

# The Long-term Follow-up of Axillary Lymphadenopathies Developed After COVID-19 Vaccination and Their Relationship with Types of Vaccines

COVID-19 Aşılaması Sonrası Gelişen Aksiller Lenfadenopatilerin Uzun Dönem Takibi ve Aşı Türleriyle İlişkisi

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## Abstract

**Objective:** To evaluate the long-term effects of the coronavirus disease-2019 vaccines on axillary lymph nodes (LN) and to examine the relationship between LN size, cortical thickness, and other morphological characteristics.

**Methods:** A total of 182 patients were included in this study. Data on the size and cortical thickness of axillary LN on both sides, the vaccinated arm, the number and type of vaccines, patient height and weight was recorded. The relationships between LN size, cortical thickness, additional variables, and time were analyzed.

**Results:** No significant relationship was found between the number of vaccine doses and LN size or cortical thickness. The vaccinated arm was the left arm. There was no significant relationship between the size of the left axillary LN and the right axillary LN. A significant increase in axillary LN size was observed correlated with body mass index ( $p<0.0001$ ). When assessing the impact of the vaccine, a significant decrease in cortical thickness of the left axillary LN was observed in the patients presenting two weeks after vaccination ( $p=0.041$ ). However, in the overall evaluation, the increase in left axillary LN cortical thickness was found to be significantly greater than the right axillary LN ( $p=0.049$ ). When examining the time relationship (maximum 48 weeks), increase in left axillary LN cortex thickness was detected ( $p=0.437$ ).

**Conclusion:** Our study demonstrated that cortical thickening of LNs persisted for an extended period (up to 48 weeks). This condition creates diagnostic challenges in patients with suspicious breast cancer findings, those under follow-up for a history of breast cancer, and in those who are newly diagnosed with breast cancer. Therefore, recording the vaccination history and comparing LN imaging before and after vaccination may help prevent unnecessary invasive procedures and misdiagnoses.

**Keywords:** Breast cancer, vaccine, aksillary lymphadenopathy

## Öz

**Amaç:** Koronavirüs hastalığı-2019 aşısının aksiller lenf nodları (LN) üzerindeki uzun vadeli etkilerini değerlendirmek ve LN boyutu, korteks kalınlığı ve diğer morfolojik özellikler arasındaki ilişkiye incelemektir.



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## Öz

**Yöntem:** Bu çalışmaya toplam 182 hasta dahil edildi. Her iki taraftaki aksiller LN boyutu ve korteks kalınlığı, aşılanan kol, aşı sayısı ve türü, hasta boyu ve kilosu kaydedildi. LN boyutu, korteks kalınlığı, diğer değişkenler ve zaman arasındaki ilişkiler analiz edildi.

**Bulgular:** Aşı dozu sayısı ile LN boyutu veya korteks kalınlığı arasında anlamlı bir ilişki bulunmadı. Aşılanan kol sol koldu. Sol aksiller LN boyutu ile sağ aksiller LN boyutu arasında anlamlı bir ilişki bulunmadı. Aksiller LN boyutunda, vücut kitle indeksi ile korelasyon içinde anlamlı bir artış gözlandı ( $p<0,0001$ ). Aşının etkisini değerlendirirken, aşılamadan iki hafta sonra başvuran hastalarda sol aksiller LN korteks kalınlığında anlamlı bir azalma gözlandı ( $p=0,041$ ). Ancak genel değerlendirmede, sol aksiller LN korteks kalınlığındaki artışın sağ aksiller LN'ye kıyasla anlamlı derecede daha yüksek olduğu bulundu ( $p=0,049$ ). Zaman ilişkisi incelendiğinde (maksimum 48 hafta), sol aksiller LN korteks kalınlığında anlamlı bir artış tespit edildi ( $p=0,437$ ).

**Sonuç:** Çalışmamız, LN korteks kalınlığının uzun bir süre (48 haftaya kadar) devam ettiğini göstermiştir. Bu durum, şüpheli meme kanseri bulguları olan hastalarda, meme kanseri öyküsü nedeniyle takip edilen hastalarda ve yeni tanı almış meme kanseri hastalarında tanı zorlukları yaratmaktadır. Bu nedenle, aşılama öyküsünün kaydedilmesi ve aşılama öncesi ve sonrası LN görüntülemelerinin karşılaştırılması, gereksiz invaziv prosedürlerin ve yanlış tanıların önlenmesine yardımcı olabilir.

**Anahtar Kelimeler:** Meme kanseri, aşı, aksiller lenfadenopati

## Introduction

Pneumonia associated with coronavirus disease-2019 (COVID-19) was first reported in December 2019 in Wuhan, China<sup>(1)</sup>. The pandemic later reached a global scale and became the focus of worldwide attention. Various COVID-19 vaccine technologies, including mRNA (Moderna, Pfizer-BioNTech)<sup>(2)</sup>, inactivated (Sinovac), recombinant protein (novavax), and vector-based (Janssen, Oxford-AstraZeneca) vaccines, were successfully developed and used during the COVID-19 pandemic<sup>(3)</sup>. Bar-On et al.<sup>(4)</sup> demonstrated the effectiveness of the third dose in protecting individuals aged 60 and above from COVID-19. Spitzer et al.<sup>(5)</sup> also reported the effectiveness of the third dose in individuals aged 18 and older. Therefore, the third dose of the vaccine became a routine practice in many countries worldwide. However, as vaccination rates increased, some vaccinated individuals experienced adverse reactions. One such reaction was ipsilateral axillary lymphadenopathy. Some researchers have stated that this condition is a short-term and harmless response, indicating vaccine effectiveness<sup>(6-8)</sup>. Axillary lymphadenopathy associated with vaccination can pose challenges in the treatment planning and prognosis assessment of patients diagnosed with or suspected of having breast cancer. In routine practice, this condition can also cause difficulties in the follow-up of patients with a history of breast cancer surgery, particularly if the lymph nodes (LN) size does not decrease over time or if signal enhancement persists on an 18-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) scan. These issues lead to repeated interventional procedures to clarify the clinical picture. The aim of this study is to

investigate the long-term effects of the vaccine on axillary LNs by correlating the type of vaccine administered and the time elapsed since vaccination.

## Materials and Methods

Ethical approval for this retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval no: 0043, date: 15.02.2024).

## Patient Selection

Turkey initiated its COVID-19 vaccination program on January 13, 2021. Therefore, a total of 198 patients with a history of vaccination who presented to the breast imaging unit between January 2021 and March 2022 were reviewed. Two patients were excluded from the study due to newly detected malignant breast masses, and histopathologically confirmed axillary LN metastases. Fourteen patients were also excluded due to a left mastectomy and vaccination in the right arm. The remaining 182 patients who received the vaccine in the left arm were included in the study.

## Radiological Evaluation

All patients included in the study underwent routine breast and axillary ultrasonography. The ultrasonographic examination was performed by a radiologist with five years of experience in breast imaging. Patient age, weight, and height were recorded. During the sonographic evaluation, the largest LNs in both axillae were measured in terms of long-axis diameter and cortical thickness. In follow-up ultrasonographic examinations, changes in LN size and

biopsy results if performed, were also assessed. Additionally, data on the number of vaccine doses received, the types of vaccines administered, and the arm in which the vaccine was given were recorded.

## Statistical Analysis

Statistical analyses were performed using the SPSS (version 26) software package. Descriptive statistics for quantitative variables were presented as mean, standard deviation, median, minimum, and maximum values. The normality of quantitative variables was assessed using the Shapiro-Wilk test. The Wilcoxon signed-rank test was used to compare medians between two dependent groups. Pearson correlation analysis was used to evaluate relationships between quantitative variables. A p-value of  $<0.05$  was considered statistically significant.

## Results

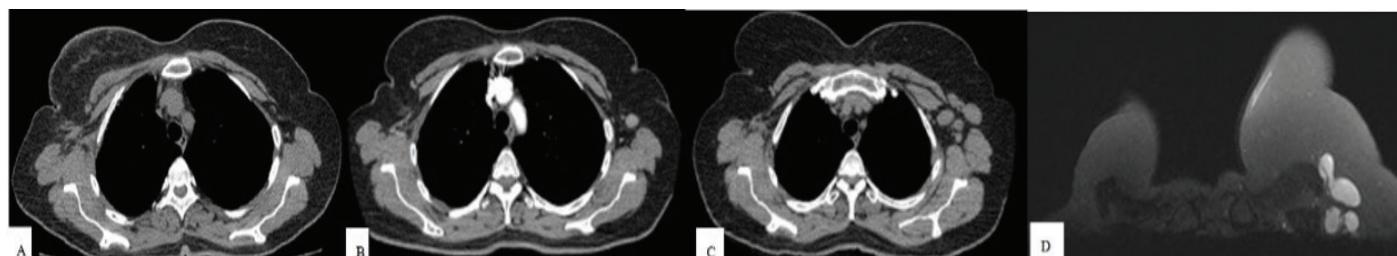
Fine-needle aspiration biopsy (FNAB) was performed on the axillary LNs of eight out of 182 patients in the study group. Two patients were excluded from the study due to malignant histopathology findings. In the remaining six patients, histopathology results confirmed reactive LNs. One year after inclusion in the study, pathological sonographic findings persisted in the axillary LNs of three patients. Two of these patients had a known history of malignancy, and the vaccine had been administered in the contralateral axilla. Due to high standardized uptake value ( $SUV_{max}$ ) values in 18F-FDG PET/CT scans, FNAB was performed on both patients. Since FNAB results were benign and pathological LNs persisted in follow-up examinations, core biopsy was performed. The biopsy results confirmed benign/reactive LNs. The patients with increased LN size and  $SUV_{max}$  values in 18F-FDG PET/CT scans are still being monitored. In one patient without a

history of malignancy, FNAB results were benign. However, the cortical thickening of the axillary LN persisted at the 18-month follow-up after the last vaccination, and the patient remains under surveillance. Patient data, including age, weight, body mass index (BMI), vaccine type, and number of doses, are presented in Table 1. Sonographic evaluation of LNs showed no statistically significant difference between the mean long-axis diameters of the right and left axillary LNs ( $p=0.109$ ).

However, the mean cortical thickness of the left axillary LNs was significantly higher than that of the right axillary LNs ( $p=0.049$ ) (Table 2).

Comparisons of LN size and cortical thickening among different vaccine types revealed no statistically significant differences between the right and left axillary LNs (Table 3). When assessing the relationship between LN size and other variables, BMI was found to be significantly correlated with the sizes of both right and left axillary LNs, with the right axillary LN ( $r=0.343$ ;  $p<0.001$ ) and the left axillary LN ( $r=0.343$ ;  $p<0.001$ ) (Table 3). Regarding the relationship between time elapsed since the last vaccine dose and sonographic findings, cortical thickening of the left axillary LN significantly decreased after the second week post-vaccination, ( $p=0.041$ ) (Table 4). The measured parameters included time since the last vaccination (1 to 48 weeks), left axillary LN cortical thickness (0.6–6.6 mm), and right axillary LN cortical thickness (0.3–3.5 mm). The time elapsed since the last vaccination and the cortex thickness of the left axillary LN were found to be not significantly associated ( $p=0.437$ ) (Table 5).

In daily clinical practice, we have observed cases of vaccine-induced lymphadenopathy in the contralateral axilla of patients with a history of breast cancer surgery (Figure 1A–D),

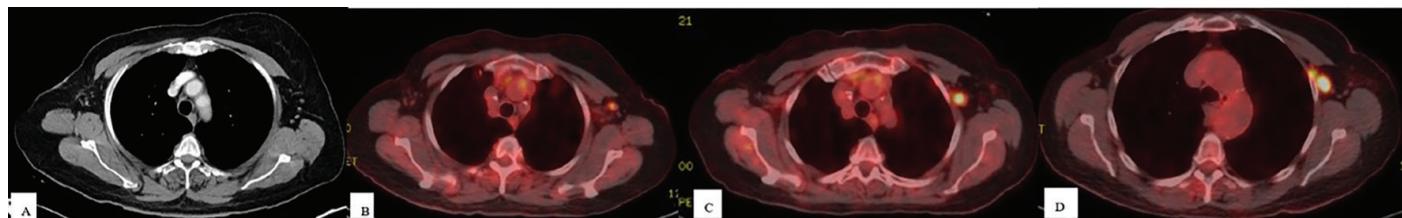


**Figure 1.** **A)** In a patient with a history of right partial mastectomy, no pathological lymph node was observed in the left axilla on the pre-COVID-19 vaccine thoracic CT scan (2020). **B)** In the post-vaccine thoracic CT scan (2022), a lymph node with cortical thickening was detected. FNAB was performed, and the result was benign. **C)** In 2023, an increase in the size of the lymph nodes was observed. **D)** In 2023, MRI was performed on the same patient. Due to the progression of lymphadenopathy, a tru-cut biopsy was performed, and the result was reported as benign

COVID-19: Coronavirus disease-2019, CT: Computed tomography, FNAB: Fine-needle aspiration biopsy, MRI: Magnetic resonance imaging

Figure 2A-D). These patients underwent long-term follow-up, multiple biopsies, and 18F-FDG PET/CT scans. Although these LNs exhibited pathological characteristics, repeated biopsies confirmed benign findings. This suggests that vaccines may cause prolonged lymphadenopathy in some

patients. Our study supports this observation, as the cortical thickness of the left axillary LNs was significantly increased compared to the right, regardless of the time elapsed since the last vaccine dose. Overall, we found a significant reduction in the cortical thickness of the left axillary LN after



**Figure 2.** **A)** In a patient with a history of right mastectomy, reactive lymph nodes were observed in the left axilla in 2020. **B)** In 2022, after vaccination, a lymph node with an  $SUV_{max}$  of 3.6 was detected on 18F-FDG PET/CT. FNAB was performed, and the result was benign. **C)** In February 2023, FNAB was repeated for a lymph node with an  $SUV_{max}$  of 8.6. The result was benign. **D)** In September 2023, an increase in both size and number of lymph nodes was observed, with an  $SUV_{max}$  of 8.4. A tru-cut biopsy was performed and interpreted as reactive growth

SUV: Standardized uptake value, 18F-FDG: 18-fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, FNAB: Fine-needle aspiration biopsy

**Table 1. Patient data, including age, weight, BMI, vaccine type, and number of doses**

	Age	Number of doses	Biontech	Sinovac	Weight	Height	BMI
Mean	50.21	3.21	2.27	0.87	70.33	7.6331	27.2863
Median	51.00	3.00	2.00	0.00	68.00	1.6000	26.4463
Standard deviation	13.731	1.123	1.185	1.315	14.564	79.78060	6.26935
Minimum	18	1	0	0	44	1.46	14.53
Maximum	80	6	5	5	130	1057.00	50.15

BMI: Body mass index

**Table 2. Sonographic evaluation of lymph nodes showed no statistically significant difference between the mean long-axis diameters of the right and left axillary lymph nodes ( $p=0.109$ ). However, the mean cortical thickness of the left axillary lymph nodes was significantly higher than that of the right axillary lymph nodes ( $p=0.049$ )**

Measurement	Mean	Median	Standard deviation	Minimum	Maximum	p-value
Right axillary lymph node long-axis (mm)	18.392	16.7	6.9825	1.2	41.1	0.109
Left axillary lymph node long-axis (mm)	17.751	16.7	5.8354	1.1	38.5	
Right lymph node cortex thickness (mm)	1.6438	1.5	1.19506	0.3	13.0	0.049
Left lymph node cortex thickness (mm)	1.7562	1.6	1.19791	0.38	12.3	

**Table 3. Comparisons of lymph node size and cortical thickening among different vaccine types revealed no statistically significant differences between the right and left axillary lymph nodes**

Variable	Right size (r)	Right size (p)	Right cortex (r)	Right cortex (p)	Left size (r)	Left size (p)	Left cortex (r)	Left cortex (p)
Age	0.101	0.188	0.089	0.248	0.027	0.724	0.027	0.721
Weight	0.367	<0.001	0.078	0.316	0.285	<0.001	0.092	0.235
Height	-0.009	0.913	-0.032	0.683	0.001	0.986	-0.013	0.864
BMI	0.343	<0.001	0.086	0.271	0.273	<0.001	0.087	0.264

BMI: Body mass index

**Table 4. The mean cortical thickness of the left lymph node in patients who were more than two weeks post-vaccination was significantly lower than in those who were two weeks or less post-vaccination (p=0.041)**

Measurement	r	p-value
Right size	0.013	0.871
Right lymph node cortex thickness	0.047	0.543
Left size	0.003	0.965
Left lymph node cortex thickness	0.06	0.437

**Table 5. The increase in cortex thickness of the left axillary lymph node was found to be significantly higher as more time elapsed since the last vaccination (p<0.437)**

Measurement	Mean	Median	Minimum	Maximum	Standard deviation	p-value
Right size ( $\leq$ 2 weeks)	18.343	19.9	7.4	29.2	7.1246	0.838
Right size ( $>$ 2 weeks)	18.425	16.7	1.2	41.1	7.0095	
Right lymph node cortex thickness ( $\leq$ 2 weeks)	2.0057	2.1	0.64	4.0	1.10675	0.263
Right lymph node cortex thickness ( $>$ 2 weeks)	1.6285	1.5	0.3	13.0	1.20309	
Left size ( $\leq$ 2 weeks)	17.15	16.45	12.2	22.7	4.3876	0.880
Left size ( $>$ 2 weeks)	17.764	16.6	1.1	38.5	5.9068	
Left lymph node cortex thickness ( $\leq$ 2 weeks)	2.2833	2.5	1.1	2.9	0.70828	0.041
Left lymph node cortex thickness ( $>$ 2 weeks)	1.7374	1.5	0.38	12.3	1.2126	

two weeks. This indicates that findings are more pronounced during the first two weeks post-vaccination. Long-term follow-up suggests that COVID-19 vaccines can cause reactive lymphadenopathy in the vaccinated axilla. More extensive studies could help prevent unnecessary biopsies in these cases.

## Discussion

With the start of the COVID-19 vaccination process in our country and around the world, many people presented to breast clinics with painful and enlarged axillary LNs after vaccination<sup>(9-11)</sup>. Managing a patient with only lymphadenopathy may be relatively easier. However, in patients with newly diagnosed breast cancer or a history of breast cancer surgery this condition after vaccination may create complexities regarding axillary metastasis. Axillary LN involvement in breast cancer is an important factor that negatively affects the prognosis of the disease and determines the clinical and surgical approach<sup>(12,13)</sup>. In breast cancer, cortical thickness greater than 3 mm is considered suspicious<sup>(12)</sup>.

This study evaluated the association of COVID-19 vaccine types, number of doses, and the time elapsed since vaccination with ipsilateral axillary lymphadenopathy, and

compared these findings with contralateral axillary LNs. There are studies in the literature evaluating the incidence of hypermetabolic axillary LNs detected by 18F-FDG PET/CT and factors affecting these LNs in oncology patients<sup>(14,15)</sup>. Especially after the second COVID-19 vaccine injection, an increase in metabolism was detected in ipsilateral axillary LNs<sup>(16)</sup>. In another study, no relationship was found between the number of doses and axillary lymphadenopathy, similar to the findings of our study<sup>(9)</sup>.

In our study, no significant difference related to vaccination was detected in axillary LNs. There is no direct relationship between the size of LNs and malignancy; however, increased cortical thickness can be seen in cases of malignancy, systemic disease-related LN involvement, and vaccination<sup>(12)</sup>.

The increase in size, thickness, and metabolic activity in axillary LNs, known to develop after vaccination, may pose challenges in breast cancer diagnosis and follow-up, leading to unnecessary invasive procedures. Therefore, the National Comprehensive Cancer Network and the Society of Breast Imaging recommend that breast imaging should be performed 4 to 6 weeks after the second COVID-19 vaccination<sup>(14)</sup>. In our study, the cortical thickness of the axillary LNs decreased over time.

Our study revealed a significant correlation between BMI and axillary LN size, indicating that patients with higher BMI tend to present with larger LNs. These findings imply that BMI may exert an influence on LN morphology. Consistent with our results, a previous investigation assessing the relationship between BMI and LN dimensions also reported a significant association between obesity and LN size<sup>(15)</sup>.

In our study, LNs on the non-vaccinated side (contralateral) were also included, which is a distinction from other studies. No lymphadenopathy was detected in the contralateral axilla, thus reducing the likelihood of systemic disease-related LN involvement. In our study, it was demonstrated that there was a statistically significant increase in cortical thickness in the left axillary LN compared to the right axilla, in long-term follow-up. Increased cortical thickness in LNs can also be seen in metastasis or primary LN malignancies. Therefore, vaccination-related lymphadenopathy should be considered in the differential diagnosis of these patients.

COVID-19 vaccines such as Sinovac (inactivated) and BioNTech (mRNA) have been developed to prevent COVID-19. When comparing the side effects of both vaccine groups, it was found that people vaccinated with the mRNA group experienced more frequent and severe side effects. Swelling in the LNs was also more frequently observed after mRNA vaccinations<sup>(3)</sup>. In a study by Cohen et al.<sup>(16)</sup> ipsilateral axillary swelling/tenderness was seen in 11.6% and 16.0% of participants after the first and second doses, respectively, and was identified as the second most common local reaction following the Moderna (mRNA) COVID-19 vaccine. In the Moderna cohort, clinically detected axillary and supraclavicular lymphadenopathy was reported as an undesirable side effect in 1.1% of study participants within 2-4 days after vaccination<sup>(16)</sup>. In the Pfizer-BioNTech (mRNA) COVID-19 vaccine trial<sup>(8)</sup>, the rate of ipsilateral axillary and supraclavicular lymphadenopathy was reported as 0.3%. In a study by B et al.<sup>(17)</sup> lymphadenopathy was most commonly observed in the first 2 weeks after mRNA vaccination; regardless of the vaccine type, it gradually decreased. These findings are similar to the results of our study. In a study involving 49 women with a 12-week follow-up ultrasonography (USG) after the first vaccination, persistent lymphadenopathy was observed in 25 of them (51%). It was found that in more than half of the patients with lymphadenopathy after the second vaccination, the cortical thickness returned to normal within a month<sup>(17)</sup>. Another study found that the regression time of reactive lymphadenopathy varied, and

persistent axillary lymphadenopathy was detected up to 43 weeks after vaccination<sup>(18)</sup>. In our study, no significant difference was found between the effects of different vaccine types. There are also publications suggesting that human papilloma virus and influenza vaccines may cause similar effects<sup>(11)</sup>. Due to the different timing of these vaccinations, the incidence of such effects may be too low to be detected or reported. It should be kept in mind that similar results may be observed after future global vaccination campaigns. There are only a few studies in the literature that include long-term follow-up<sup>(18)</sup>.

Although a study describing persistent lymphadenopathy exists, long-term data on COVID-19 vaccines are still lacking<sup>(17,18)</sup>. However, unexplained reactive lymphadenopathies continue to be observed in daily practice. Overall, our findings are particularly important for cancer patients. After COVID-19 vaccination, the imaging features of lymphadenopathy and its changes over time remain uncertain.

### Study Limitations

There were several limitations of this study. Our study was conducted in a single institution. Different results may be obtained in different institutions. Secondly, the limited number of patients may limit the representativeness of the sample for the entire population. More valid results can be obtained with larger cohorts. Additionally, the USG examinations were evaluated by a single radiologist. Interobserver consistency could be calculated with evaluations by different radiology specialists.

### Conclusion

In conclusion, COVID-19 vaccination is associated with ipsilateral axillary reactive lymphadenopathy. Consistent with the findings of our study, vaccination was associated with a significant long-term increase in cortical thickness of ipsilateral LNs compared to contralateral LNs. In breast cancer diagnosis and follow-up, querying the vaccination history in such cases may prevent unnecessary invasive procedures and misdiagnoses.

### Ethics

**Ethics Committee Approval:** Ethical approval for this retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of Izmir Katip Çelebi University (approval no: 0043, date: 15.02.2024).

**Informed Consent:** Retrospective study.

## Footnotes

## Authorship Contributions

Surgical and Medical Practises: S.Ü., Concept: S.Ü., Design: S.Ü., Data Collection or Processing: S.Ü., Ö.P., Analysis or Interpretation: Ö.P., Literature Search: S.Ü., M.G., Writing: S.Ü., M.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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