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Original article

# THE COVID-19 PANDEMIC IN THE PLEVEN REGION FOR A THREE-YEAR PERIOD (MARCH 2020 – MARCH 2023)

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**ABSTRACT:**

The COVID-19 pandemic had a major impact on the capacity of health systems to continue the delivery of essential health services. While health systems were being challenged by increasing demand for care of COVID-19 patients, it was critical to maintain preventive and curative services, especially for vulnerable populations.

**Materials and methods:** A retrospective analysis was conducted on epidemiological and demographic characteristics of the COVID-19 pandemic in the Pleven region (March 2020 – March 29 2023). Data were obtained from annual reports of the National Statistical Institute and annual epidemiological analyses of Regional Health Inspectorate–Pleven and were analyzed using statistical software (IBM SPSS Statistics 19.0).

**Results:** There were 36,308 confirmed cases of COVID-19 (medical workers – 2,176 confirmed cases), with 1,895 deaths. The cases during the years were 5,646 (2020), 16,258 (2021), 15,225 (2022). The incidence of COVID-19 in the region was 2,389; 6,964, and 6,668 at 100,000 populations in 2020, 2021 and 2022, respectively. The prevalence of the disease was 93%, 98% and 94% of all registered respiratory transmitted cases ($p<0.0005$). There were four waves with the highest incidence (November 2020, March 2021, October 2021, and January 2022, in concordance with registered for Bulgaria). The highest mortality of COVID-19 (15% of deaths) was registered during 2021 – 456 and 368 at 100,000 population for males and females, respectively (16% and 15% of deaths, respectively; 81% – at ages 65+).

**Conclusion:** The global implementation of different interventions had a significant impact on slowing down the community transmission of SARS-CoV-2. Health care and resources must be focused on the vulnerable populations.

**Keywords:** COVID-19, incidence, mortality,

## INTRODUCTION

During the present century, three zoonotic β-coronaviruses (CoVs) have crossed the inter-species barriers, infected humans, and caused outbreaks and epidemics of severe pneumonia. The first was severe acute respiratory syndrome coronavirus (SARS-CoV), appeared in 2003 [1,2]. Nine years later, the Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in 2012 [3]. Novel β-coronavirus appeared in Hubei province, China, in December 2019, causing a global disaster [4,5]. It was named 2019-novel coronavirus (2019-nCoV). The World Health Organization (WHO), on January 12 2020, named the new infection caused by the virus COVID-19 disease [6,7]. One month later (on February 11 2020), the International Committee on Taxonomy of Viruses (ICTV) study group renamed it severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [8]. The WHO changed the state of Public Health International Emergency (on January 30 2020) to a pandemic (on March 11 2020) [6]. Despite global efforts to control the pandemic, it rapidly spread worldwide. Two years after the COVID-19 appearance, the number of confirmed infections reported to WHO was more than 435 million, with a death toll of 5,952,215 until March 2022 [9].

Nearly 85% of COVID-19 patients were asymptomatic or with mild symptoms. Severe course with ARDS had been observed in 10% of the cases, and at least 5% were critical with need of treatment in the intensive care unit (ICU), of which nearly half die. The average mortality rate was approximately 2.4% [10,11]. Children and teenagers with COVID-19 infections had a milder course of the disease than adults. Fatal cases were more common in elderly patients, especially those with chronic and multiple comorbidities, such as hypertension, diabetes mellitus, heart disease, pathology of the endocrine system, chronic respiratory diseases, gastrointestinal disorders, nervous system diseases, and malignancy, due to weakened immune function [12,13,14]. In the study of Guo et al. (2019), most of the patients were males (with an average age of 55.5 years), 41.9% were females, and 0.9% of the patients were younger than 15 years [15]. Although SARS-CoV-2 and previous SARS-CoVs have phylogenetic similarity, the severity and fatality rate of COVID-19 are lower than those of SARS and MERS [15,16].

The COVID-19 pandemic had a major impact on the capacity of health systems to continue the delivery of essential health services. While health systems were being challenged by increasing demand for care of COVID-19 patients, it was critical to maintain preventive and curative services, especially for vulnerable populations. Globally, by March 29, 2023, there were 761,402,282 confirmed cases of COVID-19, of which 6,887,000 were fatal, according to WHO. For the same period, 274,567,136 cases were registered in Europe [17], 1,299,702 confirmed cases in Bulgaria.

Our **purpose** was to study the epidemiological process of the COVID-19 pandemic in the Pleven region for three years (March 2020 – March 2023) with emphasis on two major characteristics of public health – incidence and mortality, comparing these with identical for Bulgaria.

**MATERIALS AND METHODS:**

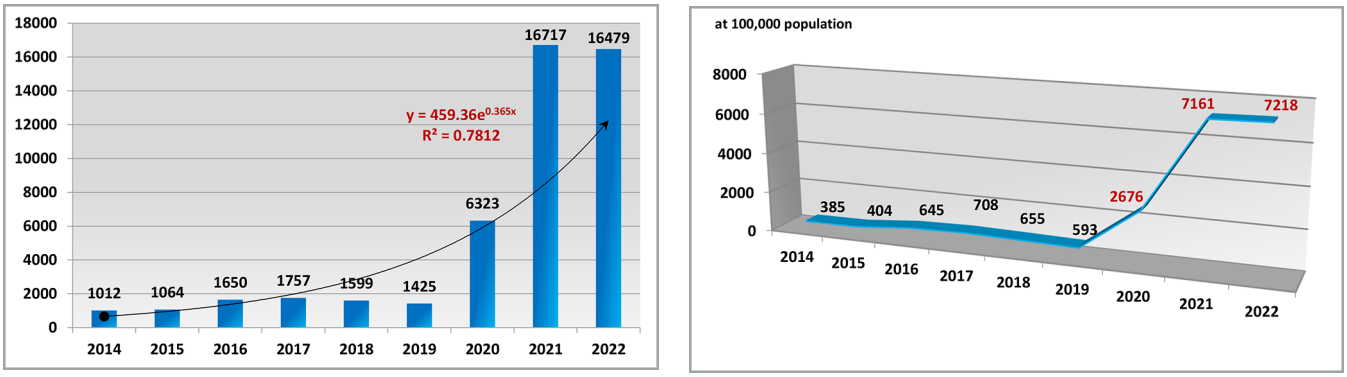
A retrospective analysis was conducted on epidemiological and demographic characteristics of the COVID-19 pandemic in the Pleven region (March 2020 – March 29 2023). The emphasis was placed on two important public health aspects – morbidity and mortality from COVID-19.

The data were obtained from: 1) Unified information portal - COVID-19 | coronavirus.bg; 2) Graphical analysis of data from the National Information System for COVID-19, Bulgaria (site of the National Center for Infectious and Parasitic Diseases; 3) the annual reports of the National Statistical Institute and 4) the annual epidemiological analyses of the Regional Health Inspectorate – Pleven and were analyzed using statistical software (IBM SPSS Statistics 19.0).

**RESULTS:**

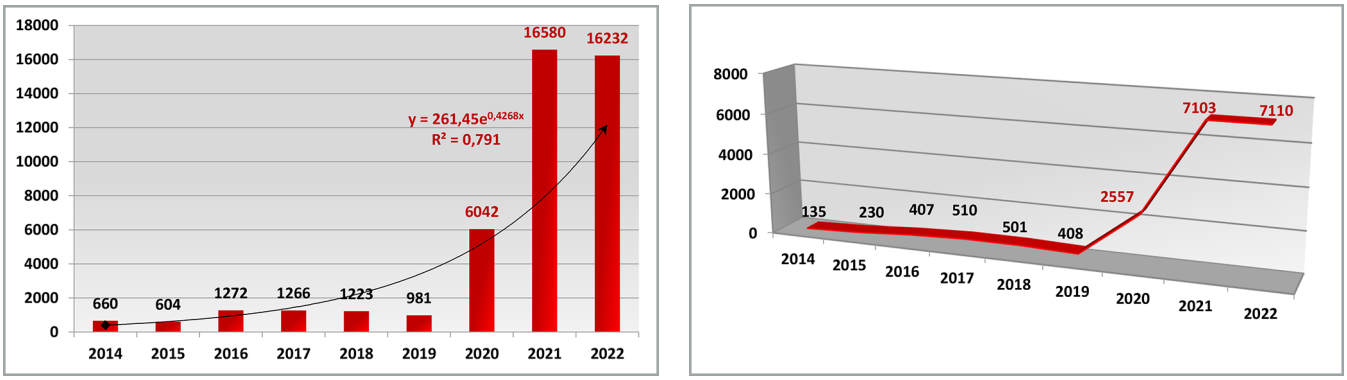
Until the onset of the COVID-19 pandemic, 8,503 cases of infectious diseases were registered in the Pleven region for six years (2014-2019). On March 7 2020, the first two cases of confirmed SARS-CoV-2 infection had been reported in University Hospital "Dr Georgi Stranski", Pleven. These cases noted the onset of the COVID-19 pandemic in Bulgaria. Since that time, 39,519 cases of infectious diseases were reported for three years (March 2020 – March 2023) (fig. 1).

**Fig. 1.** Number of cases and incidence of infectious diseases (per 100,000 population) in Pleven region (2014-2022)



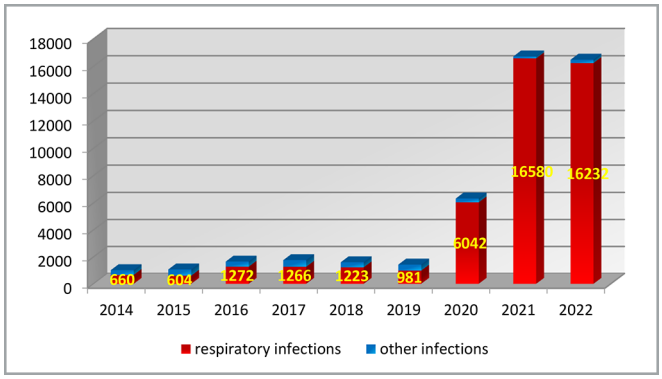

The incidence of respiratory infections in the Pleven region before the outbreak of the pandemic ranged from 135 to 510 per 100,000 population (mean 380 ± 160) and had increased fifteenfold since the beginning of March 2020, ranging from 2,557 to 7,110 per 100,000 population (mean 5,589 ± 2,626) (p<0.005) (fig. 2).

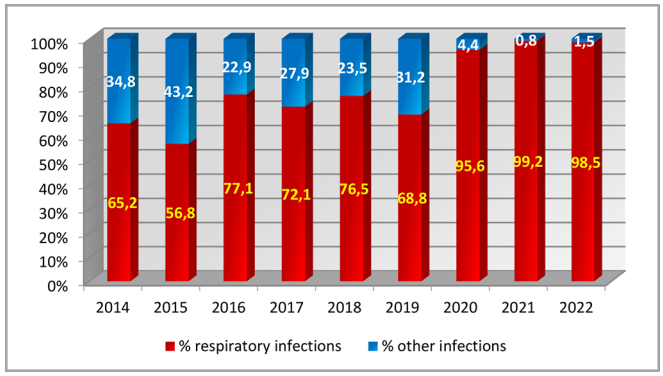
**Fig. 2.** Number of cases and incidence of respiratory infections (per 100,000 population) in Pleven region (2014-2022)




After the onset of the COVID-19 pandemic, the structure of infectious diseases dramatically changed. The prevalence of registered respiratory infections had risen from 68.8% in 2019 to 99.2% in 2021 (p<0.0005) (fig. 3).

**Fig. 3.** Number of cases and prevalence of respiratory and other infections in the Pleven region (2014-2022)




In the Pleven region, there were 36,308 confirmed cases of COVID-19 (medical workers – 2,176 confirmed cases), with 1,895 deaths. The cases during the years were 5,646 (2020); 16,258 (2021); 15,225 (2022). The incidence of COVID-19 in the region was 2,389; 6,964, and 6,668 at 100,000 population in 2020, 2021 and 2022, respectively. The prevalence of the disease was 93%, 98% and 94% of all registered respiratory transmitted infections ($p<0.0005$).

There were four waves with the highest incidence of COVID-19 (with peaks in November 2020, March 2021, October 2021, and January 2022, in concordance with registered for Bulgaria) (fig. 4 and fig.5). The total number of registered confirmed cases of COVID-19 in Pleven region and Bulgaria for 2020, 2021, 2022 and 2023 (from January to March) year is shown on Table 1**.**

**Fig. 4.** Confirmed cases of COVID-19 in Pleven region (March 2020 – March 2023)

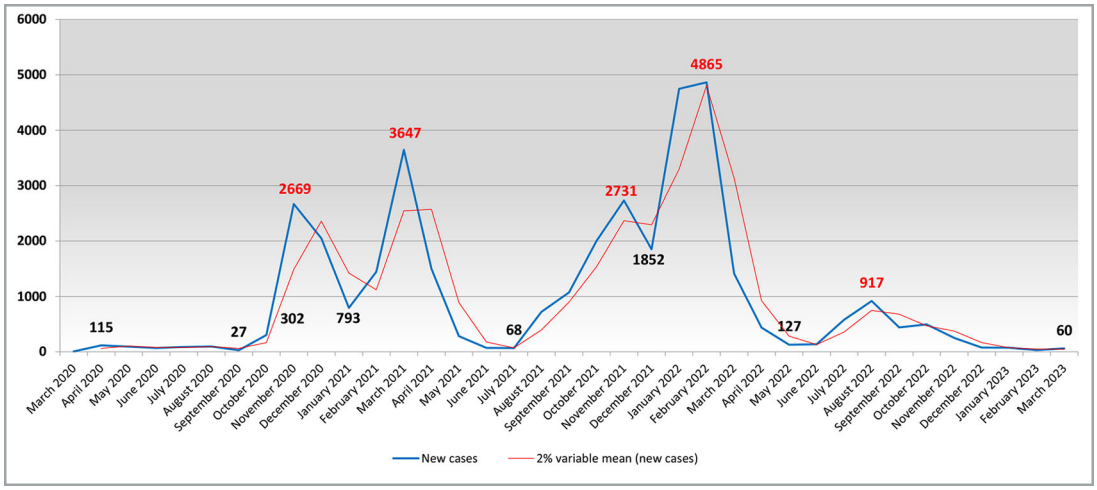



**Fig. 5.** Confirmed cases of COVID-19 in Bulgaria (June 2020 – March 2023)

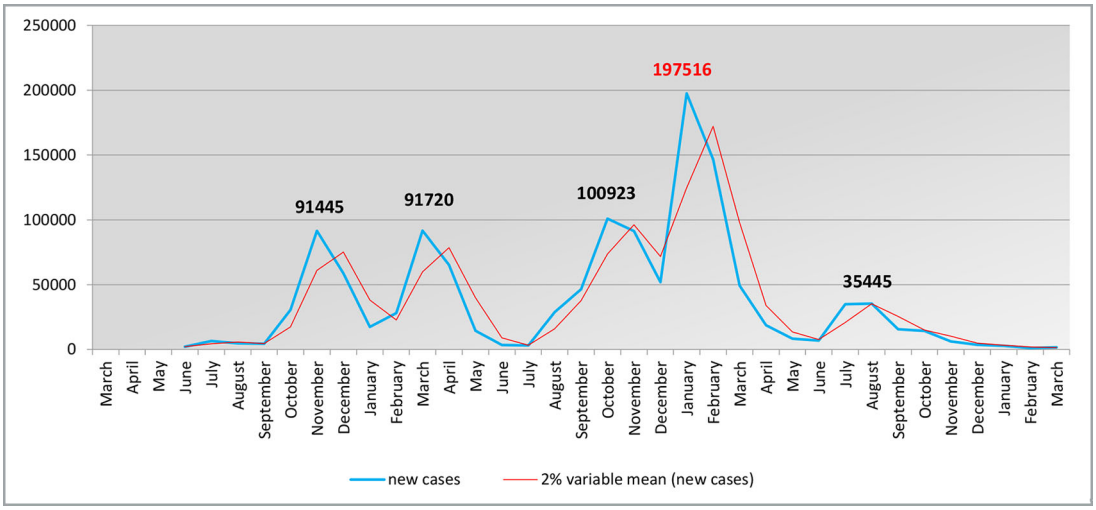


**Table 1.** Total number of registered confirmed cases of COVID-19 in Pleven region and Bulgaria for 2020, 2021, 2022 and 2023 (from January to March) years.

| | 2020 | 2021 | 2022 | 2023 | TOTAL |
|---|---|---|---|---|---|
| **Pleven region** | **5646** | **16258** | **15225** | **162** | **37291** |
| **Bulgaria** | **201220** | **542898** | **547105** | **7229** | **1298452** |

Regarding mortality, the highest mortality from COVID-19 (15% of all fatal cases) was recorded in 2021 – 456 and 368 per 100,000 population for males and females, respectively (16% and 15% of fatal cases, respectively) (Table 2).

**Table 2.** Mortality from COVID-19 in Bulgaria and Pleven region (2020-2022).

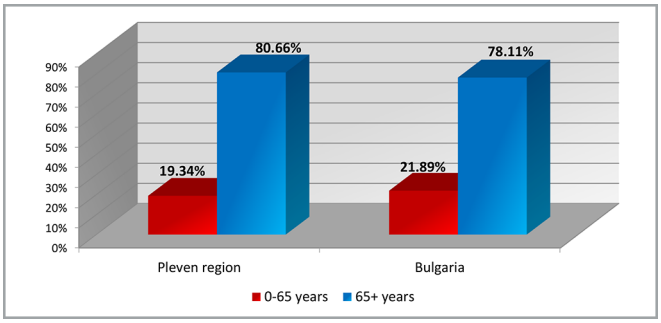
| Year | Region | Number of deaths | | | Per 100,000 population | | | Prevalence of deaths from COVID-19 out of all deaths | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Males | Females | Total | Males | Females | Total | Males | Females |
| **2020** | Pleven | 243 | 151 | 92 | 103.5 | **132.6** | **76.1** | 4.8 | **5.6** | **3.8** |
| | Bulgaria | 8554 | 5284 | 3270 | 123.4 | 157.3 | 91.5 | 6.9 | 8.0 | 5.6 |
| **2021** | Pleven | 948 | 510 | 438 | 410.6 | **456.5** | **367.6** | 15.4 | **16.0** | **14.8** |
| | Bulgaria | 27588 | 14731 | 12857 | 401.1 | 442.3 | 362.5 | 18.5 | 19.1 | 17.9 |
| **2022** | Pleven | 298 | 164 | 134 | 134.3 | **153.4** | **116.5** | 6.1 | **6.4** | **5.8** |
| | Bulgaria | 8993 | 4967 | 4026 | 139.1 | 159.8 | 120.0 | 7.6 | 8.1 | 7.0 |

Regarding mortality in different age groups, the most affected are the people older than 65 years. This trend is valid not only for the Pleven region but also for Bulgaria (Table 3), and comparative analysis did not show a significant difference – 80.66% for the Pleven region versus 78.11% for Bulgaria ($p>0.05$) (fig. 6).

**Table 3.** Number of deaths in different age groups in Pleven region and Bulgaria (2020-2022)**.**

| Age years | 2020 | | 2021 | | 2022 | | TOTAL | |
|---|---|---|---|---|---|---|---|---|
| | Pleven region | Bulgaria | Pleven region | Bulgaria | Pleven region | Bulgaria | Pleven region | Bulgaria |
| **0-4** | - | 2 | - | 5 | - | 6 | - | 13 |
| **5-9** | - | - | - | 2 | - | 3 | - | 5 |
| **10-14** | - | 2 | - | 4 | - | 1 | - | 7 |
| **15-19** | - | 7 | 1 | 11 | - | 2 | 1 | 20 |
| **20-24** | - | 6 | - | 27 | - | 4 | | 37 |
| **25-29** | - | 10 | - | 57 | 1 | 10 | 1 | 77 |
| **30-34** | - | 34 | 1 | 108 | 1 | 17 | 2 | 159 |
| **35-39** | - | 60 | 4 | 180 | - | 40 | 4 | 280 |
| **40-44** | 6 | 124 | 16 | 363 | 3 | 67 | 25 | 554 |
| **45-49** | 3 | 206 | 19 | 608 | 4 | 105 | 26 | 919 |
| **50-54** | 3 | 328 | 30 | 962 | 3 | 170 | 36 | 1460 |
| **55-59** | 13 | 594 | 33 | 1397 | 8 | 323 | 54 | 2314 |
| **60-64** | 33 | 990 | 90 | 2475 | 16 | 570 | 139 | 4035 |
| **65-69** | 37 | 1281 | 126 | 3761 | 39 | 964 | 202 | 6006 |
| **70-74** | 43 | 1625 | 185 | 5333 | 78 | 1559 | 306 | 8517 |
| **75-79** | 55 | 13811 | 189 | 4976 | 51 | 1727 | 295 | 8084 |
| **80-84** | 27 | 1074 | 142 | 3976 | 48 | 1608 | 217 | 6658 |
| **85+** | 23 | 830 | 112 | 3343 | 46 | 1817 | 181 | 5990 |
| **TOTAL** | **243** | **8554** | **948** | **27588** | **298** | **8993** | **1489** | **45135** |

**Fig. 6.** Mortality rate of COVID-19 in age groups 0-65 years and 65+ years in Pleven region and Bulgaria (2020-2022).




Analysis of the mortality rate in all twenty-eight regions in Bulgaria regarding the structure of different age groups had shown that in eight regions, 65+ age groups were affected in more than 80% off all COVID-19 deaths as follows – Vidin (82.17%), Gabrovo (81.97%), Smolyan (81.71%), Kyustendil (80.88%), Pleven (80.66%), Ruse (80.43%), Veliko Tarnovo (80.17%), and Sofia (Capital) (80.11%). In thirteen regions, this parameter is from 75% to 80%, and in the remainder - <75% (Table 4).

**Table 4.** Mortality rate in age groups 65+ in different regions of Bulgaria (2020-2022).

| Region | Mortality rate in age groups 65+ (>80%) | Region | Mortality rate in age groups 65+ (75-80%) | Region | Mortality rate in age groups 65+ (<75%) |
|---|---|---|---|---|---|
| **Vidin** | **82.17** | Lovech | 79.97 | Dobrich | 74.97 |
| **Gabrovo** | **81.97** | Plovdiv | 79.26 | Razgrad | 74.62 |
| **Smolyan** | **81.71** | Montana | 78.90 | Silistra | 74.10 |
| **Kyustendil** | **80.88** | Stara Zagora | 78.12 | Shumen | 73.69 |
| **Pleven** | **80.66** | Haskovo | 78.07 | Yambol | 73.37 |
| **Ruse** | **80.43** | Pernik | 77.59 | Targovishte | 72.70 |
| **Veliko Tarnovo** | **80.17** | Sofia (region) | 77.14 | Kurdzhali | 72.52 |
| **Sofia (Capital)** | **80.11** | Blagoevgrad | 77.14 | | |
| | | Vratsa | 76.69 | | |
| | | Pazardzhik | 76.14 | | |
| | | Sliven | 76.11 | | |
| | | Varna | 75.83 | | |
| | | Burgas | 75.41 | | |

**DISCUSSION:**

COVID-19 infection can cause mild, moderate, severe, and even life-threatening disease. The most common symptoms of COVID-19 infection are fever, running nose, cough, and body aches. These symptoms may develop in different SARS-CoV-2 variants, such as Alpha, Mega, Delta, and Omicron. In severe cases of COVID-19, losses of smell and taste and difficulty in breathing have been observed. The patients infected by the Omicron variant did not have severe dyspnea [18]. The incubation period of the SARS-CoV-2 infection ranges from 2 to 14 days, compared to a 4-day incubation period in cases caused by the Delta variant of SARS-CoV-2 [19,20,21]. COVID-19 infection may develop in severe acute respiratory failure due to alveolar damage [22]. The patients with mild COVID-19 infection present with fever, sore throat, cough, weakness, headache, dyspnea, and myalgia. They have normal or decreased leukocyte counts [23] and might show increased blood levels of transaminases (ASAT, ALAT), lactate dehydrogenase (LDH), creatine kinase (CK), C-reactive protein (CRP), and erythrocytes sedimentation rate (ESR) [19]. Patients with moderate infection often have dyspnea. Patients with severe COVID-19 infection rapidly progress to severe pneumonia with acute respiratory failure, acute respiratory distress syndrome (ARDS), severe metabolic acidosis and coagulation disorders. A septic shock is possible, which can result in multi-organ failure, including altered functions in the liver and kidneys and even death. Pathological investigations reveal inflammation, infiltration of immune cells, necrosis, and hyperplasia in the secretions and infected tissues [15]. The damage to the pulmonary interstitial arteriolar walls shows that the primary determinant of the course of the disease is the immune response [24]. Together with the clinical and pathological findings, patients with severe COVID-19 infection also have laboratory abnormalities, such as leucopenia, lymphocytopenia, and thrombocytopenia [15]. Patients with indications for admission to intensive care units have high blood levels of pro-inflammatory cytokines (IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α). The massive production of these inflammatory mediators leads to cytokine storm and is

highly relevant to the severity of the disease and even to the final outcomes [25]. An early rise of the serum levels of pro-inflammatory cytokines can lead to severe disease [26]. In patients who have increased levels of IL-6, IL-10, CRP, ALAT, ASAT, and CK; increased neutrophils, and decreased lymphocytes, the clinical course of the disease is more severe, and the mortality rate is higher [25]. In contrast, high levels of IL1B, IFNγ, IP10, and MCP1 lead to an activation of the T-helper-1 (Th1) cell responses and increases the secretion of T-helper-2 (Th2) cytokines (IL4 and IL10), that suppress inflammation [27]. The majority of the patients with COVID-19 infection have lymphocytopenia, suggesting that the virus acts on the lymphocytes (especially T lymphocytes). The virus overcomes the respiratory mucosa and infects other cells, inducing a cytokine storm and generating multiple immune responses. This leads to alterations in the number and functional activity of peripheral white blood cells such as lymphocytes. The decreased total number of lymphocytes inhibits the cellular immune functions of the host. The damage to the T lymphocytes might be an important factor in worsening the patient's condition [28]. Together with this process, the total count of other immune cells, such as CD4+T, CD8+T, dendritic cells (DCs), macrophages, and natural killer cells (NKCs), significantly decreases. It is confirmed that CD4+T cells are important for worsening the SARS-CoV-2 infection [29,30].

Epidemiologic studies have revealed that patients older than 60 and those with chronic or preexisting diseases (such as diabetes mellitus and hypertension) are more likely to present with severe course and to have lethal outcomes of COVID-19 infection than younger cases without comorbidity. This difference is possibly associated with systemic inflammation or cytokine storm [31], considering suboptimal innate and adaptive responses to viral infection in older patients with comorbidity. It is suggested that differences in immune response, gene expression levels, or even genetic background might explain the variations in the susceptibility to SARS-CoV-2 infection, the severity, and even the mortality rate. In cases without an adequate immune response, the virus replicates aggressively, and the critical phase of the disease follows rapidly. Severe pneumonia and respiratory failure in COVID-19 infection is a result of an exaggerated immune response and severe inflammation rather than a direct effect of the virus [32]. The study by Yao H-P et al. (2020) demonstrated that patients over 60 years have a lower T-cell count, indicating that TNF-α might be directly involved in the process, leading to a weak immune response against viral infection. Children are not immune to COVID-19 and are vulnerable to most of the circulating common coronaviruses. The adults are exposed to many respiratory infections, and numerous memory cells are found in adults [33]. Children younger than nine years of age infected with SARS-CoV-2 show mild symptoms compared to older patients. It is probably due to insufficient memory cells specific to SARS-CoV-2 antigens, leading to a milder cell-mediated immune response and milder inflammation. Studies on S-protein RBD and ACE2 demonstrated that a higher binding affinity of RBD to ACE2 leads to higher virus infectivity and pathogenicity. The RBD of SARS-CoV-2 exhibits a stronger affinity to ACE2 in elderly patients with a weaker immune system or accompanying underlying diseases, and this fact might be related to a lower level of ACE2 expression in those people, resulting in a high virulence of SARS-CoV-2 [32]. The fact that the older people suffer significantly more severely than the younger is strongly confirmed by our study. The most affected are the people older than 65 years. In the Pleven region, 80.66% of lethal cases are in this age group, versus 78.11% for Bulgaria ($p>0.05$).

Regarding sex differences in mortality, it is visible the higher vulnerability of the male gender. Sex steroids (estrogen and androgen) are regulators of immune responses. Their function is exerted by binding to estrogen receptors (ER), androgen receptors (AR), and progesterone receptors (PR). These receptors are expressed by immune cells such as B- and T-lymphocytes, monocytes, macrophages, NKCs, myeloid cells, and dendritic cells. The androgen receptors might be one of the important factors responsible for gender differences in the presentation of COVID-19. As an anti-inflammatory hormone, androgen has a significantly higher expression in males than in females [33,34,35]. The androgen suppresses pro-inflammatory responses by reducing the secretion of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines. An investigation found a higher expression of IL-16, IL-7, ILCs, and IL-18 in males with COVID-19 infection than in females, which may promote a COVID-19-related cytokine storm. Most of the patients with severe COVID-19 infection have experienced cytokine storm that can trigger the immune system to attack the body aggressively, leading to an ARDS and multiple organ failure. A previous study demonstrated a positive correlation between the severity of pneumonia and the cytokine storm and inflammatory response caused by COVID-19 infection. These findings might answer why the risk of severe COVID-19 and case fatality rate (CFR) in males is higher than in females [20,33,36]. In our study, the highest mortality from COVID-19 (15% of all fatal cases) was recorded in 2021 – 456 and 368 per 100,000 population for males and females, respectively (16% and 15% of fatal cases, respectively).

**CONCLUSION:**

Finally, the global implementation of different preventive measures such as vaccination, isolation of the patients and the contact people, etc. significantly slowed down the community transmission of SARS-CoV-2. But the risk factors, including age, gender and comorbidity, are permanently valid, independent of the globally and regionally decreased incidence of COVID-19. Health care and resources must be focused on the vulnerable populations.

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