RISK FACTORS ASSOCIATED WITH MORTALITY FROM OMICRON VARIANT OF SARS-COV-2 IN REPUBLIC OF NORTH MACEDONIA

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Abstract

Introduction: In 2019, Wuhan registered an epidemic of a severe form of pneumonia. On January 7, 2020, the pathogen was identified as SARS-CoV-2. COVID-19 causes acute and fatal disease with an average mortality rate of 2%. Based on evidences, risk factors include older age, male gender, and ethnicity, as well as presence of comorbidities. Five variants of concern have been identified by WHO. The original variant of Omicron was first reported in Botswana and South Africa in November 2021.

Aim: The research aimed to analyze the risk factors associated with mortality from Omicron variant of SARS-CoV-2 in the Republic of North Macedonia.

Material and methods: The research was a prospective cross-sectional study that elaborated the mortality from Omicron variant of SARS-CoV-2 in the Republic of North Macedonia during the period December 2021/2022. The analysis included demographic characteristics, symptomatology, comorbidities, and vaccination status.

Results: The analysis showed that the male gender (OR=1.83; 95%CI=1.66-2.02), the age ≥60 (OR=33.98; 95%CI=28.53-40.47), the positive comorbidity status (OR=37.26; 95%CI=30.62-35.54), and hospitalization (OR=362.7; 95%CI=309.7-424.8) significantly positively associated with death from Omicron variant.

Complete vaccination and/or booster dose significantly negatively associated with hospitalization and mortality of Omicron variant reducing the probability for hospitalization (46%) and death (56%) respectively.

Conclusion: Male patients, older age group and comorbidities positively associated with death from the Omicron variant of SARS-CoV-2. The results of this study can be used to prepare the national health system for similar future epidemic crises.

Keywords: Omicron SARS-CoV-2, mortality, hospitalization, vaccination

Introduction

Coronaviruses are named after the Latin word corona because of the spikes on the crown of the surface that can be seen under the electron microscope [1].

In December 2019, the Chinese city of Wuhan registered an epidemic of a severe form of pneumonia from an unknown cause. On January 7, 2020, the pathogen was identified as a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2].

WHO designated the disease as coronavirus disease 2019 (COVID-19) and declared a global pandemic on March 11, 2020 [3,4,5]. COVID-19 causes an acute and fatal disease with an assumed average mortality rate of 2%. However, this new coronavirus is usually associated with mild to severe respiratory illness in humans.

Based on current evidence, risk factors for developing COVID-19 in adults include older age, male gender, and ethnicity, as well as presence of comorbidities such as cardiovascular disease, hypertension, and chronic obstructive pulmonary disease (COPD) [6].

Younger children with specific comorbidities such as obesity are at greater risk for infection and potentially more serious consequences from COVID-19 [7].

In addition to these factors, major risk factors for the severity and mortality of COVID-19 also include laboratory indices, proinflammatory cytokine levels, and complications [8].

According to WHO estimates, one in 20 people needed intensive care treatment, which includes sedation and mechanical ventilation. [9]. In this protracted pandemic, effective vaccination against COVID-19 was the most critical strategy for inducing a protective immune response and prevention of progression to severe illness and death [14].

Five variants of concern have been identified by WHO: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2 and AY lineage), and Omicron (B.1.1.529, then reclassified into BA subclasses, in particular, BA.1 and BA.2).

The original variant of Omicron was first reported in Botswana and South Africa in November 2021. After that, it was spread rapidly over the world including Republic of North Macedonia from December 2022 [17-18].

The research aimed to analyze the risk factors associated with mortality from Omicron variant of SARS-CoV-2 in the Republic of North Macedonia.

Material and methods

The research was a prospective cross-sectional study study conducted at the Institute of Public Health of the Republic of North Macedonia and the Institute of Epidemiology and Biostatistics with Medical Informatics, Medical Faculty, University "Ss. Cyril and Methodius", Skopje. The study elaborated mortality from the Omicron variant of SARS-CoV-2 in the Republic of North Macedonia during the period from December 2021/2022 while the circulation of the Omicron variant of SARS-CoV-2.

The survey included all deaths from Omicron variant of SARS-CoV-2 registered in the national system for surveillance of COVID-19. People from abroad registered in this system as treated and died from Omicron variant of SARS-CoV-2 in the Republic of North Macedonia, were excluded from the research.

According to the general WHO case definition of death, death from COVID-19 was defined as death resulting from clinically compatible disease in a confirmed case of COVID-19, unless there was no clear alternative cause of death. By definition, there should be no period of complete recovery between illness and death.

An analysis was made according to demographic characteristics, symptomatology, comorbidities and vaccination status. The research was conducted in compliance with the code of ethics to ensure the impossibility of connecting the obtained data with the source/personal data of the death cases.

The data obtained with the research were processed in SPSS software package, version 26.0 for Windows, and presented in tables and graphs.The qualitative series were processed by determining the coefficient of relations, proportions, and rates, and were shown as absolute and relative numbers. Quantitative series were analyzed with measures of central tendency (mean, median, minimum values, maximum values), as well as by dispersion measures (standard deviation). The risk calculation was determined using Odd ratio (OR). A two-sided analysis with a significance level of $p<0,05$ was used to determine the statistical significance.

Results

In the period from 01.12.2021-31.12.2022, the period of circulation of the Omicron variant of SARS-CoV-2, a total of 129,868 cases of COVID-19 (I=7,070.7/100,000) were reported in the Republic of North Macedonia. For the same period, a total of 1,794 death cases were reported with a mortality rate of 97.7/100,000 and a case fatality rate of 1.4%.

As of December 31, 2022, a total of 876,010 (47.7%) citizens of the Republic of North Macedonia were vaccinated with at least one dose, and 857,247 (46.7%) were vaccinated with two doses of the COVID-19 vaccine. The coverage of booster doses among the general population was 8.9% for one and 0.5% for two booster doses.

According to the pre-set inclusion and exclusion criteria of the study, the further analysis included 117,223 cases and 1,659 deaths from the Omicron variant of SARS-CoV-2. About 1,474 (88.8%) of deaths happened in the inpatient clinics, and 185 (11.2%) were at home setting.

Out of the total number of 1,659 death from the Omicron variant of SARS-CoV-2, 989 (59.6%) were male, and 670 (40.4%) were female.

The male gender significantly positively associated with death from Omicron variant of SARS-CoV-2 - p=0,0001[OR=1.83; 95% CI=1.66-2.02] (Table 1).

The average age of people who died from Omicron variant of SARS-CoV-2 was 74.5±10.9 years with min/max of 0 to 97 years. Most of the death cases (n=601; 36.2%) were registered in the age group over 80 years.

In total, 138 cases were aged <60years (8.3%), while 1,521 cases were aged over ≥60 years (91.7%).

The analysis showed that the age ≥60 significantly positively associated with the risk of death from Omicron variant of SARS-CoV-2 compared to people aged <60 years - p=0.0001[OR=33.98; 95% CI=28.53-40.47] (Table 1).

Table 1. Binary logistic regression analysis for predictive role of gender and age for death from Omicron variant of SARS-CoV-2 (December 2021- December 2022).

Indicators		N	p	OR	95% CI
Gender	Female	670	0.0001*	1.83	1.66-2.02
	Male	989			
Age	<60	138	0.0001*	33.98	28.53-40.47
	≥60	1,521			
ref. gender=female; ref. age <60				*significant for p<0,05	

A total of 1,552 (93.6%) death cases were among people with positive comorbidity status. The analysis showed that the presence of comorbidities significantly positively associated with death from Omicron variant of SARS-CoV-2 - p=0.0001[OR=37.26; 95% CI=30.62-35.54] (Table 2).

Most of the death cases or 930 (59.9%) were registered with three or more comorbidities. Presence of ≥3 comorbidities significantly positively associated with death from Omicron variant of SARS-CoV-2 and increased the probability for death by 4.92 times compared to presence of <3 comorbidities - p=0,0001[OR=4.92; 95% CI=4.43-5.46] (Table 2).

The most common comorbidities present among the death cases were cardiovascular diseases (n=1,336), diabetes mellitus (n=515), neuromuscular diseases (n=370) and lung diseases (n=226) (Table 2).

The comorbidities that significantly positively associated with death from Omicron variant of SARS-CoV-2 were:

a) neuromuscular disease that increased the probability for death compared to its absence - p=0.0001[OR=19.61; 95% CI=17.30–22.23]

b) cardiovascular diseases that increased the probability for death compared to its absence - p=0.0001[OR=15.67; 95% CI=13.87-17.71];

c) diabetes is positively associated with death compared to its absence - p=0.0001[OR=7.16; 95% CI=6.44-7.97]; and

d) lung disease that increased the probability for death compared to its absence - p=0.0001[OR=4,97; 95% CI=4.30-5.74] (Table 2).

The analysis showed that the death from Omicron variant of SARS-CoV-2 among hospitalized was higher compared to non-hospitalized patients - p=0.0001 [OR=362.7; 95% CI= 309.7-424.8] (Table 2).

Table 2. Binary logistic regression analysis for predictive role of hospitalization and comorbidity status for death from Omicron variant of SARS-CoV-2 (December 2021- December 2022).

Indicators		N	p	OR	95% CI
Hospitalization	No	185	0.0001*	362.7	309.7-424.8
	Yes	1,474			
Comorbidities	No	107	0.0001	37.26	30.62-35.54
	Yes	1,552			
	≤3	622	0.0001	4.92	4.43-5.46
	>3	930			
Cardiovascular diseases	No	323	0.0001	15.67	13.87-17.71
	Yes	1,336			
Diabetes mellitus	No	1,144	0.0001	7.16	6.44-7.97
	Yes	515			
Neuromuscular disease	No	1,289	0.0001	19.61	17.30-22.23
	Yes	370			
Lung disease	No	1,433	0.0001	4.9	4.30-5.74
	Yes	226			
ref. Hospitalization No; comorbties No; comorbidities ≤3; cardiovascular No; diabetes melitu No; meuromuscular diseases No; lung disease No; *significant for p<0,05					

Regarding the vaccination status of the cases (n=117,217), 47,834 (40.8%) were unvaccinated, 186 (0.95%) were partially vaccinated. Fully vaccinated (received two doses of vaccine) were 56,035 (47.8%).

A total of 12,072 people received one, while 161 people received two booster doses of the vaccine against COVID-19.

Regarding the vaccination status of the death cases (n=1,658), 996 (60.1%) were unvaccinated, 27 (1.6%) were partially vaccinated. Fully vaccinated (received two doses of vaccine) were 565 (34.1%). A total of 69 people received one, while 1 person received two booster doses of the vaccine against COVID-19 (Table 3).

The analysis showed that complete vaccination with or wiuthout booster dose significantly negatively associated with hospitalization and mortality of Omicron variant of SARS-CoV-2 reducing the probability for hospitalization by 46% and the probability for death by 56%.

Additionaly, complete vaccination with or wiuthout booster dose among hospitalized cases reduces death from Omicron variant of SARS-CoV-2 by 30% compared to unvaccinated/ partially vaccinated cases.

Table 3. Binary logistic regression analysis for predictive role of COVID 19 vaccination status for hospitalization and death from Omicron variant of SARS-CoV-2 (December 2021-December 2022).

COVID-19 Vaccination status	Hospitalization				Death			
	N	p	OR	95% CI	N	p	OR	95% CI
Unvaccinated/ partially vaccinated	2,239	0.0001	0.54	0.51-0.57	1,023	0.0001	0.44	0.40-0.49
2+ doses	1,718				635			
ref. Unvaccinated/ partially vaccinated								*significant for p<0,05

Discussion

The mortality from COVID-19 in general have not been investigated in the Republic of North Macedonia. This epidemiological study aimed to analyze the mortality from Omicron variant of SARS-CoV-2 in the Republic of North Macedonia indicates original insights regarding this problem.

The results of our research suggest that in the Republic of North Macedonia during the circulation of the Omicron variant of SARS-CoV-2, men have almost twice the odds of death associated with the Omicron variant of SARS-CoV-2.

A meta-analysis of 59 studies with 36,470 patients showed that men have a higher risk of disease severity, intensive care unit admission, and death than women [10].

According to the results of our study, the odds of death associated with the Omicron variant of SARS-CoV-2 increases with age, and people over 60 years of age have higher odds for death outcome.

A study in England [19] found that the risk of severe outcomes following SARS-CoV-2 infection is substantially lower for omicron than for delta, with higher reductions for more severe endpoints and significant variation with age. Analysis of COVID-19 mortality by wave in Australia, with a focus on deaths occurring during the Omicron wave showed that at the start 5.5% of people who died from COVID-19 were aged under 60, but this proportion has decreased to under 2%.

Those aged over 90 years have comprised approximately one third of COVID-19 deaths during the Omicron wave [11].

The presence of three or more comorbidities was shown to be a significant factor for death from Omicron variant of SARS-CoV-2 in the Republic of North Macedonia.

The death associated with COVID-19 was significantly higher in patients with cardiovascular and neuromuscular disease. Similar findings were observed in a study China [12], wherein, adverse outcome was significantly higher in patients with comorbidities compared to those without as for consequently hypertension (19.7% vs 5.9%), diabetes (23.8% vs 6.8%), and COPD (50% vs 7.6%).

A pan-India study in 2022, highlighted the significant risk factor for mortality in COVID-19 patients with diabetes (OR=2.39), hypertension (OR=2.31) and heart disease (OR=2.19). [19] In England, diabetes was independently associated with a significant increase in COVID-19 related mortality (OR=2.86)[13].

The results of studies [14-16] have revealed that vaccines against COVID-19 have successfully reduced severity, hospitalization and mortality in various populations since the introduction of the vaccines, but also during the circulation of the Omicron variant of SARS-CoV-2. Similar, our research showed that complete vaccination and/or application of booster dose/doses has a protective factor in relation to the need for hospitalization, which indirectly indicates the fact that the vaccine plays a role in reducing severe clinical forms of the disease.

Also, according to the results, the vaccine against COVID-19 showed a protective factor in relation to the occurrence of death associated with the Omicron variant of SARS-CoV-2.

Conclusion

Male patients, older age group and comorbidities positively associated with death from the Omicron variant of SARS-CoV-2.

Republic of North Macedonia did not meet the target for vaccination in the general population which resulted with significantly more hospitalized and death cases among unvacinated.

The results of this study can be used to prepare the health system for similar future epidemic crises.

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