

## PAPER DETAILS

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PAGES: 1390-1393

ORIGINAL PDF URL: <https://dergipark.org.tr/tr/download/article-file/2456794>

# Association of COVID-19 vaccine with lymph node reactivity: An ultrasound-based study

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**Cite this article as:** Çevik B. Association of COVID-19 vaccine with lymph node reactivity: An ultrasound-based study. J Health Sci Med 2022; 5(5): 1390-1393.

## ABSTRACT

**Aim:** Millions of people worldwide have been infected and died due to the pandemic caused by COVID-19. Vaccination is the most effective way to deal with the pandemic. Though vaccines are safe, they are not completely risk-free, and some side effects can occur after vaccination such as lymphadenopathy. This study, it was aimed to measure the lymph node reactivity that may develop after mRNA vaccination.

**Material and Method:** A total of 50 healthy people were included in the study. Left axillary and supraclavicular ultrasound examinations were performed before and one week after the administration of the mRNA vaccine. Each patient was assessed for supraclavicular and level 1 axillary lymph region in terms of the presence, size (long and short axis), and cortex thickness of the lymph nodes.

**Results:** Of the patients participating in the study, 23 (46 %) were male, 27 (54 %) were female, and the median age was 33. In comparison, the difference in long, short axis and cortex diameter measurements of the supraclavicular lymph node before and after vaccination was found to be statistically significant ( $p=0.034, 0.021, 0.004$ , respectively). Similarly, the difference in the long, short axis, and cortex thickness of the left axillary lymph node before and after vaccination was statistically significant ( $p<0.001, <0.001, <0.001$ , respectively).

**Conclusion:** Anti-Covid-19 vaccines may cause lymphadenopathy as a result of reactivation in lymph nodes in the left axillary and supraclavicular regions. When lymphadenopathy is detected in these regions, the vaccine should be questioned in the clinical history and ultrasound follow-up should be performed on the patient.

**Keywords:** Lymphadenopathy, COVID-19 vaccines, ultrasound

## INTRODUCTION

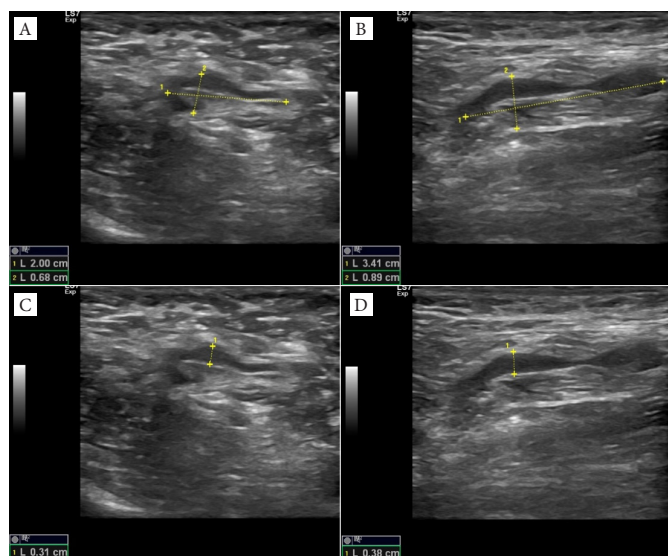
According to the statistics of the World Health Organization (WHO), millions of people around the world were infected and died due to the pandemic caused by COVID-19. One of the effective methods of dealing with the epidemic is vaccination (1). With the mass adoption of vaccination, both prevention of COVID-19 infection and reduction in morbidity and mortality can be achieved (2). However vaccines are highly safe methods, they are not completely risk-free, and some side effects can occur after vaccination (3). The development of lymphadenopathy in patients receiving the COVID-19 vaccine has recently been described in the literature (4). In addition, unilateral axillary and supraclavicular lymphadenopathy cases have been reported in recent articles (5). Sometimes, supraclavicular and axillary lymph nodes (LN) may mimic pathological lymph nodes after the COVID-19

vaccine. Ultrasound (US) examination of lymph nodes may represent a first-line imaging modality due to its rapid application, low cost, and reproducibility (6). The sonologists should consider that anti-COVID-19 vaccines may be involved in the etiology of supraclavicular and axillary lymphadenopathy with suspicious US features. This study, it was aimed to measure the lymph node reactivity that may develop after vaccination.

## MATERIAL AND METHOD

This study was approved by the Lokman Hekim University Non-interventional Clinical Researches Ethics Committee (Date 15.02.2022, Decision No: 2022017). All procedures applied in the study were carried out in accordance with the Declaration of Helsinki and ethical principles.

Before and one week after the administration of mRNA vaccine to the health personnel working in the hospital, the presence of lymph nodes in the left axillary and supraclavicular regions, if any, the short and long axis (**Figure 1 a-b**) and the thickest part of the cortex were measured (**Figure 1 c-d**). Patients with any known oncological, hematological, or autoimmune diseases were not included in the study.



**Figure 1.** A-36-year-old female patient has reactive lymph nodes (a-b) and cortex thicknesses (c-d) in the left axillary region before and after vaccination.

### US protocol

All ultrasonographic procedures were performed by the same radiologist (19 years of experience) using a GE Logiq S7 Expert with a linear 9L-D MHz array probe. The presence of lymph nodes in the level 1 left axillary and supraclavicular regions, the size of the largest lymph node (long and short axis), location, and cortex thickness were recorded in detail for each patient.

### Statistical Analysis

Distribution was determined by the Shapiro-Wilk test, skewness and kurtosis values, and histogram graphics. The median (min-max) values of the numerical variables that do not fit the normal distribution are given. Categorical variables were expressed as numbers (percentage distributions). Wilcoxon Signed Ranks Test was used to compare lymph node US measurements before and after vaccination. A p-value of <0.05 was considered statistically significant in all analyzes and these analyzes were performed using the SPSS 25.0 program.

### RESULTS

Of the patients participating in the study, 23(46 %) were male, 27 (54 %) were female, and the median age was 33 years. The median time to US controls after vaccination was 7 days.

The comparison of left axillary lymph node measurements measured by the US before and after vaccination is given in **Table 1**. In comparison, the difference in supraclavicular LN long, short axis, and cortex diameter measurements before and after vaccination was found to be statistically significant ( $p=0.034$ ,  $0.021$ , and  $0.004$ , respectively) (**Table 2**). Similarly, the difference in the long, short axis, and cortex thickness of the axillary LN before and after vaccination was statistically significant ( $p<0.001$ ,  $<0.001$ ,  $<0.001$ , respectively). There was no statistically significant difference between the long/ short axis ratios of both evaluated lymph nodes before and after vaccination.

**Table 1.** Comparison of left axillary LN measurements before and after vaccination (n=48)

	Before vaccination median (min-max)	After vaccination median (min-max)	Z value	P-value*
Left Axillary LN long axis	18.0 (12.0-28.0) <sup>1</sup>	22.0 (15.0-37.0)	-5.663	<0.001
Left Axillary LN short axis	6.0 (4.0-11.0) <sup>1</sup>	8.0 (5.0-11.0)	-4.921	<0.001
Left Axillary L/S ratio	2.7 (1.7-4.6) <sup>1</sup>	2.6 (1.8-5.2)	-0.435	0.664
Left Axillary LN cortex thickness	2.0 (1.0-4.0) <sup>1</sup>	3.0 (1.3-6.4)	-5.908	<0.001

\* Wilcoxon Signed Ranks Test

**Table 2.** Comparison of people with positive supraclavicular LN before vaccination with post-vaccine measurements (n=16)

	Before vaccination median (min-max)	After vaccination median (min-max)	Z value	P-value*
Supraclavicular LN long diameter	4.0 (0.0-12.0)	8.5 (0.0-12.0)	-2.123	0.034
Supraclavicular LN short diameter	1.5 (0.0-6.0)	4.0 (0.0-6.0)	-2.307	0.021
Supraclavicular L/S ratio	0.7 (0.0-3.0)	2.0 (0.0-2.6)	-1.790	0.073
Supraclavicular LN cortex thickness	0.7 (0.0-2.7)	2.4 (0.0-5.0)	-2.870	0.004

\* Wilcoxon Signed Ranks Test

## DISCUSSION

In our study, it was found that mRNA vaccines may cause reactivity in axillary and supraclavicular lymph nodes ipsilateral to the injection site. However, distinguishing lymphadenopathy from abnormal lymph nodes after COVID-19 vaccines has posed a diagnostic challenge (7). We observed those who are generally suspicious of malignancy, such as cortical thickening in some of the patients studied.

The most important criteria to distinguish between normal and abnormal lymph nodes are; the shape of the lymph nodes, their hilum features, and their cortical thickness. Cortical thickness >3 mm, round shape, and change in the echogenic hilum often suggest a pathological process (8,9). Axillary lymphadenopathy has been observed following vaccination with influenza, human papillomavirus vaccines, and recently with COVID-19 mRNA vaccines (10). Garreffa et al. (11) reported in a study they conducted that the frequency of lymphadenopathy detected by imaging varies between 14.5% and 53%.

Hanneman et al. (12) showed that a patient with no history of malignancy who underwent cardiac fluorine 18 F- FDG) PET/MRI investigation the day after injection of the COVID-19 vaccine caused unilateral left axillary lymphadenopathy with moderately increased FDG uptake.

In patients with malignancy, lymphadenopathy may be found incidentally on routine screening or imaging tests such as mammography, CT, or MRI. In such cases, the US examination becomes important (13,14). In some patients, the lymph nodes in the US have a rounded shape, there is no echogenic hilum. These US features may be of concern, especially in cancer patients (15).

In their study, El-Sayed et al. (16) emphasized that if the lymph node reactivity after the COVID-19 vaccination is not taken into account in malignancy patients who underwent PET CT, it would lead to errors in upgrading. Johnson et al. (17) emphasized that considering the vaccination history in patients who underwent 18F-FDG PET/CT for cancer staging or control would be important in the differential diagnosis. Hagen et al. (18) performed needle biopsy in 5 patients who were admitted with post-vaccine lymph node enlargement with a diagnosis of malignancy and proved that lymph node enlargement was caused by the vaccine.

Özütemiz et al. (19) presented five cases of axillary lymphadenopathy mimicking metastasis after the COVID-19 vaccination. Histopathological evaluation was performed in two cases. However, other cases

were recently associated with vaccination. Xu et al. (20) presented that axillary lymphadenopathy cluster in a follow-up FDG PET/CT scan of a patient with mantle cell lymphoma who had a complete metabolic response to treatment was due to COVID-19 vaccine. It is important to know the potential for ipsilateral lymphadenopathy associated with the COVID-19 vaccine to avoid unnecessary biopsy and/or treatment changes. A multidisciplinary expert panel recommended deferring imaging for at least 6 weeks after completion of vaccination to avoid misdiagnosis (21).

Mehta et al. (22) evaluated four cases vaccinated with Pfizer and Moderna vaccine. Unilateral axillary lymphadenopathy was detected in the cases. They concluded that in such cases, in addition to breast cancer, the COVID-19 vaccine should be added to the differential diagnosis. In one case, lymphadenopathy developed 9 days after vaccination. However, other cases were found incidentally. It is not known when the lymph node reaction started after receiving the COVID-19 vaccine. In this study, we found that lymph node reactivity appeared within the first 7 days.

This study has some limitations. First of all, the number of patients included is small. Second, the study has been limited by the absence of a histopathological correlation. Moreover, studies with a longer duration may give us an idea about the outcomes of those lymphadenopathies.

## CONCLUSION

Anti-COVID-19 vaccines may cause lymphadenopathy in the axillary and supraclavicular regions. Knowing those patients' history of recent vaccination prevents radiologists from performing unnecessary and costly histopathological evaluations of lymph nodes. Short-interval US control facilitates the follow-up of patients and would give us data about the outcomes of these patients.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** This study was approved by the Lokman Hekim University Non-interventional Clinical Researches Ethics Committee (Date 15.02.2022, Decision No: 2022017).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

**Acknowledgments:** I would like to thank Hulya Sirin, MD, for her help with the statistical evaluations.

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