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THE COMPARISON OF THE LABORATORY PARAMETERS OF INACTIVATED CORONAVIRUS VACCINATED AND NON-VACCINATED COVID-19 PATIENTS APPLIED HOSPITAL

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Abstract

Objectives: The comparison of laboratory parameters of non-vaccinated and inactivated coronavirus-vaccinated patients who came down with COVID-19.

Materials and Methods: The study was designed as a retrospective cross-sectional study between March 2020 and April 2021. 154 patients who had no vaccination(n=77) and one-dose (n=28) or two-dose (n=49) inactivated coronavirus vaccination, demographical data's, hemogram, C-reactive protein (CRP), ferritin and D-dimer levels were evaluated.

Results: In total, 154 patients were included in the study (84 female, 54.5%). The mean age was 65.1±14.5 years. The ferritin level was 449.93±443.48 ml/ng in one-dose vaccinated patients, 297.68±340.32 ml/ng in two-dose vaccinated patients and 568.70±539.41 ml/ng in unvaccinated patients; this difference was statistically significant (p=0.008). The D-dimer level was 0.86±0.89 µg/L in one-dose vaccinated patients, 0.67±0.79 µg/L in two-dose vaccinated patients and 1.62±1.93 µg/L in unvaccinated patients; again, a statistically significant difference existed (p=0.002). The rates of hospitalization in the ward and intensive care unit (ICU) and D-dimer levels were lower in two-dose vaccinated patients than in unvaccinated patients (p=0.015). No significant difference was detected concerning hemogram and CRP level of non-vaccinated, one-dose vaccinated and two-dose vaccinated patients.

Conclusion: Even if vaccinated, individuals can get COVID-19, but disease progression is milder, and ferritin and D-dimer levels related to disease severity are higher in unvaccinated patients.

Keywords: Inactivated coronavirus vaccine, COVID-19, lymphocyte, CRP, ferritin, D-dimer.

Introduction

The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020. To prevent the spread of the COVID-19 pandemic and to control the disease, among other measures, a mass COVID-19 vaccination program has been implemented in our country and worldwide. Since the beginning of the epidemic, numerous vaccines have been formulated worldwide, including inactivated, live virus, recombinant protein, vector, DNA or RNA vaccines developed by various companies. In our country, risk groups were established on January 13, 2021, and the CoronaVac vaccine, an inactivated SARS-CoV-2 vaccine, was used for the first time.[1]

In viral diseases that affect respiratory passage, consistent correlations are reported among C-reactive protein (CRP), ferritin, erythrocyte sedimentation speed, fibrinogen, haptoglobulinemia, serum amyloid A, acute phase proteins like procalcitonin and lymphocyte, and D-dimer levels with the progression of the disease. CRP, ferritin, and d-dimer levels were increased in the serum of the organisms that were affected by the viruses that caused respiratory passage disease compared to healthy samples. Acute-phase proteins are a good marker for showing the severity of viral replication, evaluating the individual immune response to the virus, diagnosing the disease, and evaluating the response to antiviral agents. As with other viral infections, vascular damage occurs in COVID-19 disease in association with the systemic inflammatory response.[2] The severity of vascular damage and mortality in COVID-19 disease is thought to be related. D-dimer and troponin are other laboratory parameters used to predict cardiovascular damage and mortality in coronavirus disease.[3,4]

In our study, we aimed to compare the patients' hemogram, CRP, ferritin, and d-dimer levels who caught COVID-19 after having inactivated coronavirus vaccination and the patients' hemogram, CRP, ferritin, and d-dimer levels who caught COVID-19 before being vaccinated.

Materials and Methods

The study was designed as a retrospective cross-sectional study. Between March 2020 and April 2021, patients older than 18 years who were hospitalized in the ward or intensive care unit (ICU) for COVID-19 in the pre-vaccination period and patients who developed COVID-19 and who were hospitalized in the ward or ICU in the post-vaccination period (one- or two-doses) were enrolled (77 vaccinated, 77 unvaccinated). Patients who had received Biontech's mRNA vaccine were excluded.

COVID-19 patients were divided into three groups based on treatment site: outpatients, inpatients in the ward, and inpatients in the ICU.

Patients were administered CoronaVac, an inactivated viral vaccine. We divided patients according to their vaccination status into unvaccinated, one-dose vaccinated, and two-dose vaccinated patients (unvaccinated patients n=77, one-dose vaccinated patients n=28, two-dose vaccinated patients n=49).

Non-vaccinated patients: The patients were composed of the ones who caught COVID-19 before the vaccination period and were outpatients or received treatment in a ward or intensive care unit.

The patients who had one-dose CoronaVac: The patients were composed of the ones who had COVID-19 after one-dose vaccination and were outpatients or received treatment in a ward or intensive care unit.

The patients who had two-dose CoronaVac: The patients were composed of the ones who had COVID-19 after two-dose vaccination and were outpatients or received treatment in a ward or intensive care unit.

Patient demographic characteristics and laboratory data (hemogram, CRP, ferritin, D-dimer) were obtained from the hospital database. Hemogram, CRP, ferritin, and D-dimer values of patients were measured in blood drawn at the time of hospital admission.

Statistical Analysis

All analyses were performed via SPSS V22 for Windows program (SPSS Inc., Chicago, IL, USA). Frequencies and percentages of categorical variables: mean, median and standard deviation values of numerical variables were calculated. T-tests or One-way ANOVA were conducted for numerical variables showing homogeneous distribution. Categorical variables were tested with the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

In total, 154 patients were included in the study (one-dose vaccinated patients: 28, two-dose vaccinated patients: 49, unvaccinated: 77), of whom 70 were male and 84 (54.54%) were female. The mean age was 65.14±14.5 years (vaccinated: 65.40±15, unvaccinated: 64.71±14.17). There was no statistical difference between vaccinated and unvaccinated patients in terms of age and gender ratio. Comorbidities were found in 127 patients. The most common comorbidities were hypertension (n=104, 67.53%), heart failure (n=42, 27.27%), asthma (n=32, 20.77%), and COPD (n=31, 20.12%), respectively. Of the exitus patients with a rate of %19.49, 56.66% (n= 17) were unvaccinated, 23.33% (n= 7) were two-dose vaccinated, and there was no statistical significance between vaccination status and mortality rate (Table 1).

Table 1. Demographic characteristics of patients with COVID-19 (n=154)

	1-dose vaccinated patients	2-dose vaccinated patients	Unvaccinated patients
Age, year (mean±SD)	68.57±8.15	63.73±17.62	64.71±14.17
Gender (n, %)			
Male	13(8.44)	22(14.28)	35(22.72)
Female	15(9.74)	27(17.53)	42(27.27)
Comorbidity (n, %)			
Hypertension	24(23.07)	32(30.76)	48(46.15)
Heart failure	15(35.71)	14(33.33)	13(30.95)
Asthma	4(12.50)	12(37.50)	16(50)
COPD	8(25.80)	9(29)	14(45.16)
Diabetes mellitus	1(4)	8(32)	16(64)
Cerebrovascular Event (CVE)	5(23.80)	10(47.61)	6(28.57)
Alzheimer's disease	1(11.11)	3(33.33)	5(55.55)
Malignancy	3(60)	1(20)	1(20)
Obesity	1(25)	2(50)	1(25)
Chronic Renal Insufficiency	3(75)	0(0)	1(25)
Disease severity (n, %)			
Outpatient	17(11.03)	0(0.00)	17(11.03)
Inpatient	22(14.28)	20(12.98)	43(27.92)
İntensive care unit	10(6.49)	8(5.19)	17(11.03)
Survival (n,%)	7(4.54)	6(3.86)	17(11.03)
Non-survival (n,%)	25(16.23)	22(14.28)	43(27.92)

When comparing laboratory parameters between one-dose vaccinated, two-dose vaccinated and unvaccinated patients, no statistical significance was found in leukocyte, neutrophil, lymphocyte, monocyte and CRP levels. Ferritin level was 449.93±443.48 ml/ng in one-dose vaccinated patients, 297.68±340.32 ml/ng in two-dose vaccinated patients and 568.70±539.41 ml/ng in unvaccinated patients and was statistically significant (p=0.008). The D-dimer level was 0.86±0.89 µg/L in one-dose vaccinated patients, 0.67±0.79 µg/L in two-dose vaccinated patients and 1.62±1.93 µg/L in the unvaccinated patients and was statistically significant (p=0.002) (Table 2).

While the rate of those with D-dimers <0.5 µg/L was 12.98% (n=20) in the unvaccinated patients, it was 20.12% (n=31) in two-dose vaccinated patients (p=0.001). The rate of those with D-dimers ≥1.0 µg/L (20.77%, n=32) was significantly higher in unvaccinated patients than in two-dose vaccinated patients (6.49%, n=10) (p=0.001) (Table 3).

In those with severe disease who were hospitalized in the ICU, ferritin and D-dimer levels were significantly higher in unvaccinated patients than in one-dose vaccinated and two-dose vaccinated patients (D-dimer

p=0.015; ferritin p=0.029). In outpatients with milder disease, D-dimers were lower in two-dose vaccinated patients than in unvaccinated patients, which was statistically significant (p=0.002) (Figure 1-2).

Table 2. Comparison of laboratory parameters in vaccinated and unvaccinated COVID-19 patients

	1-dose vaccinated patients	2-dose vaccinated patients	Unvaccinated patients	p
Leukocyte $X10^3/\mu l$	8.73±5.33	8.23±4.00	9.06±4.60	0.606
Neutrophil $X10^3/\mu l$	7.07±4.94	6.04±3.56	7.24±4.52	0.302
Lymphocyte $X10^3/\mu l$	1.01±0.53	1.46±0.90	1.20±0.83	0.051
Monocyte X103/µl	0.59±0.41	0.60±0.36	0.56±0.45	0.838
CRP mg/L	69.21±54.60	62.01±68.67	82.90±66.70	0.203
Ferritin, ml/ng	**449.93±443.48**	**297.68±340.32**	**568.70±539.41**	**0.008***
D-dimer, µg/L	**0.86±0.89**	**0.67±0.79**	**1.62±1.93**	**0.002***

CRP= C-reactive protein, p<0.05 The means of the groups were analyzed with the One-Way ANOVA test.
*A post-hoc test was performed for Ferritin and D-dimer levels. For Ferritin Mean Square=0.61, F= 1.69; for D-dimer Mean Square: 0.61, F= 1.14 was determined.

Discussion

The goal of vaccines developed against viral diseases is to completely prevent the disease, ameliorate the severity of the disease, or prevent mortality and morbidity. Studies of vaccine efficacy have shown that the efficacy of two doses of an mRNA vaccine ranges from 95 to 81%. [4,5] The host immune response to the coronavirus vaccine is highly variable, and even when vaccinated, COVID-19 can occur in the vaccinated population because the effect of the vaccine on new variants is not yet known. According to the WHO report, the success of the inactivated coronavirus vaccine used in China, Chile, Turkey, Indonesia, and Brazil varies between 84-50% in preventing symptomatic disease and between 100-85% in preventing hospitalization.[6] When the disease emerges, the effect of vaccination is not known on laboratory parameters (lymphocyte, CRP, D-dimer and ferritin). This study showed that ferritin and D-dimer levels are higher in non-vaccinated patients when compared to the severity of disease among two-dose vaccinated ones.

Vaccinations have a role as an immunomodulator in the emergence of disease by generating immune body against viruses. The roles of CRP, ferritin, erythrocyte sedimentation rate, fibrinogen, haptoglobulinemia, serum amyloid A, and acute phase proteins such as procalcitonin.[2] The APPs, which are the indicator of individual immune response in COVID-19 disease, are significant parameters in evaluating disease severity, indicating organ damage and mortality.

Although CRP level is known to be elevated in noninfectious diseases, it is also an APP that has been routinely used in clinical practice for many years to assess disease progression and response to treatment of infectious

diseases. In a meta-analysis, CRP was found to indicate disease severity but did not increase mortality.[7] A study by Liu et al. reported that COVID-19 disease progressed severely in cases with a CRP > 41.8 mg/L.[8] Yormaz et al. emphasized that 67.47% of cases with COVID-19 disease had high CRP levels.[9] It is not clear how CRP levels develop in people with the disease, even if they are vaccinated. We detected no significant difference between CRP levels considering non-vaccinated one-dose vaccinated and two-dose vaccinated in our study.

Ferritin, often used to diagnose iron-deficiency anemia, is another APPs that can increase with viral infections.[10] A retrospective study of COVID-19 mortality by Ruan et al. concluded that IL-6, ferritin, and CRP were higher in non-survivors than in survivors.[11] Moreover, ferritin level was an independent APP in COVID-19, ARDS and mortality in different studies. CRP, lymphopenia and D-dimers have been shown to have an effect on survival, but ferritin has not been shown to be related to survival.[12,13] In our study, ferritin levels were significantly lower in two-dose vaccinated patients than in one-dose vaccinated and unvaccinated patients.

D-dimer level is a good marker to indicate thrombi as well as a good APP associated with fibrin degradation, leading to activation of the fibrinolytic system and reflecting coagulation activity.[14] In a study by Yu et al. comparing D-dimer level in bacterial pneumonia and COVID-19 pneumonia, it was revealed that D-dimer level in COVID-19 disease was associated with inflammation.[15] Again, several studies have reported that high D-dimer levels increase the risk of thrombosis and mortality.[16,17] Similar to other studies, Tang et al. showed that D-dimer level in COVID-19 was associated with mortality and that prophylactic anticoagulant therapy reduced 28-day mortality by 20%.[18] There is no study examining D-dimer level and mortality in people with COVID-19 who had been previously vaccinated. In our study, the D-dimer level in unvaccinated individuals was approximately twice that in two-dose vaccinated individuals. We found that in patients hospitalized in the ICU, D-dimer levels were 4.4 times higher in unvaccinated patients than in two-dose vaccinated patients

The lower hospitalization rate in vaccinated individuals suggests that vaccinated individuals have a mild disease course, even if they had a prior disease due to COVID-19. The high hospitalization rate in the unvaccinated patients and the higher D-dimer level in this group led us to believe that the vaccine might also be effective in preventing microthrombus formation. This result should be supported by other studies, as the information in the literature is insufficient.

There are many studies showing an association between the severity of COVID-19 and lymphopenia.[19,20] Lymphopenia has been associated with severe disease requiring hospitalization. 80% of patients hospitalized for severe COVID-19 disease and 25% of patients for moderate COVID-19 disease had lymphopenia.[13] In our study, lymphocyte levels were lower in unvaccinated patients than in two-dose vaccinated patients. When comparing hospitalizations due to COVID-19 disease, indicating the severity of the disease, the lymphocyte

count was lower in unvaccinated hospitalized patients, especially in the ICU, than in two-dose vaccinated patients.

Our limitations were having a limited number of patients, evaluating the data retrospectively, and as the first practiced vaccination was inactivated coronavirus vaccination and later practiced mRNA vaccination's effect on laboratory figures could not be evaluated. The strength of our study is using inactivated SARS-CoV-2 vaccine is valuable as it reflects real-world experience.

In conclusion, even when unvaccinated patients were vaccinated and became ill, the COVID-19 disease is milder and ferritin and D-dimer levels related to disease severity are higher. Although the vaccine is not sufficient to completely prevent the disease, it may lead to a milder course, and this should be supported by further clinical studies.

Ethical Considerations: Ethics committee approval (Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee permission dated 06.05.21 and numbered 12) was obtained for this study.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Balaban GB, Tanyeri Y, Tokyay BK et al. Vaccines and Production Methods Developed Against SARS-CoV-2. JHIT 2021; 14-32
2. Perez L. Acute phase protein response to viral infection and vaccination. Arch Biochem Biophys. 2019 August 15;671: 196-202
3. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res. 2020 Dec;69(12):1181-9.
4. Soleimanpour S, Yaghoubi A. COVID-19 vaccine: where are we now and where should we go? Expert Rev Vaccines. 2021 Jan; 20(1): 23-44.
5. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 December 31;383(27):2603-15.
6. Strategic Advisory Group of Experts on Immunization-SAGE (WHO). Evidence Assessment:Sinovac/CoronaVac COVID-19 vaccine. Report from 29/04/2021. https://translate.google.com/website?sl=en&tl=tr&hl=tr&prev=search&u=https://cdn.who.int/media/docs/defaultsource/immunization/sage/2021/april/5_sage29apr2021_critical-evidence_sinovac.pdf (accessed May 26, 2021).
7. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020 Oct;26(10):1636-43.
8. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020 Jun;127:104370
9. Yormaz B, Ergun D, Tulek B, et al. The evaluation of prognostic value of acute phase reactants in the COVID-19. Bratisl Lek Listy. 2020;121(9):628-33
10. Branco RG, Garcia PC. Ferritin and C-Reactive Protein as Markers of Systemic Inflammation in Sepsis. Pediatr Crit Care Med. 2017 Feb;18(2):194-6.
11. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 May;46(5):846-8.
12. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020 Jul;92(7):856-62.
13. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-81
14. Sathe PM, Patwa UD. D Dimer in acute care. Int J Crit Illn Inj Sci. 2014 Jul;4(3):229-32
15. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. J Thromb Thrombolysis. 2020 Oct;50(3):548-57

16. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. Eur Respir J. 2020 Jul 30;56(1):2001365.
17. Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol. 2020 Aug;190(4):e192-e95
18. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 May;18(5):1094-9.
19. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020 Jul;95(7):834-47.
20. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020 Jun;42 Suppl 1:11-8.