PREDICTIVE FACTORS FOR MORTALITY FROM DELTA 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 age, underlying health conditions, vaccination status, and immune response. Five variants of concern have been identified by WHO. The Delta variant was first reported in India in late 2020.

Aim: The research aimed to analyze the predictive role of gender, number and type of comorbidities, hospitalization and vaccination status for mortality from Delta variant of SARS-CoV-2 in the Republic of North Macedonia.

Material and methods: The research was a analitical cross-sectional study that included 56,030 cases and 2,292 deaths and elaborated the mortality from Delta variant of SARS-CoV-2 in the Republic of North Macedonia during the period June-November 2021.

Results: The analysis showed that the male gender (OR=1.30; 95% CI=1.20-1.42), the age ≥60 (OR=14.13; 95% CI=12.71-15.72), the positive comorbidity status (OR=13.69; 95% CI=12.25-15.29), and hospitalization (OR=208.1; 95% CI=178.6-242.5) significantly positively associated with death from Delta variant.

Complete vaccination and/or booster dose had significant protective role reducing the probability for hospitalization and death from Delta variant for 38% and 47% respectively.

Conclusion: Male patients, older age and comorbidities positively associated with death from the Delta variant of SARS-CoV-2. The findings of this study can be utilized to compare mortality rates among different variants of SARS-CoV-2.

Keywords: Delta SARS-CoV-2, mortality, hospitalization, vaccination, comorbidity, age

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%. [4,5,6].

The SARS-CoV-2 genome has undergone several mutations since the beginning of the pandemic in December 2019. A number of these mutants were associated with higher transmissibility, higher mortality as well as hospitalization rates, which were named the variants of concern.

The B.1.617.2 or the Delta variant has made a lot of concern as it has been responsible for COVID-19 outbreaks throughout the world. The Delta variant was first reported in India in late 2020 [7]. After that, it was spread rapidly over the world including Republic of North Macedonia from June 2021.

Previous studies have highlighted various demographic, clinical, and socio-economic factors associated with severe outcomes and mortality in COVID-19 patients across different variants. Age, underlying health conditions, vaccination status, and immune response have consistently emerged as key determinants influencing COVID-19 mortality rates [8,9,10,11].

Several studies have highlighted the increased transmissibility and potential for immune evasion exhibited by the Delta variant [12].

Furthermore, emerging evidence suggests that infection with the Delta variant may be associated with an elevated risk of hospitalization and severe disease outcomes compared to earlier strains of SARS-CoV-2 [9,13,14].

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 [15].

Vaccines in 34 countries in the European region reduced deaths by 57% overall (country range: 15% to 75%), representing ~1.4 million lives saved in those aged ≥25 years: 96% of lives saved were aged ≥60 years and 52% were aged ≥80 years; first boosters saved 51%, and 67% were saved during the Omicron period [16].

As of November 30, 2021, a total of 839,596 (40.6%) citizens of the Republic of North Macedonia were vaccinated with at least one dose, and 800,599 (38.7%) were vaccinated with two doses of the COVID-19 vaccine. The coverage of booster doses among the general population was 3.4% for one booster dose.

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

Material and methods

The research was a analitical 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 Delta variant of SARS-CoV-2 in the Republic of North Macedonia during the period June-November 2021 while the circulation of the Delta variant of SARS-CoV-2.

The survey included all COVID-19 associated deaths during the circulation of the Delta variant of SARS-CoV-2 registered in the national system for surveillance of COVID-19. Forigners registered in this system as treated and died in the Republic of North Macedonia, were excluded.

WHO case definition of 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, 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.

The data were processed in SPSS software package, version 26.0 for Windows.

The quantitative series underwent analysis using measures of central tendency (mean, minimum, maximum values) alongside dispersion measures (standard deviation). Risk assessment was conducted using Odds Ratio (OR). A two-tailed analysis was conducted with a significance level set at $p<0.05$ to ascertain statistical significance.

Results

A total of 60,853 cases of COVID-19 during the circulation of the Delta variant of SARS-CoV-2 (I=3,313.1/100,000) were reported in the Republic of North Macedonia from June to November 2021. In the same period, a total of 2,318 death cases were reported with a mortality rate of 126.2/100,000 and a case fatality rate of 3.8%.

According to the pre-set inclusion and exclusion criteria of the study, the further analysis included 56,030 cases and 2,292 deaths. About 2,100 (91.6%) of deaths happened in hospital, and 192 (8.4%) were at home setting.

Of total number of 2,292 COVID-19 associated deaths during the circulation of the Delta variant of SARS-CoV-2, 1,219 (53.2%) were male, and 1,073 (46.8%) were female. The male gender significantly positively associated with death from Delta variant of SARS-CoV-2 - p=0,0001[OR=1.30; 95% CI=1.20-1.42] (Table 1).

The average age of death cases during the circulation of the Delta variant of SARS-CoV-2 was 69.2±13 years ranging from 1 to 100 years. In total, 438 (19.1%) cases were aged <60years, while 1,854 (80.9%) cases were aged over ≥60 years.

The analysis showed that the age ≥60 significantly positively associated with the risk of death from Delta variant of SARS-CoV-2 compared to people in the age group <60 years - p=0.0001[OR=14.13; 95% CI=12.71-15.72] (Table 1).

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

Indicators		N	p	OR	95% CI
Gender	Female	1,073	0.0001*	1.30	1.20-1.42
	Male	1,219			
Age	<60	438	0.0001*	14.13	12.71-15.72
	≥60	1,854			
ref. gender=female; ref. age <60				*significant for p<0,05	

A total of 1,905 (83.1%) death cases were among people with positive comorbidity status. The presence of comorbidities significantly positively associated with death from Delta variant of SARS-CoV-2 - p=0.0001[OR=13.69; 95% CI=12.25-15.29] (Table 2).

About 1,000 (52.5%) deats were registered among patients with two or more comorbidities. Presence of ≥2 comorbidities significantly positively associated with death from Delta variant of SARS-CoV-2 increasing the probability for death by 3,49 times compared to presence of one comorbidity - p=0,0001[OR=3.85; 95% CI=3.49-4.25] (Table 2).

The most common comorbidities presented among the death cases were cardiovascular diseases (n=1,676), diabetes mellitus (n=645), lung diseases (n=319) and neuromuscular diseases (n=217) (Table 2).

The comorbidities that significantly increased the probability of death from Delta variant of SARS-CoV-2 compared to their absence were: a) cardiovascular diseases by 31,34 times [95% CI=27.25-36.03; p=0.0001] b) neuromuscular disease by 10,49 times - [95% CI=8.93-12.33; p=0.0001]; c) diabetes mellitus by 8.09 times - p=0.0001[95% CI=7.31-8.95], and d) lung disease –by 6,83 times - p=0.0001 [95% CI=6.00-7.78] (Table 2).

The analysis showed 208,1 times significantly higher probability of death from Delta variant of SARS-CoV-2 among hospitalized compared to non-hospitalized patients - p=0.0001[95% CI=178.6-242.5] (Table 2).

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

Indicators		N	p	OR	95% CI
Hospitalization	No	192	0.0001*	208.1	178.6-242.5
	Yes	2,100			
Comorbidities	No	387	0.0001	13.69	12.25-15.29
	Yes	1,905			
	1	905	0.0001	3.85	3.49-4.25
	≥2	1,000			
Cardiovascular diseases	No	229	0.0001	31.34	27.25-36.03
	Yes	1,676			
Diabetes mellitus	No	1,260	0.0001	8.09	7.31-8.95
	Yes	645			
Lung disease	No	1,586	0.0001	6.83	6.00-7.78
	Yes	319			
Neuromuscular disease	No	1,688	0.0001	10.49	8.93-12.33
	Yes	217			
ref. Hospitalization No; comorbities No; comorbidities 1; cardiovascular No; diabetes melitu No; meuromuscular diseases No; lung disease No; *significant for p<0,05					

Regarding the vaccination status of the death cases (n=2,292), 1,670 (72.9%) were unvaccinated, 126 (5.5%) were partially vaccinated. A total of 494 (21.6%) received two doses of vaccine while 2 people received one booster dose of the vaccine against COVID-19 (Table 3).

Two doses of the vaccine against COVID-19 significantly negatively associated with hospitalization and mortality of Delta variant of SARS-CoV-2 reducing the probability for hospitalization by 38% and the probability for death by 47%. Additionally, among hospitalized cases it reduces death from the Delta variant of SARS-CoV-2 by 90% 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 Delta variant of SARS-CoV-2 (June 2021- November 2021).

COVID-19 Vaccination status	Hospitalization				Death			
	N	p	OR	95% CI	N	p	OR	95% CI
Unvaccinated/ partially vaccinated	3,605	0.0001	0.62	0.57-0.66	1,796	0.0001	0.53	0.48-0.58
2+ doses	1,178				496			
ref. Unvaccinated/ partially vaccinated								*significant for p<0,05

Discussion

The mortality from COVID-19 in general have not been fully investigated in the Republic of North Macedonia. This epidemiological study aimed to analyze the mortality from Delta variant of SARS-CoV-2 provides original insights concerning this issue.

The results of our research suggest that during the circulation of the Delta variant of SARS-CoV-2, men have 1.3 times the odds of death. 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 [17].

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

A study in England [18] 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 Delta wave showed the Delta wave was the only wave where more than half of the deaths (53.2%) occurred in people younger than 80 years old. This contrasts to Wave 2 where close to 80% of all people who died were aged over 80 years. During the Omicron wave, 71.0% of deaths were of people aged 80 or older [19].

The presence of two or more comorbidities was shown to be a significant factor for death from Delta variant of SARS-CoV-2 in the Republic of North Macedonia, especially in patients with cardiovascular and neuromuscular disease. Similar findings were observed in a study in China [20], 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). [21] In England, diabetes was independently associated with a significant increase in COVID-19 related mortality (OR=2.86) [22].

The analysis in our study showed that the death among hospitalized from Delta variant of SARS-CoV-2 was higher compared to non-hospitalized patients.

The results from a study in England suggest that patients with the delta variant had more than two times the risk of hospital admission and worse outcome compared with patients with the alpha variant [23].

The results of studies [15,24,25] 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 Delta variant of SARS-CoV-2. Likewise, our research findings indicate that receiving two doses of the COVID-19 vaccine offers protection against hospitalization, suggesting its effectiveness in reducing severe cases of the illness. Additionally, our results demonstrate that the COVID-19 vaccine are a protective factor against death linked to the Delta variant of SARS-CoV-2.

Results from the study in England suggest that outbreaks of the delta variant in unvaccinated populations might lead to a greater burden on health-care services than the alpha variant [23.]

Conclusion

Male patients, older age group and comorbidities positively associated with death from the Delta variant of SARS-CoV-2. Low complete vaccination coverage in the general population resulted with higher mortality among unvacinated.

The findings of this study can be utilized to compare mortality rates among different variants of SARS-CoV-2.

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