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# Using hormonotherapy in breast cancer and its relationship with metabolic syndrome

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## ABSTRACT

**Aims**: This study aims to investigate whether the use of hormonotherapy pharmaceuticals causes metabolic syndrome-like symptoms in patients diagnosed with breast cancer and to compare the long-term effects of the drugs.

**Methods**: This retrospective file analysis was conducted on breast cancer patients who presented to the Radiation Oncology clinic between January 2019 and April 2022. Files of 75 patients diagnosed with breast cancer, postmenopausal, and without any previous chronic diseases such as diabetes or hypertension were included in the study. Patients who were started on medications with different active ingredients (tamoxifen citrate, letrozole or anastrazole) in the adjuvant period were examined in 3 groups. Waist circumference thickness, body weight, blood pressure, and blood biochemical tests (blood glucose, lipid levels) were measured before and 6 months after the start of the drugs, and the values were compared retrospectively.

**Results**: Of the 75 patients included in the study, the average age of patients using tamoxifen was 59.6; The average age of patients using letrozole was 59.12 years and the average age of patients using anastrozole was 63.56 years. There was an increase in fasting blood sugar (p:0.014) and waist circumference (p:0.009) in the tamoxifen group. There was an increase in fasting blood sugar, weight, waist circumference, blood pressure and lipid levels in the letrozole and anastrazole arms ($p<0.0001$ for all). Furthermore, comorbidities such as diabetes mellitus and hypertension that developed after using drugs were ascertained.

**Conclusion**: We think that there is a significant association between hormonotherapy medicines used in breast cancer and metabolic syndrome. While we found increases in blood lipids, FBG, body weight, and waist circumference in most of the patients, we observed that these increases were significantly higher in the groups using aromatase inhibitors. These patients should be examined in detail before starting hormone therapy. Diet, active lifestyle, and sports should be recommended.

Keywords: Aromatase inhibitor in breast cancer, metabolic syndrome, hormone receptor-positive breast cancer

## INTRODUCTION

Breast cancer is the most prevalent form of cancer in women and the second leading cause of cancer-related deaths globally.[1]

Breast cancer risk can be associated with many factors including genetics, hormonal parameters, metabolic syndrome (MS), and lifestyle.[2] As is well known, hormonotherapy is an important part of the treatment of patients who are diagnosed with breast cancer and have positive hormone receptors (estrogen and progesterone receptors). Hormonotherapy drugs are classified as tamoxifen citrate (TMX) and aromatase inhibitors (letrozole, anastrozole).[3]

It has been shown that estrogen hormone has an important role in the development of breast cancer. This carcinogenic effect can be prevented by receptor blockade through antiestrogens or by inhibiting estrogen synthesis with aromatase inhibitors. While the main site of estrogen production in the premenopausal period is the ovary, in the postmenopausal period it is fat and muscle tissue.[3,4]

TMX is a non-steroidal anti-estrogenic agent with weak estrogen agonist effects and is used in palliative and adjunctive treatment of breast cancer, also reduces the incidence of breast cancer in women at high risk and the risk of invasive breast cancer in women with ductal carcinoma in situ (DCIS). Because of the competition between estrogen and TMX for binding to estrogen receptors (ER) in the breast, TMX abolishes the augmentation effect of estrogen on breast cancer patients.[4-6]

Aromatase inhibitors have been used in hormone receptor-positive postmenopausal breast cancer patients for many years and have been proven to reduce recurrence and increase survival in many studies.[7-9]

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Many hormonal, metabolic, and inflammatory mechanisms are known to play a role in the progression of breast cancer.[10] Increased visceral fat, increased insulin resistance, and insulin biosynthesis lead to increased extra-glandular estrogen production and elevated estradiol levels, which exert mitogenic effects on breast epithelial cells.[11]

Especially menopause is a triggering factor for metabolic syndrome. According to the data of the World Health Organization, metabolic disorders were observed 2 times more in patients with breast cancer in 5000 women aged 50-80 years, and these rates were higher after menopause.[12,13]

Metabolic syndrome (MS), described as a cluster of metabolic abnormalities including abdominal adiposity, insulin resistance, hypertension, and dyslipidemia, has been linked to an increased risk of various cancers.[14,15]

Increased waist circumference, elevated triglycerides (TG), low HDL cholesterol, elevated blood pressure, and fasting blood glucose (FBG) are the main components of MS, the incidence of which has increased in our country and worldwide in recent years. The presence of at least 3 of these parameters is required for diagnosis.[16,17]

It is a known fact that type 2 diabetes, dyslipidemia, and hypertension are more common in women with breast cancer compared to other healthy individuals.[18]

The factors recognized as features of the metabolic syndrome are well known. However, the general consensus is that at least 3 of the following factors are required for diagnosis:

- Central, visceral, abdominal obesity and large waist circumference.
- Elevated fasting blood glucose levels (>100 md/dl)
- High blood pressure (hypertension) (systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg)
- High TG levels (>150 mg/dl)
- Low HDL (male <40 mg/dl, female <50 mg/dl)

Having three or more of these factors signifies the risk of cardiovascular diseases such as heart attack or stroke and type 2 diabetes, which is regarded as a late-onset disorder but is increasingly seen in young people with these risk factors.[3,19,20]

In our previously published hypothesis, we reported that aromatase inhibitors may have a role in glucose intolerance in obese men.[21]

In our study, we aimed to investigate the relationship between the use of hormonotherapy (TMX and aromatase inhibitors) and the development of metabolic syndrome in postmenopausal breast cancer patients.

## METHODS

Ethics committee approval of Ankara Training and Research Hospital Ethics Committee (Date: 07.09.2022, Decision No: 1067/2022) was taken. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Total 98 patients with positive hormone receptors (estrogen and progesterone receptors) who were diagnosed with breast cancer and started treatment between January 2019 and April 2022 were evaluated. All patients had undergone surgery. All patients received anthracycline and taxane-based chemotherapy in the adjuvant period. The number of chemotherapy sessions and the drugs used were the same.

**Criteria for inclusion in the study:**

- Those diagnosed with breast cancer,
- Postmenopausal patients,
- Those in stages I, II, or III Women patients,
- Patients who have undergone surgery and completed chemotherapy.

**Criteria for exclusion from the study:**

- Cancers other than breast cancer,
- Pre- or perimenopausal patients,
- Stage IV (metastatic) patients,
- Patients who have not undergone surgery or chemotherapy,
- Patients with previous diabetes, hypertension, heart disease, or hyperlipidemia, and male patients.

As a result of the screening, 23 patients were excluded from the study because their metabolic values were abnormal. As a result of the scanning, 75 postmenopausal patient files were eligible for the study.

Before starting adjuvant hormonal therapy, a routine gynecological examination and bone densitometry were performed. According to the results, TMX was started in 25 postmenopausal patients with severe osteoporosis. Letrozole and anastrazole were started in patients without osteoporosis.

In addition, blood pressure (mmHg), waist circumference (cm) and body weight (kg) were measured in all patients before starting treatment. Hemogram and biochemical blood tests (FBG (md/dl), TG (mg/dl), LDL (mg/dl), cholesterol (mg/dl), HDL (mg/dl)) were analyzed and noted in their files. During patient follow-up, the same measurements were repeated every 6 months and noted in our routine clinical practice for the monitorization of patients weight management, blood pressure and metabolic status. We compared the data in the files for the study and presented statistical analysis. Bone densitometry is performed every 2 years for patient follow-up, while gynecological examination is repeated every year.

Patients diagnosed with diabetes, hypertension (HT), hyperlipidemia and heart disease were also identified and the necessary medical examinations and treatments were arranged. All patients took their medications.

For hormonotherapy, 25 patients were given TMX 20 mg/day PO, 25 patients were given letrozole 2.5 mg/day PO, and 25 patients were given anastrozole 1 mg/day PO. They were planned to be used for 5 years.

### Statistical Analysis

All data were analyzed using SPSS v25. Categorical variables were expressed as counts and percentages. In the comparison of the parameters before and after the use of drugs, the Shapiro-Wilk test was used to determine whether the variables were normally distributed. Wilcoxon signed ranks test was used to compare the parameters before and after the use of drugs if at least one variable was not normally distributed before and after. Also, a Paired sample t-test was used if both data before and after the use of drugs were normally distributed. Kruskal Wallis test was used for age distribution. The chi-square test was also used. A value of P<0.05 was considered statistically significant.

## RESULTS

The mean age of the patients using TMX was 59.6 years (min 50, max 81); the mean age of patients using letrozole was 59.12 years (min 50, max 77); and the mean age of patients using anastrozole was 63.56 years (min 49, max 82). There is no statistically significant difference between the ages of the participants according to the drugs they use (p=0.08) (**Table 1**).

For each of the drugs, baseline and follow-up data were compared. Accordingly, TMX, letrozole, and anastrozole are shown in **Table 2**.

**Table 1.** Distribution of patient ages according to the medications they use

| | Tmx (n=25) | | | Letrazol (n=25) | | | Anastrazol (n=25) | | | P Kruskal Wallis Test |
|---|---|---|---|---|---|---|---|---|---|---|
| | Median | Min.-Maks. | mean.±SD | Median | Min.-Maks. | mean±SD | Median | Min.-Maks. | mean±SD | |
| Age | 56 | 50-81 | 59.6± 9.2 | 56 | 50-77 | 59.12± 7.3 | 63 | 49-82 | 63.56± 9.3 | 0.08 |

Tmx: Tamoxifen, SD: standart deviation

**Table 2.** Distribution and statistics before/afterTMX, letrozole and anastrozole use

| TMX (n=25) | Before use | | | After use | | | p |
|---|---|---|---|---|---|---|---|
| | Median | Min.-Max. | mean.±SD | Median | Min.-Max. | mean.±SD | |
| FBG | 88 | 81-96 | 88.08±4.6 | 90 | 82-101 | 90.8±5.1 | 0.014* (1) |
| HDL | 40 | 31-73 | 42.72±9.1 | 43 | 33-84 | 46.28± 10.5 | 0.014* (2) |
| LDL | 85 | 42-154 | 91.68±27 | 92 | 62-150 | 96.72± 24.7 | 0.052 (2) |
| Cholesterol | 156 | 46-234 | 152.92± 45.9 | 160 | 105-240 | 161.96± 38.4 | 0.122 (1) |
| Waist circumference (cm) | 92 | 60-126 | 90.04± 19.3 | 101 | 60-127 | 93.28± 20.7 | 0.009** (1) |
| TG | 130 | 70-250 | 145.16± 52.4 | 151 | 67-360 | 154.96± 58.6 | 0.166 (2) |
| Weight (kg) | 74 | 45-101 | 69.68± 15 | 72 | 44-103 | 70.64±16 | 0.058 (1) |
| **Letrozole (n=25)** | **Before use** | | | **After use** | | | **p** |
| | **Median** | **Min.-Max.** | **mean.±SD** | **Median** | **Min.-Max.** | **mean.±SD** | |
| FBG | 92 | 82-109 | 92.36±6 | 122 | 86-226 | 132.08± 38.3 | <0.001**(2) |
| HDL | 46 | 33-113 | 52±16.5 | 48 | 35-130 | 52.92±18 | 0.431 (2) |
| LDL | 121 | 53-210 | 122.04± 38.8 | 156 | 64-220 | 155.48± 39.7 | <0.001**(2) |
| Cholesterol | 182 | 45-239 | 170.72± 41 | 248 | 111-360 | 243.8± 51.8 | <0.001**(2) |
| Waist circumference(cm) | 96 | 60-131 | 97.4±17.8 | 105 | 59-138 | 106.52± 18 | <0.001**(1) |
| TG | 153 | 75-273 | 153.64± 57 | 235 | 96-378 | 246.12± 77.2 | <0.001**(1) |
| Weight (kg) | 70 | 45-107 | 72.92± 14.6 | 79 | 45-110 | 79.84± 14.7 | <0.001**(1) |
| **Anastrozole (n=25)** | **Before use** | | | **After use** | | | **p** |
| | **Median** | **Min.-Max.** | **mean.±SD** | **Median** | **Min.-Max.** | **mean.±SD** | |
| FBG | 91 | 84-100 | 91.88±4.2 | 128 | 85-194 | 129.76± 34 | <0.001**(2) |
| HDL | 46 | 31-68 | 47.92±9.3 | 48 | 36-138 | 52.4±19.5 | 0.681 (2) |
| LDL | 114 | 70-159 | 109± 27.8 | 138 | 86-600 | 158.56± 98.4 | <0.001**(2) |
| Cholesterol | 161 | 46-240 | 165.8± 46.4 | 245 | 116-329 | 234.04± 53.1 | <0.001**(1) |
| Waist circumference (cm) | 101 | 60-132 | 97.8±16.6 | 108 | 61-134 | 106.16± 17.4 | <0.001**(1) |
| TG | 160 | 70-277 | 158.24± 51.4 | 260 | 95-829 | 264.68± 144.7 | <0.001**(2) |
| Weight (kg) | 73 | 45-98 | 74.04± 14.7 | 77 | 46-109 | 79.76± 15.1 | <0.001**(1) |

*: p<0.05; **: p<0.01, HDL: High-density lipid (mg/dl), TG: Triglyceride(mg/dl), LDL: Low-density lipid (mg/dl), FBG: Fasting blood glucose(100 md/dl), (1): Paired samples t test, (2): Wilcoxon signed ranks test

There is a statistically significant increase after TMX therapy regarding FBG (p=0.014), HDL (p=0.014), and waist circumference (p=0.009) values of the patients.

There is no statistically significant difference between LDL (p=0.052), cholesterol (p=0.122), TG (p=0.166), and weight (p=0.058) values before and after the use of TMX. Increased blood pressure was detected in 4 patients (16%).

There is a statistically significant increase regarding FBG (p<0.001), LDL (p<0.001), cholesterol (p<0.001), waist circumference (p=0.001), TG (p<0.001), weight (p<0.001) after the use of letrozole.

There is no statistically significant difference between HDL values before and after the use of letrozole (p=0.431). Increased blood pressure was detected in 11 patients (44%).

There is a statistically significant increase regarding FBG (p<0.001), LDL (p<0.001), cholesterol (p<0.001), waist circumference (p<0.001), TG (p<0.001), body weight (p<0.001) values of patients after anastrozole use.

There is no statistically significant difference between HDL values before and after anastrozole use (p=0.681). Increased blood pressure was detected in 13 patients (52%).

**Table 3** shows the statistical data of changes in FBG, HDL, LDL, cholesterol, waist circumference, TG, and weight for all drugs (**Table 3**).

**Table 3.** Descriptive statistics of FBG, lipid levels, waist circumference, and weight gain after drugs

| Medicine | N | Min | Max | Avg. | SD |
|---|---|---|---|---|---|
| Tmx | | | | | |
| FBG increase | 25 | -9 | 16 | 2.72 | 5.1 |
| HDL increase | 25 | -5 | 33 | 3.56 | 7.8 |
| LDL increase | 25 | -80 | 72 | 5.04 | 25.2 |
| Cholesterol | 25 | -29 | 114 | 9.04 | 28.2 |
| Waist circumference increase | 25 | -3 | 19 | 3.24 | 5.7 |
| TG increase | 25 | -58 | 133 | 9.80 | 37.7 |
| Weight increase | 25 | -3 | 5 | 0.96 | 2.4 |
| Letrozole | | | | | |
| FBG increase | 25 | 1 | 132 | 39.72 | 38.9 |
| HDL increase | 25 | -20 | 17 | 0.92 | 8.3 |
| LDL increase | 25 | -2 | 94 | 33.44 | 29.1 |
| Cholesterol | 25 | -24 | 221 | 73.08 | 53.3 |
| Waist circumference increase | 25 | -1 | 25 | 9.12 | 7.6 |
| TG increase | 25 | 3 | 254 | 92.48 | 63.5 |
| Weight increase | 25 | -1 | 21 | 6.92 | 6.3 |
| Anastrozole | | | | | |
| FBG increase | 25 | -4 | 102 | 37.88 | 33.4 |
| HDL increase | 25 | -11 | 107 | 4.48 | 22.1 |
| LDL increase | 25 | -26 | 523 | 49.56 | 107.5 |
| Cholesterol | 25 | -21 | 213 | 68.24 | 67.1 |
| Waist circumference increase | 25 | -5 | 36 | 8.36 | 9.7 |
| TG increase | 25 | -29 | 658 | 106.44 | 137.2 |
| Weight increase | 25 | -3 | 21 | 5.72 | 6.5 |

HDL: High-density lipid TG: Triglyceride, LDL: Low-density lipid, FBG: Fasting blood glucose

In the 6th month or later months after the initiation of the medication, some of the patients were disturbed by the increase in blood values such as glucose, lipids, and blood pressure, and these patients were re-examined by internal medicine and cardiology, and medication was started for these additional diseases. Statistical data on the use of antihypertensive drugs are given, and cardiac drugs, antidiabetic drugs, and anti-lipid drugs are shown in **Table 4**.

**Table 4.** Statistical data on the use of antihypertensive drugs, cardiac drugs, antidiabetic drugs and anti-lipid drugs

| | | Anti HT | | Total |
|---|---|---|---|---|
| | | Not present | Present | |
| Tmx | n | 21 | 4 | 25 |
| | % | 84% | 16% | 100% |
| Letrozole | n | 14 | 11 | 25 |
| | % | 56% | 44% | 100% |
| Anastrozole | n | 12 | 13 | 25 |
| | % | 48% | 52% | 100% |
| Total | n | 47 | 28 | 75 |
| | % | 62.7% | 37.3% | 100.0% |
| | | Heart medication | | Total |
| | | Not present | Present | |
| Tmx | n | 25 | 0 | 25 |
| | % | 100.0% | 0.0% | 100.0% |
| Letrozole | n | 22 | 3 | 25 |
| | % | 88.0% | 12.0% | 100.0% |
| Anastrazol | n | 22 | 3 | 25 |
| | % | 88.0% | 12.0% | 100.0% |
| Total | n | 69 | 6 | 75 |
| | % | 92.0% | 8.0% | 100.0% |
| | | Anti DM | | Total |
| | | Not present | Present | |
| Tmx | n | 25 | 0 | 25 |
| | % | 100.0% | 0.0% | 100.0% |
| Letrozole | n | 10 | 15 | 25 |
| | % | 40.0% | 60.0% | 100.0% |
| Anastrozole | n | 10 | 15 | 25 |
| | % | 40.0% | 60.0% | 100.0% |
| Total | n | 45 | 30 | 75 |
| | % | 60.0% | 40.0% | 100.0% |
| | | Anti-lipid | | Total |
| | | Not present | Present | |
| Tmx | n | 23 | 2 | 25 |
| | % | 92.0% | 8.0% | 100.0% |
| Letrozole | n | 5 | 20 | 25 |
| | % | 20.0% | 80.0% | 100.0% |
| Anastrozole | n | 8 | 17 | 25 |
| | % | 32.0% | 68.0% | 100.0% |
| Total | n | 36 | 39 | 75 |
| | % | 48.0% | 52.0% | 100.0% |

Tmx: Tamoxifen, AntiHT: Antihypertensive AntiDM: Antidiabetitic

There is a statistically significant difference between drugs in terms of the formation of HT after starting the use of drugs (p=0.022). The highest presence of HT was observed in anastrozole (52%) and the least presence of HT was observed in TMX drugs (16%).

There is no statistically significant difference between drugs in terms of the use of cardiac medication after the initiation of medications (p=0.196). The highest use of cardiac medication was seen in letrozole and anastrozole (12%), while no patient was found to use the cardiac medication after TMX use.

There is a statistically significant difference between drugs in terms of the occurrence of DM after the initiation of the drugs (p=0.0001) (p=0.0001). The presence of DM was highest in letrozole and anastrozole (60%), while the presence of DM was not detected after the use of TMX.

There is a statistically significant difference between drugs in terms of lipid formation results after the initiation of drugs (p=0.0001). The highest anti-lipid drug use was detected in those using letrozole (80%) and the lowest in those using TMX (8%).

## DISCUSSION

As seen in our study, we observed that aromatase inhibitors in particular, which we used in the treatment of patients who had no chronic disease prior to the diagnosis of breast cancer, caused the formation of metabolic syndrome or there was an indirect link between them.

In most of the studies, it is stated that breast cancer is already more common in patients with metabolic syndrome, and the frequency increases, especially in menopausal patients.[10,22]

Breast cancer is more associated with type 2 diabetes, hyperlipidemia, and hypertensive heart diseases, while it has also been stated in publications that all these metabolic disorders trigger each other.[23]

Few studies have investigated whether chemotherapy and hormonotherapy used for adjuvant breast cancer treatment are associated with the syndrome.[24,25]

We excluded hormone receptor-negative, premenopausal, and perimenopausal patients from the study. As a result of our personal observations, we decided to investigate more scientifically, especially after we noticed an increase in waist circumference and lipid levels following the initiation of aromatase inhibitors in postmenopausal patients.

In most of the studies, patients already had diabetes, hypertension, and hyperlipidemia before treatment.25 However, we conducted the study by excluding patients with chronic diseases. And we wanted to investigate whether we really triggered such a risk. We followed up the patients who already had chronic diseases with other standard clinical follow-up methods.

The effects of TMX were also investigated in perimenopausal and premenopausal patients, but no significant relationship was found between metabolic syndrome and TMX use. Its estrogenic properties have been found to reduce the risk of cardiovascular disease.[26,27]

Considering the cardioprotective effect of TMX, we aimed to have a control group in postmenopausal patients. In our study, we showed that TMX was not significantly associated with metabolic syndrome.

As reported in a review of 6 articles published in Pubmed, some studies were conducted on the effects of chemotherapy and drugs used on insulin and glucose levels in breast cancer patients, and although there was no scientific significance, it was observed that drugs such as Taxanes increased metabolic syndrome-like findings.[24-29] Since all patients received the same chemotherapeutic agents in the same way in our study, the effect of chemotherapy was not analyzed in this study.

When the lipid profiles of the patients were analyzed, TG levels increased by 70.7% in all patients, with the highest increase in those using anastrozole. Statistically, the increase was significant in the letrozole and anastrozole groups (p<0.0001). HDL levels decreased by 26.7% in all patients but were statistically significant only in those using TMX (p:0.014).

While an overall 50.7% increase in FBG levels was observed in all patients, the highest increase was found in the letrozole group. The increase was statistically significant in all groups.

In our cases, the initial weight and waist circumference of the patients were measured and the increase or decrease was monitored in the following period, so overweight patients were enrolled in the study.

An increase in waist circumference thickness was observed in 58.7% of all patient groups. This increase was highest in the letrozole group. It was statistically significant in all groups. While weight gain was observed in all drugs, it was statistically significant in the letrozole and anastrozole groups.

In our study, anti-lipid drugs were started in 52% of the patients in the early period. Of these patients, 94.8% were in the group receiving aromatase inhibitors (AI) (letrozole+anastrozole).

Again, 37.3% of patients started to use antihypertensive drugs in the early period, and 86% of this group was in the AI group.

While 40% of the patients started to use oral antidiabetics, 20% of them (6 patients) started to use insulin.

Another 34.6% (26 patients) continued their hormone therapy without any medication, only diet arrangements, increased activity, and an active lifestyle.

### Limitations

There were some limitations to this study. Firstly, TMX was preferred over an aromatase inhibitor in patients with severe osteoporosis, since our study was conducted on postmenopausal patients. Second, the number of patients in the study was not large, as patients with any chronic disease were excluded before starting treatment, but still statistically significant results were obtained. Conducting the study on a larger number of patients will help obtain more robust results. Metastatic patients were not included in the study. In this group of patients, the use of chemotherapy and targeted drugs was preferred instead of only hormone therapy. Another limitation is whether metabolic syndrome develops in patients who do not use any hormone medication, but we consider it unethical to follow up without treatment. Therefore, all patients received hormone therapy. 6th month data is presented in the study. However, the data obtained will be more accurate when patient follow-up is completed for at least 5 years.

## CONCLUSION

The study first revealed that the drugs lead to metabolic syndrome-like effects. We notice that metabolic syndrome develops especially in patients diagnosed with breast cancer who are treated with aromatase inhibitors. We think that we can reduce the risk of developing metabolic syndrome with a strict diet, sports, and active social life from the very beginning, regardless of whether it is due to breast cancer or the use of hormone therapy. In the patient group where these do not help, it is our recommendation to start treatment for the metabolic disorder in the early period.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ankara Training and Research Hospital Ethics Committee (Date: 07.09.2022, Decision No: 1067/2022).

### 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.

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