (46 per 100,000 population) in Serbia died from COVID-19, and in 2021, this number increased to 9525 (139 per 100,000 population). The ratio of reported COVID-19 deaths to calculated EM was 20% in 2020 and 27% in 2021, respectively (Figure 2). Number of reported COVID-19 death cases in 2022 was 4927 (74 per 100,000 population). The ratio between COVID-19 reported deaths and EM was 64% in 2022.

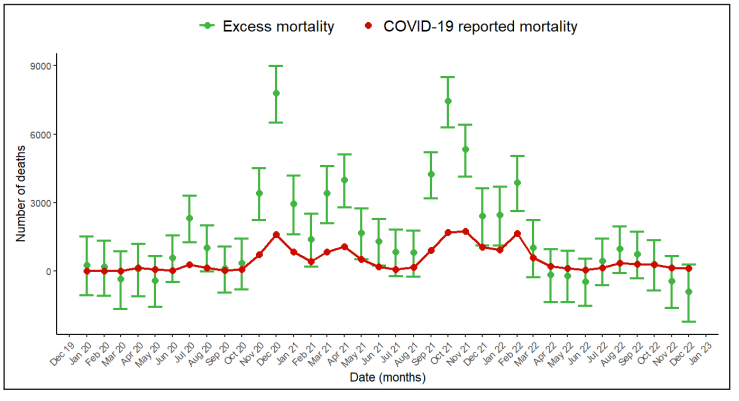

Figure 2. Excess mortality based on the negative binomial regression with 95% confidence interval and COVID-19 reported mortality from January 2020 to December 2022 in Serbia.

Sex and excess mortality

In 2020 and 2021, the sex-specific mortality rate per 100,000 population was higher in men than in women (1,799 vs 1,594 in 2020 and 2,101 vs 1,902 in 2021). Both men and women reached their annual peak mortality rates per 100,000 in the same months: December 2020 (277 vs 220) and October 2021 (235 vs 223).

EM was also higher among men than among women. The NBR method estimated that excess in males was 9,363 (279 per 100,000) in 2020 and 19,093 (574 per 100,000) in 2021. EM in females was estimated at 6,078 (172 per 100,000) in 2020 and 16,745 (477 per 100,000) in 2021.

The NBR method's sex-related *P-scores* show that all scores from April 2020 onwards were positive for both sexes, except for May 2020 (both sexes) and September 2020 (negative for females). *P-score* values were higher for men except for October 2020, June, July, August, and October 2021.

The mortality rate per 100,000 was 1695 for men, with the mimunum of 111 in June and maximum of 203 in February of 2022. The rate for female was 1585 per 100,000 in the range of 105 in June and 185 in February. The EM for man in 2022 was 3833 (118 per 100,000). For female EM was 3900 (114 per 100,000). Unlike the previous two years, the *P-score* varied with negative and positive values in 2022 (46% for men and 40% for women). It had the highest value in February. In April, May and June, it had negative values for both sexes. Then it was negative again in November and December, when the lowest *Pscore* values were recorded (-10% for men -9% and for women).

Age groups and excess mortality

All age groups had positive EM during 2019-2020 (Table 1). The oldest age group (>85) had the greatest reported excess rate. An analysis of *P-scores* by month provides a comprehensive perspective (Figure 3). In December 2020, April 2021, and October 2021, the age group 65-74 had the highest *P-score* values in three pronounced periods. Record annual *P-score* values were documented in this age group in December 2020 with a value of 108% and in October 2021 with 101% using the NBR method, meaning observed deaths in this group were more than double the expected.

In 2022, excess mortality rates decreased sharply compared to 2021 in all age groups (Table 1). Especially among those under 65. Among those over 85, it halved in comparing to a year before and was slightly higher than in the first year of pandemic.

Table 1. Reported all-cause mortality with a rate per 100 000 population, the excess death rate by age groups based on the negative binomial regression (NBR) for 2020-2022 in Serbia.

	Reported all-cause mortality		NBR: Excess death
Age group	N	Rate	Rate
		2020	
0-14	432	44	0
15-44	2576	100	14
45-64	18696	990	147
65-74	29694	3308	600
74-84	37683	8938	1001
85+	27693	20231	1758
Unknown	76		
		2021	
0-14	426	44	1
15-44	3002	118	33
45-64	20797	1113	289
65-74	36247	3978	1234
74-84	43951	10816	2852
85+	32134	23508	4527
Unknown	65		
		2022	
0-14	374	39	-6
15-44	2409	101	8
45-64	16042	866	6
65-74	28081	2995	402
74-84	34383	8317	218
85+	27847	23521	2147
Unknown	67		

Source: Statistical Office of the Republic of Serbia (RZS) and authors calculations.

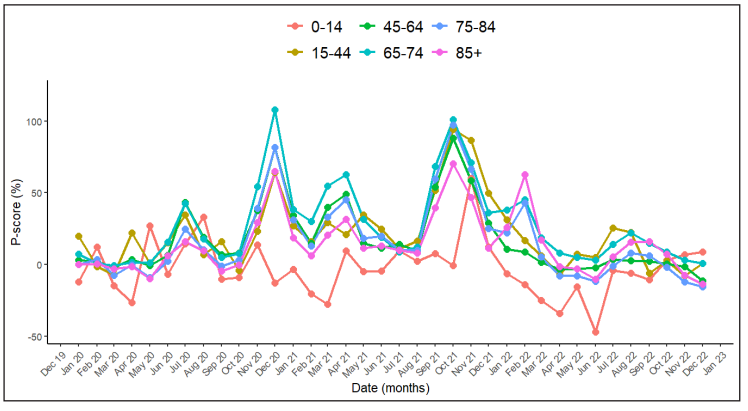

Figure 3. Monthly P-scores for age groups based on the negative binomial regression method from January 2020 to December 2022 in Serbia (The "Unknown age group" was removed from the plot).

DISCUSSION

The study aimed to estimate excess mortality during the first two pandemic years in Serbia. Most countries underwent increased mortality and significant excess during 2020-2021 in various intensities (Galjak 2021; Msemburi et al., 2023; Sanmarchi et al., 2021). Some were less, and some more affected. The Russian Federation, North Macedonia, Turkey, Montenegro, and Bulgaria were the European countries with the largest excess (Msemburi et al., 2023). Unfortunately, Serbia was among them (Msemburi et al., 2023). All these countries are from the East or South-East of Europe. A comparable discrepancy existed in some Latin American countries (Sanmarchi et al., 2021; World Health Organization, 2023a). Our NBR analysis found that the total mortality excess was 51,273 over the two years. For comparison, the annual mortality from 2010 to 2019 was between 100,300 and 103,722 (Statistical Office of the Republic of Serbia, 2020). Only a tiny fraction of this excess is documented COVID-19 deaths. The second year was particularly challenging, with an excess rate of 524 per 100,000. For the same period, the average excess rates per 100,000 across the WHO European Region were 141 in 2020 and 199 in 2021 (Msemburi et al., 2023). This implies that the excess of total mortality in Serbia was far higher than the European average and that the health consequences of the pandemic in Serbia were far higher than the European average.

The prominent difference between Serbia and Western Europe is the absence of a significant mortality increase in the spring of 2020 (Rossen et al., 2022). Under-reporting in Serbia during the initial wave might be one of the reasons (Mussino et al., 2024). On the other side, Serbia experienced a third wave of infection, which peaked in November 2021. This difference could stem from variations in data collection, different sources of the initial outbreak, and a different percentage of vaccinated (Konstantinoudis et al., 2022). Indubitably, there were significant differences between countries in the population health and well-being before 2020. Such disparities became even more noticeable during the pandemic. Documented factors that reduced the mortality excess were public trust in authorities, trust in others, equal distribution of resources, and government care for the most vulnerable through financial support and food aid (da Silva et al., 2024). Public health should use some of these tools in the future, and data transparency is undoubtedly one of the best ways to establish trust between decision-makers and society (Stivas & Cole, 2023).

The level of COVID-19 testing plays a vital role in understanding the factors behind excess. Generally, countries with a high testing capacity reported low levels of COVID-19 mortality and low all-cause excess.

Denmark, Mongolia, Iceland, Australia, New Zealand, South Korea and Singapore were the countries with high testing capacities and negative excess deaths during 2020. Finland and Norway had a small but positive excess of deaths compared to previous years, despite a relatively high test-to-case ratio(Oliu-Barton et al., 2021; Sanmarchi et al., 2021). These countries testing and tracing systems effectively restrained the virus's spread and overall health consequences. Karanikolos and McKess suggested that the actual number of COVID-19 cases was likely higher than reported in countries with limited testing (Karanikolos & McKee, 2020). As testing resources in Serbia were pretty restricted, there is a good chance that Serbia's COVID-19 mortality was higher than the reported one. Figure 2 supports this claim, showing how the documented number of deaths from COVID-19 follows the trend of mortality excess.

Mortality depends on the likelihood of infection and the death of infected persons. Both probabilities vary depending on demographic and socioeconomic characteristics, including age structure, ethnicity, poverty, and environmental conditions (Konstantinoudis et al., 2022; Mussino et al., 2024). This research showed that from March 2020 to March 2021, the youngest age group had a negative *P-score*, except for May, July, August, and November 2020. In contrast, the excess rate among those over 65 increased with each age group. This gradient was particularly noticeable for 2021. Thus, the over-85 group had twice the rate of those aged 75-84 and almost four times the rate of those aged 65-74 during the second pandemic year. According to reported national data on total mortality, one in four people over 85 passed away in 2021. From 2015 to 2019, the mortality rates in this age group were between 18% and 20% for comparison (Statistical Office of the Republic of Serbia, 2023b). In 2022, excess mortality rates decreased sharply compared to 2021 in all age groups (Table 1). Especially among those under 65. Among those over 85, it halved in comparing to a year before and was slightly higher than in the first year of pandemic.According to studies, from July 2020 to spring 2021, the *P-scores* for males significantly increased. This indicates higher male mortality than expected. As with the difference between age groups, future studies should answer which part of this excess was associated with COVID-19 and which was not. We know from previous studies that men had higher mortality from the coronavirus, viruses in general, and chronic respiratory diseases (Geldsetzer et al., 2022; Karlberg, Chong & Lai, 2004; Twitchell et al., 2022). A possible reason might be the generally poorer health of men compared to women of the same age (Alwani et al., 2021; Geldsetzer et al., 2022). Men also practice harmful behaviors more often, such as smoking and drinking alcohol (GBD 2015 Tobacco Collaborators, 2017). Additionally, men were less likely to adhere to preventive measures against virus transmission (Solomou & Constantinidou,

2020). Besides everything mentioned, men were more often exposed to sick and asymptomatic carriers of the virus (Dehingia & Raj, 2021; Grzelak et al., 2021; Mussino et al., 2024). In Serbia, men dominate in professions that did not cease during the lockdown (Statistical Office of the Republic of Serbia, 2023a). The work engagement made them more exposed to the virus. On the contrary, women constitute a higher proportion in retail, education, and social protection, making them relatively protected during the closure of schools, kindergartens, and non-essential shops and restaurants. How significant the difference in exposure of the sexes to dying was demonstrated by the disappearance of the gap between the sexes soon after the easing of restrictive measures.

LIMITATIONS

Our study has limitations due to data availability and quality. We could not access individual death records. Therefore, there might be some mistakes in our data. Different or more extended reference periods for expected mortality may provide different results. The biggest limitation can be that the impact of changes in the age structure and specific mortality rates are not considered. Data grouped monthly can mask genuine variations on a weekly or daily basis. Especially if there is irregular reporting with days of delay in data submission. Thus, data from one month can easily be transferred to the next month. It's good to remember that things in society and among people are constantly changing. It is the same with demographic trends that may coincide with the pandemic without any impact of pandemic, virus, or emergency measures (Garber, 2021). It would be interesting to monitor the EM and whether the ACM might fall later.

CONCLUSIONS

Serbia experienced a significant increase in deaths during 2020 and 2021 compared to the previous five years. EM fluctuated with peaks in winter 2020, spring, and late 2021. The reported deaths from COVID-19 likely represent only a fraction of the total excess deaths. High, above-expected death rates were recorded among older age groups, among males, and in certain administrative regions. These differences warrant additional attention to protect vulnerable populations and reduce avoidable deaths. It is crucial to prioritize the needs of vulnerable populations in future health emergencies and protect them from exposure to reduce preventable deaths.

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PROCENA SMRTNOSTI TOKOM PANDEMIJE COVID-19 VIRUSA U REPUBLICI SRBIJI, U PERIODU OD 2020 DO 2022. GODINE

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SAŽETAK

Rani izveštaji ukazivali su na to da je Srbija bila među najuspešnijim evropskim zemljama u suočavanju sa zdravstvenim izazovima tokom pandemije Covid-19, na osnovu relativno niske stope mortaliteta uzrokovane ovim virusom. Ovaj uspeh se delimično može pripisati brzom reagovanju Vlade i implementaciji restriktivnih mera kako bi se suzbilo širenje virusa. Takođe, može se primetiti da je visok nivo solidarnosti među građanima doprineo efikasnom suzbijanju pandemije, pridržavajući se propisanih mera i preporuka stručnjaka. Srbija je postala primer dobre prakse u borbi protiv Covid-19, što je rezultiralo pozitivnim ocenama međunarodnih organizacija i stručnjaka. Međutim, mortalitet prouzrokovan isključivo virusom nije dovoljan za opisivanje zdravstvenih efekata pandemije, za razliku od viška mortaliteta od svih uzroka. Upravo zbog toga, važno je sagledati i druge posledice pandemije, poput ekonomskih, socijalnih i mentalnih. Mnogi ljudi su izgubili posao, preduzeća su propala, a povećan je i broj slučajeva mentalnih oboljenja. Zbog toga je neophodno da se država, zajedno sa stručnjacima, fokusira ne samo na suzbijanje virusa, već i na oporavak društva u celini. Cilj ovog rada je da analizira višak smrtnosti u Srbiji u periodu 2020–2022. godine i da uporedi procenjene podatke o smrtnosti sa prijavljenim slučajevima smrti uzrokovanim Covid-19. Višak je procenjen primenom negativne binomne regresije na istorijske podatke iz perioda 2015–2019. Procena pruža P-indeks kao procentualnu razliku između prijavljenog i očekivanog broja smrtnih slučajeva. U Srbiji je višak smrtnosti iznosio 15.437 tokom 2020. i 35.836 tokom 2021. godine, sa stopama od 224 i 524 na 100.000 stanovnika, dok su P-indeksi iznosili 15% i 36%, redom. Uočena su tri izražena talasa viška smrtnosti: tokom zime 2020. godine, proleća i poslednjeg kvartala 2021. Najveći mesečni višak zabeležen je u decembru 2020. godine, sa stopom od 113 na 100.000 stanovnika i P-indeksom od 84%. Odnos prijavljenih smrtnih slučajeva od Covid-19 prema izračunatom višku smrtnosti bio je 20% u 2020. i 27% u 2021. godini. Višak smrtnosti se dramatično povećava sa starošću. Srbija se suočila sa visokim nivoima viška smrtnosti u 2020. i 2021. godini, posebno među starijom populacijom. U 2022. godini zabeležen je pad smrtnosti u

odnosu na pandemijske godine. Te godine je umrlo 109.203 ljudi, sa stopom od 1.639 na 100.000 stanovnika. Višak smrtnosti u 2022. godini iznosio je 7.733 (116 na 100.000) sa P-indeksom od 8%.

Ključne reči: SARS-CoV-2, višak smrtnosti, mortalitet svih uzroka, negativna binomna regresija

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