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Aydın Ulaş



# Does Covid-19 affect lower urinary tract symptoms (luts) of male patients?

Soner Çoban<sup>1</sup>, Atilla Satır<sup>1</sup>, Salim Zengin<sup>1</sup>, Özgür Ekici<sup>2</sup>, Anıl Erkan<sup>1</sup>,  
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## ABSTRACT

**Objectives:** We investigated the effect of COVID-19 on lower urinary tract symptoms (LUTS) in male patients.

**Methods:** 110 patients diagnosed with COVID-19 were prospectively included in the study. Fifty-five male patients over the age of 40 who were hospitalized with the diagnosis of COVID-19 at University of Health Sciences, Bursa Yüksek İhtisas Education and Research Hospital between May 2020 and April 2021, who did not meet the exclusion criteria, were included in the study. As a control patient, 80 patients in the same age group who applied to the urology outpatient clinic for reasons other than LUTS were included. Demographic data of the patients such as age, total prostate specific antigen (tPSA), free PSA (fPSA), International Prostate Symptom Score (IPSS), height and weight were recorded and analyzed. Patients were classified as mild (0-7), moderate (8-19), and severe (20-35) according to their IPSS. These forms were filled in by patients to avoid possible influence from the practitioner. All patients with 5 or more nocturia numbers were considered to have 5 nocturia numbers.

**Results:** There was no age difference between the groups ( $p = 0.29$ ). Although the IPSS value in the COVID-19 group was lower than the patients in the control group who applied to the outpatient clinic, the difference was found to be statistically insignificant ( $p = 0.07$ ). Similarly, although nocturia and prostate volume was lower than the control group, the difference was not statistically significant. The tPSA and fPSA examined were found to be statistically significantly lower in the COVID 19 group ( $p = 0.01$ ,  $p = 0.009$ , respectively). However, there was no difference between f/t PSA ( $p = 0.3$ ).

**Conclusion:** We found that COVID 19 did not affect LUTS in male patients.

**Keywords:** COVID-19, free/total PSA, lower urinary system symptoms, nocturia



**B**enign prostatic hyperplasia (BPH) is a histologic definition that develops because of the simultaneous overgrowth of epithelial and stromal cells of the prostate

[1]. It is the most common cause of benign prostatic obstruction. Lower urinary tract symptoms (LUTS), which are closely related to benign prostatic obstruction, develop

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because of disruption of both bladder and prostate dynamics [1]. International prostate symptom score (IPSS), prostate specific antigen (PSA) and finger rectal examination are the first tests for the diagnosis of LUTS which increases with age and significantly impairs quality of life.

Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2), which was first isolated in Wuhan province of China in November 2019, has been in our lives for more than 2 years and despite improved vaccines, it causes more than 100 deaths per day according to data from the Turkish Ministry of Health. Although the organs and systems most responsible for deaths are the lungs, heart and cardiovascular system, the virus has been isolated in many organs [2, 3]. SARS-CoV-2 enters the cell through cells expressing angiotensin converting enzyme-2 (ACE-2) and transmembrane serine protease-2 (TMPRSS2). In a study examining the distribution of ACE-2 expression using RNA sequences from different organs, it was reported that it was expressed at a rate of 4% in renal proximal tubule cells and 2.4% in bladder uroepithelial cells [4]. According to this study, the most sensitive organs were lung, heart, esophagus, kidney, ileum and bladder.

Although typical symptoms include fever, cough, headache and diffuse muscle pains, new symptoms related to the involvement of many organs emerge as the disease becomes better understood. Symptoms and findings may also be observed in urinary system involvement, including tightness due to uroepithelium involvement, increased urinary frequency, microscopic haematuria, and acute renal failure [5, 6]. According to the results of a multicentre study, although no lower urinary system symptoms were reported in any patient, the virus was isolated in urine in 19% of the patients [7]. Such a high incidence of uroepithelium has led urologists to investigate the relationship between LUTS and COVID-19 [6, 8].

Our study aimed to investigate whether coronavirus infection affects LUTS in male patients.

## METHODS

This prospective study was conducted in accordance with the Declaration of Helsinki and the Ethical Principles of Clinical Research. It was approved by the Clinical Research Ethics Committee of Health Sciences University Bursa Yuksek Ihtisas Education and Research Hospital (decision number 2011-

KAEK-25 2020/05-14 dated 27.05.2020). 55 male patients over 40 who were hospitalised with a diagnosis of COVID-19 at University of Health Sciences, Bursa Yuksek Ihtisas Education and Research Hospital between May 2020 and April 2021 were included in the study. As control patients, 100 patients of the same age group who applied to the urology outpatient clinic with complaints other than LUTS were included. Patients included in the study signed an informed consent form.

Exclusion criteria were patients with a PSA value >10 ng/ml or prostate malignancy detected as a result of prostate biopsy with a PSA value between 4-10 ng/ml, previous use of alpha-blockers or 5-alpha reductase inhibitors, Diabetes Mellitus, Chronic Obstructive Pulmonary Disease, TUR-P and/or any interventional treatment for BPH, patients with urethral stricture and/or lower urinary tract surgery (such as urethrotomy, urethroplasty, hypospadias repair, cystolithotomy) for any reason, patients diagnosed with prostate cancer and/or radical prostatectomy, patients with neurological examination findings and/or neurological disease (such as cerebrovascular accident, spinal trauma, multiple sclerosis), patients with a history of diuretic and alcohol use. The patients included in the study were divided into COVID-19 and control groups. The COVID-19 group included hospitalised patients who were definitively diagnosed with reverse transcriptase-polymerase chain reaction (RT-PCR) (Device-Biorad (USA), Kit-Qiagen (USA) test. PCR tests were performed in the acute period when symptoms started the patients whose symptoms regressed after treatment were routinely discharged without PCR testing.

Demographic data of the patients, including age, total PSA (tPSA), free PSA (fPSA), IPSS, prostate volume measured by USG, number of nocturia, height, weight, and medical history, were recorded. According to IPSS, 7 questions were asked to the patients, each receiving a score between 0 and 5 (9). Patients were classified as mild (0-7), moderate (8-19) and severe (20-35) according to IPSS. The quality-of-life index of the IPSS form was used as a quality-of-life scale [10]. The patients filled in these forms to prevent the possible influence of the practitioner. However, it was stated that patients could request information from us for questions they needed help understanding. The number of nocturia was accepted as 5 in all patients with 5 or more than 5 nocturia.

Data were analysed using Statistical Package for Social Sciences (SPSS) version 22.0™ (IBM Corpo-

**Table 1. Mean age of patients and results of investigations**

	COVID-19 group (n = 55)	Control group (n = 80)	p - value
Age (year) mean ± SD	59.46 ± 11.3	61.6±7.8	0.29
Creatinine (mg/dl) mean ± SD	0.9 ± 0.2	0.9±0.1	0.36
Total PSA (ng/ml) median (IQR)	0.8(1.1)	1.3(2.2)	0.01*
Free PSA (ng/ml) median (IQR)	0.3(0.3)	0.5(0.7)	0.009*
f/t PSA median (IQR)	0.4(0.2)	0.3(0.2)	0.3

PSA: prostate specific antigen \* $p < 0.05$

ration). The distribution of variables was measured using the Shapiro-Wilk test. Statistical analyses were performed using Student's ttest, the Mann-Whitney U test with and without normal distribution, respectively. Categorical variables were compared using chi-squared test.  $P < 0.05$  was considered statistically significant.

## RESULTS

The study included 110 patients hospitalised in the COVID-19 ward. Of these patients, 7 were excluded because of a PSA result  $> 10$  ng/ml, 38 were excluded because they were using alpha-blockers and/or 5-alpha reductase inhibitors due to LUTS, and 10 were excluded because they had a history of previous prostate and/or urethral surgery. The data of the remaining 55 people in the COVID-19 group were analysed. In the control group, 100 people who were not diagnosed with COVID-19 and who applied to the urology outpatient clinic for reasons other than LUTS were included. In this group, 9 patients were excluded because the PSA result was  $> 10$  ng/ml, 5 patients were excluded because prostate cancer was detected as a result of a biopsy taken between 4-10 ng/ml, 3 patients were excluded because they had a history of active or previous malignancy of the urological system, and

3 patients were excluded because renal function tests were impaired and/or chronic renal failure was diagnosed. The data of the remaining 80 patients in the control group were analysed.

The mean age of the patients and the results of the tactics are shown in Table 1. The values in the table are given as mean ± standard deviation or median (interquartile range), with and without normal distribution, respectively.

Information about IPSS, number of nocturia, quality of life scale score and prostate volume are summarised in Table 2. The data in the table are shown as mean ± standard deviation. Although the IPSS value in the COVID-19 group was lower than that in the control group of patients presenting to the outpatient clinic due to LUTS, the difference was statistically insignificant ( $p = 0.07$ ). Similarly, although nocturia and prostate volume was lower in the COVID-19 group compared to the control group, the difference was not statistically significant.

Twenty (36%) patients in the COVID-19 group and 11 (13.8%) in the control group were mildly symptomatic, and the difference was statistically significant ( $p = 0.002$ ) (Table 3). However, the groups in moderate and severe symptomatic patients had no significant difference, according to IPSS. The relationship between IPSS and prostate volume is shown in Figure 1.

**Table 2. Comparison of COVID-19 group and control group values**

	COVID-19 group (n = 55)	Control group (n = 80)	p - value
IPSS	13.3 ± 9.5	15.5 ± 6.6	0.07
Number of nocturia	2.2 ± 1.5	2.6 ± 1.1	0.61
Quality of life scale score	2.8 ± 2.2	4.3 ± 1.5	$< 0.001^*$
Prostate volume	44.3 ± 19.1	52.1 ± 25.9	0.18

IPSS: International Prostate Symptom Score, \*  $p < 0.05$

**Table 3. Frequency of nocturia and IPSS**

	COVID-19 group (n = 55)	Control group (n = 80)	p - value
<b>Nocturia</b>			
0	6 (10.9%)	0	< 0.001*
1	14 (25.5%)	7 (8.8%)	0.009*
2	13 (23.6%)	39 (48.7%)	0.003*
3	11 (20%)	15 (18.7%)	
4	4 (7.3%)	14 (17.5%)	
5	7 (12.7%)	5 (6.3%)	
<b>IPSS severity</b>			
Mild	20 (36.4%)	11 (13.8%)	0.002*
Moderate	21 (38.2%)	42 (52.5%)	
Severe	14 (25.4%)	27 (33.7%)	

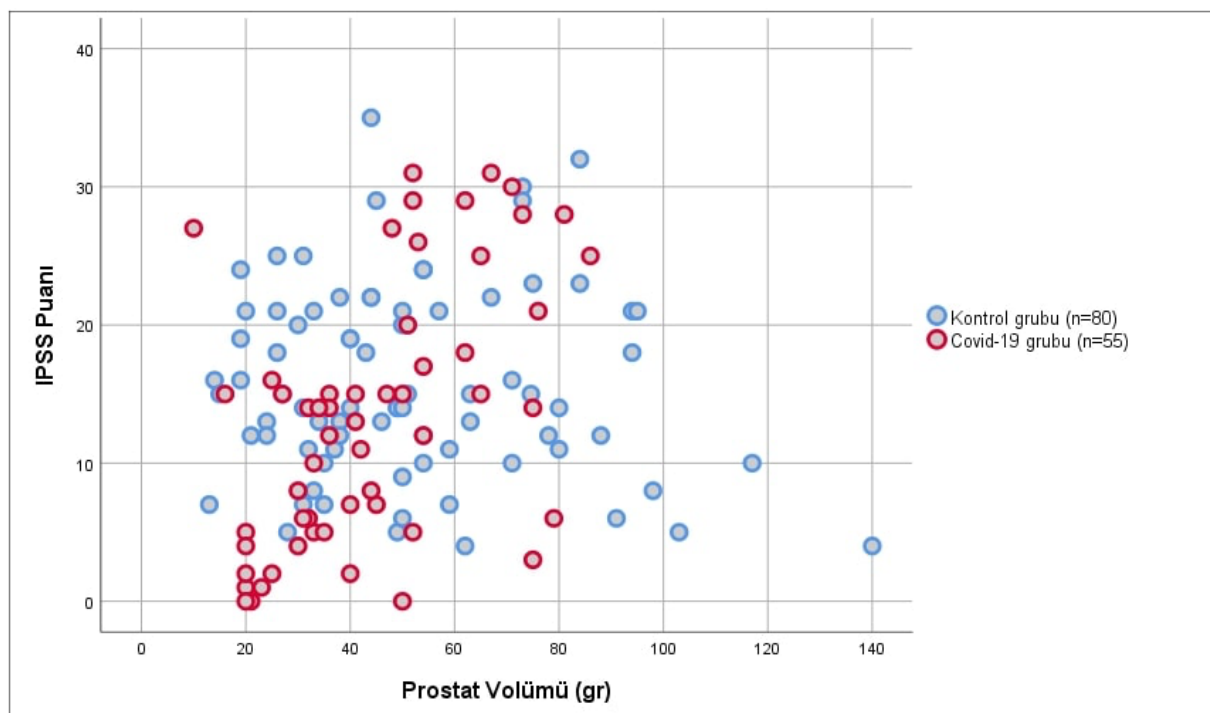
IPSS: International Prostate Symptom Score, \* $p < 0.05$

## DISCUSSION

COVID-19 primarily affects the lungs, causing respiratory symptoms. On the other hand, it can involve all organs and systems through ACE-2 receptors. Bladder and prostate involvement may lead to de novo lower urinary system symptoms or worsening of existing symptoms, increased urinary frequency, and microscopic haematuria [11]. These complaints and the COVID-19-related cystitis picture are thought to

be related to the cytokines released. In fact, it has been reported that the cytokine storm, which is responsible for the disease's rapid progression, causes demyelination in central and peripheral nerves and leads to acute urinary retention [12]. However, in the present study, we showed that COVID-19 did not change the symptom scores, the number of nocturia, and prostate volume of BPH patients and only caused changes in PSA values.

The prostate is a target for SARS-CoV-2, just as



**Figure 1. Distribution graph of prostate volume and international prostate symptom score of the patients**

other organs are targets via ACE-2 and TMPRSS2 receptors. The possible mechanism is related to tissue damage and disruption of the structure of the ductus, as in prostatitis. Disruption of this structure may lead to an increase in the level of PSA in the blood. In their study investigating the effect of COVID-19 on PSA levels in BPH patients, Cinislioğlu *et al.* found that the PSA value during the COVID period was statistically significantly higher than before and after COVID-19 [13]. In the present study, total and free PSA values of COVID patients in our study population were statistically significantly lower than in the non-COVID control group. According to the authors of the study, antibiotics, anti-virals or steroids taken by inpatients to prevent bacterial co-infections may have led to lower PSA values compared to the control group.

Our study found no difference between the COVID and the control groups regarding IPSS. In their research, including both genders, Kaya *et al.* had patients hospitalised and discharged due to COVID-19 fill out IPSS and Urinary Symptom Profile (USP) before, during and after hospitalisation. In male patients, only the storage scores of IPSS were found to be different between the three periods. In female patients, stress incontinence and overactive bladder symptoms significantly differed in three periods [14]. Can *et al.* divided COVID-19 patients into low-moderate-severe groups according to lung involvement and analysed the correlations of these groups with IPSS. According to the analysis, no correlation was found between the severity of CT findings and IPSS. In the group over 50 years of age, an increase in IPSS during the COVID period compared to the previous period was found to be statistically significant [15]. Nabeeh *et al.*, in their study including 50 BPH patients, found that the IPSS value increased statistically significantly during hospitalisation and in the 1st and 3rd months after discharge compared to the pre-COVID period [16]. In addition, the quality-of-life score worsened during the COVID-19 period in this study. In our research, on the contrary, the quality-of-life score was found to be lower in the COVID-19 patient group.

In our study, there was no difference between the COVID-19 group and the control group regarding the number of nocturia. Swatesitipun *et al.*, in their study including 136 COVID-19 patients, reported that 44.85% of patients had storage symptoms, and the group with storage symptoms had a significantly higher number of nocturia than the other group [17]. Although not in a comparative study, Dhar *et al.* reported that all patients had nocturia symptoms, and

87% of patients had nocturia >4 in a study including COVID-19 patients of both sexes with 39 diseases [5]. The prominence of nocturia is probably because viral infections lead to storage disorders. For example, according to a study conducted on patients infected with the HTLV-1 virus, the most common urological finding in these patients was nocturia, with 35.8% [18]. Studies in which cytokine increase was detected in urine samples of patients with storage phase disorders support this theory [19]. Lamb *et al.* reported that IL-6, IL-8 and IL-10 levels were increased in all COVID-19 patients in their study conducted with 4 COVID-19 patients with de novo urinary system symptoms and 4 patients in the control group. They defined the new-onset lower urinary system symptoms associated with COVID-19 as COVID-19-related cystitis [19].

According to the results of our study, COVID-19 does not negatively affect lower urinary tract symptoms and nocturia. The findings in the literature generally contradict our results. However, studies that partially support our results have also been published. For example, Welk *et al.*, in their study comparing 5617 COVID-19 patients with 11225 patients who did not have COVID-19, did not observe a significant difference in the COVID-19 group in terms of the use of medication, urology consultation and cystoscopy necessity in terms of the overactive bladder within 2-5 months after COVID-19. Therefore, they stated that it did not lead to significant bladder dysfunction after the acute period [20].

In contrast to our research question, in a study on the effect of lower urinary tract symptoms on COVID-19 prognosis, Karabulut *et al.* divided COVID-19 patients into low-medium-high risk groups in terms of IPSS. They found more hospitalisation time, more intensive care unit hospitalisation and higher mortality rate in the high-risk group compared to patients in the low-risk group [21]. According to the study's authors, lower urinary tract symptoms can be used to predict the prognosis and severity of COVID-19.

Among the study's limitations, antibiotics, and the amount of fluid intake, which may affect nocturia and PSA levels in the patient groups, were not known. These factors may have caused changes in nocturia and PSA levels.

## CONCLUSION

We found that COVID-19 did not affect LUTS in male patients. On the other hand, tPSA and fPSA

were statistically significantly lower in the COVID-19 group, which may delay the diagnosis of prostate cancer. Therefore, the decision for biopsy in patients with COVID-19 should be based on the f/t PSA ratio.

### Conflict of Interest

There is no conflict of interest between the authors.

### Ethics Committee Decision

It was approved by the Clinical Research Ethics Committee of Health Sciences University Bursa Yuksek Ihtisas Education and Research Hospital (decision number 2011-KAEK-25 2020/05-14 dated 27.05.2020).

### Authors' Contribution

Authors' Contribution Study Conception: AA,; Study Design: SZ, ÖE, AE,; Supervision: AG, MK, AB,; Materials: AK, MÖ, AA,; Data Collection and/or Processing: SÇ, AS,; Statistical Analysis and/or Data Interpretation: SZ, ÖE, AE; Literature Review: AG, MK, AK,; Manuscript Preparation: ART, MG and Critical Review: AK, MÖ, AA.

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# Evaluation of Patients Receiving Home Health Services

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## ABSTRACT

**Objectives:** In this study, it is aimed to determine the health status of the patients who need home health services in Bursa, and to contribute to the accurate and effective planning of home health services according to this analysis.

**Methods:** The universe of this descriptive cross-sectional study consists of individuals over the age of 16 who are registered in the home health services unit of Bursa Ali Osman Sönmez Oncology Hospital. No sample was selected in the study, and all patients in the last year were evaluated. The data were taken from the patient information forms in the computer environment.

**Results:** Between July 2022 and July 2023, 655 patients who requested home health services were reached. The mean age of the patients was determined as 82.4. It was observed that 57% (n = 373) of the patients were female and 43% (n = 282) were male. As a result of the evaluation according to the Barthel Index, 66 (9.3%) of the patients were fully dependent, 482 (67.6%) were severely dependent, 165 (22.9%) were moderately dependent and 2 (0.3%) was found to be mildly dependent.

**Conclusion:** The prolongation of life expectancy at birth, the most important public health problem that we will encounter in our developing world with new diagnoses and treatments, is the increasing number of patients over 65 years of age, with more than one chronic disease and in the fragile group who need care. Each service to be provided to the vulnerable group will help the person to take care of himself/herself, and will reduce the burden of caregivers.

**Keywords:** Home care services, public health, family medicine practice

In parallel with the developments in technological, scientific and medical fields, there are many changes in the way of providing services to patients. As a concept, home health care services are mostly a medical service, although they include personal care services at home [1]. As an approach, home health care services include protecting and improving the health of people and, when necessary, intervening without the

need for long rehabilitation services when the health condition deteriorates, providing medical care to reintegrate the person into society [2].

Home health service in our country, in the Regulation on the Delivery of Home Care Services published in the Official Gazette dated 10.03.2005 and numbered 25751; It is defined as “providing health and care and follow-up services to patients in line with



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the recommendations of physicians, in the environment they live with their families, by the healthcare team in a way that meets their medical needs, including rehabilitation, physiotherapy, and psychological treatment” [3].

Age groups to which home health services are directed; Although there are mostly elderly patients aged 65 and over who need chronic and long-term care, this group includes babies and children of all ages with chronic diseases. With home health services, all these featured groups can receive multi-faceted care services under safe home conditions. In addition, home health services can be provided in order to enable terminal cancer patients to spend their last days of life better [4].

On the other hand; The increasing cost of health services in hospitals, the continuing need for care after discharge, the aging of the society and the emergence of various health needs due to old age cause the population in need of home health services to increase [5]. As a result of people preferring home health services more, the frequency of going to the hospital and the duration of hospitalization are decreased [6].

Reduction of the side effects that may occur due to hospitalization, the fact that the family and friends of the person do not adhere to the hospital routine when they want to visit, and the appropriate patients benefit from health services in this way without leaving the home environment they are used to and love, reducing the occupancy of hospital beds and reducing the costs of tertiary care hospitals and the tertiary care costs of the patients in need. It facilitates access to services [7].

In this study, it is aimed to provide a detailed analysis of the reasons for the need for home health services of patients in the province sample and to contribute to the correct and effective planning of home health services according to this analysis.

## METHODS

Data were obtained by examining the physical and electronic files of 655 patients selected by the Simple Random Sampling Method among the patients who received service from the Home Health Services Coordination Center affiliated to the Bursa Provincial Health Directorate Public Hospital Services Presidency. During the study period, the number of patients registered to the Center was 18,718.

The health status of the patients was examined

during the period of July 2022-July 2023. In these analyzes, variables such as demographic characteristics of patients (age, gender), number of visits, addiction levels, disease diagnoses, nutritional status, vaccination rates, incidence of constipation, urinary tract infection and decubitus ulcer, and medical devices used were examined. The study was planned as retrospective, descriptive and cross-sectional, and numerical variables were summarized as ‘mean  $\pm$  SD’, categorical variables as number and ratio (%).

Dependence levels of the patients were evaluated with the Barthel Activities of Daily Living Index, a scale used to measure the performance of individuals in activities of daily living. The scale was developed by Barthel and Mahoney in 1965 and modified by Shah *et al.* in 1992. It was adapted into Turkish by Küçükdeveci *et al.*, and its internal consistency was found to be 0.93 and 0.88 [8].

The index evaluates ten different activities of daily living. These life activities; nutrition (10 points), transition from wheelchair to bed and from bed to wheelchair (15 points), self-care (5 points), toilet activities (10 points), bathing activities (5 points), walking on a flat surface (15 points), stairs going up and down (10 points), dressing (10 points), bowel care (10 points) and bladder care (10 points) [9].

Prior to the study, approval was obtained from Bursa Provincial Health Directorate Scientific Research Commission (Committee Approval dated 25.08.2023 and numbered 2023/8).

## RESULTS

The mean age of the patients was determined as 82.4. While the mean age for women is 83.2, it is 81.5 for men (Table 1). It was observed that 57% (n = 373) of the patients were female and 43% (n = 282) were male (Table 1).

As a result of the evaluation according to the Barthel Index, 66 (9.3%) of the patients were fully de

**Table 1. Sociodemographic information of home health care patients**

Gender	Ratio
Female	57% (n = 373)
Male	43% (n = 282)
The average age	Number
Female	83,2
Male	81,5

**Table 2. Dependence status of home health care patients**

Dependence status	Number
Severely dependent	67.8% (n = 482)
Mildly-Moderate dependent	23% (n = 163)
Fully dependent	9.2% (n = 66)

pendent, 482 (67.6%) were severely dependent, 165 (22.9%) were moderately dependent and 2 (0.3%) was found to be mildly dependent (Table 2).

In the study, the most common disease diagnoses were; Alzheimer's/dementia (48.9%), hypertension (31.6%), heart diseases (21.4%) and DM (11.6%) were found.

When the past records of 655 patients included in the study were examined, the total number of visits made from the date all patients started to receive service until 2020 was 4,524 (Table 4). It was determined that 67 of 655 patients had a permanent disability report. It was determined that 316 of the patients died during the research period (Table 4).

33 (5%) patients could not be fed orally and 230 (35%) patients were fed with formula supplementation. The number of patients with decubitus ulcer was 20 (3%).

Of the 655 patients participating in the study, 46 use at least one medical device. The distribution of 46 people using medical devices according to the devices they use is as follows; The walker uses 10 people, an air bed for 15 people, a wheelchair for 8 people, an oxygen cylinder for 15 people, and a ventilator for 3 people (Graph 1).

Among the patients participating in the study, the number of people who had flu vaccine was 4, and the number of people who had pneumococcal vaccine was 4.

**Table 3. Chronical disease status of home health care patients**

Chronical disease	Number
Hypertension	207
Diabetes mellitus	76
Alzheimer's disease/Dementia	320
Cancer	25
Heart diseases	140
Chronic Obstruktive Pulmonary Disease	27
Osteoporosis	40
Cerebrovascular disease	57
Epilepsy	10

**Table 4. number of visits and Disability report in home health care patients**

Number of visits	4524
Disability report	655
Death	316

## DISCUSSION

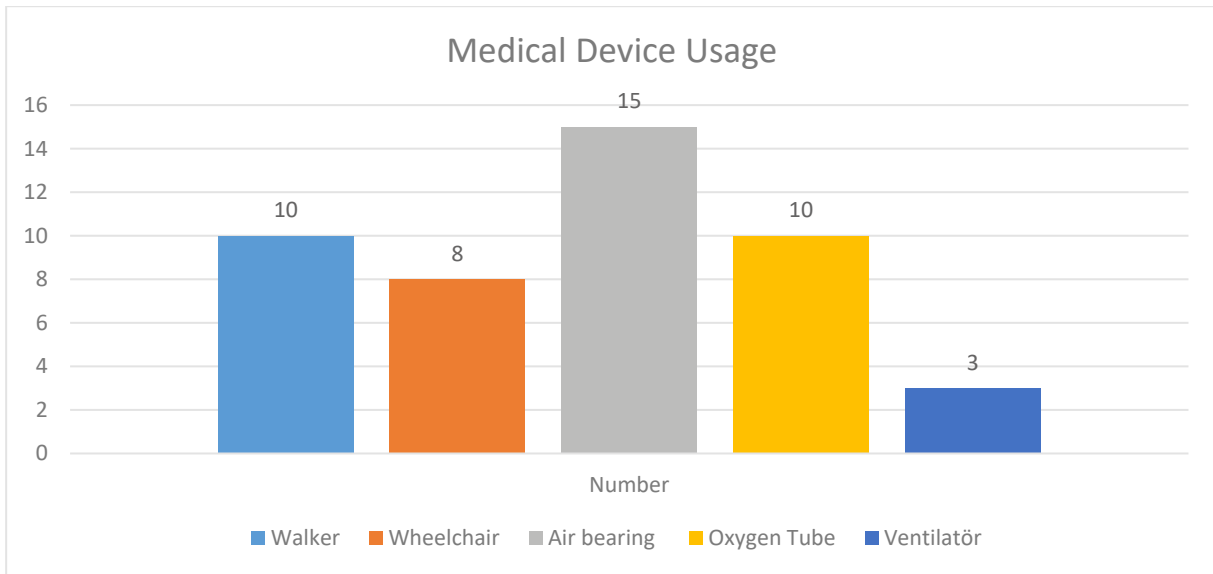
The high average age of the group needing home care brings along many chronic diseases and moderate-to-advanced addiction levels. In our study, it was found that mildly moderately dependent 23% (n = 163), severely dependent 67.8% (n = 482), and fully dependent 9.2% (n = 66). When the literature of our country was reviewed, it was found that it was 37.3% moderate and advanced in one study, 61.2% fully dependent, and 8%, advanced 20%, fully dependent 37% in another study [7, 10]. It is possible that the level of addiction varies between studies and may be affected by multifactorial causes such as age group, chronic diseases and cancer status of the population under consideration.

When evaluated in terms of mean age in our study, the mean age of patients receiving home health services in this study was found to be 82.3. Looking at the literature, the mean age was found to be 79.6 years, similar to our study [10, 11]. In our study, gender weight was found to be in favor of women with a frequency of 57% (n = 373). Similarly, in previous studies, it was reported that patients receiving home care were predominantly female [10, 12].

The most common chronic diseases in our study were; Alzheimer's/dementia in 35.4%, hypertension in 22.9% and cerebrovascular diseases in 8% (Graphic 2). In a previously reported study, the frequency of chronic diseases was cerebrovascular accident (21.40%), hypertension (15.20%) and Alzheimer's disease (12.20%) [10]. In another study, 20.80% of the patients who received home health services had cerebrovascular disease [13]. Neurological diseases appear to be the cause of general disability in patients receiving home care services.

Malnutrition leads to malnutrition and accompanying biopsychosocial problems. This situation causes sarcopenia and thus loss of resistance in the frail group, falls, prolongation of the healing time, and development of decubitus ulcer [14]. According to the findings of our study, 5% (n=33) of the patients cannot be fed orally and 35% (n = 230) of them take nutritional supplements. Looking at the literature, in a



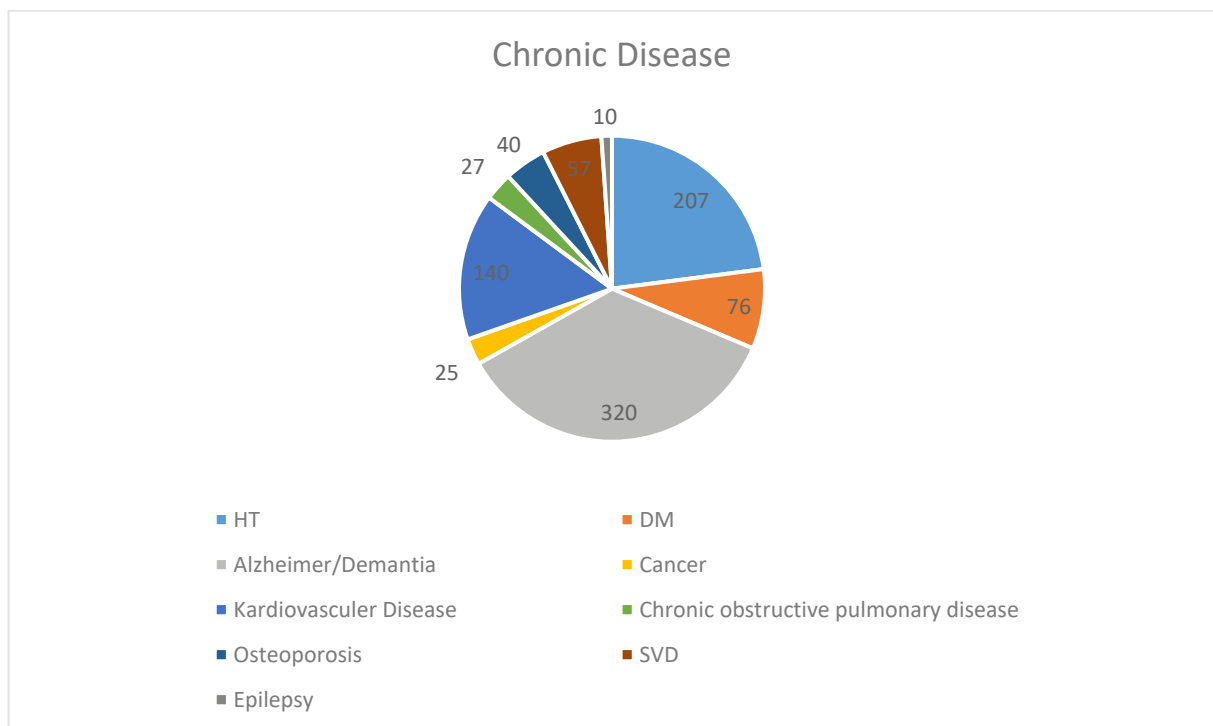


**Graph 1. Medical device usage of home health care patients**

study, 7% of the patients could not be fed orally and 32% of them took nutritional supplements [7]. Another study found the rate of patients who could not be fed orally as 33% [15]. In another study, 10.5% of patients were fed enterally [16]. In home care patients, close follow-up is important in terms of the fact that nutritional status follow-up invites many negativities.

In our study, the incidence of pressure ulcers in patients receiving home health services was found to be

3% (n = 20). When we look at the literature of our country, the rate of pressure sores in similar groups has been reported with a wide margin of 12-37% [7, 15-17]. Looking at the world literature, it was stated in a study that one out of every three patients receiving home health care needed wound care, and 37% of them had decubitus ulcers (18). Compared to other studies on home care patients in our country, the incidence of decubitus ulcer among patients in this study



**Graph 2. Chronical disease status of home health care patients**

was found to be lower than in other studies [7, 15-17]. Considering that decubitus ulcers, malnutrition, infection status and quality of care are affected by many factors, it is clear that groups with larger patient populations are needed.

There is a free immunization service in our country for individuals over 65 years of age with chronic diseases [19]. In our study, 0.6% (n = 4) with pneumococcal vaccine, 0.6% [n = 4] with influenza vaccine in the last 1 year, and in a study conducted in Samsun, 35 (6.5%) patients received influenza vaccine and only 2 (0.5%) the patient had pneumococcal vaccine; In a study conducted in Ankara, the rates of getting the influenza vaccine were 22.03%, while the rates of getting the pneumococcal vaccine were 6.44% [10, 20]. Our study shows similarity with other studies in our country in terms of pneumococcal immunization and lower than other studies in terms of influenza. In order to spread free preventive services to the entire population, a lot of work falls on the primary care and family medicine.

The most frequently provided medical services are home health services, patient visits by the home health team and wound dressing. Patients were visited an average of 2.8 times per year. In a previous study conducted in Samsun, it was reported that the frequency of visits was 2.5 per year, similar to our study [10]. Our study is similar to the literature.

## CONCLUSION

The prolongation of life expectancy at birth, the most important public health problem that we will encounter in our developing world with new diagnoses and treatments, is the increasing number of patients over 65 years of age, with more than one chronic disease and in the fragile group who need care. Each service to be provided to the vulnerable group will enable the person to take care of himself/herself and hold on to life and will reduce the burden of caregivers. Home health services are carried out by health professionals at home, where the person will feel psychologically comfortable. It is important to carry out studies that depict the general of our country, such as this study, in terms of determining the need and expectation of home health services. Home health care, which is one of the best examples for the effective use of health resources, should also be evaluated in terms of easing the workload of the 2nd and 3rd steps.

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For the frequency of home care visits, more than 2 visits per year are within the quality standards of the Ministry of Health, and it is admirable that the frequency of home health visits in Bursa is well above the target value. We would like to thank the whole team, especially in the presence of Bursa Provincial Health Director Dr.Fevzi YAVUZYILMAZ, for the support given by the home health services coordination center, which is affiliated to the Bursa provincial health directorate.

## Ethical Approval

For the protocol of the study, permission was obtained from the Bursa Provincial Health Directorate with the letter dated 25.08.2023 and numbered 222981783.

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# Thyroid dysfunction is associated with poor COVID-19 outcomes

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## ABSTRACT

**Objectives:** We aimed to investigate the effects of the thyroid hormone level on the hospitalization rate and prognosis of COVID-19 patients.

**Methods:** Patients with a positive PCR test result and having their TSH, fT3, and fT4 values tested. The patients were classified according to their thyroids' functional status. The hospitalization rates in the hospital and intensive care unit and the mortality rate were evaluated.

**Results:** A total of 708 patients were included in the study. 225 (31.8%) patients were euthyroid. The rates of hospitalization to the intensive care unit ( $p < 0.001$ ) and the clinic ( $p < 0.001$ ) and also the mortality rate (0.012) were lower. 483 (68.2%) were classified as a euthyroid sick syndrome. In 305 (43.1%) patients, only the fT3 level was low, whereas in 47 (6.6%), both fT3 and fT4 were low, and in 131 (18.5%) patients, the fT3, fT4, and TSH levels were low. In patients with thyroid dysfunction, the levels of BUN, creatinine, D-dimer, neutrophil %, troponin T, CRP, procalcitonin, LDH were higher, and the aPTT was longer. In contrast, the leukocyte count and percentage were lower.

**Conclusions:** The intensive care hospitalization rate, the duration of hospitalization in the clinic, and the mortality rate were lower in euthyroid patients. ICU hospitalization and mortality rates were higher in patients in whom both fT3 and fT4 levels were low. Thyroid dysfunction is common in COVID-19 patients. The variations in serum TSH and T3 levels may significantly indicate disease severity in COVID-19.

**Keywords:** COVID-19; intensive care; euthyroid sick syndrome

Since the first coronavirus disease 2019 (COVID-19) cases due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in late 2019, COVID-19 has spread worldwide. As a result, in March 2020, a global pandemic was declared by the World Health Organization [1]. The virus infection is known to have a complex interaction with the thyroid gland and related inflammatory-immune responses. SARS-CoV-2 uses ACE2 jointly with transmembrane protease serine 2 (TM-

PRSS2) as the key molecular complex for infecting host cells. Surprisingly, in the thyroid gland, the expression levels of ACE2 and TMPRSS levels are higher than in the lungs [2].

In COVID-19 patients, thyroid dysfunction may be comorbidity. Besides, the low triiodothyronine (T3) status is considered as an indicator of the euthyroid sick syndrome (ESS) and observed in critical patients [3-5]. For this reason, alterations of thyroid functions during the coronavirus infection have



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drawn attention. Moreover, in observational studies, the thyroid hormone and TSH levels were lower in patients who died due to COVID-19 when compared to survivors [6, 7]. A cohort study conducted in China showed that in COVID-19 patients followed up in the hospital, the mortality rate was higher in the patients with thyroid dysfunction than those with no dysfunction [8]. Furthermore, investigators have reported that thyroid dysfunction was related to mortality among critical patients hospitalized in the intensive care unit [9, 10].

In euthyroid sick syndrome (ESS), low fT3, normal TSH, and normal fT4 were defined as ESS- mild disease, low fT3, normal/low TSH, and normal/low/high fT4 as ESS-moderate disease, low fT3, low fT3, and low TSH as ESS-severe disease [11]. This retrospective study aimed to investigate the effects of thyroid hormone levels on COVID-19 patients' hospitalization rates and prognosis.

## METHODS

### Study Design and Participants

The Local Ethics Committee (01.09.2021/ethics no.: 15 / 8) approved this study. Seven hundred eight patients with reverse-transcription polymerase chain reaction- (RT-PCR)-confirmed COVID-19 who were admitted to Our Hospital between April 2020 and December 2020 were enrolled. None of them had previous thyroid disease, used any thyroid medications, or had a pregnancy. Covid pcr positive patients were included in the study. Exclusion criteria were defined as using thyroid medication, having a history of thyroid disease, pregnancy and being under 18 years of age.

### Data Collection

All patients were evaluated for thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4). In addition, the results for complete blood counts, alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, creatinine, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, PT, aPTT, troponin T, and procalcitonin values were recorded from the laboratory information system.

The patients' age and gender distributions, hospitalization rates (%), duration of hospitalization in the clinics and ICU, and discharge status were evaluated.

The patients were divided into four groups: Euthyroid group, Group 1 - only low fT3; group 2 - low fT3

and low fT4; group 3 - low TSH, low fT3, and low fT4. It was determined as overt hyperthyroidism (low TSH, high fT3, and/or fT4) and overt hypothyroidism (elevated TSH and low fT4 and/or fT3). The patients' clinic and ICU hospitalization duration and discharge/exitus status were classified according to the groups.

### Biochemical Analysis

The parameters of AST, ALT, creatinine, and LDH were analyzed with Roche Cobas 8000 c 702. In addition, the parameters of PT, INR, APTT were measured with Coagulation Analyzer Cobas T711. The troponin T level was measured with sandwich principle Roche Cobas 8000-e801. The procalcitonin levels were measured with Sandwich Roche Cobas 800-e801 (ECLIA). CRP levels were measured with Particle-enhanced immunoturbidimetric assay-c702 (ECLIA). The D-dimer level was measured with particle-enhanced turbidimetric immunoassay - Roche Cobas T711. Ferritin values were measured with sandwich principle electrochemiluminescence- C801 (ECLIA). Complete blood counts were measured with Sysmex XN1000. TSH, free thyroxine (fT4), and fT3 were evaluated at admission before the administration of in-hospital medications using the sandwich principle electrochemiluminescence- e 801 (ECLIA) (Roche, Mannheim, Germany). The reference range for TSH was 0.27–4.20 mIU/L, for fT3 2.04–4.44 ng/L, and for fT4 0.93–1.71 ng/dl.

### Statistical Analysis

The study's statistical analysis was performed using the JASP 0.14.1 and RStudio 1.0.959 software packages. Descriptive statistics for qualitative variables in the study were given as frequency and percentage, and quantitative variables as the mean, standard deviation, median, minimum, and maximum values. In addition, the conformity of the study's quantitative variables with a normal distribution was analyzed with the Shapiro Wilk test. The Mann-Whitney U test was used for independent two-group comparisons of quantitative variables not having a normal distribution; the Kruskal Wallis test compared three or more groups. The Mann Whitney U test with the Bonferroni correction was used for two-subgroup comparisons of variables with significant inter-group differences. For qualitative variables' inter-group comparisons, Pearson's Chi-square test was used. In the study's statistical analysis, the results with a p-value below 0.05 were considered statistically significant.

**Table 1. Distribution of Euthyroid and ESS groups**

	n	%	Age (Mean ± SD)	Male (n, %)
Euthyroid	225	31.8	62.01 ± 15.6	132 (58.7%)
Group 1	305	43.1	63.75 ± 14.78	176 (57.7%)
Group 2	47	6.6	62.51 ± 14.11	28 (59.6%)
Group 3	131	18.5	63.66 ± 13.88	76 (58.0%)
Total	708	100	63.10 ± 14.84	412 (58.2%)

## RESULTS

Patients hospitalized in the our hospital between April 2020 and December 2020 were screened. Seven hundred eight patients with a positive PCR test and who were tested for TSH, fT3, fT4 were included in the study. Of 708 patients, 412 (58.2%) were male, and 296 (41.8%) were female. Six hundred three patients were discharged from the hospital, whereas 105 died. The number and percentage distributions of the

groups are presented in Table 1.

Of 708 patients, 225 were in Euthyroid group. In 305 (43.1%) patients, only the fT3 value was low.

In 47 (6.6%) patients, both fT3 and fT4 values were low, and in 11 (18.5%), fT3, fT4, and TSH levels were low. Overt hypothyroidism was present in 11 patients, whereas overt hyperthyroidism in 30 patients.

Comparison of Euthyroid and ESS groups regarding the laboratory parameters

No statistically significant difference was deter-

**Table 2. The mean, minimum, and maximum values of the parameters**

	Euthyroid	Mild disease	Moderate disease	Severe disease	<i>p</i>
Alt	23 (7-3113)	22 (5-303)	27 (5-111)	23 (5-251)	0.608
Ast	28 (10-1927)	32 (6-378)	30 (8-271)	30 (11-219)	0.376
BUN	13.7 (3.6-139.2)	16.5 (4.7-109.1)	19.10 (7.9-78.4)	16.10 (6.2-70)	< 0.001
Creatinine	0.91 (0.44-3.02)	0.96 (0.41-3.64)	1.11 (0.42-2.04)	0.93 (0.53-3.99)	0.001
Hgb	13.4 (5.6-18.4)	13.1 (5.2-17.7)	13.3 (8.4-16.5)	13 (9.1-18.2)	0.052
Wbc	6.75 (1.38-450.40)	7.13 (0.92-58.91)	7.23 (2.70-20.07)	7.07 (1.61-27.74)	0.610
Leu	1.21 (0.17-298.57)	1.17 (0.20-48.77)	1.19 (0.47-2.96)	0.98 (0.15-3.13)	0.007
Leu %	18.5 (2.1-88.5)	17.9 (2.2-84.8)	16.3 (4.9-39.6)	14.5 (2.4-50.9)	0.004
Neu	4.53 (0.66-24.99)	5.19 (0.65-39.45)	5.05 (1.71-17.64)	4.96 (1.23-25.91)	0.304
Neu %	71.8 (2.3-97)	73.7 (10.7-96.3)	75.5 (52-93.6)	77.1 (43.1-93.7)	0.001
Plt	215 (22-724)	220 (52-697)	217 (57-483)	217 (72-620)	0.607
Ldh	250 (74-1343)	298 (98-1226)	305 (0.03-1352)	315 (138-767)	< 0.001
Prc	0.08 (0.02-13)	0.10 (0.02-81.59)	0.10 (0.02-16.50)	0.11 (0.02-5.59)	0.007
Crp	32.1 (0.2-313.5)	63.2 (0.8-497.8)	66 (3.8-345.5)	64.1 (1.8-324.3)	< 0.001
D-Dimer	0.46 (0.20-20.50)	0.54 (0.20-20.80)	0.58 (0.20-15.30)	0.63 (0.20-8.78)	0.028
Ferritin	294.5 (3-16931)	395 (14-4293)	284 (59-4745)	374.5 (5-6838)	0.005
Pt	9.07 (7.45-15.60)	9.09 (7.68-19.10)	9 (8.04-13.60)	9.05 (7.48-12.80)	0.664
INR	1.01 (0.84-1.70)	1.02 (0.86-2.05)	1.01 (0.91-1.47)	1.02 (0.85-1.41)	0.670
aPtt	30.5 (15-53.9)	31.40 (17.8-56.6)	31.6 (18.5-66.4)	31 (16.3-45.8)	0.046
Trop T	7.20 (3-6650)	12.75 (3-430.3)	15.7 (3-464)	11.3 (3-285)	< 0.001
TSH	1.17 (0.27-16.80)	0.64 (0.27-19.80)	1.49 (0.29-97.20)	0.15 (0.03-0.26)	< 0.001

#Kruskal Wallis test

**Table 3. The duration of hospitalization in Euthyroid and ESS groups (days)**

	Euthyroid	Group 1	Group 2	Group 3	<i>p</i>
Duration of Hospitalization in ICU	9 (1-36)	10 (1-51)	19 (1-53)	11 (1-25)	0.126
Duration of Hospitalization in the Clinic	8 (1-31)	10 (1-47)	11 (2-60)	9.5 (1-44)	< 0.001
Duration of Total Hospitalization	9 (2-38)	12 (3-61)	16 (3-88)	12 (3-60)	< 0.001

#Kruskal Wallis test

mined among the groups regarding the values of ALT, AST, Hgb, WBC, PLT, PT, INR, and neutrophil count ( $p = 0,608, p = 0,376, p = 0,052, p = 0,610, p = 0,607, p p = 0,664, p = 0,670, p = 0,610$ ). On the other hand, significant differences were present among the groups regarding other parameters as presented in the Table 2.

Comparison of Euthyroid and ESS groups regarding hospitalization duration in the clinic and ICU The average ICU hospitalization duration was nine days in Euthyroid patients, whereas ten days, 19 days, and 11 days in Groups 1, 2, and 3, respectively ( $p = 0.126$ ). The hospitalization duration of Euthyroid patients in the clinic was significantly shorter than Groups 1, 2, and 3 ( $p = 0.001, p = 0.007, \text{ and } p = 0.026$ ). In Euthyroid patients, it was eight days on average, whereas in Groups 1, 2, and 3, 10 days, 11 days, and 9.5 days, respectively ( $p < 0.001$ ). The total hospitalization duration of Euthyroid patients was significantly lower than Groups 1, 2, and 3. On average, it was determined as nine days in Euthyroid patients, whereas 12 days, 16 days, and 12 days in Groups 1, 2, and 3, respectively ( $p < 0.001$ ). The duration of hospitalization in Euthyroid and ESS groups (days) in the Table 3.

Comparison of Euthyroid and ESS groups regarding hospitalization rates in the clinic and ICU, and the mortality rate

The ICU hospitalization rate of Euthyroid patients

was 16.6% and significantly lower than the patients with TD. This ratio was 30.6%, 40.4%, and 31.3% in Groups 1, 2, and 3, respectively ( $p < 0.001$ ). The rate of hospitalization in the clinic was 97.4% in Euthyroid patients, whereas 97.4%, 95.7%, and 99.2% in Groups 1, 2, and 3, respectively ( $p = 0.502$ ). The mortality rate was 9.8% in Euthyroid patients and was lower than the patients with TD. This ratio was 16%, 27.7%, and 16% in Groups 1, 2, and 3, respectively ( $p < 0.001$ ). The relationship between hospitalization and mortality rate in Euthyroid and ESS groups in the Table 4.

The relationship between hospitalization in the clinic, ICU, and mortality in the hypothyroid and hyperthyroid patients

The ICU hospitalization rate was 36.4% in the hypothyroid group, whereas 40% in the hyperthyroid group ( $p = 1.000$ ). On the other hand, the mortality rate was 18.2% in the hypothyroid group, whereas

26.7 in the hyperthyroid group ( $p = 0.012$ ). The relationship between hospitalization and mortality rate in Hypothyroid and Hyperthyroid patients in the Table 5.

**DISCUSSION**

Our study determined ESS in 483 (31.8%) of the 708 COVID-19 patients. Thyroid dysfunction was

**Table 4. The relationship between hospitalization and mortality rate in Euthyroid and ESS groups**

		Euthyroid n (%)	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	<i>p</i>
Hospitalization in ICU	No	186 (83.4)	211 (69.4)	28 (59.6)	90 (68.7)	< 0.001
	Yes	37 (16.6)	93 (30.6)	19 (40.4)	41 (31.3)	
Hospitalization in the Clinic	No	5 (2.2)	8 (2.6)	2 (4.3)	1 (0.8)	0.502
	Yes	218 (97.8)	296 (97.4)	45 (95.7)	130 (99.2)	
Final situation	Discharged	203 (90.2)	256 (84)	34 (72.3)	110 (84)	0.012
	Exitus	22 (9.8)	49 (16)	13 (27.7)	21 (16)	

#Kruskal Wallis test

**Table 5. The relationship between hospitalization and mortality rate in Hypothyroid and Hyperthyroid patients**

		Hypothyroid n (%)	Hyperthyroid n (%)	<i>p</i>
Hospitalization in ICU	No	7 (63.6)	18 (60.0)	1.000
	Yes	4 (36.4)	12 (40.0)	
Hospitalization in the Clinic	No	-	-	-
	Yes	11 (100)	30 (100)	
Final situation	Discharged	9 (81.8)	22 (73.3)	0.012
	Exitus	2 (18.2)	8 (26.7)	

# Pearson's Chi-square test

associated with a longer duration of hospitalization and a higher mortality rate. In the study conducted by Zhang *et al.*, 16.9% (n=71) of the COVID-19 patients had ESS, and it was associated with a high mortality rate. Besides, the neutrophil count, CRP, LDH, and CK were high, and the lymphocyte count was low [8]. In Gao *et al.*'s study involving 100 patients with severe COVID-19, thyroid functions were assessed, and a higher mortality rate was determined in those with a low fT3. [12]. In our study, hospitalization rates in both the ICU and the clinic and the mortality rate were higher in ESS patients. On the other hand, the mortality rate was 18.2% in the Hypothyroid group and was higher, 26.7% in the Hyperthyroid group.

The ICU hospitalization rate in Euthyroid patients was 16.6%, lower than in the patients with TD. This rate was 30.6%, 40.4%, and 31.3% in Groups 1, 2, and 3, respectively. In addition, the mortality rate was 9.8% in Euthyroid patients and was lower than in the patients with TD. This ratio was 16%, 27.7%, and 16% in Groups 1, 2, and 3, respectively.

The pathophysiology of ESS varies according to the type, severity, and stage of the disease. In the acute phase of the disease, the plasma concentration of T3 decreases rapidly, and the reverse T3 level increases. These alterations can be partially explained by decreased thyroid hormone-binding protein and albumin levels and reduced binding activity. Additionally, an acute change in T4's peripheral conversion due to reduced Type 1 deiodinase (D1) activity and increased Type 3 deiodinase (D3) activity can explain these changes. It is known that circulatory cytokines reduce D1

activity and increase D3 activity, leading to acute reduction of T3 levels in critical patients [13, 14]. In COVID-19, the disease's course and severity are closely related to the effects of various cytokines

such as interleukin-6 and tumor necrosis factor-alpha (15). In our study, the levels of inflammatory markers (CRP, procalcitonin, LDH) were higher in ESS patients than in Euthyroid patients. Elevations of inflammatory cytokine levels can suppress central TSH and 5'-deiodinase activity. ESS might have occurred in COVID-19 patients due to SARS-CoV-2 directly infecting the thyroid glandular cells.

In our study investigating the ESS subgroups, the higher mortality rate determined in the group with low fT3 and low fT4 (Group 2) suggests that the fT4 and fT3 levels being low together may indicate significance in mortality and ICU hospitalization. In our study, TD did not affect the duration of ICU hospitalization, whereas it led to prolongation of hospitalization in the clinic and the total length of stay in the hospital.

In a multi-center study in the U.S.A., Khoo *et al.* evaluated the thyroid functions of the COVID-19 patients at admission and follow-up examinations. They reported that the TSH and fT4 levels were

relatively lower in COVID-19 patients than those without COVID-19 [16].

The study's main limitations were its retrospective nature, lack of a control group, lack of thyroid antibody measurements, absence of oxygen support and treatment modality status, lack of data collection on mechanical ventilation requirement, inotropes, and other comorbidities.



Our study may be representational due to the investigation of ESS subgroups. However, the effect mechanisms of TD on COVID-19 should be investigated thoroughly with large-scale studies in the future. On the other hand, should thyroid hormone replacement therapy be encouraged in the non-thyroidal illness syndrome? Studies related to its prognostic effect may also be conducted in the future.

## CONCLUSION

### *Ethical Approval*

The protocol of the study was approved by the Medical Ethics Committee of Bursa City Hospital, Bursa, Turkey. (Decision number: 2021 15/8, date: 1.09.2021).

### *Financing*

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# Leptospirosis presenting with acute kidney injury, Case Report

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## Case Report

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## ABSTRACT

Leptospirosis is very common in the tropical regions, with 73% of cases occurring in this region, particularly in South-East Asia, Eastern Sub-Saharan Africa, the Caribbean and Oceania. Farmers who are in contact with livestock and exposed to rodents in their workplaces, and people living in areas with poor sanitation are at highest risk.

A 47-year-old male patient presented to the emergency room with complaints of weakness, fever, nausea and vomiting that continues for 4-5 days. He was found to be hypotensive (blood pressure arterial 83/55 mmHg) and tachycardic (pulse: 125 beats/minute) at the time of admission. The patient who had no history of chronic disease, was engaged in farming. In the laboratory tests performed in the emergency room, Leukocyte count: 7470 103/ $\mu$ L, hemoglobin:13.4 g/dL, platelet: 15000 103/ $\mu$ L in the complete blood count. Biochemistry parameters: urea:113 mg/dL, creatinine: 2.5 mg/dL, AST:138 IU/L, ALT:80 IU/L, total bilirubin: 6.29 mg/dL, direct bilirubin: 3.78 mg/ dL, LDH:264 IU/L, c-reactive protein: 322 mg/L were detected. Patient was consulted to infectious disease thus It was recommended to send salmonella, brucella and leptospirosis samples, as well as hepatitis A-B-C, toxoplasma, cytomegalovirus (CMV), ebstein barr virus (EBV) serology. The patient was started empirically with doxycycline 2x100 mg/PO and ceftriaxone 2x1gr iv with their recommendations. On the 5<sup>th</sup> day of his treatment, the leptospirosis PCR test was positive. Liver function tests, bilirubin, kidney function tests and acute phase reactants decreased to normal values with antibiotic treatment.

The diagnosis of leptospirosis is made based on the presence of questionable clinical features with a history of risk exposure. Renal failure is often non-oliguric and is associated with hypokalemia. Supportive renal replacement therapy may be required in the acute phase, but renal function recovery is rapid and complete after six months. In our case, the platelet count was 15,000 103/ $\mu$ L at the time of admission and back to normal values within 1 month of the treatment. Leptospirosis which is a zoonotic disease should be considered in the differential diagnosis in patients presenting with acute kidney injury, thrombocytopenia, hyperbilirubinemia, liver function test disorders, and acute phase reactant elevation.

**Keywords:** leptospirosis, acute kidney injury, hyperbilirubinemia



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**L**eptospirosis is very common in the tropical regions, with 73% of cases occurring in this region, particularly in South-East Asia, Eastern Sub-Saharan Africa, the Caribbean and Oceania.

It is common among rural farmer populations and poor urban and semi-urban populations, particularly affecting young male adults.

Farmers who are in contact with livestock and exposed to rodents in their workplaces, and people living in areas with poor sanitation are at highest risk [1]. Human leptospirosis has a variety of clinical manifestations. While clinical disease in humans presents with mild, self-limiting mostly uncomplicated fever, approximately 10% of them present with multi-organ dysfunction and may constitute a serious and life-threatening condition (2-3).

Serious complications such as acute kidney injury, liver injury, myocardial involvement and pulmonary hemorrhage, and numerous other manifestations have been reported [3, 4].

Conjunctival redness, jaundice, and acute kidney injury with classic presentation constitute Weil's syndrome. Pulmonary bleeding has recently been shown to be an important cause of mortality [3-5]

The diagnosis of leptospirosis is made on the basis of characteristic clinical findings revealed by a history of risk exposure, by demonstration of bacterial DNA or culture providing direct evidence of infection and /or by demonstration of antibodies to leptospirosis providing indirect evidence of infection [6].

While patients with suspected or confirmed leptospirosis who have mild clinical findings and no comorbidity can be followed up as an outpatient, patients with comorbidities and organ involvement should be hospitalized. Early initiation of antibiotic therapy affects the prognosis positively [6]

## CASE

A 47-year-old male patient presented to the emergency room with complaints of weakness, fever, nausea and vomiting that continues for 4-5 days. He was found to be hypotensive (blood pressure arterial 83/55 mmHg) and tachycardic (pulse: 125 beats/minute) at the time of admission. In the physical examination performed in the emergency room, the patient was conscious, oriented and cooperative, and had an icteric appearance. Respiratory system, abdomen and neurological system examination were normal. In the

emergency service follow-up, there is 550 cc urine output in 6 hours. The patient who had no history of chronic disease, was engaged in farming.

In the laboratory tests performed in the emergency room, Leukocyte count: 7470 103/ $\mu$ L, neutrophil: 6670 103/ $\mu$ L, lymphocyte: 430 103/ $\mu$ L, hemoglobin: 13.4 g/dL, platelet: 15000 103/ $\mu$ L in the complete blood count. In urinalysis density: 1022, erythrocyte: 1352 / HPF (large magnification), leukocyte: 5/ HPF, protein 2+, bilirubin 2+, urobilinogen was negative. Biochemistry parameters: urea: 113 mg/dL, creatinine: 2.5 mg/dL, sodium: 133 mmol/L, potassium: 3.9 mmol/L, pH in venous blood gas: 7.42, HCO<sub>3</sub>: 27.8 mmol/L, pCO<sub>2</sub>: 42.9 mmHg, AST: 138 IU/L, ALT: 80 IU/L, total bilirubin:

6.29 mg/dL, direct bilirubin: 3.78 mg/dL, LDH: 264 IU/L, c-reactive protein: 322 mg/L were detected.

No pathology was detected in the chest X-ray in the imaging performed in the emergency department. In the abdomen USG, the liver dimensions were larger than normal and 162 mm in size, the spleen dimensions were normal, and the gallbladder wall thickness was increased and measured as 4 mm. With these signs and symptoms, the patient was followed up in the intensive care unit with the prediagnoses of acute kidney injury, sepsis, microangiopathic hemolytic anemia (MAHA), and cholangitis. Urgent hemodialysis was not considered in the patient who did not have any uremic symptoms due to the current clinical and laboratory findings. No signs of hemolysis (fragmented erythrocytes, polychromasia, etc.) were found in the peripheral smear, and the platelet count was found to be decreased in line with the hemogram. MAHA and pseudothrombocytopenia were ruled out.

Patient was consulted to infectious disease thus It was recommended to send salmonella, brucella and leptospirosis samples, as well as hepatitis A-B-C, toxoplasma, cytomegalovirus (CMV), ebstein barr virus (EBV) serology. The patient was started empirically with doxycycline 2x100 mg/PO and ceftriaxone 2x1gr iv with their recommendations.

As the general condition of the patient improved and his vitals were stable, he was followed up in the Nephrology clinic. No pathology was detected in MR-cholangiopancreatography performed with the preliminary diagnosis of cholangitis. The serological tests for hepatitis, toxoplasma, CMV and EBV were negative.

On the 5<sup>th</sup> day of his treatment, the leptospirosis PCR test was positive. Liver function tests, bilirubin

bin, kidney function tests and acute phase reactants decreased to normal values with antibiotic treatment. The patient, whose antibiotic treatment was completed for 7 days with the recommendation of infectious diseases, was discharged with the recommendation of outpatient follow-up.

## DISCUSSION

The diagnosis of leptospirosis is made based on the presence of questionable clinical features with a history of risk exposure. Renal failure is often non-oliguric and is associated with hypokalemia.

Urinalysis often shows proteinuria, pyuria, granular casts, and less often microscopic hematuria. Histological findings include interstitial nephritis and acute tubular necrosis. Supportive renal replacement therapy may be required in the acute phase, but renal function recovery is rapid and complete after six months [7]. In our case, proteinuria, pyuria, and microscopic hematuria were observed in the urine examination performed during the emergency admission. There was also non-oliguric acute renal injury. The creatinine level at the time of admission was 2.5 mg/dL and back to normal values within 1 month of the treatment. (Graphic Kreatinin !)

In a retrospective study involving icterohemorrhagic leptospirosis cases in Iran, thrombocytopenia was observed in more than 88% of the cases and azotemia was observed in approximately one third of the cases [8]. In our case, the platelet count was 15,000  $10^3/\mu\text{L}$  at the time of admission and back to normal values within 1 month of the treatment. (Graphic Trombosit!)

Hyperbilirubinemia is frequently seen in Weil's disease. Bilirubin elevation can be mild or severe. In a case report from Puca E. et al, it was reported that the total bilirubin level reached 73.4 mg/dl on the 4th day of treatment [9]. In our case, the total bilirubin level, which was 6.29 mg/dl at the time of admission, progressed to 14.75 mg/dl on the 4<sup>th</sup> day of treatment.

Leptospirosis which is a zoonotic disease should be considered in the differential diagnosis in patients presenting with acute kidney injury, thrombocytopenia,

hyperbilirubinemia, liver function test disorders, and acute phase reactant elevation. With early diagnosis and medical treatment, mortality and morbidity are significantly reduced.

## CONCLUSION

### Authors' Contribution

Study Conception: MU,; Study Design: MU,; Supervision: SA,; Materials: ÖBK,; Data Collection and/or Processing: ÖBK,; Statistical Analysis and/or Data Interpretation: SA,; Literature Review: SA,; Manuscript Preparation: SA and Critical Review: ÖBK.

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# Nijmegen breakage syndrome in fraternal twins and synchronous development of non-hodgkin's lymphoma

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## ABSTRACT

Nijmegen breakage syndrome (NBS) is an uncommon autosomal recessive chromosomal instability that is usually characterized by microcephaly, a facial structure resembling a bird, growth retardation, radiation hypersensitivity, immunodeficiency, and a propensity for malignancies. NBS patients are more likely to develop lymphomas, primarily non-lymphoma Hodgkin's (NHL). Among NBS patients, diffuse large B-cell lymphoma ranks among the most prevalent types of lymphoma. The prognosis remains poor. Here, we report the synchronous development of NHL and NBS in fraternal twins for the first time.

**Keywords:** Nijmegen Breakage Syndrome, Non-Hodgkin's Lymphoma, fraternal twins. chromosomal instability

**N**ijmegen breakage syndrome (NBS), is an extremely uncommon autosomal recessive chromosomal instability disorder that is brought on by homozygous or compound heterozygous mutations in the NBS1 gene (NBN) on chromosome 8q21. Symptoms of NBS include microcephaly, facial features resembling birds, growth retardation immunodeficiency, a propensity for malignancies and radiation hypersensitivity.

The underlying NBN gene (c.657 661del5), which codes for a protein involved in repairing DNA double-strand breaks, contains a founder mutation that makes it more common in Slavic populations. It is associated with childhood mortality, mostly due to lymphoid malignancies [1]. In a Turkish family, a homozygous 657del5 mutation was discovered before [2]. In the majority of patients, development of secondary neo-



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plasms is considered a fatal complication. Patients with immunodeficiencies, such as NBS and ataxia telangiectasia (AT), have a 250-fold increased risk of lymphomas, primarily non-lymphoma Hodgkin's (NHL), and a 50-fold increased risk of developing malignancy [3]. The conclusive evaluation of NBS is based on the common clinical symptoms, elevated cell membrane responsivity to radiation exposure in an in vitro environment, and genetic and molecular research that support homozygous mutations in the NBN coding region. The 657del5 mutation of the NBN gene on 8q21 is present in approximately 85% of cases [1].

Herein, we, for the first time, report NBS in fraternal twins and synchronous development of NHL.

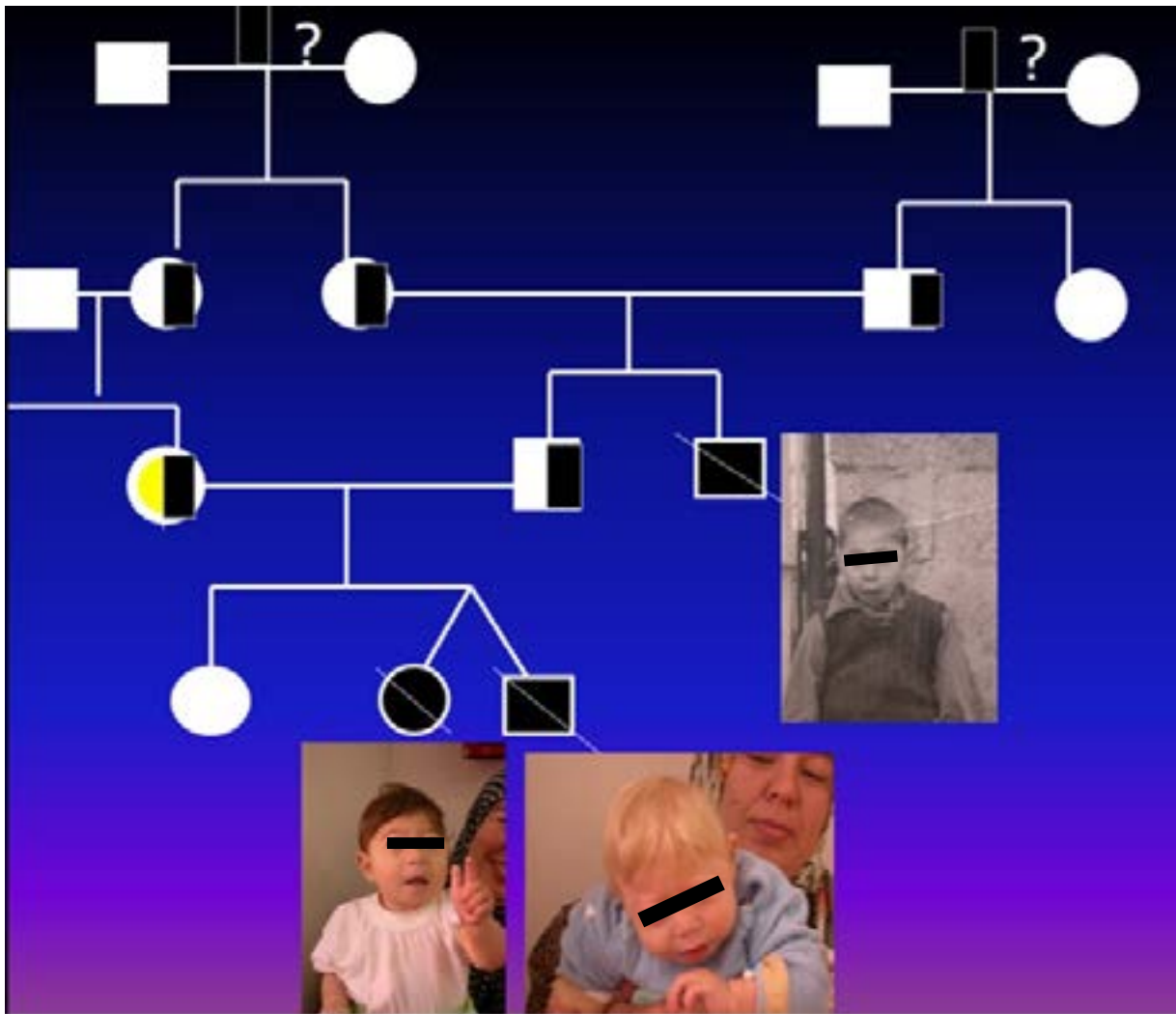
## CASE REPORT

Two nine-month-old twins with an enlarged cervical lymph node were referred to our center with same complaints. They were born at 38th gestational week with low birth weight and microcephaly. Although immunodeficiency was not thought to be present, both twins experienced respiratory infections during infancy, including pneumonia, otitis media, and bronchiolitis. The family was of Turkish origin, who had migrated from Albania many years ago. There was no information that they were of Slavic origin. At the time of admission, both twins had a typical bird-like

face appearance of NBS with microcephaly (Figure 1). When he was ten years old, the children's uncle, who also had a typical facial appearance, passed away from a lung infection (Figure 2). Physical examination of the twins revealed significant growth retardation, bilateral tonsillar enlargement, cervical lymphadenopathy, and hepatomegaly. Blood tests showed mild leukopenia with slightly increased lactic dehydrogenase (LDH) levels (596 U/l) (normal range 220-450 U/L). Immunological studies demonstrated low serum immunoglobulin (Ig) A and IgG levels with a high serum IgM concentration. Bone marrow examination results of both patients were normal. The NBS1 gene mutation analysis of theof both twins showed homozygosity for typical 5bp deletion (657del5). Anterior mediastinum was slightly enlarged on chest computed tomography (CT) scan and X-ray, and mediastinal adenopathy to right- and left-sided nodular lesions connected to pulmonary neoplastic infiltration were also seen. (Figure 3A). Tru-Cut biopsies of the tonsils were performed on both twins. Histopathological and immunohistochemical examination findings were compatible with NHL (diffuse large B-cell lymphoma [DLBCL]) in both children. A lymphoma-like growth pattern and atypically large lymphocytes with prevalent nuclei and abundant cytoplasm are seen upon histological examination. There are mitotic figures (Figure 3B). Pediatric chemotherapy regimen was initiated with Berlin-Frankfurt-Münster (BFM) protocol with reduced doses of the cytotoxic agents. Following the



**Figure 1.** Typical facial appearance of fraternal twins. Male(A) and female (B).



**Figure2.** The family pedigree

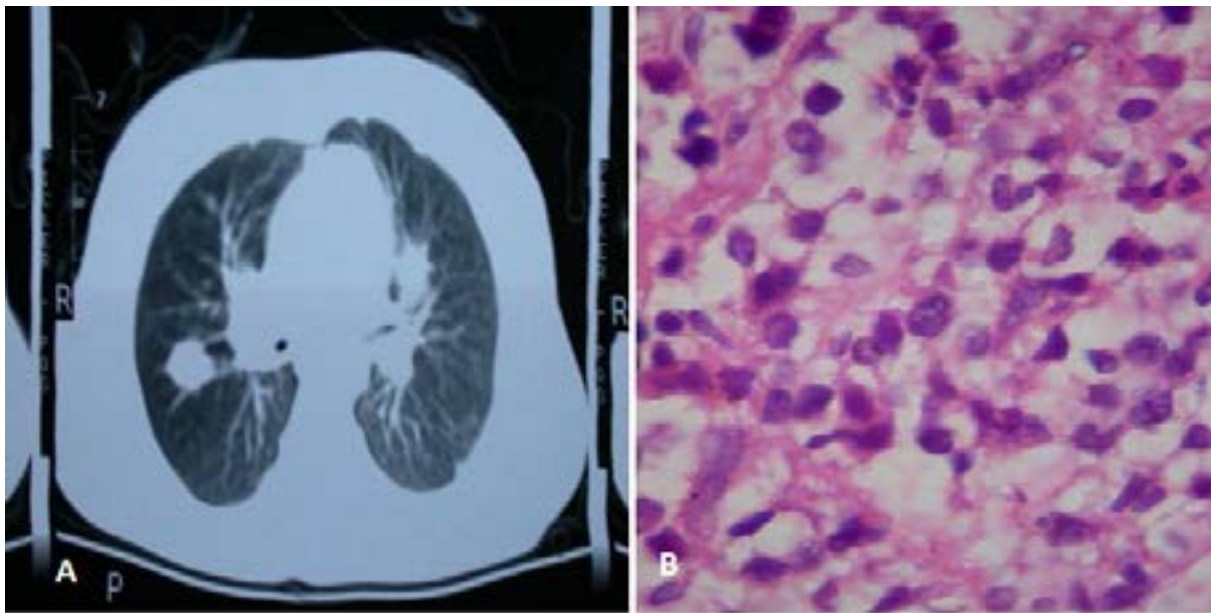
first cycle of chemotherapy, severe febrile neutropenia and infections occurred and both patients died from sepsis and massive hemorrhage within three weeks.

## DISCUSSION

Nijmegen breakage syndrome is a relatively uncommon condition DNA repair disorder. Recent studies have demonstrated that NBS is caused by mutations in the gene that code for nibrin. [1]. Malignancies usually develop in nearly half of NBS patients before the age of 21 years [4]. The most frequent neoplasms related with NBS are lymphoblastic T cell lymphoma (T-LBL) and diffuse large B-cell lymphoma (DLBCL); even though medulloblastoma and rhabdomyosarcoma are also documented in the literature. [1]. Fanconi anemia, Xeroderma pigmentosum, Rothmund-Thomson syndrome, and Werner syndrome are the most fre-

quent cancers in people without immunodeficiency, whereas immune-deficient patients of disrupted DNA repair, such as above with an NBS, Bloom Syndrome, Ataxia-telangiectasia (AT), and, show a higher propensity to develop lymphomas. [5]. Although several biomarkers predicting malignant transformation have been widely investigated in recent studies, but the reasons for an increased predisposition of immunocompromised patients for lymphoproliferative diseases have not been fully understood, yet.

In general, patients with primary immunodeficiencies and NHL are younger than non-immunocompromised patients with NHL. In a BFM study with 1,569 newly diagnosed NHL patients, it was found that 0.06 percent of the patients had NBS (n = 4) or AT (n = 5) [6]. In this study, the median age of NHL diagnosis was nine years old, which was similar to other pediatric NHL cases (median 9.3 years) [7]. Similar to our patients, two of these patients with NBS were diag-



**Figure 3.** (A), A thoracic computed tomography (CT) image of male case. (B) Tru-Cut biopsies of the tonsils from male case. Mitotic figures are present (arrows). (Hematoxylin and Eosin stain x100).

nosed based on immunological examination after the diagnosis of NHL. In their previous article, it was also reported 19 patients with primary immunodeficiency (NBS n=4) in BFM studies. Two of them were siblings aged 6.5 (female) and 9 (male) years, respectively [8].

17 NBS patients with a median age of 9.5 years who received treatment for NHL were the subject of another study [9]. Their youngest patient with NHL was 3.8 years old. There were also reported 38 patients with primary lymphoid cancer and chromosomal instability syndromes (NBS n = 19 and AT n = 19 and) [10]. The youngest patient with NBS who was diagnosed with NHL was 4.3 years old and five of them were not considered syndromic cases, until the definite diagnosis of lymphoma. More recently, the European Society for Immunodeficiencies (ESID) dataset between 2004 and 2012 revealed that 63 (42%) of a total of 149 patients were diagnosed with 80 malignancies, with the median age for the initial episode of neoplasms being 10.25 years (range, 2 to 26). However, there is no NBS case with lymphoma aged under two years in this database [11].

As far as we are aware, there are no published cases of NBS and NHL occurring before the age of two. Similarly, there is no reported case of fraternal twins with NBS and NHL. Therefore, we believe that our cases are the first NBS cases who synchronously developed NHL. In addition, DLBCL is one of the most prevalent types of lymphoma in NBS patients, as in our cases.

However, NBS patients have demonstrated signifi-

cant variation in immunodeficiency over time in both the same patient as well as between different patients [1]. Our patients were IgA and IgG-deficient which were unable to be detected before the diagnosis of NHL.

Serious infectious side effects may develop during treatment in cancer patients with DNA repair abnormalities like NBS, making clinical management and diagnosis difficult. In addition to available treatment options, there is also growing evidence in recent years on successful treatment of NBS with hematopoietic stem cell transplantation (HSCT) before life-threatening complications or secondary malignancies occur [1].

Despite all efforts, the outlook for NBS and NHL remains dismal. According to one of the biggest sequence of Polish NBS patients of NHL, some patients could be healed and their chances of survival were better if they had B-cell NHL as opposed to T-cell lymphoma [9]. Therefore, it is crucial to diagnose the illness as early as possible. Furthermore, it has been shown that NBS is associated with reduced tolerance to chemotherapy and toxic deaths mainly from sepsis [1, 6-8]. Similarly, our both patients died from toxicity-related sepsis, despite low dose regimen.

## CONCLUSION

In conclusion, this case report is the first to present NBS cases who synchronously developed NHL



in fraternal twins which highlights the importance of recognizing underlying immunodeficiencies or NBS in patients who develop NHL at an uncommonly early age or who experience unusually severe chemotherapy toxicity. Therefore, interdisciplinary clinical diagnosis and long-term actually follow should be encouraged, and clinicians should be aware of these issues and the disease's natural course. However, more prospective multicenter studies are required to determine the effectiveness of NHL treatment in NBS patients.

#### *Authors' contributions*

Study Conception: EGK, HG, FGI, AE, CV,; Study Design: EGK, HG, FGI, AE, CV,; Supervision: DG,; Materials: EGK, HG, SA,; Data Collection and/or Processing: DG,; Statistical Analysis and/or Data Interpretation: DG,; Literature Review: EGK,; Manuscript Preparation: EGK, DG and Critical Review: EGK, HG, FGI, AE, CV.

#### *Conflict of interests*

No potential conflicts of interests relevant to this article were reported.

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# Large intraductal papilloma in the breast: A case report and review of the literature

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## ABSTRACT

Most of the patients who come to the breast clinic present with the complaint of a palpable mass. Some of the pathological lesions that cause this picture are intraductal papillomas. Most intraductal papillomas are smaller than 5 mm. In this article, we aimed to present an unusually large intraductal papilloma case seen as a cystic structure, together with its diagnosis and treatment features, in the light of literature.

A 58-year-old female patient was admitted to our hospital with the complaint of retraction of palpable lumps on the left breast. In ultrasonography; A complex cystic mass lesion with a thick wall, smooth contours, a diameter of 56x48 mm in the cystic component and a diameter of 19.2x13.3 mm in the solid component was observed. It was removed with clean surgical margins by excisional biopsy. It reported as low grade papillary ductal intraepithelial neoplasia (Atypical Papilloma). Some researchers have reported that the rate of transformation of benign intraductal papilloma into malignancy with surgical excision may vary between 2% and 10%.

We think that in the management of intraductal polypoid lesions, the effectiveness of each of the radiological follow-up, tru-cut biopsy and surgical excision methods should be evaluated on a patient basis.

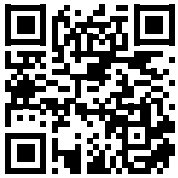
**Keywords:** Intraductal papilloma, papillary breast lesions, surgical excision

Most of the patients who come to the breast clinic present with the complaint of a palpable mass. Some of the pathological lesions that cause this picture are intraductal papillomas. Intraductal papillomas are usually seen in premenopausal women and originate from the major duct [1]. Intracystic papillary lesions of the breast are rare and constitute approximately 1-3% of all breast lesions [2].

Papillomas are formed by the development of ductal epithelial proliferation together with a fibrovascular stalk. Papilloma when papillary lesions are central and solitary; When they are located peripherally

and in more than one terminal ductal lobular unit, it is called papillomatosis [3]. Papillary lesions are classified as benign (papilloma) and malignant (papillary carcinoma). Most of the lesions are benign [4]. On ultrasonography (USG), papillary lesions can be seen as a solid mass in an enlarged duct or a cyst, or as a pure solid mass [5]. Most of the intraductal papillomas are smaller than 5 mm [6]. The risk of malignancy increases as the size of the cyst and the ratio of its solid component increase [7].

In this article, we aimed to present an unusually large intraductal papilloma case seen as a cystic structure, together with its



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diagnosis and treatment features, in the light of literature.

## CASE REPORT

A 58-year-old female patient was admitted to our hospital with a complaint of palpable left breast for about 2 months and nipple retraction in the last 15 days. The patient had no complaints of pain and nipple discharge. There were no features of breast cancer risk factors in the family history. On physical examination, a well-circumscribed, round mass was palpated near the areola at the junction of the left breast outer quadrant. Breast ultrasonography and mammography examinations were requested. In ultrasonography, A

complex cystic mass lesion with a thick-walled, smooth contour, cystic, solid component inside, showing increased internal vascularity, with a cystic component diameter 56 mm and a solid component diameter of 19 mm was observed (Figure 1).

In mammography, A dense nodular area of diameter 6.4 cm with sharp edges and smooth contours was observed compressing the glandular parenchyma (Figure 2). He was informed that the possible pathology result of the detected cystic mass might be benign rather than malignancy, but malignancy could not be

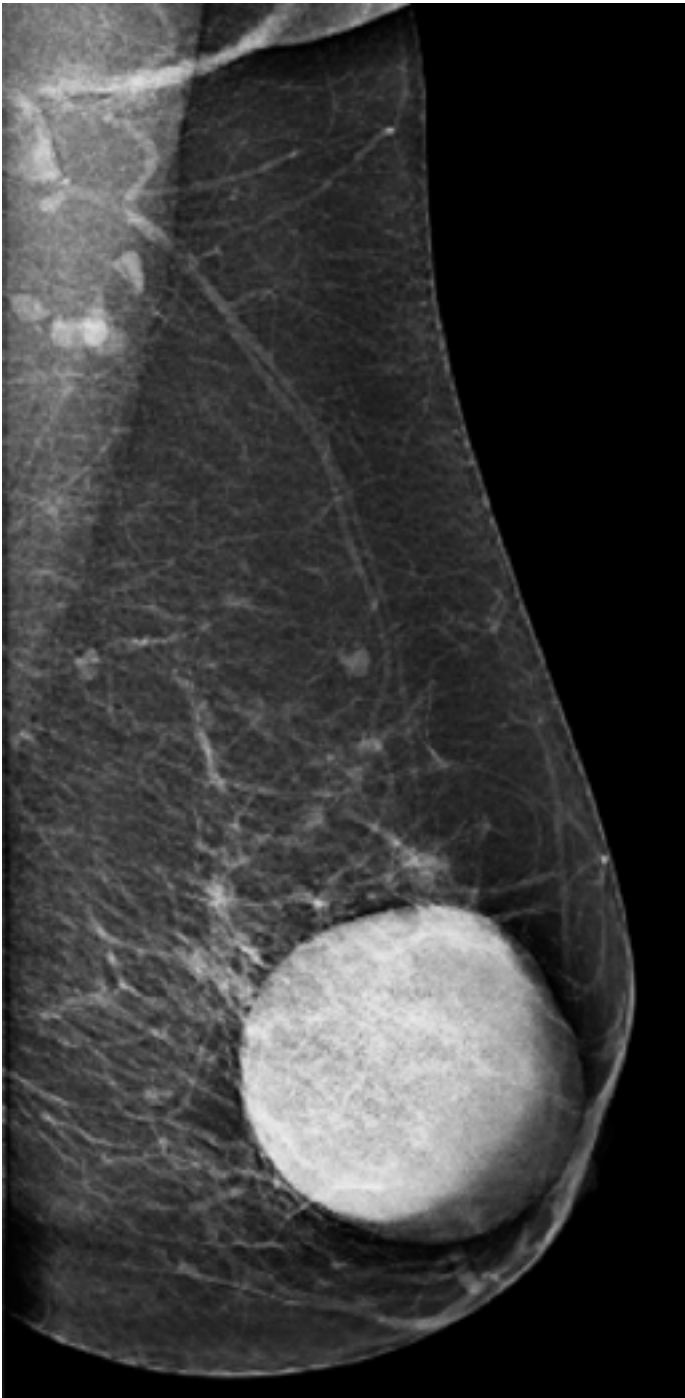
ruled out by radiological imaging alone, and histopathological examination was recommended to the patient. Information was given about the use of core biopsy and excisional biopsy methods accompanied by ultrasonography. At the patient's request, the cystic intraductal polypoid lesion was excised by excisional biopsy with clean surgical margins (Figure 3). In its pathology, Papillary and solid proliferation areas were observed in the dilated duct lumens in the breast parenchyma. In some papillary structures, especially in the areas of solid array pattern, atypia and increased mitosis were noted in the cells. It was reported as low grade papillary ductal intraepithelial neoplasia (Atypical Papilloma).

## DISCUSSION

Nipple retraction, discharge and palpable breast stiffness are the main complaints that cause patients to worry and apply to the hospital. As a result of the frequent use of imaging methods such as mammography or ultrasonography in breast cancer screening, papillary lesions can be detected as an asymptomatic mass or calcified lesion [8]. US findings in papillary breast lesions depend on the macroscopic appearance of the lesion [9]. On US, papillary lesions can be seen



**Figure 1.** Ultrasound image of a complex cystic mass lesion



**Figure 2.** Mammography image of a dense nodular area of diameter 6.4 cm with sharp edges and smooth contours.

as a solid mass in an enlarged duct or a cyst, or as a pure solid mass [5, 9]. If the lesion is small, a focal enlarged canal without a mass may be the only US finding. In this case,

the presence of nipple discharge in the patient should suggest the diagnosis of papillary lesion, even if the mass is not observed [5]. Han *et al.* [10] classified papillary lesions in US into four groups as intraluminal, extraductal, completely solid and solid-cystic

mixed type. Masses localized in the breast, especially behind the nipple-areola complex, may present with skin and nipple retraction as a clinical symptom due to a fibrous process. Pathologically, there are signs of fat necrosis, ductal ectasia, Mondor's disease, and skin retraction in carcinoma [11]. Since ductal ectasia is associated with advanced fibrosis of the duct wall, the nipple may be flattened or completely collapsed in this disease [12].

Intraductal papillomas are usually seen in premenopausal women and originate from the major duct. It is usually less than 0.5 cm in size but can reach up to 5 cm [1]. In our case, there was an uncommon intraductal papillomatoid lesion with a size of approximately 2 cm within the 5 cm ductal cystic component. She complained of nipple recession due to being near the areola.

While papillary neoplasia constitutes 40-70% of pathological nipple discharges, bloody or pathological discharge is observed in only half of the patients diagnosed with papilloma. Papillary carcinomas are rare and account for 1% to 2% of all breast malignancies. It is frequently seen in the postmenopausal group, and complaints of palpable mass and nipple discharge are present [13]. In our case, there was postmenopausal age but no nipple discharge. The absence of this finding was a feature that strengthened the benign character of the lesion. Cysts containing papilloma are smaller in size than papillary carcinoma, and intracystic papillary lesions smaller than 3 cm are usually



**Figure 3.** Excised cystic intraductal polypoid lesion.

benign [14]. In our case, there was a polypoid mass of approximately 2 cm in line with the literature, and this finding supported the idea that the lesion was benign.

Although it greatly reduces the rate of excisional biopsy, there is no standard treatment approach for which patients to undergo excision in the management of benign papillary

lesions after tru-cut biopsy or FNAB. Excisional biopsy is recommended because a significant portion of the cases diagnosed with Tru-cut biopsy or FNAB are upgraded to in-situ or invasive cancer after surgical excision [15]. However, some authors suggest removal of only lesions with atypia [16]. One reason for concern in this regard is the possibility that areas of atypia or a focus of carcinoma may be missed in the biopsy specimen. In recent studies, it has been shown that upgrading is detected in one-fifth of the patients, and therefore the treatment approach has changed in favor of surgery [16, 17].

Differentiation of benign and malignant papillary lesions is difficult in the absence of specific radiological and histological findings, and surgical excision is required [18]. Some investigators have reported that the rate of benign intraductal papilloma becoming malignant with surgical excision may vary between 2% and 10% [19]. For this reason, some suggest follow-up with clinical and imaging methods, while others recommend resection. Benign IDPs proven by radiology and core biopsy compatibility rarely turn into malignancy [20].

Various studies in the literature have shown a relationship between advanced age, postmenopausal status, complex cystic echo pattern on imaging, peripheral localization, microcalcifications, large lesion, pathology-radiology mismatch, high Breast Imaging Reporting and Data Systems (BI-RADS) score, and nipple discharge and malignancy. detected [21]. Since the USG finding was BIRADS 4C, the patient was informed, and excisional biopsy was performed without tru-cut biopsy. Pathology result was reported as Low grade papillary ductal intraepithelial neoplasia (Atypical Papilloma).

## CONCLUSION

Intraductal papillomas constitute approximately 1-3% of all breast lesions and 1% to 2% of all breast malignancies. As the lesion size increases, the malignancy potential increases. Diagnosis can be made with less invasive methods such as tru cut biopsy,

but the possibility of pathological upgrade of 2-10% should be considered. For this reason, we think that the efficacy of radiological follow-up, tru-cut biopsy and surgical excision methods should be evaluated on a patient basis in the management of intraductal polypoid lesions.

## Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

## Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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