Comparative Analysis of COVID-19 Severity and Mortality Among Vaccinated and Unvaccinated Individuals During the Delta Variant Surge in a Tertiary Care Center

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Article

Comparative Analysis of COVID-19 Severity and Mortality among Vaccinated and Unvaccinated Individuals during the Delta Variant Surge in a Tertiary Care Center

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Abstract: Introduction: On March 11, 2020, the World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) as a pandemic. The spread of the Delta variant of coronavirus started in June 2021 and accounted for the fifth peak of COVID-19 in Iran in July 2021. According to reports from other countries, vaccination protects against severe diseases caused by COVID-19, including the Delta variant. Studies have also shown that vaccination provides strong protection against SARS-CoV-2 infection, COVID-19-related hospitalization, and mortality. This retrospective cohort study was designed based on the medical care monitoring center (MCMC) database of Sayyad Shirazi Hospital. **Methods:** The following patient data were extracted for this study: demographic characteristics, signs and symptoms, ICU admission, need for aggressive oxygen therapy, including intubation, mortality, and vaccination status. **Results:** Being vaccinated was associated with a 4.14-fold increase in survival (adjusted OR=4.14; 95% CI: 2.22 to 7.69; P<0.01), and individuals in a younger age group demonstrated a 5.58-fold higher likelihood of surviving (adjusted OR=5.58; 95% CI: 4.25 to 8.14; P<0.01). The risk of severe COVID-19 was significantly lower in vaccinated individuals, showing a 3.12-fold decrease in risk (adjusted OR=3.12; 95% CI: 2.06 to 4.72; P<0.01), and in younger age groups, the risk exhibited a 3.28-fold decrease (adjusted OR=3.28; 95% CI: 2.66 to 4.04; P<0.01). **Conclusion:** The present results suggest that receiving at least one dose of COVID-19 vaccine had a significant relationship with decreased COVID-19 severity and mortality in vaccinated patients compared to unvaccinated patients.

Keywords: coronavirus disease 2019 (COVID-19); delta variant; tertiary care; mortality; Vaccination; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which originated from Wuhan, China, started to spread around the world since November 2019. On March 11, 2020, the World Health Organization (WHO) declared it as pandemics around the world. From December, 2019 until November 8, 2021, more than 250 million cases of COVID-19 were reported. Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is the virus responsible for COVID-19. According to WHO reports, this virus is responsible for the death of over five million people in more than 200 countries [1].

The spike glycoprotein on the surface of virion binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is the main target for the virus and is located on the surface of host cells. ACE2 receptors help the virus enter its RNA to the host cell cytoplasm and cause infection [2]. As of May 31, 2021, the World Health Organization (WHO) reported four variants of concern (VOCs): Alpha, Beta, Gamma, and Delta. These variants, particularly those with mutations in the receptor binding domain of the spike gene (S gene), have been associated with increased transmission and severity of the disease. The prevalence and spread of the Delta variant of coronavirus has surpassed

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other variants in most countries. This variant's elevated transmission ability can substantially reduce vaccine effectiveness, increasing the likelihood of breakthrough infections [3–9].

The spread of the Delta variant of coronavirus started in June 2021 and accounted for the fifth peak of COVID-19 in Iran in July 2021 [10]. According to reports from other countries, vaccination protects against severe diseases caused by COVID-19, including the Delta variant. Studies have also shown that vaccination provides strong protection against SARS-CoV-2 infection, COVID-19-related hospitalization, and mortality. Moreover, it has been reported that both full and partial vaccination can be greatly effective against the severe outcomes of COVID-19-related hospitalization and mortality [11,12].

Iran, with a population of 83 million people, is one of the top 10 countries in terms of COVID-19-related mortality. As of November 8, 2021, Iran reported more than six million confirmed cases of COVID-19 and over 127,000 deaths [12]. Vaccination was initiated in January 2021. The first vaccinated groups included the healthcare personnel and frontline workers. Also, mass vaccination started in May 2021. The present study aimed to evaluate the mortality and severity of the Delta variant in vaccinated patients versus unvaccinated patients, admitted to Sayyad Shirazi Hospital in Gorgan, Iran, during the fifth peak of COVID-19, caused by the Delta variant in summer 2021.

MATERIAL AND METHODS

Study design and patients

This study was conducted on the population of Golestan province. Golestan with a population of 1.8 million (2016) is located in the north-west of Iran. People of this province are from different ethnicities like Mazandarani, Turkmen, Baluch, Persian, Kazakh, Kurd, and Azeri[13]. This retrospective cohort study was designed based on the medical care monitoring center (MCMC) database of Sayyad Shirazi Hospital in Golestan Province, Iran.

The inclusion criteria for patient selection encompassed adults aged 18 and above, with confirmation through PCR testing. Additionally, individuals with negative polymerase chain reaction (PCR) results but presenting clinical manifestations consistent with COVID-19 and corresponding findings on chest CT scans were also considered. Between June 22, 2021, and September 22, 2021, a total of 2,964 COVID-19 cases were admitted to this hospital during the Delta variant spread. The study considered all COVID-19 admitted patients within this timeframe. All the patients were examined for a history of confirmed COVID-19 infection, based on standard laboratory protocols. The available findings of PCR and chest computed tomography (CT) for typical COVID-19 were examined in this study.

The following patient data were extracted from medical records and MCMC database of Sayyad Shirazi Hospital for this study: demographic characteristics, signs and symptoms, ICU admission, need for aggressive oxygen therapy, including intubation, mortality, and vaccination status. Individuals receiving one or two doses of vaccine were considered to be vaccinated. Available vaccines during study period in Golestan province were AstraZeneca, Sinopharm, Sputnik, Co-Iran Barakat, and Co- pars.

We defined Severe COVID-19 according to the 2019 clinical practice guideline of the Infectious Diseases Society of America [13].

Statistical analysis

Statistical analyses were performed in SPSS version 16. Numerical variables are reported as mean, standard deviation (SD). Categorical variables were presented as frequency and proportion. A multivariate logistic regression analysis was performed to assess the association of COVID-19 severity and mortality with vaccination and other covariates. Crude and adjusted odds ratios (OR) and their 95% confidence intervals (CIs) were also calculated. For sensitivity assessment, a similar analysis was carried out by restricting the data to only PCR-positive cases. A P-value less than 0.05 was considered statistically significant.

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Ethics approval

The local ethics committee at Golestan University of Medical Science approved this retrospective study (IR.GOUMS.REC.1400.307) according to the 1964 Helsinki declaration and its later amendments. The patient data was appropriately anonymized and maintained with confidentiality. Informed consent was obtained from all individual participants included in the study.

RESULTS

A total of 2,962 confirmed cases of COVID-19, with a mean (SD) age of 51.33 (16.22) years, who were admitted to Sayyad Shirazi Hospital in Shiraz, Iran, were included in this study. Among all participants, 1,597 (53.9%) were female. The demographic characteristics of the patients are presented in Table 1. Among all patients, 524 (17.8%) had severe COVID-19. Overall, 5.2% (27/524) of the patients were vaccinated, while 94.8% (497/524) were unvaccinated. Severe COVID-19 was significantly related to vaccination (adjusted OR=3.12; 95% CI: 2.06 to 4.72; P<0.01) and age (adjusted OR=3.28; 95% CI: 2.66 to 4.04; P<0.01).

Table 1. Demographic characteristics of confirmed COVID-19 patients admitted to Sayyad Shirazi Hospital.

Variable		Number	Percent
Gender			
	Male	1365	46.1
	Female	1597	53.9
Age			
	≤50	1466	49.5
	>50	1496	50.5
COVID-19 diagnosis method			
	PCR	1737	58.6
	Clinical/CT	1225	41.4
Vaccination status			
	Vaccinated	281	9.5
	Unvaccinated	2681	90.5
Health staff			
	Yes	30	1.0
	No	2932	99.0

A total of 269 (9.0%) patients died during the study. Out of the patients who died, only 4.1% were vaccinated, while 95.9% were unvaccinated. Based on the results, being vaccinated (adjusted OR=4.14; 95% CI: 2.22 to 7.69; P<0.01) and a younger age group (adjusted OR=5.58; 95% CI: 4.25 to 8.14; P<0.01) were significantly associated with a lower mortality (Table 2).

The results of sensitivity analysis on 1737 PCR confirmed cases suggested that severe COVID-19 had a significant relationship with vaccination (adjusted OR= 3.04, 95% CI: 1.64 to 5.65, P< 0.01) and age (adjusted OR= 3.71, 95% CI: 2.83 to 4.86, P< 0.01). Overall, 169 PCR-confirmed cases expired, including 162 (95.8%) unvaccinated cases and 139 (82.2%) cases older than 50 years. Vaccination (adjusted OR=2.74; 95% CI: 1.25 to 6.04; P<0.01) and age (adjusted OR= 6.01, 95% CI: 3.99 to 9.05, P< 0.01) were significantly related to mortality in PCR-positive cases (Table 3).

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Table 2. Association between vaccination status and severity or mortality of COVID-19 in patients admitted to Sayyad Shirazi Hospital, Gorgan, between June 22 and September 22, 2021.

		Severe COVID-19							Mortality						
			Crude			Adjusted				Crude			Adjusted		
Variable		N (%)	OR	95% CI	P-value	OR	95% CI	P-value	N (%)	OR	95% CI	P-value	OR	95% CI	P-value
Gender															
	Male	257/1356 (18.8)	1.15	0.96-1.39	0.13	1.15	0.95-1.39	0.16	132/1365 (9.7)	1.14	0.89-1.47	0.30	—	—	—
	Female	267/1597 (16.7)	Ref.	Ref.	—	Ref.	Ref.	—	137/1597 (8.6)	Ref.	Ref.	—	—	—	—
Age															
	≤50	149/1466 (10.1)	Ref.	Ref.	—	Ref.	Ref.	—	47/1466 (3.2)	Ref.	Ref.	—	Ref.	Ref.	—
	>50	375/1496 (25.0)	2.96	2.41-3.63	P< 0.01	3.28	2.66-4.04	P< 0.01	222/1496 (14.8)	5.26	3.87-7.27	P< 0.01	5.88	4.25-8.14	P< 0.01
Vaccine															
	Yes	27/281 (9.6)	Ref.	Ref.	—	Ref.	Ref.	—	11/281 (3.9)	Ref.	Ref.	—	Ref.	Ref.	—
	No	497/2681 (18.5)	2.14	1.423-3.221	P< 0.01	3.12	2.06-4.72	P< 0.01	258/2681 (9.6)	2.61	1.41-4.84	0.002	4.14	2.22-7.69	P< 0.01

Table 3. Association between vaccination status and severity or mortality of COVID-19 in PCR-positive patients admitted to Sayyad Shirazi Hospital, Gorgan, from June 22 to September 22, 2021.

		Severe COVID-19							Mortality						
			Crude			Adjusted				Crude			Adjusted		
Variable		N (%)	OR	95% CI	P-value	OR	95% CI	P-value	N (%)	OR	95% CI	P-value	OR	95% CI	P-value
Gender															
	Male	157/795 (19.7)	1.18	0.922-1.499	0.19	1.16	0.90-1.49	0.25	85/795 (10.6)	1.22	0.89-1.68	0.21	—	—	—
	Female	163/942 (17.3)	Ref.	Ref.	—	Ref.	Ref.	—	84/942 (8.9)	Ref.	Ref.	—	—	—	—
Age															
	≤50	88/891 (9.8)	Ref.	Ref.	—	Ref.	Ref.	—	30/891 (3.3)	Ref.	Ref.	—	Ref.	Ref.	—
	>50	232/846 (27.4)	3.45	2.64-4.50	P< 0.01	3.71	2.83-4.86	P< 0.01	139/846 (16.4)	5.64	3.75-8.48	P< 0.01	6.01	3.99-9.05	P< 0.01
Vaccine															
	Yes	12/116 (10.3)	Ref.	Ref.	—	Ref.	Ref.	—	7/116 (6.3)	Ref.	Ref.	—	Ref.	Ref.	—
	No	308/1621 (19.0)	2.03	1.10-3.74	0.02	3.04	1.64-5.65	P< 0.01	162/1621 (9.9)	1.73	0.79-3.78	0.17	2.74	1.25-6.04	0.01

Table 4. Symptoms observed in COVID-19 patients admitted to Sayyad Shirazi Hospital, Gorgan, between June 22 and September 22, 2021.

Sign and symptoms	Number	Percent
Fever	1365	46.1
Respiratory symptoms	2077	70.1
Myalgia	807	27.2
Gastrointestinal symptoms	718	24.2
Neurological symptoms	555	18.7

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DISCUSSION

Iran has experienced five waves of the COVID-19 pandemic until the end of summer 2021, with the death of over 127,000 people and major economic, medical, and social consequences. The number of COVID-19 patients began to rise in June, reaching the peak during the fifth wave caused by the Delta variant in July 2021. Since June 2021, the majority of new COVID-19 cases in Iran have been caused by the Delta variant [4]. The present results suggest that COVID-19 severity is 3.12 times higher in unvaccinated patients, and also, COVID-19 mortality is 4.14 times higher in unvaccinated patients. However, the present study was performed when most of the patients were partially vaccinated. We also found strong evidence of age dependence in the extent of risk reduction.

Based on the current findings, vaccination demonstrated a significant positive association with a lower risk of severe COVID-19 and a decrease in mortality rates. In a study published in 2021, Noa Dagan et al. estimated that the effectiveness of COVID-19 vaccination against severe disease and death was 80% (95% CI: 59 to 94) and 84% (95% CI: 44 to 100), respectively. They enrolled 596,618 participants in each vaccinated and unvaccinated groups [13]. Abhilash et al. in a cohort study contained 4183 patients, estimated the mortality rate of COVID-19 to be 0.2% (95% CI: 0.2% to 0.7%) and 12.9% (95% CI: 11.8-14.1%) in fully vaccinated and unvaccinated patients, respectively. They also indicated that full vaccination was significantly associated with a lower disease severity, need for respiratory support, ICU admission, and mortality (P<0.001). Their findings showed that at least one dose of vaccine reduced the need for oxygen therapy, non-invasive ventilation, hospitalization, ICU admission, and mortality [14]. The rate of severe COVID-19 was 18.5% in unvaccinated patients in the current study. In a systematic review of 12 studies, consisting of 2,794 COVID-19 patients, 21.33% had a severe disease [23]. In another meta-analysis which also included 12 studies on 2,445 patients, admitted to the hospitals of China, 479 (19.9%) cases had a severe illness or were admitted to the ICU [24]. In our study, 21.2% of patients in the unvaccinated group had a critical disease related to COVID-19, which is consistent with the findings of other systematic reviews (19.9% and 21.33%), respectively [24,25].

Other studies have also indicated the effectiveness of COVID-19 vaccination. In a large retrospective cohort study on 15,244 patients during the Delta variant spread in North India, two doses of vaccine caused greater protection against reinfection [15]. Moreover, in a large integrated health system study conducted in Southern California (N=3,436,957), Tartof et al. reported that fully vaccinated individuals had an adjusted vaccine effectiveness of 73% (95% CI: 72 to 74) against SARS-CoV-2 infection and 90% (95% CI 89–92) against COVID-19-related hospitalization [16]. Besides, Ali Pormohammad et al. in a meta-analysis of 15 studies concluded that vaccination can prevent COVID-19 infection, and reduce the severity of disease and hospitalization against the Delta variant [17].

Eric J Haas et al. used the national surveillance data to show that in all age groups, by increasing vaccine coverage, the incidence of negative SARS-CoV-2 outcomes declined. Their findings indicated that vaccine effectiveness was 95.3% against SARS-CoV-2 infection (95% CI: 94·9 to 95·79), 97.2% against COVID-19-related hospitalization (95% CI:96.8 to 97.5), 97.5% against severe or critical COVID-19-related hospitalization (95% CI: 97.1 to 97.8), and 96.7% against COVID-19-related death (95% CI: 96.0 to 97.3). The findings of this study, similar to the current study, showed the high effectiveness of vaccination in reducing death and preventing the increased severity of this disease [18]. Another study by Jamie Lopez Bernal et al. with a population of 174731, indicated that vaccination could significantly reduce COVID-19 symptoms in older adults and protect against a severe disease. The effectiveness of vaccination was 43% in reducing the risk of emergency hospital admission (33% to 52%) and 51% (37% to 62%) in reducing the risk of mortality in vaccinated patients compared to unvaccinated ones [11].

Our study confirmed that older age is a risk factor for severe COVID-19 (OR: 3.28; 95% CI: 2.66-4.04) and COVID-19 mortality (OR: 5.88; 95% CI: 4.28-8.14). In line with the current findings, Xiaochen Li et al. reported that age over 65 years was significantly associated with severe COVID-19 (OR: 2.2; 95% CI: 1.5-3.5) [19]. Moreover, in a study by J. Zhang et al., it was found that age above 60 years was associated with a lack of improvement in hospitalization, poor condition, and poor outcomes. Overall, older COVID-19 patients were significantly more likely to expire (P=0.004) [20]. It seems that

age-related changes in the adaptive immune response can lead to an increased risk of infection in elderly patients, as defects in both cell-mediated and humoral immunity progressively increase with age, resulting in a marked increase in the incidence of severe infection [21,22].

Limitations: Unfortunately, reliable comorbidity data was not available for this study. This study combines individuals who are partially and fully vaccinated into one group due to the low ratio of fully vaccinated individuals. However, the immunity provided by one dose versus two doses can significantly differ, and combining these two groups can misrepresent the actual impacts. The definitions of COVID-19 related severity can be based on different guidelines in studies, so it should be considered when interpreting the results. Another limitation of the study is the inclusion of patients with negative PCR results but positive CT findings as COVID-19 cases. This approach may introduce bias if the CT findings are not confirmed with COVID-19-specific symptoms or repeat PCR testing.

Conclusion: According to findings elucidated in this study, which underscore a substantial positive association between vaccination and diminished severity of COVID-19 coupled with a noteworthy reduction in mortality rates, it is imperative to direct attention towards future research endeavors to delve into the longitudinal effects of vaccination, the potential efficacy of booster doses, and the intricate dynamics of emerging variants, thereby contributing valuable insights to the ongoing discourse on public health strategies.

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Conflict of interest: The authors declare that there are no conflicts of interest associated with this manuscript.

References

1. Bodrud-Doza M, Shammi M, Bahlman L, Islam ARM, Rahman M. Psychosocial and socio-economic crisis in Bangladesh due to COVID-19 pandemic: a perception-based assessment. Front Public Health. 2020;8: 341.
2. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444-8.
3. World Health O. COVID-19 weekly epidemiological update, edition 42, 1 June 2021. Geneva: World Health Organization; 2021 2021-06-01. https://apps.who.int/iris/handle/10665/341622.
4. World Health O. COVID-19 weekly epidemiological update, edition 64, 2 November 2021. Geneva: World Health Organization; 2021 2021-11-02. https://apps.who.int/iris/handle/10665/348063.
5. Williams SV, Vusirikala A, Ladhani SN, et al. An outbreak caused by the SARS-CoV-2 Delta (B. 1.617. 2) variant in a care home after partial vaccination with a single dose of the COVID-19 vaccine Vaxzevria, London, England, April 2021. Euro Surveill. 2021;26(27):2100626.
6. Ogawa J, Zhu W, Tonnu N, et al. The D614G mutation in the SARS-CoV2 Spike protein increases infectivity in an ACE2 receptor dependent manner. bioRxiv. 2020:2020.07.21.214932.
7. Farinholt T, Doddapaneni H, Qin X, Menon V, et al. Transmission event of SARS-CoV-2 Delta variant reveals multiple vaccine breakthrough infections. BMC Med. 2021;19(1):1-6.
8. Allen H, Vusirikala A, Flannagan J, et al. Household transmission of COVID-19 cases associated with SARS-CoV-2 delta variant (B. 1.617. 2): national case-control study. Lancet Reg Health Eur. 2021:100252.
9. Campbell F, Archer B, Laurenson-Schafer H, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill. 2021;26(24):2100509.
10. COVID-19 Delta Variant Hits Iran. Available at: https://iranprimer.usip.org/blog/2021/jul/13/delta-variant-hits-iran . Accessed June 23, 2022.
11. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021;373:n1088.

12. Scobie HM, Johnson AG, Suthar AB, et al. Monitoring incidence of covid-19 cases, hospitalizations, and deaths, by vaccination status—13 US jurisdictions, April 4–July 17, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(37):1284.
13. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67.
14. Golestan province. Available at: https://en.wikipedia.org/wiki/Golestan_province. Accessed July 3, 2022.
15. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. NEJM. 2021;384(15):1412-23. https://doi.org/10.1056/NEJMoa2101765
16. Abhilash KPP, Mathiyalagan P, Krishnaraj VRK, et al. Impact of prior vaccination with CovishieldTM and Covaxin® on mortality among symptomatic COVID-19 patients during the second wave of the pandemic in South India during April and May 2021: a cohort study. Vaccine. 2022;40(13):2107-13. https://doi.org/10.1016/j.vaccine.2022.02.023
17. Malhotra S, Mani K, Lodha R, et al. SARS-CoV-2 Reinfection Rate and Estimated Effectiveness of the Inactivated Whole Virion Vaccine BBV152 Against Reinfection Among Health Care Workers in New Delhi, India. JAMA Netw Open. 2022;5(1):e2142210-e. https://doi.org/10.1001/jamanetworkopen.2021.42210
18. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021;398(10309):1407-16. https://doi.org/10.1016/S0140-6736(21)02183-8
19. Pormohammad A, Zarei M, Ghorbani S, et al. Effectiveness of COVID-19 Vaccines against Delta (B.1.617.2) Variant: A Systematic Review and Meta-Analysis of Clinical Studies. Vaccines. 2022;10(1):23. https://doi.org/10.3390/vaccines10010023
20. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397(10287):1819-29. https://doi.org/10.1016/S0140-6736(21)00947-8
21. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8. https://doi.org/10.1016/j.jaci.2020.04.006
22. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020;26(6):767-72. https://doi.org/10.1016/j.cmi.2020.04.012
23. Grubeck-Loebenstein B, Wick G. The aging of the immune system. Adv Immunol. 2002. https://doi.org/10.1016/S0065-2776(02)80017-7
24. Weksler ME. Changes in the B-cell repertoire with age. Vaccine. 2000;18(16):1624-8. https://doi.org/10.1016/S0264-410X(99)00497-1
25. Del Sole F, Farcomeni A, Loffredo L, et al. Features of severe COVID-19: A systematic review and meta-analysis. Eur J Clin Invest. 2020;50(10):e13378. https://doi.org/10.1111/eci.13378
26. Li J, He X, Yuan Y, et al. Meta-analysis investigating the relationship between clinical features, outcomes, and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. Am J Infect Control. 2021;49(1):82-9. https://doi.org/10.1016/j.ajic.2020.06.008