Efficacy of COVID-19 vaccination on mortality

ABSTRACT

Background: In this research we aimed to demonstrate the clinical-radiological and laboratory characteristics of patients hospitalized for COVID-19 pneumonia despite having COVID-19 vaccine compared to unvaccinated patients.

Materials-Methods: Patients hospitalized in the COVID-19 clinic between *February 2022 and August 2022* were included in the study. Demographic, clinical features and treatment results furthermore COVID-19 vaccination status of the cases were recorded. The cases were divided into two groups as those with and without the COVID vaccination and compared respectively.

Results: A total of 215 cases were included in the study, 53.5% *(n=115)* were vaccinated. The presence of comorbid chronic diseases and cancer was less in the unvaccinated group. The duration of hospitalization was longer in the unvaccinated group*(9.6 and 7.1 days, respectively).* The number of segments affected were significantly higher in the unvaccinated group*(p<0.05).* Patients who received high-dose glucocorticoid therapy in the unvaccinated group was higher *(28 cases vs. 11 cases; p<0.001).).* The 11.3% *(13/115)* of the patients in the vaccinated group deceased, whereas 14% (14/100) in the unvaccinated group. Vaccination was found to be an independent factor affecting mortality *(p=0.034 CI: 0.108 - 0.918).*

Conclusion: The vaccinated cases were who were infected with COVID-19 had shorter duration of hospitalization and lower severity of radiological involvement. The requirement of pulse steroids were also less compared to unvaccinated individuals. Despite having chronic diseases and cancer, which is considered to have a significant effect on mortality in COVID-19. Additionally although the vaccinated group was older, they had similar mortality rates with unvaccinated subjects.

Keywords: Covid-19, covid-19 related mortality, vaccination

1.Introduction

COVID-19 disease, which emerged in Wuhan, China in 2019, has been one of the deadliest pandemics in recent history. At the time this article 759 408 703 people were infected all over the world, and 6 866 434 people died from this disease.[1,2]

Vaccination is an effective and economical way to combat infectious diseases. While there was only symptomatic treatment against COVID-19 disease at the beginning of the pandemic, vaccine studies started in March 2020, immediately after outbreak of pandemic. Today, it is thought that a more effective fight against the disease is made with more than one COVID-19 vaccine, whose phase 2 and phase 3 studies have been completed urgently.[3]

In pandemic periods, especially in rapidly spreading diseases such as COVID-19, the development of effective and safe vaccines, require comprehensive testing and mass production is a difficult process. This has been achieved via today's cutting-edge technology but the effects and side effects of vaccines should be followed-up closely.[4]

Until now, studies on vaccination in COVID-19 have mostly focused on reducing symptomatic infections and hospitalizations.[5,6]

In this study, the clinical and radiological features of the cases with and without the COVID-19 vaccine inoculations were compared, and the clinical radiological effectiveness of the vaccine was investigated.

2.Materials-Method

RT – PCR positive cases who were hospitalized in the COVID chest diseases clinic of our institution between *February 2022 and August 2022* were included in this retrospective analysis. The research was planned in accordance with the International Declaration of Helsinki and approved by the ethics committee of our hospital *(Ethics Committee approval number 2022/0032).*

Demographic information of the cases such as age, gender, smoking history, and additional chronic diseases were recorded. Routine radiological and laboratory tests, clinical characteristics of the cases, treatment histories, COVID vaccine status, follow-up periods, and treatment results were recorded for all hospitalized patients with the diagnosis of COVID-19 pneumonia. İndividuals were divided into two groups as those with and without effective COVID vaccination. Clinical, radiological and laboratory features of both groups were compared.

Cases <18 years old, with RT – PCR test, unknown COVID-19 vaccination, who were not vaccinated effectively, and pregnant women were not included in the study.

2.1.COVID-19 Pneumonia case definition and treatment

All of the study population consisted of individuals that were found to be positive in real-time reverse transcription polymerase chain reaction *(rRT – PCR)* with combined swab sample *(oropharyngeal and nasal swab)* according to the COVID-19 diagnosis and treatment guideline of the Ministry of Health. Bilateral diffuse *(>50%)* lung involvement and/or respiratory rate ≥24/minute, and/or room air SpO_2 level ≤93% has been observed in hospitalized patients.

The treatment of the cases was regulated according to the COVID-19 diagnosis and treatment guideline of the Ministry of Health of Turkey, and if there were no contraindications,

low molecular weight Heparin was used for thrombosis prophylaxis, favipravir as antiviral treatment, oxygen support in cases who have passed the viral replication phase *(first 5 – 7 days),* 6 mg/day dexamethasone or 0.5 – 1 mg/kg prednisolone has been administered. Additionally in cases with clinical and radiological worsening with increased oxygen demand in 24 hours despite treatment and increased acute phase response, higher dose glucocorticoid *(pulse ≥250 mg/day methyl prednisolone)* has been administered.[7]

2.2Radiological evaluation of a COVID-19 pneumonia

Non-contrast chest tomography was performed for each patient as standard radiological evaluation. Thorax CT were performed by a 16-slice CT scanner *(GE Optima CT520)* with the following acquisition parameters: Tube voltage 100 kV, tube current 70–120 mAs, slice thickness 1.25 mm, automatic dose modulation, CT volume-dose index 5.60 mGy, dose length product 179.32–210.48 mGy, and effective dose 2.5–2.9 mSv. In the evaluation of thorax CTs, the involvement patterns of the lesions *(ground glass opacities, consolidation, air bronchogram, interlobular septal thickening, etc.)* were examined and recorded. In addition, considering the total number of segments out of 17, the number of segments involved with the lesion of each COVID-19 case was recorded.[8]

2.3Vaccination status

Patients who were inoculated with two types of vaccine, which were routinely used in our country at the time of the study were included in the study. Individuals were considered to be fully vaccinated if they have received inactivated SARS-CoV-2 vaccine produced by Sinovac as 2 doses *(0.5 ml)* intramuscularly and had the last dose at least 14 days ago or inoculated by 2 doses *(0.3 ml)* intramuscularly Pfizer/Biontech vaccine, last dose at least 21 days ago and did not exceed 6 months after the last dose of vaccine. [9]

2.4.Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 software. Central tendency measures (mean and standard deviation) for numerical variables, and calculated frequency distributions (number and percentage) for categorical variables were described in study data. The presence of differences between the two groups using an independent Sample t-test and a Mann–Whitney U-test were evaluated under appropriate conditions. Chi-squared test for assessing associations between categorical variables were presented. Cox regression analysis was used for the significance of factors associated with mortality. Within the confidence interval (CI) of 95%, the results were considered significant at $P < 0.05$ and highly significant at $P< 0.01$.

3.Results

The files of 273 patients hospitalized in the COVID clinic between February *2022 and August 2022* have been enrolled in this retrospective analysis. Thirty-one cases were excluded because their vaccination status was unknown and 27 cases were excluded because their PCR test was negative. A total of 215 patients were included in our study, and the patients were divided into 2 groups according to their vaccination status as those who did not have an effective COVID-19 vaccination *(n=100)* and who had an effective COVID-19 vaccination *(n=115)*. Of the COVID effective vaccination group, 67 *(58.2%)* were inoculated with inactivated vaccines and 48 *(41.8%)* RNA-based vaccines.

The mean age of the unvaccinated group was 57.66 ± 17.05 years, and the mean age of the vaccinated group was 72.27 ± 14.08 *(p<0.001)*. There was no difference between the two groups in terms of gender. Comorbid diseases and cancer were more common in the vaccinated group. The duration of hospitalization in the unvaccinated group was 9.60 ± 6.0 days, while the

hospitalization period in the vaccinated group was significantly shorter, 7.19 ± 3.77 days *(p<0.001), (Table 1).*

When the laboratory parameters of the patients were examined, statistically significant differences were observed between total leukocyte count *(WBC),* hemoglobin *(Hb),* hematocrit *(Htc),* lymphocyte percentage, neutrophil count and percentage, eosinophil count and percentage between unvaccinated and vaccinated patients *(Table 2).*

When biochemical parameters were examined, urea and creatinine values were statistically higher in vaccinated patients *(unvaccinated and vaccinated, respectively, Urea: 31.68 ± 15.28, 46.90 ± 29.92; Creatinine: 0.858 ± 0.252, 1, 02 ± 0.396).* Serum C-reactive protein *(CRP)* and Procalcitonin *(PRC)* values of the vaccinated patients were found to be significantly higher *(Table 2)*.

Although there was no difference between the two groups in terms of the involvement pattern in the radiological evaluations of the patients, the number of segments involved in the vaccinated group was statistically significantly lower *(Table 3).*

While no difference was observed between the anti-viral treatments given to both groups, individuals who were given high-dose glucocorticoid *(pulse steroid)* treatment were higher in the unvaccinated group *(28 cases vs. 11 cases; p<0.001)*. The total number of steroid used days was also significantly higher in unvaccinated cases *(8.69 ± 5.26, 6.54 ± 3.72, respectively; p<0.001) (Table 4).*

There was no statistically significant difference between the two groups in terms of intensive care unit *(ICU)* admissions *(15.6%, n=18/115 of the cases in the vaccinated group and 18%, n=18/100) in the unvaccinated group were transferred to the ICU), (p=0.703).* In terms of mortality, 11.3% *(13/115)* of the cases deceased in the vaccinated group, and 14%

(14/100) in the unvaccinated group. No statistically significant difference between the two groups has been achieved *(p=0.855).*

When the factors affecting mortality were examined with multifactorial regression analyzes, being vaccinated *(p=0.034 CI: 0.108 – 0.918),* being older than 65 years, having chronic heart disease, taking pulse steroids during treatment, and the number of days of hospitalization were among the independent factors affecting mortality *(Table 5).*

4.Discussion

In this study, we have investigated the importance of effective vaccination in COVID-19 disease whether cases with COVID-19 vaccine were hospitalized for a shorter period, the rate of radiological involvement was lower, they had less requirement for high-dose/pulse steroid treatment that had to be used in severe patients. Additionally we have also tried to observe the difference of immunological response (*higher CRP, PRC, WBC, and lower lymphocyte percentage)* in COVID-19 pneumonia. It has been observed that both groups had similar mortality rate despite the older age and the presence of more additional chronic diseases including cancer in the vaccinated group.

As in other diseases involving the lung parenchyma, thoracic CT in has an important diagnostic role in COVID-19 pneumonia, classification of its severity, and the monitoring of the response to treatment.[10] *Li Y et al* investigated 98 cases who died due to COVID-19 *(46 cases)* and survived after COVID-19 *(52 cases)* and stated that lung involvement was 53.2% in the thorax CT of the deceased group and this rate was 35% in survived cases *(p< 0.001).* [11] In our study, radiological involvement patterns *(ground glass, consolidation, interlobular septal thickening, air bronchogram)* were similar between the vaccinated and unvaccinated groups *(p>0.05).* On the other hand, there was a statistically significantly less segment involvement in the vaccinated group *(p=0.006).* This finding suggested that effective vaccination may limit the

radiological course of the disease. *Lee JE et al.* evaluated the characteristics of vaccinated and unvaccinated patients *(total n=761)* and elaborated that 41% of vaccinated cases and 78% of unvaccinated cases had pneumonia *(p <0.001)*.[12] The results of this study also emphasized that vaccination in COVID-19 disease may be associated with radiological severity, similar to our study.

In COVID-19 pneumonia, radiological methods can be used to show the severity of the disease, as well as cheaper reproducible laboratory methods without harmful radiation effect.[13] One of them is peripheral blood lymphocytes. Many studies have shown that lymphopenia is mostly seen in COVID-19 cases and this is associated with the severity of the disease. Lymphopenia has been detected in most of these studies and this has been attributed to the hypothesis that the virus directly infects lymphocytes or affects lymphatic organs, inhibition of lymphocytes by secreted inflammatory cytokines, or a decrease in the number of lymphocytes in the peripheral blood as a result of migration to inflammatory regions.[13-16]

There are few studies on the effect of COVID-19 vaccine on hematological parameters. Among them, *Sing CW et al.* found that the risk of leukopenia-neutropenia increased especially after mRNA vaccines in cases >60 years old, but they could not come to a conclusion about the exact reason for this. [17,18] The lymphocyte values of the cases included in this study were not evaluated. On the other hand, *Mulligan MJ et al* identified lymphopenia in post-vaccination cases. [19] The authors concluded that this finding was due to the fact that RNA vaccines induce type I interferon, which is associated with transient migration of lymphocytes into tissues, and does not affect the clinical situation. Our study is compatible with the literature in this sense. Lymphocyte % value was lower in the COVID-19 vaccinated group than in the unvaccinated group *(14.8 ± 10, 18.2 ± 11.2, p=0.021, respectively)*. It is known that natural COVID-19 infection causes lymphopenia, and pro-inflammatory cytokine release and acute phase reactants are increased in severe COVID-19 infection.[20,21] Although the reaction of immune system

develops against COVID-19 has not yet been solved, lymphocytes have great importance in both innate and vaccine-induced immunity *(CD8 – CD4 lymphocytes)*.[22-24] Similar to other coronaviruses, a lymphocyte-mediated *(T Lymphocyte)* protective immune response is induced in SARS-CoV-2 infections. We interpreted that the lymphocyte % values of the vaccinated cases were lower at the beginning of the disease compared to the unvaccinated cases, as the human immune system that encounters COVID-19 through vaccination has a preparation against COVID-19 from the beginning of the disease. In our study, acute phase reactants such as CRP and PRC, and WBC and Neutrophil counts were also found to be higher in vaccinated COVID-19 cases compared to vaccinated COVID-19 cases. Similarly, the higher CRP, PRC and WBC values of vaccinated cases suggested that vaccinated individuals may have a different immune response to COVID-19 disease. Although we cannot prove this hypothesis at the moment, prospective studies coud be planned to investigate the clinical features of vaccinated and unvaccinated cases in the future, CRP, PRC, WBC and lymphopenia levels were determined by evaluating the antibody level against COVID-19 in vaccinated cases with high acute phase reactant levels and low lymphopenia. Our hypothesis can be proved or disproved by examining the antibody level correlation.

Although the cause has not been fully elucidated, life-threatening pneumonia, respiratory failure and acute respiratory distress syndrome *(ARDS)* develop in some cases of COVID-19. Studies have shown that such patients have higher serum cytokine levels, and this is called cytokine storm. [25,26] There are conflicting results regarding the use of corticosteroids in COVID-19 pneumonia. *Bartoletti et al.* reported that there was no effect on mortality in pateints treated with corticosteroids in hospitalized cases, and the effect of corticosteroid treatment on mortality may be limited to COVID-19 patients with critical illness. [27] On the other hand, *Edalatifard M et al*. reported that mortality was lower and recovery time was shorter in the group who received 250 mg/day intravenous methylprednisolone for 3 days in a single-

blind, randomized controlled study.[28] While there was no difference between the two groups of antiviral and routine glucocorticoid *(0.5-1 mg/kg prednisolone)* treatments in our study, the cases in which we had to switch to pulse steroid treatment due to clinical radiological deterioration and increased oxygen demand under routine treatment were more common in the unvaccinated group. Pulse steroid was initiated in 28 cases in the unvaccinated group, this number was 11 cases in the vaccinated group *($p<0.001$).* In addition, we used glucocorticoids for a total of 8.69 ± 5.26 days in the unvaccinated group, while we used glucocorticoids for 6.54 ± 3.72 days in the vaccinated group *($p<0.001$).*

Today, it is accepted that vaccination against COVID-19 significantly reduces hospitalizations and is highly protective against severe illness and death, especially in adults older than 65 years. The Centers for disease control and prevention *(CDC)* pays particular attention to the protection/vaccination of people at high risk for severe disease.[29,30] Tenforde MW et al. have compared the characteristics of hospitalized vaccinated and unvaccinated COVID-19 cases, as in our study.[31] In their study, the unvaccinated *($n=314$)* COVID-19 cases consisted of a younger population than the vaccinated group *($n=1669$) (53-67, respectively).* Similarly, chronic diseases were less in the unvaccinated group. The authors concluded that vaccination against COVID-19 may prevent progression to invasive mechanical ventilation and death. In our study, the data of both groups were similar in terms of death and ICU course. The reason for this may be that our study was planned with a relatively small sample size. However, the fact that the vaccinated group consisted of patients with advanced age and additional disease, that is, at high risk in terms of severe disease, had a relatively low risk and similar mortality compared to the younger age group, which may be related to being vaccinated.

One of the main limitations of our study could be attribted to its retrospective nature and relatively small number of sample size in a single center. Not knowing the blood antibody levels of the vaccinated cases, not knowing the blood antibody levels, which is one of the real

indicators of immunity against COVID-19, and not knowing whether there is a correlation between antibody levels and parameters such as radiological involvement frequency and laboratory values are other limitations of our study. In addition, the inability to conduct examinations according to vaccine subgroups can be counted among the limitations. These limitations should not be ignored when interpreting the results of the study.

4.1.Conclusion

The vaccinated cases were who were infected with COVID-19 had shorter duration of hospitalisation and lower intensity of radiological involvement. The requirement of pulse steroids were also less compared to unvaccinated individuals. Despite having chronic diseases and cancer, which is considered to have a significant effect on mortality in COVID-19. Additionally although the vaccinated group was older, they had similar mortality rates with unvaccinated subjects.

References

1. Zhu N, Zhang D, Wang W, Li XX, Yang B et al. A Novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382:727-733.
2. World Health Organization [Internet]. © 2023 WHO. Coronavirus disease (COVID-19) pandemic. [Accessed March 12,2023]. Available from: https://web.archive.org/web/20230312053841/https://www.who.int/emergencies/diseases/novel-coronavirus-2019
3. Kazak A, Hintistan S, Betül Ö. COVID-19 Vaccine Development Studies in the World and Turkey. Celal Bayar University-Health Sciences Institute Journal 2020: (7); 571-575.
4. Remy, V, Largeron, N, Quilici, S, Carroll, S, The economic value of vaccination: Why prevention is wealth. Value in Health 2014;17 (7):A450.
5. Sheikh A, McMenamin J, Taylor B, Robertson C; Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet 2021;397 (10293): 2461-62.
6. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK et al. Prevention and attenuation of COVID-19 with the BNT162b2 and mRNA-1273 vaccines. N Engl J Med 2021;385(4):320-329.
7. T.C. Sağlık Bakanlığı [İnternet]. © 2023 T.C. Sağlık Bakanlığı. COVID-19 Tanı ve Tedavi Rehberi. [Accessed: 21 March 2023]. Available from: https://covid19.saglik.gov.tr/TR-66926/eriskin-hasta-tedavisi.html
8. Zhou Z, Guo D, Li C, Fang Z, Chen L et al. Coronavirus disease 2019: Initial chest CT findings. Eur Radiol 2020;30 (8):4398-4406.
9. Yavuz E. "COVID-19 vaccines." Turkish Journal of Family Practice 2020; 24(4): 227-234.

10. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. AJR Am J Roentgenol 2020;214(6):1280-86.
11. Li Y, Yang Z, Ai T, Wu S, Xia L. Association of "initial CT" findings with mortality in older patients with coronavirus disease 2019 (COVID-19). European Radiology 2020;30(11):6186-93.
12. Lee JE, Hwang M, Kim YH, Chung MJ, Sim BH et al. Imaging and Clinical Features of COVID-19 Breakthrough Infections: A Multicenter Study. Radiology 2022; 303(3):682–692.
13. Tan L, Wang Q, Zhang D, Ding J, Huang Q et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020: 27;5(1):33.
14. Wu C, Chen X, Cai Y, Xia J, Zhou X et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7): 934-43.
15. Ghweil A, Hassan MH, Khodeary A, Mohamed AO, Mohammed HG et al. Characteristics, Outcomes and Indicators of Severity for COVID-19 Among Sample of ESNA Quarantine Hospital's Patients, Egypt: A Retrospective Study. Infection and Drug Resistance 2020;13: 2375–83.
16. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020;95 (6):E131-4.
17. Sing CW, Tang CTLM, Chui CSL, Fan M, Lai FTT et al. COVID-19 vaccines and risks of hematological abnormalities: Nested case-control and self-controlled case series study. Am J Hematol 2022; 97(4): 470-480.

18. Cummins D, Wilson ME, Foulger KJ, Dawson D, Hogarth AM. Haematological changes associated with influenza vaccination in people aged over 65: case report and prospective study. Clin Lab Haematol 1998; 20(5): 285- 287.
19. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020;586(7830): 589-593.
20. Cheng LL, Guan WJ, Duan CY, Zhang NF, Lei CL, et al. Effect of Recombinant Human Granulocyte Colony-Stimulating Factor for Patients With Coronavirus Disease 2019 (COVID-19) and Lymphopenia: A Randomized Clinical Trial. JAMA Intern Med 2021;181(1):71-78.
21. Larsen MD, de Graaf EL, Sonneveld ME, Plomp HR, Nouta J, Hoepel W et al. Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Science 2021: 26;371(6532):eabc8378.
22. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol 2020;20(10):615-632.
23. Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol 2021;21(8):475-484.
24. Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. Cell Stress 2020;4(4):66-75.
25. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020: 28;395(10229):1033-1034.

26. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. Clin Chim Acta 2020;509:180-194.
27. Bartoletti M, Marconi L, Scudeller L, Pancaldi L, Tedeschi S et al. Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: a multicentre study. Clin Microbiol Infect 2021;27(1):105-111.
28. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J 2020: 24;56(6):2002808.
29. Centers For Diseases Control and Prevention; Summary of Guidance for Minimizing the Impact of COVID-19 on Individual Persons, Communities, and Health Care Systems United States, August 2022 (Accessed march 3,2023) Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7133e1.htm
30. Yuan Y, Thierry JM, Bull-Otterson L, Yeargin-Allsopp M, Clark KEN et al. COVID-19 Cases and Hospitalizations Among Medicare Beneficiaries With and Without Disabilities - United States, January 1, 2020-November 20, 2021. MMWR Morb Mortal Wkly Rep 2022:17;71(24):791-796.
31. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. JAMA 2021: 23;326(20):2043-2054.