ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effect of Vaccination on Biochemical and Inflammatory Markers in Hospitalized COVID-19 Patients

Hastanede Yatan COVID-19 Hastalarında Aşılamanın Biyokimyasal ve İnflamatuar Belirteçler Üzerine Etkisi

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ABSTRACT

Aim: *Coronavirus disease 2019 (COVID-19) vaccines have been proven beneficial in preventing hospitalization, serious illness, and death. However, whether immunization affects biochemical and inflammatory markers, prognostic factors in hospitalization remain unknown. The effects of vaccination status on blood biochemistry and inflammatory markers were investigated in our study of patients hospitalized with COVID-19.*

Material and Method: *A total of 107 patients comprising 67 unvaccinated and 40 vaccinated individuals who were hospitalized for COVID-19 from two different centers between November 1, 2021, and January 1, 2021, were included in our study. The patients' demographics, comorbidities, and biochemical and inflammatory markers were recorded during hospitalization.*

Results: *We identified 107 patients (62 men and 45 women; mean age, 63.7±14.8 years), with a mean age of 68.6±12.2 (37–89) and 60.7±15.5 (27–88) for the vaccinated and unvaccinated groups (p=0.005), respectively. Lymphocyte level in the 0–55 age group was 1.4±0.46×109/L in vaccinated patients and 0.96±0.5×109/L in unvaccinated patients. The difference was statistically significant (p=0.05). The lactate dehydrogenase (LDH) value was higher in the unvaccinated patients in all age groups (0–55 and over 55 years old) (p=0.04). Using logistic regression analysis, LDH was demonstrated to be a predictive factor for admission to the intensive care unit (ICU) in the 0–55 age range of unvaccinated patients. It was determined that the increase in LDH in all age groups elevates the ICU admission risk by 1.004 times.*

Conclusion: *Our study showed that COVID-19 vaccination is effective against lymphopenia induced by COVID-19 in people under 55 and LDH in people of all ages. The impact of vaccination status on LDH may be meaningful, considering that elevated LDH has been associated with a higher risk of ICU support, mortality, and complications.*

Key words: *COVID-19; COVID-19 vaccine; lactate dehydrogenase; lymphopenia*

ÖZET

Amaç: *Koronavirüs 2019 hastalığı (COVID-19) aşılarının hastaneye yatış, hastalık ağırlığı ve ölümleri önlemede yararlı olduğu kanıtlanmıştır. Ancak bağışıklanmanın hastaneye yatışta prognostik faktörler olan biyokimyasal ve enflamatuvar belirteçleri etkileyip etkilemediği bilinmemektedir. COVID-19 ile hastaneye yatırılan hastalarda aşılama durumunun kan biyokimyasal ve enflamatuvar belirteçler üzerindeki etkileri araştırılmıştır.*

Materyal ve Metot: *Çalışmamıza 1 Kasım 2021 – 1 Ocak 2021 tarihleri arasında iki farklı merkezden COVID-19 nedeniyle hastaneye yatırılan 67 aşısız, 40 aşılı olmak üzere toplam 107 hasta dâhil edildi. Hastaneye yatış sırasında hastaların demografik özellikleri, komorbiditeleri, biyokimyasal ve enflamatuvar belirteçleri kaydedildi.*

Bulgular: *Aşılı ve aşısız gruplar için yaş ortalaması sırasıyla 68,6±12,2 (37–89) ve 60,7±15,5 (27–88) olan 107 hasta (62 erkek ve 45 kadın; ortalama yaş, 63,7±14,8) değerlendirildi (p=0,005). Sıfır ila elli beş yaş grubunda lenfosit düzeyi aşılılarda 1,4±0,46×109/L, aşısızlarda 0,96±0,5×109/L idi. Fark istatistiksel olarak anlamlıydı (p=0,05). Tüm yaş gruplarında (0–55 ve 55 yaş üstü) aşılanmamış hastalarda laktat dehidrojenaz (LDH) değeri daha yüksek bulundu (p=0,04). Lojistik regresyon analizi kullanılarak, LDH'nin 0–55 yaş aralığında aşılanmamış hastalarda yoğun bakım ünitesine (YBÜ) yatış için öngörücü bir faktör olduğu gösterildi. Tüm yaş gruplarında LDH artışının yoğun bakıma yatış riskini 1,004 kat artırdığı belirlendi.*

Sonuç: *Çalışmamızda COVID-19 aşısının her yaştan insanda LDH'nin yanı sıra 55 yaş altı kişilerde COVID-19'un neden olduğu lenfopeniye karşı etkili olduğu izlenmiştir. Yüksek LDH düzeyinin daha fazla YBÜ desteği, mortalite ve komplikasyon riski ile ilişkili olduğu düşünüldüğünde, aşılama durumunun LDH üzerindeki etkisi önem teşkil edebilir.*

Anahtar kelimeler: *COVID-19; COVID-19 aşısı; laktat dehidrogenaz; lenfopeni*

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Introduction

The disease caused by a new coronavirus, which first appeared in Wuhan, China in late 2019 and subsequently spread to other countries, was named Coronavirus disease 2019 (COVID-19) in February 2020 and declared a pandemic in March by the World Health Organization (WHO). Pneumonia due to SARS-CoV-2 has caused significant morbidity and mortality worldwide, especially among those with comorbidities. As of April 2022, approximately 486 million individuals had been infected worldwide, with over 6 million deaths.

Infection can arise in numerous tissues of the body due to the extensive tissue distribution of the viral receptor in COVID-19. The etiology of the disease is influenced by viral and immune system factors[1]. COVID-19 is a systemic infection with major implications on the hematological system and hemostasis. Lymphopenia, thrombocytopenia, lactate dehydrogenase (LDH), C-reactive protein (CRP), and increased biomarkers, including serum procalcitonin and ferritin, appear to be poor prognostic indicators. In addition, high D-dimer levels are associated with disease severity and coagulopathy consequences[2].

Although vaccination is the most effective approach to managing the pandemic, the vaccination rates in most nations remain below the goal level. Effective vaccination has been shown to be potent against hospitalization, severe illness, and death from COVID-19[3–5]. However, whether immunization affects biochemical and inflammatory markers, which are prognostic factors in hospitalization, remains unknown. In our study, the effects of the vaccination status of patients hospitalized for COVID-19 on blood biochemical, inflammatory parameters, and disease course were investigated.

Materials and Methods

Our study comprised 67 unvaccinated and 40 vaccinated patients more than 18 years of age with positive polymerase chain reaction (PCR) who were hospitalized for COVID-19 between November 2021 and January 2021 at two different centers. Individuals who had at least two doses of COVID-19 vaccine (inactivated/mRNA) were considered vaccinated cases. Individuals who have not been vaccinated against COVID-19 or those for whom more than six months between the date of COVID-19 disease and the last vaccine have lapsed were considered unvaccinated cases. The patients with previous COVID-19 disease within the last 6 months, hematologic malignancies, active inflammatory diseases, pregnancy, previous liver diseases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) above 3 times of upper normal limit or bilirubin above 2 mg/dl) and kidney diseases (serum creatinine level above 1.5 mg/dl) were excluded from the study. At the time of hospitalization, the patients' demographics and comorbidities like diabetes mellitus, systemic hypertension, coronary heart disease, chronic lung diseases, and cerebrovascular accidents were recorded. In addition, full blood count, CRP, procalcitonin, D-dimer, LDH, ferritin, and fibrinogen levels were recorded. Oxygen saturation, oxygen support therapy, length of stay, and intensive care requirements were evaluated. All patients were evaluated for the lung involvement of more than 50% during initial hospitalization by two chest disease specialists separately. The data were analyzed using the Statistical Package for Social Sciences (SPSS) program version 22 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used as the normal distribution test. Parametric tests were prioritized in the analysis of data that fit the normal distribution, while nonparametric tests were preferred in the analysis of data that did not fit the normal distribution. The Mann-Whitney U test and binary logistic regression were used in the analysis. $P<0.05$ was considered statistically significant. The study protocol was approved by the ethics committee.

Results

We enrolled 107 patients (62 men, 45 women; mean age 63.7±14.8 years) in this study. There are two types of vaccines available in Türkiye. Amongst the vaccinated patients, eight received two doses of BNT162b2 (BioNTech), six received two doses of Sinovac (whole-virion inactivated vaccine), 13 received three doses of Sinovac, 12 received two doses of Sinovac and one dose of BioNTech, and one received two doses of Sinovac and two doses of BioNTech. The mean age of the patients in the vaccinated and unvaccinated groups was 68.6±12.2 (37–89) and 60.7±15.5(27–88) ($p=0.005$), respectively. The vaccinated group was older than the unvaccinated group, but there was no statistical difference in terms of gender or comorbidity between the two groups (Table 1). At least one comorbidity was present in 67.5% of the vaccinated individuals and 68% of the unvaccinated patients, respectively. The most common comorbidity was hypertension (42.5%) in the vaccinated group and diabetes mellitus (25.4%) in

Table 1. *Distribution of vaccinated and unvaccinated patients based on demographic and radiological features, oxygen saturation, comorbidity, and mortality*

	Vaccinated (n: 40)(%)	Unvaccinated (n: 67)(%)	p
Gender			0.17
Male	26 (65%)	36 (46%.3)	
Female	14 (35%)	31(53%.7)	
Mean age (year)	68.6±12.2 (37–89)	60.7±15.5 (27–88)	0.005
Oxygen saturation (%)	90.4±6.4 (75–98)	89.4±6.6 (70–98)	0.5
Radiological involvement >50%	10 (25%)	24 (35%.8)	0.3
Length of hospitalization (day)	12.4±8.2	13.6±13	0.11
ICU requirement	10 (25%)	21 (31%.3)	0.31
Exitus	2 (5%)	6 (9%)	0.36
Comorbidity	27 (67%.5)	46 (68%.7)	0.53
HT	17 (42%.5)	16 (23%.9)	0.037
DM	12 (30%)	17 (25%.4)	0.38
CVD	9 (22%.5)	15 (22%.4)	0.58

ICU: intensive care unit; HT: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease.

Table 2. *At the time of admission for hospitalization, 104 patients' mean (± SD) laboratory results.*

	Vaccinated (n=40)	Unvaccinated (n=67)	p
White blood cell ($\times10^9$/L)			
>55 year old	8.7 (±4.4)	9.3 (±5.9)	0.5
≤55 year old	8.8 (±1, 7)	6.84 (±3.4)	0.1
Neutrophil ($\times10^9$/L)			
>55 year old	7.01 (±3.1)	7.3 (±5.5)	0.4
≤55 year old	6.3 (±0.9)	5.4 (±3.3)	0.2
Lymphocyte ($\times10^9$/L)			
>55 year old	1.03 (±0.6)	1.25 (±1.5)	0.9
≤55 year old	1.4 (±0.5)	0.96 (±0.53)	0.05
Hemoglobin (g/dL)			
>55 year old	12 (±2.2)	12 (±2.2)	0.7
≤55 year old	12.5 (±1.2)	13.1 (±1.6)	0.5
Platelets ($\times10^9$/L)			
>55 year old	213 (±78)	229 (±139)	0.8
≤55 year old	208 (±46)	234 (±102)	0.7
LDH (U/L)			
>55 year old	375 (±255)	390 (±173)	0.05
≤55 year old	255 (±88)	455 (±238)	
Ferritin (ng/m)			
>55 year old	401 (±402)	554 (±1174)	0.6
≤55 year old	187 (±162)	495 (±811)	0.4
CRP (mg/L)			
>55 year old	120 (±94)	99 (±73)	0.4
≤55 year old	70 (±78)	63 (±47)	0.6

LDH: Lactate dehydrogenase; CRP: C reactive protein.

the unvaccinated group. There was no statistically significant difference in oxygen saturation levels between the vaccinated and unvaccinated groups (90.4±6.4 vs 89.4±6.6, p=0.5). Those with more than 50% radiological involvement in the vaccinated and non-vaccinated groups were determined to be 25% and 35.8% (p=0.3), respectively. There was no statistically significant difference between the non-vaccinated and vaccinated groups on the day of hospitalization (13.6±13 vs 12.4±8.2, p=0.11) and the requirement for intensive care (25% vs 31.3%, p=0.31). Table 1 shows the distribution of vaccination status based on demographic and radiological features, oxygen saturation during hospitalization, comorbidities, and death. Given that biochemical and inflammatory markers were evaluated between the two groups, the lymphocyte level in the 0–55 age group was 1.4±0.46 x 10^9/L in the vaccinated and 0.96±0.5x 10^9/L in the unvaccinated patients. The difference was statistically significant (p=0.05). The LDH value was higher in the unvaccinated patients in

all age groups (0–55 and over 55 years old) (p=0.04). Using logistic regression analysis, LDH was demonstrated to be a predictive factor for admission in the intensive care unit (ICU) in the 0–55 age range of unvaccinated patients. It was determined that the increase in LDH in all age groups raises the risk of admission to the ICU by 1.004 times. No significant differences in the serum levels of CRP, procalcitonin, D-dimer, ferritin, or fibrinogen levels were observed between the two groups (Table 2). Since fibrinogen and D-dimer could not be studied over a period of time in the hospital, these parameters were evaluated in only 66% and 65% of the patients, respectively.

Discussion

The results of our study showed that efficient COVID-19 vaccination is effective against lymphopenia induced by COVID-19 in people under the age of 55, as well as LDH in people of all ages. Lactate dehydrogenase was demonstrated to be a predictive factor for admission to the ICU in unvaccinated patients. It was determined that the increase in LDH in all age groups raises the risk of admission to the ICU by 1.004 times.

Despite new vaccines and diagnostic approaches, COVID-19 is still a global health issue. The immunological response to SARS-CoV2 infection remains complicated and poorly understood. Malik et al.[6] found in their systematic review and meta-analysis that specific biomarkers were associated with poor outcomes in hospitalized COVID-19 patients. These biomarkers included decreased lymphocyte count, decreased platelet count, and elevated CRP, creatine kinase, procalcitonin, D-dimer, LDH, AST, ALT, and creatinine. Other studies showed that lower lymphocyte count was a typical feature of SARS-CoV-2 infection and associated with increased mortality, ARDS, ICU care, and severe COVID-19[7,8]. In our study, lymphocyte counts were significantly higher in the vaccinated group under 55 years of age compared to the unvaccinated group. According to Huang et al.'s meta-analysis[8], the correlation between lymphopenia and severe COVID-19 was higher in younger patients. One potential hypothesis to explain such a result was that immune system aging may result in a relatively consistent decrease in lymphocyte count due to a relatively "nonreactive" immunological state. However, highly active lymphocyte kinetics may be affected by a wide range of insults and comorbidities in the younger population, resulting in a relatively higher mean difference. According to this hypothesis, the vaccine's enhanced effect on lymphocyte count in our patient population can be explained by the more active cell kinetics in the young population. Some factors have been suggested to explain lymphopenia in COVID-19. The first is that lymphocytes express ACE2, which is known as a SARS-CoV-2 receptor; thus, the virus attacks lymphocytes directly[9]. The second theory is that elevated proinflammatory cytokines in COVID-19 patients may result in lymphocyte apoptosis[10]. Another factor is concomitant lactic acid acidosis, which is common in cancer patients and may inhibit lymphocyte proliferation[2].

High LDH levels reflect cellular damage due to plasma membrane damage. Han et al.[11] found that the levels of LDH in the early stage of severe COVID-19 cases can be a good predictor of lung injury. Increased LDH has been associated with a higher risk of ARDS, ICU support, and death[2]. Das et al.[12] demonstrated that elevated peak LDH levels in MERS-CoV patients might suggest underlying lung tissue damage. High initial and peak LDH levels have also been found to be good independent predictors of poor clinical outcomes in SARS patients. Furthermore, high peak LDH levels were independent indicators of more severe lung injury in this study[13].

In recent investigations, non-survivors had higher LDH, procalcitonin, and serum ferritin levels than survivors[2]. Other laboratory values did not show a statistically significant difference between the vaccinated and unvaccinated groups in our study, which may be attributed to the limited number of patients. At the same time, the vaccinated group was composed of mostly elderly patients. The fact that the vaccinated and unvaccinated groups were different in age may have made us unable to clearly observe the response of the vaccine to inflammatory parameters. For the same reason, the more than 50% radiological involvement, hospitalization, and oxygen saturation level, which may reflect the impact of vaccination on the course of the disease, may be caused by the vaccine recipients' older age and the small number of patients in the trial. Future research should concentrate on changes in biomarker levels in a larger population. Probable discrepancies between the vaccinations administered may also become apparent.

This study has some limitations. For a certain period of time, fibrinogen and D-dimer could not be analyzed in our hospital. As a result, the number of samples tested for coagulopathy is less than the total number of

samples. Another limitation is that the vaccinated and unvaccinated groups were similar in terms of comorbidity and gender, but the vaccinated group was older. This could have an impact on the blood parameters measured in our research. Biochemical differences between the subgroups of vaccinated individuals could not be examined due to the low number of vaccinated patients.

Conclusions

The results of our study underscore that COVID-19 vaccination is effective against lymphopenia induced by COVID-19 in people under the age of 55, as well as LDH in people of all ages. Therefore, the impact of vaccination status on LDH may be important, considering that elevated LDH has been associated with a higher risk of ARDS, ICU support, mortality, and complications.

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