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Evaluation of the Frequency of Acute Kidney Injury in Hospitalized Patients with Benign Prostatic Hyperplasia Due to COVID-19 Pneumonia

COVID-19 Pnömonisi Nedeniyle Hastanede Yatarak Tedavi Gören Benign Prostat Hiperplazili Hastalarda Akut Böbrek Hasarı Sıklığının Değerlendirilmesi

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Abstract

Objective: Benign prostatic hyperplasia (BPH)-related acute kidney injury (AKI) occurs in male patients as a natural result of aging and androgen exposure. In our study, we investigated the frequency of BPH-related AKI and its relationship with disease severity in patients hospitalized for COVID-19 pneumonia.
Materials and Methods: This is a retrospective and observational study on 869 male patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), who were diagnosed with COVID-19 by real-time PCR testing and hospitalized due to COVID-19 pneumonia. None of the patients was admitted to the intensive care unit (ICU). 55 patients out of 869 had BPH. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria. BPH and non-BPH groups were statistically compared with respect to the existence, frequency, hospitalization duration and in-hospital death.
Results: Median age was 70 years for BPH group and BPH patients were significantly older than the non-BPH. Hypertension, coronary artery disease and heart failure were significantly more frequent in the BPH group. On admission, compared with normal serum creatinine, serum urea was significantly higher in the BPH patients. All AKI patients with BPH had three or more comorbidities. During hospitalization, AKI occurred in 7,3% of the BPH patients compared with the non-BPH (0,98%). The incidence of AKI was significantly higher in the patients with BPH (OR:7,94, 95% CI:2,31-27,25). In-hospital death occurred in 16,4% of the patients with BPH. The mortality was significantly lower in non-BPH group (8,6%) compared with the BPH. Our final analysis showed that age, arterial hypertension, prior coronary artery disease and heart failure were independent risk factors for occurred BPH-related AKI.
Conclusions: Older male patients with common comorbidities showed a higher risk for mortality from COVID-19 pneumonia. Also, AKI patients with BPH had a poorer prognosis and higher mortality than the non-BPH patients.

Keywords: COVID-19 pneumonia, acute kidney injury, benign prostatic hyperplasia

Öz

Amaç: Yaşlanma ve androjen maruziyetinin doğal bir sonucu olarak erkek hastalarda benign prostat hiperplazisi (BPH) ile ilişkili akut böbrek hasarı (ABH) görülmektedir. Çalışmamızda COVID-19 pnömonisi nedeniyle yatarak tedavi gören hastalarda BPH ilişkili ABH sıklığını ve hastalık şiddeti ile ilişkisini araştırdık.
Gereçler ve Yöntemler: Araştırmamız, akut solunum yolu sendromu koronavirus 2 (SARS-CoV-2) tanısı PCR testi ile onaylanmış ve COVID-19 pnömonisi nedeniyle hastanede yatarak tedavi gören 869 erkek hasta üzerinde geriye dönük ve gözlemsel bir çalışmadır. 869 hastanın 55'inde BPH vardı. Yoğun bakımda tedavi edilen hastalar çalışmaya dahil edilmedi. ABH, Böbrek Hastalığı: İyileştirici Küresel Sonuçlar (KDIGO) kriterlerine göre tanımlandı. BPH'li ve BPH'li olmayan gruplar, ABH varlığı, sıklığı, hastanede kalış süresi ve hastane içi ölüm açısından istatistiksel olarak karşılaştırıldı.
Bulgular: BPH grubu için medyan yaş 70 idi ve BPH hastaları BPH'ı olmayanlara göre anlamlı derecede ileri yaştaydı. BPH grubunda hipertansiyon, koroner arter hastalığı ve kalp yetmezliği anlamlı olarak daha fazla saptandı. Başvuruda, BPH hastalarında normal serum kreatinin ile karşılaştırıldığında serum üre anlamlı olarak daha yüksek saptandı. ABH gelişen tüm BPH'li hastaların üç veya daha fazla komorbiditesi vardı. Hastanede yatış sırasında ABH, BPH olmayanlara (%0,98) kıyasla BPH hastalarının %7,3'ünde meydana geldi. ABH insidansı BPH'li hastalarda anlamlı olarak daha yüksekti (OR:7,94, %95 GA:2,31-27,25). BPH'li hastaların %16,4'ünde hastane içi ölüm meydana geldi. Mortalite BPH olmayan grupta (%8,6) BPH ile karşılaştırıldığında anlamlı olarak daha düşüktü. Son analizimiz, yaş, arteriyel hipertansiyon, koroner arter hastalığı ve kalp yetersizliği varlığının BPH ilişkili ABH gelişimi için bağımsız risk faktörleri olduğunu gösterdi.
Sonuç: İleri yaşlı ve komorbiditesi bulunan erkek hastalarda COVID-19 pnömonisinden ölüm riski daha yüksektir. Ayrıca, BPH varlığında ABH gelişimi, BPH olmayan hastalara göre daha kötü prognoza ve daha yüksek mortaliteye sahiptir.

Anahtar kelimeler: COVID-19 pnömonisi, akut böbrek hasarı, benign prostat hiperplazisi

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Introduction

The global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or the so called "COVID-19 pandemic" is known to be associated with a high mortality all over the world. Acute kidney injury (AKI) is a commonly observed condition among hospitalized patients suffering from severe coronavirus disease 2019 (COVID-19) infection [1]. Previous studies revealed the existence of kidney injury associated with an increased risk of death in patients with SARS-CoV-1 [2]. It is widely accepted that AKI is a negative prognostic factor of disease severity and COVID-19 induces AKI in 20-40% of the patients admitted to intensive care unit (ICU) [3].

There are several mechanisms and multiple factors that might be involved in the pathogenesis of kidney damage in patients with COVID-19. These are hyperinflammation, tubular damage on SARS-CoV-2 viral entry and ACE2 expression in proximal tubules, microangiopathy and hemophagocytic macrophage activation. Additionally, cytokine storm after a viral infection influencing the kidney directly and indirectly by inducing sepsis, shock, hypoxia, rhabdomyolysis and organ interactions among lung, heart, and kidney are also considered [4,5]. Furthermore, lower oxygen delivery to kidney may cause an ischemic injury.

BPH is a histological condition caused by an excessive growth of nonmalignant proliferation of epithelial and stromal cells in the transition zone yielding an enlargement of the prostate gland. Prevalence of BPH is about 25.3% among men aged 40-79, and more than 50% among men aged 60 and over [6]. Although, the etiological basis of BPH has not been resolved yet, age-related changes and androgens are assumed to play a major role in its pathogenesis. The prevalence of BPH is observed to have a noticeable increase with age [7]. COVID-19 is more severe and fatal in men, possibly due to the existence of androgens influencing the immunological response and additional factors such as chronic comorbidities as a result of the weaker immune functions [8].

Former studies suggested that the virus was mainly infecting the lungs. Angiotensin-converting enzyme (ACE) receptors in the lung and the transmembrane serine protease 2 (TMPRSS2) enzyme group are assumed to be effective in the interaction of the virus with the pneumocytes [9]. However, co-expression of ACE2 and TMPRSS2 in other organs such as kidneys, testes, and prostate make it plausible that the virus can also affect the aforementioned organs. Recent studies have also found that a critical factor for the virus to be able to infect the organ is the co-expression of ACE2 and TMPRSS2 [10]. It is well established that the androgen receptors (AR) which are widely expressed in both epithelial and stromal prostate cells, have a key role in the development of BPH [11]. Recently, androgen-mediated regulation of the ACE receptors and the TMPRSS2 enzyme group in the patients resulted in more frequent occurrence of COVID-19 infection and higher mortality in men [12-14].

As it is well known, the urinary tract obstruction – 10% (most often due to BPH in older men) is a common cause of AKI in hospitalized patients [15]. Since BPH has a high prevalence and is more common in older men who are more prone to COVID-19, recent data suggest a closer monitoring of older patients who are more susceptible to both BPH and also COVID-19 infection during this pandemic [16]. Although BPH is believed to cause an increased risk of developing AKI, data on BPH related AKI in the presence of COVID-19 infection are rather scarce. This is the first study on COVID-19 pneumonia course that developing AKI in BPH patients in the literature, to our knowledge. We performed a retrospective study to investigate the AKI in hospitalized COVID-19 pneumonia patients having BPH and we evaluated its relationship to disease severity and in-hospital death.

Materials and Methods

Study Design and Cohort

We performed a retrospective observational study on 1509 patients who were diagnosed with COVID-19 by real-time PCR testing, by radiologic involvement for CT scan and hospitalized due to COVID-19 pneumonia at our Hospital, Level-3 pandemic, from September 01, 2020 to December 31, 2020. After screening the database, we excluded those patients from the study who did not have any clinical or laboratory data or who had pneumonia arising from other causes. Duplicate records, erroneous data and outliers were excluded. Patients with chronic kidney disease (CKD), those who had a prior kidney transplant, or those who had fewer than two serum creatinine (Cr) measurements during the admission were also excluded. Other criteria for exclusion to reduce the confounding effects were the existence of chronic dialysis, terminal conditions due to cancer and reception of chemotherapy for cancer treatment.

CKD was defined by past medical history and the presence of diagnosis and stages of CKD based on Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria, recommending that two values of estimated glomerular filtration rate (eGFR) obtained in a period of least three months apart, should be less than 60 ml/min/1.73 m2 in order to assume that the patient had CKD [15].

After exclusion, 869 adult male patients were recruited to the study. None of the patients was admitted to the intensive care unit (ICU). Demographic data, comorbidities, COVID-19 related examinations such as respiratory rate, oxygen saturation by pulse oximetry (SpO2), and mean oxygen requirement at hospitalization duration were recorded. We categorized the data as moderate or severe based on severity classification with reference to the Chinese Guidelines for Diagnosis and Treatment of Novel Coronavirus Pneumonia (Trial Version 7) [17]. Moderate COVID-19 patients had fever (>37.30C) and they had respiratory symptoms identified by radiological findings suggesting pneumonia. The existence of any one of the following criteria was assumed to be a sufficient condition for considering the patient to be severe: (1) respiratory distress (≥30 breaths/min), (2) oxygen saturation ≤93% at rest, (3) arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300mmHg (1 mmHg=0.133 kPa). Computerized tomography (CT) scans were obtained from all the patients when they were admitted to the hospital. CT results were classified into mild, moderate and severe involvement by an expert radiologist [18].

European Urological Association's diagnostic criteria were used for the diagnosis of BPH [19]. All BPH patients were medicated using drugs as alpha-adrenergic receptor antagonists (i.e., Tamsulosin, Doxazosin, and Terazosin), possibly combined with a 5-alpha reductase inhibitor (i.e., Finasteride or Dutasteride). In addition to that, some patients had undergone surgery.

We used the KDIGO criteria to define AKI following: Stage 1 – increase in serum creatinine by 0,3 mg/dL within 48 hours or a 1,5-1,9 times increase in serum creatinine from baseline within 7 days; Stage 2-2 to 2.9 times increase in serum creatinine within 7 days; Stage 3-3 times or more increase in serum creatinine within 7 days or initiation of renal replacement therapy. Patients were classified based on the highest AKI stage they have attained during the hospitalization [15]. Serum creatinine value on admission was adopted as the baseline serum creatinine. All of the cases enrolled in the study were managed in accordance with the COVID 19 treatment protocol of Turkish Health Ministry [20]. The research was first registered in the data of Turkish Health Ministry Scientific Research Committee and then reviewed and approved by the Local Ethics Committee (Dr. Sadi Konuk Training and Research Hospital Ethics Committee approval no: 2021/347).

Statistical Analysis

Mean ± standard deviation values were estimated as descriptive statistics. Deviations from normality were assessed using the median and percentage values in the distributions. Student's t-test was used for the continuous variables having normal distributions. Categorical data were analyzed using Chi-square test. Continuous variables having abnormal distribution were evaluated by Mann-Whitney U test. A $p<0,05$ was accepted as statistically significant. All statistical analyses were performed in commercially available SPSS software v.21 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Receiver operating characteristic (ROC) curves were used to obtain the best parameters for predicting the mortality from BPH-related AKI which were later incorporated into the cox regression model. Possible factors identified with multivariate analyses were further entered into the Cox regression model, with backward selection, to determine independent predictors of occuring BPH-related AKI, disease severity and death. The univariate effects of age, arterial hypertension, prior coronary artery disease and heart failure on occurred BPH-releated AKI of patients were investigated using the log rank test. The proportional hazards assumption and model fit was assessed by means of residual (Schoenfeld and Martingale) analysis.

Results

Baseline Characteristics

A total of 869 patients were included in our study. 55 had BPH and 814 had non-BPH. **Table 1** shows the clinical features and comorbidities of patients with COVID-19 pneumonia. Median age was 70 years for BPH group and BPH patients were significantly older than the non-BPH. Hypertension, coronary artery disease and heart failure were significantly more frequent ($p<0,001$, $p=0,002$, $p=0,02$, respectively) among BPH patients than in the non-BPH (OR:3,67, 95% CI:2,04-6,62, OR:2,5, 95% CI:1,37-4,58, OR:2,83, 95% CI:1,13-7,06, respectively). No significant difference was observed in almost all of the laboratory findings when the two groups were studied. Additionally, there were no significant difference between groups in terms of their inflammatory responses indicating poor prognostic laboratory findings, such as ferritin, fibrinogen, D-dimer, and C-reactive protein. The duration of hospitalization, CT involvement results and disease status was also found to be similar between groups **(Table 2)**. On the other hand, mean serum lactate dehydrogenase, platelets and urea were significantly higher in BPH patients than in the non-BPH.

Table 1. Evaluation of baseline characteristics and comorbidities for BPH and non BPH patients

	BPH (n=55)	Non BPH (n=814)	P values
Age, years	70.6±9.06	57.99±14.87	**<0.001**
Respiratory rate, per minute	22.74±5.86	21.2±5.39	NS
Baseline SpO2 (%)	94(87-98)	95(94-99)	NS
SpO_2¶(%)	94.05±2.04	94.18±1.98	NS
O2 support (L/per min)	7.56±9.12	5.23±7.42	**0.02**
Body temperature, °C	36.92±0.71	36.98±0.71	NS
Heart rate, per minute	81.60±16.31	83.52±14.4	NS
Systolic blood pressure, mmHg	133.15±22.02	126.59±18.28	**0.01**
Diastolic blood pressure, mmHg	71.22±11.3	71.53±10.4	NS
Arterial hypertension on treatment	38(69%)	310(38%)	**<0.001**
Diabetes mellitus on treatment	17(30.9%)	248(30.5%)	NS
Coronary artery disease on treatment	17(30.9%)	124(15.2%)	**0.002**
Chronic atrial fibrillation	2(3.6%)	36(4.4%)	NS
Heart Failure	6(10.9%)	34(4.2%)	**0.02**
COPD¶¶	3(5.5%)	39(4.8%)	NS
Asthma bronchiale	4(7.3%)	38(4.7%)	NS
Prior stroke	4(7.3%)	26(3.2%)	NS
Neurodegenerative diseases	1(1.8%)	20(2.5%)	NS

¶SPO2: median; under oxygen support; ¶¶ COPD: chronic obstructive pulmonary disease

Table 2. Evaluation of laboratory tests, CT results and mortality for BPH and non-BPH patients

Characteristics Count	BPH (n=55)	Non BPH (n=814)	P values
Neutrophil, cells/mL	5.84±3.22	5.69±2.94	NS
Lymphocytes, cells/mL	1.04±0.53	1.13±0.56	NS
Platelets, cells/mL	251.01±110.88	218.35±97.54	**0.03**
Hematocrit, %	38.4±5.49	38.93±4.44	NS
Glucose, mg/dL	152.11±67.4	153.18±72.34	NS
Urea, mg/dL	52.1±25.42	42.86±27.22	**0.01**
Basal creatinine, mg/dL	1.08±0.33	1.04±0.95	NS
ALT, U/L	47.85±35.99	47.68±33.72	NS
AST, U/L	44.16±36.25	50.39±42.92	NS
Lactate dehydrogenase, U/L	379.21±182.17	335.39±116.91	**0.01**
Potassium, mEq/L	4.24±0.6	4.27±0.51	NS
Sodium, mEq/L	136.73±3.83	136.93±3.92	NS
Magnesium, mg/dL	1.95±0.26	2.07±0.29	**0.004**
Calcium, mg/dL	8.63±0.57	8.69±0.62	NS
Phosphorus, mg/dL	3.05±0.74	3.15±0.78	NS
C-reactive protein, mg/L	113.44±98.61	117.15±79.78	NS
Procalcitonin, ng/mL	0.28±0.64	0.58±4.38	NS
Ferritin, mcg/L	514.95±424.32	681.41±644.91	NS
D-dimer, mcg FEU/mL	1.2±1.88	0.9±1.26	NS
Fibrinogen, mg/dL	505.27±124.88	536.44±140.78	NS
Troponin I, ng/mL	19.08±31.55	25.2±12.35	NS
Albumin, g/dL	34.93±5.34	35.64±5.38	NS
CT results (n, %)			NS
Mild involvement	15(27.3%)	148(18.2%)	
Moderate involvement	24(43.6%)	389(47.8%)	
Severe involvement	16(29.1%)	277(34%)	
Disease status			**0.009**
Moderate	17(30.9%)	308(37.9%)	
Severe	38(69.1%)	506(62.1%)	
AKI	4(7.3%)	8(0.98%)	**<0.001**
Stage 1	1(25%)	4(50%)	
Stage 2	1(25%)	3(37.5%)	
Stage 3	2(50%)	1(12.5%)	
Peak serum creatinine, mg/dL	9.62±4.81	4.56±2.79	**<0.001**
Duration of hospitalization, day	12.67±7.34	11.69±6.74	NS
In-hospital death	9(16.4%)	70(8.6%)	0.05

AKI: acute kidney injury; NS: not significant

Kidney Abnormalities, Incidence of AKI and In-Hospital Death

On admission, BPH patients had higher serum urea and normal serum creatinine levels. AKI patients with BPH (7,3%) had peak serum creatinine level of 9,62±4,81 mg/dL during hospitalization. Two (50%) patients were in stage 3 and only one patient needed renal replacement therapy in the form of hemodialysis. All AKI patients with BPH had >3 or more comorbidities. Relatively fewer non-BPH patients (12,5%) were in stage 3- and none of them needed to receive renal replacement therapy. One patient died from respiratory failure in the AKI with BPH group. During hospitalization, AKI occurred in (7,3%) of BPH patients compared with the non-BPH (0,98%). The incidence of AKI was significantly higher in BPH group (OR:7,94, 95% CI:2,31-27,25) than in the non-BPH. In-hospital death occurred with a rate of (16,4%) in BPH group resulting in a mortality which is significantly lower in the non-BPH group (8,6%) (Table 2).

Finally, our univariate analysis showed that coronary artery disease, hypertension and heart failure were significantly more frequent among BPH patients than in the non-BPH since BPH patients were significantly older than the non-BPH. Our analysis also showed that age, prior coronary artery disease, heart failure and arterial hypertension were independent risk factors for the existence of BPH-related AKI **(Table 3)**.

Discussion

AKI is one of those diseases which has a clinical importance affecting the management of primary conditions in patients in terms of the treatment options. AKI denotes a sudden and often reversible reduction in kidney function, as measured by glomerular filtration rate (GFR). The existence of AKI may result in an accumulation of metabolic products such as water, sodium and several disturbances may be observed in electrolyte concentrations. AKI is a serious factor ending up in longer hospital stays and higher patient morbidity [21]. Although most of the AKI cases recover completely with the help of supportive treatment; its prognosis is predominantly determined by its etiology and the existence of previous kidney disease or deteriorated eGFR. Today, in-hospital mortality for patients with AKI is reported as varying between 30-50%, especially when dialysis is required. Negative prognostic factors include advanced age, oliguria, use of vasopressors, multiorgan dysfunction, need for blood transfusions and hypotension [21,22]. So far, no specific treatment is proposed for COVID-19 induced AKI.

Several studies report that AKI is an important non-respiratory clinical condition observed in COVID-19, independent of any prior kidney injury or malfunction [23,24]. However, reported detection rates are controversial for AKI non-ICU patients with COVID-19. In a large observational study, about 0,5% of the patients were diagnosed with AKI during hospitalization with COVID-19 [25]. However, studies with small sample size showed a detection rate of AKI about 5% in patients with COVID-19 [7,23,24,26]. Cheng Y et al., found similar results in their prospective design, including a large cohort [27]. Almost all the above cited studies included the CKD, female patients, and other confounding effects. However, BPH-related, or post-renal etiological data are lacking in these studies.

Multiple factors may be operational in the kidney disease involvement in patients with COVID-19. There are several mechanisms responsible for the high prevalence of kidney involvement in hospitalized patients with COVID-19. Kidneys are involved through direct or indirect mechanisms [28]. BPH is also a known etiological factor for the development of AKI through an indirect mechanism. The existence of a correlation between the development of BPH and chronic inflammation has been widely accepted. Etiological factors such as bacterial or viral infection may trigger inflammation. Prostatic inflammation is also shown to be a risk factor for BPH progression [29]. Studies evaluating the development of AKI due to hospitalized COVID-19 pneumonia patients with BPH are lacking. We have not found any studies investigating the potential of BPH progression as a complication of COVID-19 so far and only a few have proposed BPH management during the COVID-19 pandemic [16,30].

Our results showed that AKI was associated with a higher risk

Table 3. Multivariate cox regression analysis on the risk factors associated with the occured BPH-related AKI in patients with COVID-19

Variable	Univariate			Multivariate		
	HR	95%	p	HR	95%CI	p
Age (years)	0.97	0.96-0.98	**0.001**	1.25	1.13-1.36	**0.005**
Systolic blood pressure, mmHg	1.47	1.36-1.59	**0.01**			
Diastolic blood pressure, mmHg	0.97	0.96-0.98	**0.02**			
Diabetes mellitus on treatment	1.283	0.753-2.186	0.360			
Arterial hypertension on treatment	1.42	1.18-1.72	**0.001**	1.8	1.71-1.99	**0.015**
Coronary artery disease on treatment	1.897	1.055-3.412	**0.032**	1.349	0.618-2.944	0.451
Heart Failure	1.002	1.000-1.004	**0.02**	1.002	0.999-1.004	0.135
Urea, mg/dL	2.43	1.88-3.14	**0.01**			
Lactate dehydrogenase, U/L	0.99	0.99-0.99	**0.01**			
Troponin I	1.001	0.999-1.002	0.260			
D-dimer	0.962	0.814-1.136	0.645			
Disease status	0.97	0.96-0.98	**0.009**			

of BPH in hospitalized patients during COVID-19 pneumonia. Factors as old age and common comorbidities, particularly arterial hypertension, heart failure and coronary artery disease, in BPH patients impose a higher risk of mortality from COVID-19 pneumonia. Additionally, it has been shown that patients having a heart failure cardio-renal syndrome (CRS) had more AKI severity [15]. In our study, hypertension, coronary artery disease and heart failure were significantly more frequent among the BPH patients than in the non-BPH. In our results, we showed that the AKI with BPH was a condition with a poorer prognosis and a higher mortality than the AKI without BPH. On the other hand, larger scale follow-up studies are required to explore the COVID-19 effects on BPH.

This study has several limitations. First, it is a retrospective study. Second, we have a relatively low number of patients (55/814) with BPH. In addition, BPH patients had various comorbidities who were also under commonly prescribed medication. Additionally, their renal functions might have changed dynamically because of the underlying primary disorder. Finally, the potential role of AKI related-BPH in COVID-19 needs to be investigated further.

Conclusion

In our study, AKI is shown to be associated with a higher risk of in BPH in hospitalized patients having COVID-19 pneumonia. Patients, particularly exhibiting mild respiratory symptoms and altered kidney function are recommended to be monitored for their kidney functioning after their admission to the clinical environment. The importance of early detection and treatment of the renal abnormalities combined with adequate hemodynamic support should not be underestimated for the improvement of vital prognosis of COVID-19.

Ethics Committee Approval: All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This article does not contain any studies with animal subjects performed by any of the authors. The study was approved by the medical research ethics committee of the University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Approval number, and registration number: 21.06.2021/347). We are committed to protecting the privacy of patients and to comply with the Declaration of Helsinki. **Informed Consent:** An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
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Authorship Contributions: Any contribution was not made by any individual not listed as an author. Muge Bilge; design of the work, the acquisition, analysis and interpretation of data, Isil Kibar Akilli, Sengul Aydin Yoldemir, Ramazan Korkusuz and Esra Canbolat Unlu; the acquisition of data, Ekrem Guner and Kadriye Kart Yasar; analysis and interpretation of data. **Conf ict of Interest:** The authors declare that they have no conflict of interest.
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