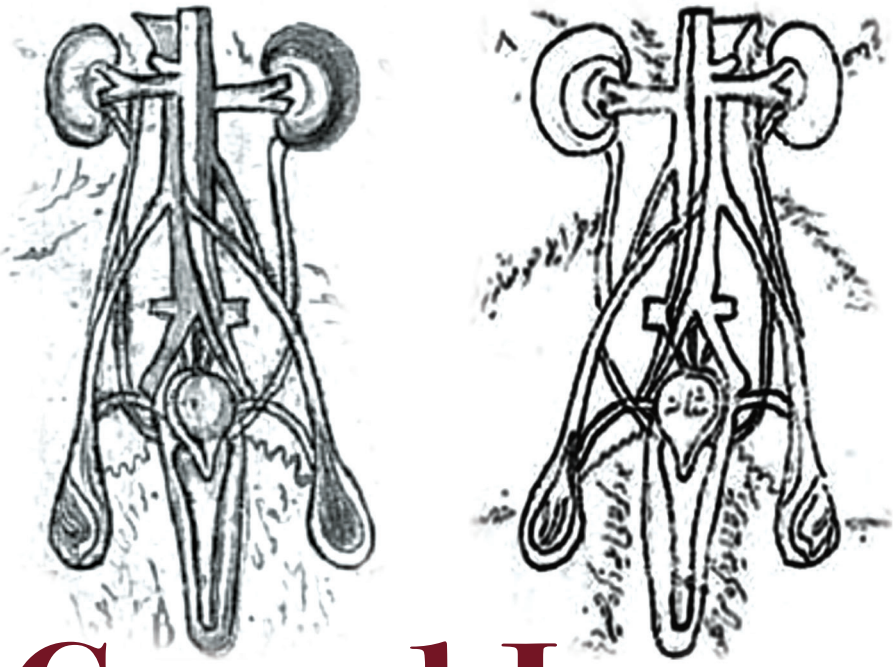
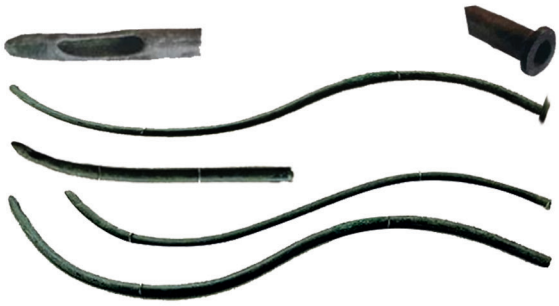
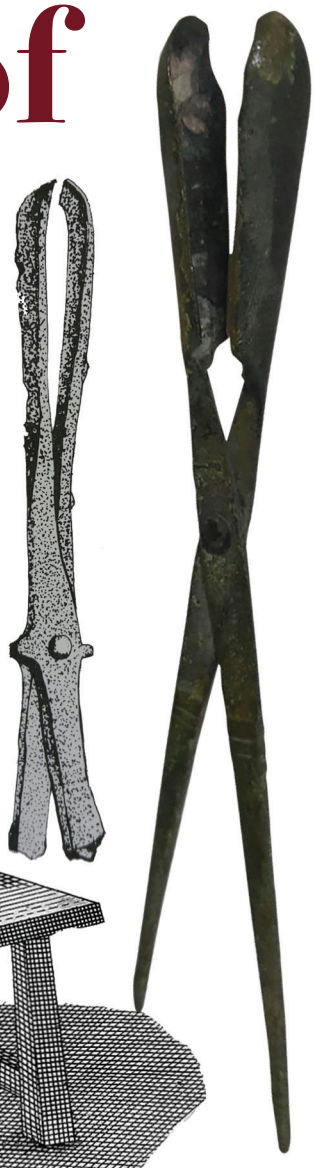
ISSN: 2757-7163

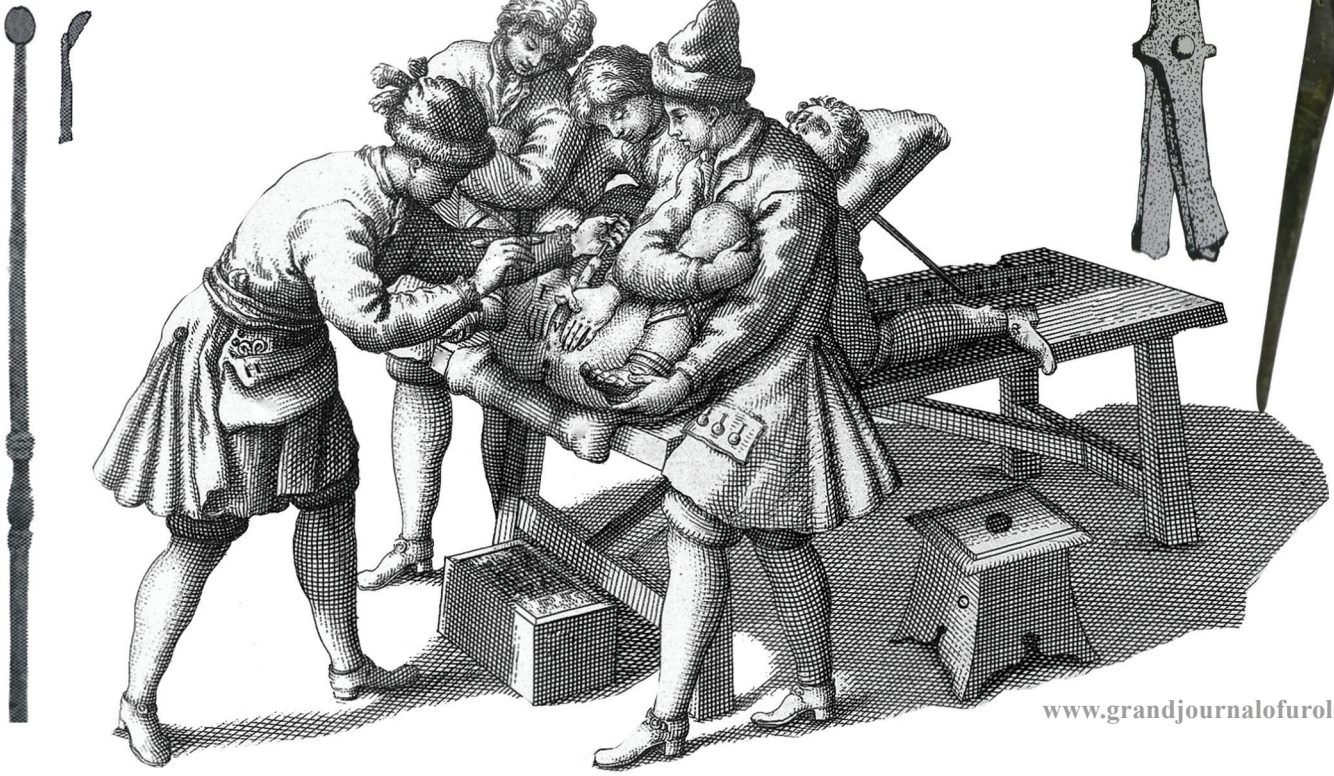




Grand Journal of UROLOGY

January 2022 | Volume: 2 | Issue: 1





www.grandjournalofurology.com

www.grandjournalofurology.com

Publication Type
Periodicals Electronic

Administrative Office
Address: Atakent Mah., 222. Cad., 2 AH., Daire No: 22,
34307, Kucukcekmece, Istanbul, Turkey
E-mail: info@grandjournalofurology.com

ISSN: 2757-7163 | January 2022 | Volume: 2 | Issue: 1

Grand Journal of UROLOGY

Grand Journal of Urology is published three times a year
(January, May, September)
GJU is an open access, free and peer-reviewed journal

You can reach publication policies and writing guides from
www.grandjournalofurology.com

Advisory Board

Advisory Board

Advisory Board

Contents

Contents

Editorial

Dear colleagues,

I am honored to share with you the first issue of 2022 of the Grand Journal of Urology (Grand J Urol) with the contributions of many respected researchers and authors.

Our journal has been indexed in EBSCOhost, J-Gate, Index Copernicus International ICI World of Journals, EuroPub and SciLit international databases. As of these achievements, the Grand Journal of Urology (GJU) has taken its place among the journals indexed by international databases. With this result, GJU was entitled to be included in the journals in category 1b defined in the application criteria for associate professorship.

In this issue of our journal, there are many valuable articles under the subheadings of Andrology, Endourology, General Urology, Genitourinary Radiology, and Urological Oncology. There are three original articles related to COVID-19 and Urology, which reflect the ongoing pandemic process under the sub-title of General Urology. I hope that these carefully prepared articles will make important contributions to valuable readers, researchers and the urology literature.

On this occasion, I would like to express my heartfelt gratitude to our authors who have contributed to our journal with their articles, to our reviewers who have meticulously evaluate the articles.

Respectfully yours
January 2022
Assoc. Prof. Ekrem GUNER, MD
Editor-in-Chief

Original Article – Urological Oncology

Grand J Urol 2022;2(1):1-7
DOI: 10.5505/GJU.2022.41636

The Relation Between Multifocality and Clinical, Pathological and Histological Results in Renal Tumors

Böbrek Tümörlerinde Multifokalitenin Klinik, Patolojik ve Histolojik Bulgularla İlişkisi

Bahadir Ermec[1], Metin Ishak Ozturk[2], Bilal Eryildirim[3], Erbil Ergenekon[4]

[1]Department of Urology, University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey
[2]Department of Urology, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey
[3]Department of Urology, University of Health Sciences, Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey
[4]Department of Urology, University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

Cite as: Ermec B, Ozturk MI, Eryildirim B, Ergenekon E. The relation between multifocality and clinical, pathological and histological results in renal tumors. Grand J Urol 2022;2(1):1-7.

Submission date: 21 June 2021 **Acceptance date:** 06 October 2021 **Online First:** 11 October 2021 **Publication date:** 20 January 2022

Corresponding Author: Bahadir Ermec / University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital, Department of Urology, Istanbul, Turkey / drbahadir76@hotmail.com / ORCID ID: 0000-0002-7680-9119

Abstract

Objective: In this study, histological, pathological and clinical characteristics that may affect multifocality rate and multifocality in renal tumors were investigated.
Materials and Methods: A total of 162 patients who underwent radical nephrectomy with the diagnosis of renal tumor from our urology clinic and urology clinics in two other hospitals between May 2002 and April 2006 and whose results were available were included in the study. Kidney samples were evaluated regarding multifocality through sections made macroscopically at an interval of 3 mm.
Results: Of the patients included in the study, 92 (56.8%) were male and 70 (43.2%) were female. The mean age of the patients was 59.98 years (22-87). In 11 (6.7%) of 162 patients, a multifocality focus was pathologically observed. Satellite lesions were radiologically identified in two (18.2%) of the patients with multifocality. On the other hand, satellite lesions could not be identified radiologically in nine patients (5.5%). Univariate and multivariate analyzes were performed to determine the relation between pathological, histological, and clinical characteristics and multifocality. There was no significant relation between age, gender, smoking, the location of the tumor, pathological stage, lymph node involvement, the presence of metastasis, the size of the tumor, and histology of the tumor. Univariate analysis results showed a statistically significant relation between renal capsule involvement and renal vein involvement and multifocality (p=0.015 and p=0.004, respectively); however, only renal capsule involvement was found to be associated with multifocality in multiple logistic regression analysis (p=0.008).
Conclusion: In our multicentric study including 162 patients, the multifocality rate in renal tumors was 6.7% (11 patients). There was a significant relationship between capsule involvement and multifocality (p=0.015 – p=0.008). Meta analysis is required to determine the rate of multifocality in renal tumors and identify with which clinical, pathological, and histological characteristics it is associated.

Keywords: renal tumor, radical nephrectomy, multifocality

Öz

Amaç: Biz bu çalışmamızda, böbrek tümörlerinde multifokalite oranını ve multifokaliteyi etkileyebilecek histolojik, patolojik ve klinik özellikleri araştırdık.
Gereçler ve Yöntemler: Mayıs 2002- Nisan 2006 tarihleri arasında üroloji kliniğimiz ve diğer iki hastanedeki üroloji kliniklerinden böbrek tümörü tanısı ile radikal nefrektomi yapılan ve bulgularına ulaşılan 162 hasta çalışmaya alındı. Böbrek spesmenleri makroskobik ve 3 mm'lik aralıklarla ince kesit yapılarak multifokalite açısından değerlendirildi.
Bulgular: Çalışmaya alınan hastaların 92'si (%56,8) erkek, 70'i (%43,2) kadındı. Hastaların ortalama yaşları 59,98 (22-87) idi. 162 hastanın 11'inde (%6,7) patolojik olarak multifokalite odağı görüldü. Multifokalite belirlenen hastaların 2'sinde (%18,2) radyolojik olarak satellite lezyon saptandı. Buna karşılık 9 hastada (%5.5) radyolojik olarak satellite lezyon saptanamadı. Patolojik, histolojik ve klinik özelliklerin multifokalite ile olan ilişkisini saptamak için univariate ve multivariate analizler yapıldı. Hasta yaşı, cinsiyet, sigara kullanımı, yerleşim yeri, patolojik evre, lenf nodu tutulumu, metastaz varlığı, tm boyutu, tm histolojisi arasında anlamlı bir ilişki saptanmadı. Univariate analiz sonucu hem renal kapsül tutulumu hem de renal ven tutulumu ile multifokalite arasında istatistiki anlamlı ilişkili saptanırken (sırasıyla p=0,015 ve p=0,004), multipl logistic regression analizinde sadece renal kapsül tutulumu multifokalite ile ilişkili olarak bulundu (p=0,008).
Sonuç: Multisentrik, 162 vakalık çalışmamızda böbrek tümörlerinde multifokalite sıklığını 11 hasta (%6,7) olarak saptadık. Bizim çalışmamızda kapsül tutulumu (p=0,015 – p=0,008) ile multifokalite arasında anlamlı bir ilişki bulunmuştur. Böbrek tümörlerinde multifokalite oranının ve hangi klinik, patolojik ve histolojik özelliklerle ilişkili olduğunun saptanması için meta-analize ihtiyaç vardır.

Anahtar kelimeler: böbrek tümörü, radikal nefrektomi, multifokalite

ORCID ID: M.I. Ozturk 0000-0001-9369-8206 **B. Eryildirim** 0000-0002-2213-3985 **E. Ergenekon** 0000-0002-6806-2473

Introduction

Currently, renal cell carcinoma (RCC) represents about 3% of all cancers and the highest incidence occurs in Western countries [1]. High duration of survival achieved by radical nephrectomy, made this method the gold standard in the treatment of early-stage renal tumors. However, in a surgery to be performed in patients with a solitary kidney, chronic renal failure, or a systemic disease that will affect contralateral renal function, or who have bilateral tumors, the intact kidney should be preserved. Achieving a longer survival that is comparable to radical nephrectomy in nephron-sparing surgery (NSS), which means removing the tumor by sparing the most functional parenchyma, and the improvements in surgical technique (development of prevention methods against ischemic renal damage, increased renal vascular surgery experience) have increased the interest in this method [2]. Moreover, the indications of NSS have enlarged with the application of partial nephrectomy in small, early-stage, peripherally located, and incidentally detected renal tumor cases [3].

Partial nephrectomy has the disadvantage that it may cause local recurrence due to the inability to remove the satellite tumor in multifocal cases, as well as the advantages of preventing the removal of the entire kidney with benign tumors and reducing the risk of long-term renal failure [4,5].

There is no precise information about the biological potential of these multifocal microscopic residual tumors [6]. The multifocality rate in renal cortical tumors was within a wide range of 4.7% - 25% in various studies [7-16]. In this multicentric study including 162 patients, the histological, pathological and clinical characteristics that may affect the multifocality rate and multifocality in renal tumors were analyzed.

Materials and Methods

Patient Selection

The study was approved by the Institutional Review Board Ethics Committee of Istanbul Training and Research Hospital (Approval no: 2021/2911). An informed consent was obtained from all the patients. A total of 210 patients who underwent surgery between May 2002 and April 2006 with the diagnosis of renal tumor from our urology clinic and urology clinics in two other hospitals were retrospectively evaluated. Radical Nephrectomy was performed in 178 of 210 patients, and nephron-sparing (partial) nephrectomy was performed in the remaining 32 patients. The patients who underwent partial nephrectomy were excluded from the study. Moreover, 16 of the patients who underwent radical nephrectomy were excluded from the study as some information was missing. None of the patients were excluded from the study based on primary tumor size and the TNM classification. A total of 162 renal tumor patients who underwent radical nephrectomy were included in the study and their preoperative-peroperative-postoperative results were analyzed.

Clinical Evaluation

All of the 162 patients diagnosed with renal tumor were evaluated based on an anamnesis (age, gender, occupation, initial complaint, and smoking), a complete physical examination, complete urinalysis, hemogram, sedimentation, urea-creatinine ratio, liver-function tests, calcium, ferritin, chest radiography, abdominal ultrasonography (US), and computed tomography (CT). In addition, abdominal magnetic resonance imaging (MRI), MR angiography, and Doppler USG were performed in some patients for differential diagnosis, clinical staging, and surgery method. Based on these data, the patients were clinically staged according to the 2002 tumour–node–metastasis (TNM) classification.

The patients were staged by taking the TNM classification as a reference following the pathological examination, and they were included in the follow-up protocol.

Pathological Evaluation

All kidney samples were evaluated by a pathologist in the pathology clinics of the hospitals included in the study according to the same protocol developed **(Table 1)**. Accordingly, the samples were first examined macroscopically for primary tumor size and the presence of satellite lesions. Then, multifocality was investigated through thin sections made at 3 mm intervals on the samples. Histological classification of the primary tumor and the satellite tumor was made according to the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). The differential diagnosis of adenoma and carcinoma was made histologically. Accordingly, histologically papillary masses of ≤5mm with a low Fuhrmann nuclear grade were accepted as adenoma. Adenomas were not considered multifocal lesions and were not included in the study.

Statistical Analysis

Demographic results and distribution of tumor characteristics of the patients were compared using the Chi-Square Test. Univariate and multivariate analysis were performed using logistic regression to determine the relation between clinical and pathological characteristics and multifocality. Variables included patient age, gender, smoking history, primary tumor size, the location of the tumor, pathological stage (pT), lymph node involvement, the presence of distant metastasis, capsule involvement, renal vein involvement, and histological diagnosis.

Results

Of the patiens included in the study, 92 (56.8%) were male and 70 (43.2%) were female. The mean age of the patients was 59.98 (22-87). In 11 (6.7%) of the 162 patients, the multifocality focus was observed pathologically. The demographic results and tumor characteristics of the patients are shown in **Table 2**. Satellite lesions were identified radiologically in 2 (18.2%) of the 11 patients with multifocality. Both of these satellite lesions were demonstrated by a CT scan and/or MRI. The rate of multifocality (occult) that could not be diagnosed with preoperative imaging was 9 patients (5.5%) in 162 patients.

When all renal tumors were examined histologically using

Table 1. Multifocality in renal tumors (A multi-center study)

NAME-SURNAME:
Age: Profession:
Phone: Address:
COMPLAINT:
Hematuria: Mass: Weight loss: Anemia: Pain:
Polycythemia: Hypertension: Hepatic Dysfunction: Other:
LABORATORY:
Hb: Hct: Leucocyte: Urea: Creatinine: SGOT: SGPT:
Calcium: Ferritin: Other:
USG: Right Kidney:
Left Kidney:
IVP: Right Kidney:
Left Kidney:
CT: Right Kidney:
Left Kidney:
MR: Right Kidney:
Left Kidney:
Chest radiography:
Other Imagings:
CLINICAL STAGING: cT: cN: cM:
METHOD OF SURGERY:
Suspected macroscopic satellite lesion noticed during the surgery (cortical irregularity):
MACROSCOPY:
Kidney weight: Kidney sizes: x x cm
Tm Size: x x cm Tm Location:
Necrosis: Yes ( ) No ( ) Explanation:
Histopathology:
Tm type: Clear cell ( ) Papillary ( ) Chromophobe ( ) Collecting tubules ( ) Medullary ( )
Nuclear Grade: Grade 1 ( ) Grade 2 ( ) Grade 3 ( ) Grade 4 ( )
Renal capsule involvement: Renal vein invasion:
Surgical margins: Ureteral ( ) Renal vein ( ) Soft tissue ( ) Adrenal ( ) Lymph nodes ( )
PATHOLOGICAL STAGING: pT: pN: pM:
MULTIFOCALITY:
Number: Size: Nuclear Grade: Grade1 ( ) Grade2 ( ) Grade3 ( ) Grade4 ( )
Histological type:
Distance to the primary: Location: Subcapsular ( ) Intraparenchymal ( )
NOTE OF PATHOLOGY: When the renal capsule is peeled off, the cortex is examined, if possible, for irregular areas under magnification, and the intraparenchymal lesion is investigated with serial sections of 1 cm and then 3 mm following taking the necessary samples for the primary tumor.

the UICC and AJCC classification systems, it was identified that 106 (65.4%) had conventional clear cell carcinoma, 32 (19.8%) had papillary cell carcinoma, 9 (5.6%) had chromophobe cell, five (3.1%) had oncocytoma, two (1.2%) had collecting tubules carcinoma, two (1.2%) had medullary cell carcinoma, and six (3.7%) patients had unclassifiable type renal cell carcinoma. On the other hand, five patients (45.5%) had papillary cell carcinoma, five (45.5%) had conventional clear cell carcinoma, and one (9%) had chromophobe cell carcinoma concerning multicentric tumors. Discordance was observed in two patients (18.2%) between primary renal tumor and satellite lesion histology; these were chromophobe-papillary and clear cell-papillary cell carcinoma. There was no discordance between primary tumor grade and satellite tumor grade in any patient.

The tumor size was mean 8.12 cm (2 cm to 17 cm) in primary tumors. Radical nephrectomy was performed for tumors smaller than 4 cm because it is completely endophytic and close to the collecting system. Tumor sizes regarding multifocality and unifocality were mean 7 cm (2 cm – 12 cm) and 8.01 cm (2 cm – 17 cm), respectively. Multifocality was identified in nine patients

Table 2. Demographic characteristics and pathological-histological results of the patients with renal tumors

		Unifocal	Multifocal	Total
Number of the patients (%)		151 (93.35)	11 (6.7%)	162
Age (mean)		58.88 (22-87)	61.4 (33-74)	59.98 (22-87)
Gender				
Male		85 (56.3%)	7 (63.6%)	92 (56.8%)
Female		66 (43.7%)	4 (36.4%)	70 (43.2%)
Smoking	(%)			
	Yes	84 (55.6%)	8 (72.7%)	92 (56.8%)
	No	67 (44.4%)	3 (27.3%)	70 (56.8%)
Location				
Right		61 (40.4%)	2 (18.2%)	63 (38.9%)
Left		90 (59.6%)	9 (81.8%)	99 (61.1%)
Pathological Stage				
pT1		63 (41.7%)	4 (36.4%)	67 (41.4%)
pT2		53 (35.1%)	4 (36.4%)	57 (35.1%)
pT3a		21 (13.9%)	2 (18.2%)	23 (14.2%)
pT3b		8 (5.3%)	1 (9%)	9 (5.6%)
pT3c		N/A	N/A	N/A
pT4		6 (4%)	N/A	6 (3.7%)
Lymph node involvement				
Yes		8 (5.3%)	4 (36.4%)	12 (7.4%)
No		143 (94.7%)	7 (63.6%)	150 (92.6%)
Existence of metastasis (%)		29 (19.2%)	N/A	29 (17.9%)
Tumor size				
≤ 4 cm		20 (13.2%)	2 (18.2%)	22 (13.6%)
> 4 cm		131 (86.8%)	9 (81.8%)	140 (86.4%)
Tumor size (cm)		8.01 (2-17)	7 (2-12)	8.12 (2-17)
Tumor histology				
Clear cell		101 (66.9%)	5 (45.5%)	106 (65.4%)
Papillary		27 (17.9%)	5 (45.5%)	32 (19.8%)
Chromophobe		8 (5.3%)	1 (9%)	9 (5.6%)
Oncocytoma		5 (3.1%)	N/A	5 (3.1%)
Unclassified		6 (4%)	N/A	6 (3.7%)
Collecting tubules		2 (1.4%)	N/A	2 (1.2%)
Medullary		2 (1.4%)	N/A	2 (1.2%)
Renal capsule involvement		44 (29.1%)	6 (54.5%) Uni. **p=0.015** Mult. **p=0.008**	50 (30.8%)

(4.3%) among 140 samples with a primary tumor size of >4 cm, and in two patients (9%) among 22 samples with a primary tumor size of ≤4 cm. While >4 multifocality foci were observed in two patients, four foci in one patient, three foci in one patient, two foci in four patients, one focus in three patient were observed. The mean distance of satellite lesions to the primary tumor was 1.33 cm (0.2 - 3.5).

When the distribution of primary tumors, according to the 2002 TNM classification, was analyzed, the frequency was T1 in 67 patients (41.4%), T2 in 57 patients (35.1%), T3a in 23 patients (14.2%), T3b in 9 patients (5.6%), and T4 in six patients (3.7%). In 12 patients (7.4%), lymph node positivity was identified, and metastasis was identified in 29 patients (17.9%) at the time of admission. In patients with multifocality, the distributions for T1, T2, T3a, and T3b were four (36.4%), four (36.4%), two (18.2%), and one (9%), respectively. Multifocality was not identified in any of the six T4 patients. There was lymph node positivity in four (36.4%) of 11 multifocal tumors. None of the patients with multifocality were metastatic at the time of diagnosis.

Univariate and multivariate analyzes were performed to determine the relation between pathological, histological, and clinical features and multifocality. While univariate analysis results showed a statistically significant relation between both renal capsule involvement and renal vein involvement and multifocality (p=0.015 and p=0.004, respectively), only renal capsule involvement was associated with multifocality in multiple logistic regression analysis (p=0.008).

Discussion

There are limited data about sporadic cases in the literature, though well defined in hereditary renal cell carcinomas, such as multifocal renal cortical tumors, Von Hippel Lindau (VHL) syndrome, hereditary renal papillary carcinoma, familial oncocytoma, and Birt-Hogg Dubé (BHD) syndrome. The multifocality rate in renal cortical tumors was in a wide range of 4.7% - 25% in various studies [7-16]. In a study with the largest series on this subject, Siracusano et al. identified a multifocality rate of 5% in 5378 renal cortical tumors [15]. The lower rate, compared to other series, may be attributed to the retrospective nature of the study, though being with a large series, and the pathological examination performed through routine pathological evaluation rather than 3mm thin-section examination. In addition, studies with higher rates were the series with a maximum of 108 patients [9-13]. In our study, multifocality was identified in 11 (6.7%) of 162 patients.

The difference between adenoma and RCC in terms of the differential diagnosis in these studies investigating multifocality may also explain the discordance in the multifocality rates. Some pathologists make adenoma diagnosis based on the size of the mass and the limit is determined as 3 cm [11,12]. However, as in the criteria of the present study, many pathologists make the differential diagnosis of adenoma and RCC based on the histological characteristics of tissues.

It is possible to show satellite lesions with imaging methods such as CT, MRI, and USG performed during preoperative period. Kletscher et al. identified multifocality using a preoperative CT scan and/or MRI in 44% of their patients [10]. However, the rates were 14% and 23% in the studies by Baltaci et al. and Schlichter et al., respectively [13,18]. In the present study, two (18.2%) of 11 patients with multifocality were diagnosed using preoperative imaging methods. The rates of multifocality (occult) that could not be diagnosed using preoperative imaging methods were between 3.5% and 29% in the same studies [10-14,16,17]. This rate was identified in 9 (5.5%) of 162 patients in the present study.

In some studies, a significant relationship was shown between various histological, pathological, and clinical features and multifocality [9-15]. In our study, there was no statistically significant difference between primary tumor histology and multifocality, and it was observed to be associated especially with papillary type renal cell carcinoma. There are contradictory results in the literature regarding the relation between tumor histology and multifocality. There was no statistically significant relation in the studies of Whang et al., Baltaci et al. and Sargin et al. [11,13,16]. Kletscher et al., Richstone et al. and Siracusano et al. found a significant relation between papillary renal cell carcinoma and multifocality [10,14,15]. When we examined the histological structure of renal tumors, we found that papillary type renal cell carcinoma was more common in multifocal samples than unifocal samples. However, Richstone et al. showed in their 1071 disease series that the distribution of histological subtypes in the multifocal group was also similar to that of the unifocal group [14]. The discordance between the primary tumor and satellite lesion histology was 18.2% (6-30%), which was similar to the studies in the literature.

The relation between tumor size and multifocality has been the most interesting point in the studies of multifocality as nephron-sparing surgery is performed in peripherally-located renal tumors of <4 cm in current urology practice. In a series of 100 patients, Kletscher et al. identified multifocal foci in 16 samples (16%), while the tumor size was < 4 cm in 8 of these 16 samples (50%) [10]. Mukamel et al. found the rate of patients with a primary tumor at a diameter of <4 cm in multifocal tumors as 31%, which supported the results of the study by Kletscher et al. [9]. Baltaci et al. identified the rate as 32%, and it was identified as 39% by Richstone et al. [13,14]. In the present series, the rate was 18.2%. These rates explain the reason for local recurrence that develops after partial nephrectomy performed in peripherally-located tumors with a size of < 4 cm.

Although it was considered to be a relation between tumor stage and multifocality, Kletscher and Gohji could not identify this correlation in their studies [10,12]. However, Richstone et al. Baltaci et al. showed that there was a significant relation between the stage and multifocality [13,14]. Siracusano et al. also showed that high stage and high tumor grade were associated with multifocality [15]. The results of other studies suggested that the tumor stage was associated with multifocality; however, the relation was not statistically significant [9,11,12]. In our series, there was no significant relation between the tumor stage and multifocality.

In prospective studies in the literature, the total renal tumor sample has usually been ≥100; however, investigating the correlation of multifocality with clinical, pathological, and histological characteristic may yield different results as the number of samples with multifocality is a maximum of 22. However, in a study with the largest series (5378 patients) Siracusano et al.

could not obtain sufficient results due to both retrospective design of the study and not making examination with a thin section of 3 mm [15].

The limitations of our study include its retrospective multicenter study. In addition, the relatively small sample sizes may lead to a higher heterogeneity of the research. Therefore, determining the multifocality rate in renal tumors and clinical, pathological, and histological parameters associated multifocality with meta-analysis will provide more reliable data.

Conclusion

In our multicentric study including 162 patients, we determined the multifocality rate as 6.7% (11 patients) in renal tumors. Although various clinical, pathological, and histological characteristics were associated with multifocality, a significant relation was found between capsule involvement (p=0.015 – p=0.008) and multifocality, especially in the present study. Meta-analysis is required to determine the rate of multifocality in renal tumors and identify with which clinical, pathological, and histological characteristic it is associated.

Ethics Committee Approval: The study was approved by the Institutional Review Board Ethics Committee of Istanbul Training and Research Hospital (Approval number: 2021/2911).
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.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – B.E., M.I.O., B.E., E.E.; Design – B.E., E.E., B.E., M.I.O.; Supervision –B.E., M.I.O., B.E., E.E.; Resources – B.E., M.I.O., B.E.; Materials –B.E., M.I.O., B.E., E.E.; Data Collection and/or Processing – B.E., M.I.O., B.E., E.E.; Analysis and/or Interpretation –B.E., B.E., M.I.O.; Literature Search – B.E., M.I.O., B.E.; Writing Manuscript – B.E., M.I.O., B.E.; Critical Review – B.E., E.E.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356-87. https://doi.org/10.1016/j.ejca.2018.07.005.

[2] Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011;59:543-52. https://doi.org/10.1016/j.eururo.2010.12.013.

[3] Kural AR, Demirkesen O, Akpınar H. Düşük evreli böbrek tümörlerinde nefron koruyucu cerrahi. In: Solok V, Erözenci NA, editors. Ürolojide ikilemler, İstanbul: Doyuran Matbaası; 1997, p. 98-105.

[4] McKiernan J, Yossepowitch O, Kattan MW, Simmons R, Motzer RJ, Reuter VE, et al. Partial nephrectomy for renal cortical tumors: pathologic findings and impact on outcome. Urology 2002;60:1003-9. https://doi.org/10.1016/s0090-4295(02)01967-2.

[5] McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. Urology 2002;59:816-20. https://doi.org/10.1016/s0090-4295(02)01501-7.

[6] Kovacs G, Akhtar M, Beekwith BJ, Bugert P, Cooper CS, Delahunt B, et al. The Heidelberg classification of renal cell tumours. J Pathol 1997;183:131-3. https://doi.org/10.1002/(SICI)1096-9896(199710)183:2%3C131::AID-PATH931%3E3.0.CO;2-G.

[7] Karadeniz T, Güzelburç V, Şahin S, Beşiroğlu H. The Relationship of Multifocality With Prognostic Factors in Renal Cell Carcinoma. Okmeydanı Tıp Dergisi 2012;28:35-41. https://www.researchgate.net/publication/315044129 .

[8] Kuzgunbay B, Soyupak B. Böbrek tümörlerinde multifokalite. Neye dikkat etmeli? Bull Urooncol 2010;9:6-8. http://cms.galenos.com.tr/Uploads/Article_8364/6-8.pdf.

[9] Mukamel E, Konichezky M, Engelstein D, Servadio C. Incidental smalI renal tumors accompanying clinically overt renal cell carcinoma. J Urol 1988;140:22-4. https://doi.org/10.1016/s0022-5347(17)41474-1.

[10] Kletscher BA, Qian J, Bostwick DG, Andrews PE, Zincke H. Prospective analysis of multifocality in renal cell carcinoma: influence of histological pattern, grade, number, size, volume and deoxyribonucleic acid ploidy J Urol 1995;153:904-6. https://pubmed.ncbi.nlm.nih.gov/7853571/.

[11] Whang M, O'Toole K, Bixon R, Brunetti J, Ikeguchi E, Olsson CA, et al. The incidence of multifocal renal cell carcinoma in patients who are candidates for partial nephrectomy. J Urol 1995;154:968-71. https://pubmed.ncbi.nlm.nih.gov/7637103/.

[12] Gohji K, Hara I, Gotoh A, Eto H, Miyake H, Sugiyama T, et al. Multifocal renal cell carcinoma in Japanese patients with tumors with maximal diameters of 50 mm or less. J Urol 1998;159:1144-7. https://pubmed.ncbi.nlm.nih.gov/9507818/.

[13] Baltaci S, Orhan D, Soyupek S, Bedük Y, Tulunay O, Gögüs O. Influence of tumor stage, size, grade, vascular involvement, histological cell type and histological pattern on multifocality of renal cell carcinoma. J Urol 2000;164:36-9. https://pubmed.ncbi.nlm.nih.gov/10840419/.

[14] Richstone L, Scherr DS, Reuter VR, Synder ME, Rabbani F, Kattan MW, et al. Multifocal renal cortical tumors: Frequency, associated clinicopathological features and impact on survival. J Urol 2004;171:615-20. https://doi.org/10.1097/01.ju.0000106955.19813.f6.

[15] Siracusano S, Novara G, Antonelli A, Artibani W, Bertini R, Carini M, et al. Prognostic role of tumour multifocality in renal cell carcinoma. BJU Int 2012;110:E443-8. https://doi.org/10.1111/j.1464-410X.2012.11121.x.

[16] Sargin SY, Ekmekcioglu O, Arpali E, Altinel M, Voyvoda B. Multifocality incidence and accompanying clinicopathological factors in renal cell carcinoma. Urol Int 2009;82:324-9. https://doi.org/10.1159/000209366.

[17] Mano R, Kent M, Larish Y, Winer AG, Chevinsky MS, Hakimi AA, et al. Partial and Radical Nephrectomy for Unilateral Synchronous Multifocal Renal Cortical Tumors. Urology 2015;85:1404-10. https://doi.org/10.1016/j.urology.2015.02.032.

[18] Schlichter A, Werner W, Wunderlich H, Schubert J. Multifocal renal cell carcinoma – diagnostic value of imaging techniques in vivo and ex vivo. J Urol, suppl 1999;161:168, abstract 647. https://www.researchgate.net/publication/246112202.

Original Article – General Urology

Grand J Urol 2022;2(1):8-14
DOI: 10.5505/GJU.2022.58067

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

Muge Bilge[1], Isil Kibar Akilli[2], Sengul Aydin Yoldemir[1], Ramazan Korkusuz[3], Esra Canbolat Unlu[3], Ekrem Guner[4], Kadriye Kart Yasar[3]

[1]Department of Internal Medicine, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[2]Department of Pulmonary Disease, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[3]Department of Infectious Disease, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[4]Department of Urology, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

Cite as: Bilge M, Kibar Akilli I, Aydin Yoldemir S, Korkusuz R, Canbolat Unlu E, Guner E, Kart Yasar K. Evaluation of the frequency of acute kidney injury in hospitalized patients with benign prostatic hyperplasia due to COVID-19 pneumonia. Grand J Urol 2022;2(1):8-14.

Submission date: 01 August 2021 **Acceptance date:** 16 November 2021 **Online First:** 22 November 2021 **Publication date:** 20 January 2022

Corresponding Author: Muge Bilge / University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Internal Medicine Istanbul, Turkey / mugebilge@yahoo.com / ORCID ID: 0000-0001-7965-3407

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

ORCID ID: **I. Kibar Akıllı** 0000-0002-4969-4512 **R. Korkusuz** 0000-0002-9988-9596 **E. Guner** 0000-0002-4770-7535
S. Aydin Yoldemir 0000-0003-4236-1181 **E. Canbolat Unlu** 0000-0003-1465-3283 **K. Kart Yasar** 0000-0003-2963-4894

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.
Peer-review: Externally and internally peer-reviewed.
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.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.
Acknowledgments: The authors wish to thank Prof. Dr. Ahmet Ademoglu and Biomedical Engineering Institute of Bogazici University for his help with statistical analyses and interpretation of data.

References

[1] Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al. AKI in Hospitalized Patients with COVID-19. J Am Soc Nephrol 2021;32:151-60. https://doi.org/10.1681/ASN.2020050615.

[2] Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int 2005;67:698-705. https://doi.org/10.1111/j.1523-1755.2005.67130.x.

[3] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323:2052-9. https://doi.org/10.1001/jama.2020.6775.

[4] Pan X-W, Xu D, Zhang H, Zhou W, Wang L-H, Cui X-G. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med 2020;46:1114-6. https://doi.org/10.1007/s00134-020-06026-1.

[5] Tolouian R, Vahed SZ, Ghiyasvand S, Tolouian A, Ardalan M. COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment. J Renal Inj Prev 2020;9:e19-e19. https://doi.org/10.34172/jrip.2020.19.

[6] Peng Y-H, Huang C-W, Chou C-Y, Chiou H-J, Chen H-J, Wu T-N, et al. Association between asthma and risk of benign prostatic hyperplasia: a retrospective population-based study. The Aging Male 2020;23:599-606. https://doi.org/10.1080/13685538.2018.1552253.

[7] Gandaglia G, Briganti A, Gontero P, Mondaini N, Novara G, Salonia A, et al. The role of chronic prostatic inflammation in the pathogenesis and progression of benign prostatic hyperplasia (BPH): Chronic prostatic inflammation in BPH pathogenesis and progression. BJU Int 2013;112:432-41. https://doi.org/10.1111/bju.12118.

[8] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13. https://doi.org/10.1016/S0140-6736(20)30211-7.

[9] Stopsack KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. TMPRSS2 and COVID-19: Serendipity or Opportunity for Intervention? Cancer Discov 2020;10:779-82. https://doi.org/10.1158/2159-8290.CD-20-0451.

[10] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically

Proven Protease Inhibitor. Cell 2020;181:271-80.e8. https://doi.org/10.1016/j.cell.2020.02.052.

[11] Izumi K, Mizokami A, Lin W-J, Lai K-P, Chang C. Androgen Receptor Roles in the Development of Benign Prostate Hyperplasia. The American Journal of Pathology 2013;182:1942-9. https://doi.org/10.1016/j.ajpath.2013.02.028.

[12] Kyprianou N, Davies P. Association states of androgen receptors in nuclei of human benign hypertrophic prostate. Prostate 1986;8(4):363-80. https://doi.org/10.1002/pros.2990080408.

[13] Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. J Am Acad Dermatol 2020;83:308-9. https://doi.org/10.1016/j.jaad.2020.04.032.

[14] Wambier CG, Goren A, Vaño-Galván S, Ramos PM, Ossimetha A, Nau G, et al. Androgen sensitivity gateway to COVID-19 disease severity. Drug Dev Res 2020;81:771-6. https://doi.org/10.1002/ddr.21688.

[15] Kellum J, Lameire N, Aspelin P, Barsoum R, Burdmann E, Goldstein S, et al. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138. https://doi.org/10.1038/kisup.2012.1.

[16] Haghpanah A, Masjedi F, Salehipour M, Hosseinpour A, Roozbeh J, Dehghani A. Is COVID-19 a risk factor for progression of benign prostatic hyperplasia and exacerbation of its related symptoms?: a systematic review. Prostate Cancer Prostatic Dis 2021;18:1-12. https://doi.org/10.1038/s41391-021-00388-3.

[17] Wei P-F. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl) 2020;133:1087-95. https://doi.org/10.1097/CM9.0000000000000819.

[18] Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. Radiol Cardiothorac Imaging 2020;2:e200047. https://doi.org/10.1148/ryct.2020200047.

[19] Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJMCH. EAU 2004 Guidelines on Assessment, Therapy and Follow-Up of Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Obstruction (BPH Guidelines). European Urology 2004;46:547-54. https://doi.org/10.1016/j.eururo.2004.07.016.

[20] Republic of Turkey Ministry of Health. Covid-19 (SARS-CoV-2 Infection) Guide. Available @:covid-19rehber ieriskinhastatedavisipdf.pdf (saglik.gov.tr), (Accessed 20/07/2020.)

[21] Palevsky PM. Endpoints for Clinical Trials of Acute Kidney Injury. Nephron 2018;140:111-5. https://doi.org/10.1159/000493203.

[22] Doi K, Nishida O, Shigematsu T, Sadahiro T, Itami N, Iseki K, et al. The Japanese Clinical Practice Guideline for Acute Kidney Injury 2016. J Intensive Care 2018;6:48. https://doi.org/10.1186/s40560-018-0308-6.

[23] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[24] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9. https://doi.org/10.1001/jama.2020.1585.

[25] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20. https://doi.org/10.1056/NEJMoa2002032.

[26] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med 2020;382:1199-207. https://doi.org/10.1056/NEJMoa2001316.

[27] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829-38. https://doi.org/10.1016/j.kint.2020.03.005.

[28] Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020;8:738-42. https://doi.org/10.1016/S2213-2600(20)30229-0.

[29] Madersbacher S, Sampson N, Culig Z. Pathophysiology of Benign Prostatic Hyperplasia and Benign Prostatic Enlargement: A Mini-Review. Gerontology 2019;65:458-64. https://doi.org/10.1159/000496289.

[30] Yee CH, Wong HF, Tam MHM, Yuen SKK, Chan HC, Cheung MH, et al. Effect of SARS and COVID-19 outbreaks on urology practice and training. Hong Kong Med J 2021;27:258-65. https://doi.org/10.12809/hkmj208822.

Original Article – Genitourinary Radiology

Grand J Urol 2022;2(1):15-20
DOI: 10.5505/GJU.2022.87599

Relationship Between SUVmax and ADC Values of Metastatic Lymph Nodes Detected by Ga-68 PSMA PET/MR in Prostate Cancer Patients

Prostat Kanseri Hastalarında Ga-68 PET/MR ile Saptanan Metastatik Lenf Nodlarına Ait SUVmaks ve ADC Değerleri Arasındaki İlişki

Fuad Aghazada, Ali Kibar, Rabia Lebriz Uslu Besli, Muhammet Sait Sager, Haluk Burcak Sayman, Kerim Sonmezoglu

Department of Nuclear Medicine, Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Istanbul, Turkey

Cite as: Aghazada F, Kibar A, Uslu-Besli RL, Sager MS, Sayman HB, Sonmezoglu K. Relationship between SUVmax and ADC values of metastatic lymph nodes detected by Ga-68 PSMA PET/MR in prostate cancer patients. Grand J Urol 2022;2(1):15-20.

Submission date: 31 August 2021 **Acceptance date:** 29 November 2021 **Online First:** 06 December 2021 **Publication date:** 20 January 2022

Corresponding Author: Fuad Aghazada / Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Department of Nuclear Medicine, Istanbul, Turkey / fuad.aghazada@gmail.com / ORCID ID: 0000-0001-9519-3455

Abstract

Objective: Our aim is to assess if there is a relationship between maximum standardized uptake (SUVmax) and apparent diffusion coefficient (ADC) values of reactive and metastatic lymph nodes, also to compare ADC values of reactive and metastatic lymph nodes in prostate cancer patients.
Materials and Methods: We have retrospectively investigated 20 patients diagnosed with prostate cancer who underwent Ga-68 PSMA PET/MR imaging. Three metastatic and three reactive lymph nodes classified according to PSMA Ga-68 uptake in PET/MR were chosen for each patient. SUVmax and ADCmean values were calculated for each lymph node separately. SPSS version 22 was used for statistical analysis.
Results: A total of 120 lymph nodes in 20 prostate cancer patients were assessed. There was a weak negative correlation between SUVmax values and ADCmean values of metastatic lymph nodes (p=0.009, r=-0.333). However, there was no significant correlation between SUVmax values and ADCmean values of reactive lymph nodes (p=0,271, r=-0,144). ADCmean values of metastatic lymph nodes were significantly lower than those of reactive lymph nodes (p=0.0001).
Conclusion: PET/MR, which combines both advantages of PET and MRI, is an important tool for the diagnosis and management of prostate cancer. We have found that SUVmax values of metastatic lymph nodes were inversely correlated with ADCmean values and combination of both parameters may increase the diagnostic accuracy of Ga-68 PSMA PET/MR in the detection of lymph node metastasis.

Keywords: prostate cancer, lymph node metastasis, Ga-68 PSMA, positron emission tomography

Öz

Amaç: Amacımız, prostat kanserli hastalarda reaktif ve metastatik lenf nodlarının maksimum standardize uptake değeri (SUVmaks) ile görünür difüzyon katsayısı (ADC) değerleri arasında bir ilişki olup olmadığını değerlendirmek, ayrıca reaktif ve metastatik lenf nodlarının ADC değerlerini karşılaştırmaktır.
Gereçler ve Yöntemler: Ga-68 PSMA PET/MR görüntüleme yapılmış prostat kanseri tanılı 20 hastanın görüntüleri retrospektif olarak incelendi. Her hasta için PSMA PET tutulumuna göre sınıflandırılan üç metastatik ve üç reaktif lenf nodu seçildi. SUVmax ve ADCortalama değerleri her bir lenf nodu için ayrı ayrı hesaplandı. İstatistiksel analiz için SPSS versiyon 22 kullanıldı.
Bulgular: Yirmi prostat kanserli hastada toplam 120 lenf nodu değerlendirildi. SUVmaks değerleri ile metastatik lenf nodu ADCortalama değerleri arasında düşük düzeyde negatif korelasyon vardı (p=0,009, r=-0,333). Ancak SUVmaks değerleri ile reaktif lenf nodlarının ADCortalama değerleri arasında anlamlı bir ilişki yoktu (p=0,271, r=-0,144). Metastatik lenf nodlarının ADCortalama değerleri, reaktif lenf nodlarından anlamlı derecede düşüktü (p=0,0001).
Sonuç: PET ve MR'ın avantajlarını bir araya getiren PET/MR, prostat kanseri teşhisi ve tedavisi için önemli bir araçtır. Metastatik lenf nodlarının SUVmaks değerlerinin ADCortalama değerleri ile ters orantılı olduğunu ve her iki parametrenin kombinasyonunun lenf nodu metastazının saptanmasında Ga-68 PSMA PET/MR'ın tanısal doğruluğunu artırabileceğini bulduk.

Anahtar kelimeler: prostat kanseri, lenf nodu metastazı, Ga-68 PSMA, positron emisyon tomografisi

ORCID ID: **A. Kibar** 0000-0003-0073-2343 **M.S. Sager** 0000-0003-2013-5845 **K. Sonmezoglu** 0000-0003-1215-5184
R.L. Uslu-Besli 0000-0003-1868-3957 **H.B. Sayman** 0000-0002-0954-5707

Introduction

According to American Cancer Society, prostate cancer is the second most common cancer among men after skin cancer and also the second most common cause of cancer related mortality among men. Early detection and treatment is crucial. Prostate specific membrane antigen (PSMA) is a type 2 integral membrane protein which is shown to be overexpressed in prostate cancer cells [1, 2]. Expression of PSMA increases with the grade of cellular dysplasia [3]. As the grade of prostate cancer increases PSMA expression also increases [4]. For imaging and therapeutic use, PSMA is radiolabeled with different radionuclides and to date Gallium-68 labeled PSMA (Ga-68 PSMA) is the most commonly used PSMA-targeted radiopharmaceutical for imaging.

Standardized uptake value (SUV) is a measure which shows uptake level in PET scan. Higher SUV values mean higher radiotracer uptake within that lesion. Apparent diffusion coefficient (ADC) is a measure of the diffusion of water molecules within tissue which is calculated for magnetic resonance imaging (MRI) lesions. Ga-68 PSMA positron emission tomography (PET) is a useful tool for the staging and follow-up of the primary disease as it shows increased uptake in PSMA- positive lesions of prostate cancer [5]. The development of integrated positron emission tomography/magnetic resonance imaging (PET/MR) devices enables simultaneous acquisition of PET and MRI, which increases the accuracy of PET imaging in prostatic as well as other soft tissue lesions [6]. Prostate cancer frequently metastasizes to regional lymph nodes and Ga-68 PSMA PET is a highly sensitive and specific imaging modality for the detection of metastatic lymph nodes [7]. Patients with higher Gleason scores show higher radiotracer uptake [8]. Maximum SUV (SUVmax) of primary prostate lesions acquired by Ga-68 PSMA PET have been shown to have positive correlation with Gleason scores [9]. Conversely, ADC values of prostate lesions, acquired from MRI images have been negatively correlated with Gleason scores [10]. Also, an inverse correlation between SUVmax and ADCmean of primary prostate lesions have been recorded and the prognostic importance of both of them for the detection of the status of lymph node metastases has been shown [11]. Similar to prostate lesions, ADC values of metastatic lymph nodes are expected to be lower than those of reactive lymph nodes [12]. In this study, we have aimed to evaluate the ADC values of metastatic and reactive lymph nodes in prostate cancer patients and to assess the relationship between ADC and PSMA SUV values, if any.

Materials and Methods

Study Population

This study was approved by the institutional Clinical Research Ethics Committee of Cerrahpasa Medical Faculty (2019/6927). Our study was conducted between 02/2017, and 04/2018. Twenty patients diagnosed with prostate cancer who underwent Ga-68 PSMA PET/MRI imaging were retrospectively included in our analysis. Mean age of the patients was 68,2±7,4 (range: 58-82 years). All patients had verified prostate biopsy results. Gleason scores of patients are given in **Table 1.** Patients with prostate cancer diagnosis, who underwent PSMA PET imaging, and had more than three metastatic and reactive lymph nodes were included in our study. Prostate cancer patients having less than three metastatic/reactive lymph nodes were not enrolled in the study.

Imaging

Patients were imaged after intravenous injection of mean activity of 6,3±1,73 mCi Ga-68 PSMA HBED-CC. Radiolabeling procedure was performed using a fully automated radiopharmaceutical synthesis device (Eckert & Ziegler Eurotope, Berlin, Germany). All PET/MRI images were acquired using an integrated 3 Tesla- PET/MRI scanner (GE Signa PET/MRI, GE Healthcare, Waukesha, Wisconsin, USA). Patients underwent whole body PET/MRI imaging at an average of 67,16±18,8 minutes after injection. Sequences obtained by PET/MRI consisted of an initial localizer scan, a 3D dual-echo fast spoiled gradient recalled echo liver-accelerated volume acquisition sequence (LAVA-FLEX) for MRI based attenuation correction (MRAC), followed by a high-resolution axial T1-weighted (T1W) 3D LAVA-FLEX sequence, diffusion-weighted imaging (DWI) with b values: 50 and 1000 s/mm2 and corresponding ADC mapping.

Image Analysis

Ga-68 PSMA PET/MRI images of 20 patients were retrospectively reviewed and analyzed using GE AW Volume Share 7 workstation (GE Medical Systems, Buc, France). Three metastatic and three reactive lymph nodes were chosen for each patient according to PSMA PET findings. Lymph nodes which showed markedly increased Ga-68 PSMA uptake compared to background activity were considered as metastatic **(Figure 1)**. Inguinal lymph nodes without significant PSMA uptake or any morphological appearance suspicious for metastasis (including

Table 1. Gleason scores and PSA values of the patients

Gleason score	Number of patients (median PSA values ng/ml)
3+3	1 (628.0)
3+4	4 (42.0; range: 0.2- 81.4)
4+3	5 (13.2; range: 1.1- 21.6)
4+4	3 (22.2; range: 8.5- 84.3)
4+5	3 (119.3; range: 52.1-155.2)
5+4	3 (207.1; range: 58.3- 934.4)
5+5	1 (18.8)

PSA: prostate specific antigen

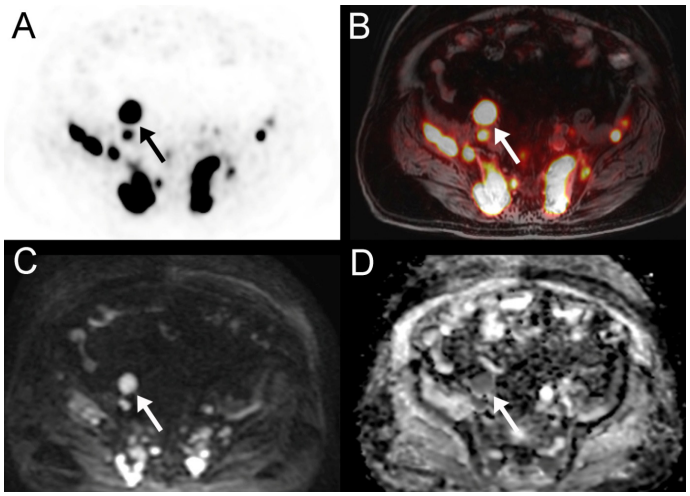


Figure 1. A 79-year-old patient with Gleason score 5+5 prostate cancer. Metastatic common iliac lymph node is shown with arrow (SUVmax 37,5 gr/ml; ADCmean 0,000812 mm^2/s). A: PET image; B: PET/MR fusion; C: DWI (b:1000); D: ADC

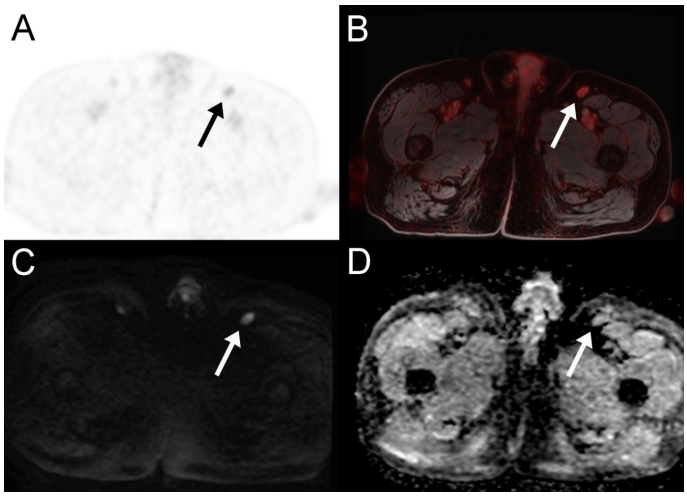


Figure 2. A 53-year-old patient with Gleason score 4+3 prostate cancer. Lower SUVmax and higher ADCmean values for reactive left inguinal lymph node is shown with arrow (SUVmax 2,51 gr/ml; ADCmean 0,00170 mm2/s). A: PET image; B: PET/MR fusion; C: DWI (b:1000); D: ADC

abnormal size, shape and cortical thickness) were regarded as reactive lymph nodes **(Figure 2)**. SUVmax and ADCmean values were calculated for each lymph node separately by drawing a region of interest (ROI) within each lymph node.

Statistical Analysis

SPSS software version 22 (IBM Corp., Armonk, New York, USA) was used for statistical analysis. $P<0.05$ was accepted as the level of statistical significance. Normal distribution of the values in the population was confirmed by both the Kolmogorov-Smirnov test and the histogram curves. Linear regression analysis was performed to determine the relationship between SUVmax and ADCmean values, and Spearman correlation analysis to determine the significance of this relationship. Student T-test was performed to analyze the relationship between ADC values. ROC analysis for ADC values was also made.

Results

A total of 120 lymph nodes in 20 prostate cancer patients with Gleason scores of 3+3 (n=1), 3+4 (n=4), 4+3 (n=5), 4+4 (n=3), 4+5 (n= 3), 5+4 (n=3), and 5+5 (n=1) were assessed **(Table 1)**. SUVmax and ADCmean values of the lymph nodes are given in **Table 2**. SUVmax values of metastatic and reactive lymph nodes were between 5.57-62.53 and 0.20-2.51, respectively. Mean (± SD) SUVmax and SUVmean values for metastatic lymph nodes were 19.17 (±13.60) and 12.63 (±7.78), respectively. Mean (± SD) ADC values for metastatic and reactive lymph nodes were 9.78 (±2.71) and 13.3 (±4.52), respectively **(Figure 3)**.

ADCmean values of metastatic lymph nodes were significantly lower than those of reactive lymph nodes (p=0.0001). Cut- off value for ADC was calculated as 0,001595 (sensitivity: 30%, specificity: 98%). There was a weak negative correlation between SUVmax values and ADCmean values of metastatic lymph nodes (p=0.009, r=-0.3) **(Figure 4a)**. However, there was no significant correlation between SUVmax values and ADCmean values of reactive lymph nodes (p=0.271, r=-0.2) **(Figure 4b)**.

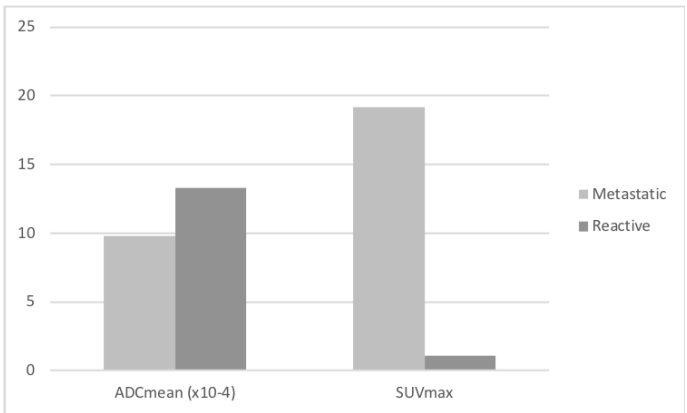


Figure 3. Comparison of ADCmean and SUVmax values of metastatic and reactive lymph nodes. Metastatic lymph nodes have lower ADC-mean values and higher SUVmax values

Discussion

PSMA PET is a relatively new diagnostic imaging tool for the detection of prostate cancer, however its demand for it increases rapidly. It shows higher radiotracer uptake in patients with higher Gleason scores [8], and also higher diagnostic sensitivity and specificity for lymph node metastasis [13]. PSMA PET changes prostate cancer management decisions for many patients [14, 15].

DWI is based upon the random Brownian motion of water molecules within the tissue and gives microstructural information about the tumor tissue. Normal or reactive lymph nodes also show a relatively restricted diffusion due to high cellular density. However, metastatic lymph nodes have higher cellular density, which further restricts diffusion compared to normal or reactive lymph nodes [16]. The resulting signal changes in restricted diffusion in MRI are high-signal intensity on DWI with corresponding reduced apparent diffusion coefficient (ADC) values. In our study we found lower ADC values in metastatic lymph nodes compared to reactive lymph nodes consistent with the current literature data.

Ga-68 PSMA PET targets PSMA, which is a membrane

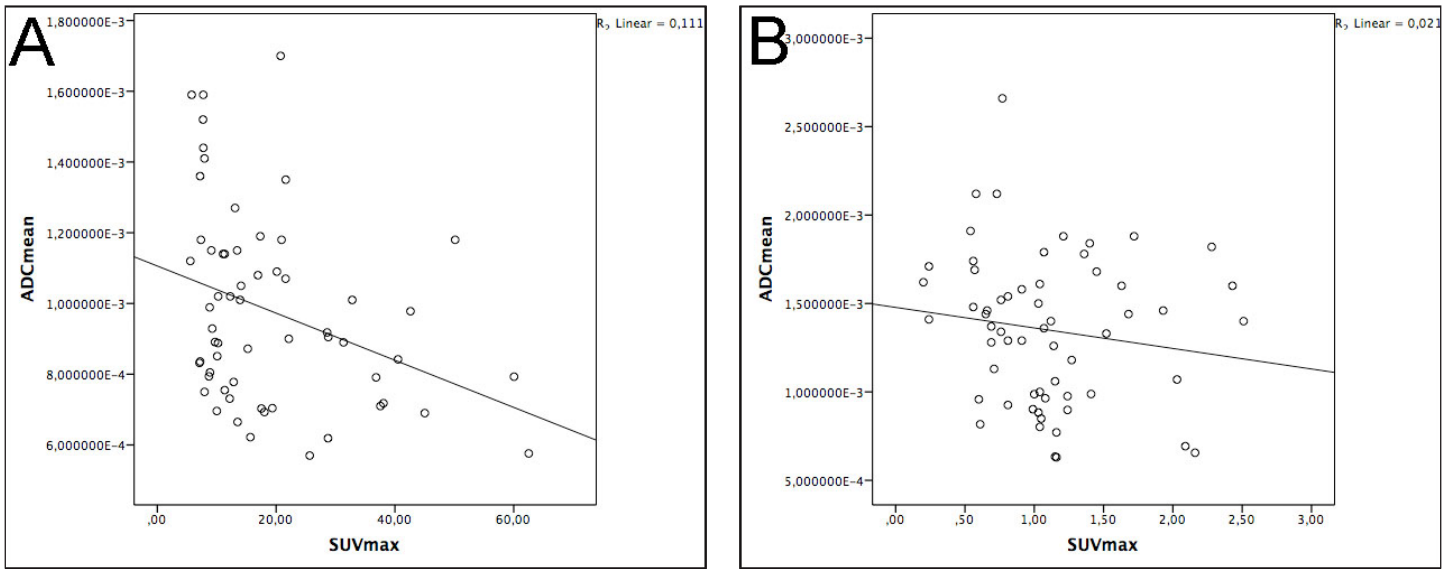


Figure 4. Correlation of ADCmean and SUVmax values. Metastatic lymph nodes have weak inverse correlation (A), whereas reactive lymph nodes do not have significant correlation (B)

Table 2. SUV and ADC values of lymph nodes

	Mean±Standard deviation	Range
Metastatic lymph nodes		
SUVmax (g/ml)	19.17±13.60	5.57-62.53
SUVmean (g/ml)	12.63±7.78	4.17-41.65
ADCmean (x10^{-4}) (mm^2/s)	9.78±2.71	5.70-17.0
Reactive lymph nodes		
SUVmax (g/ml)	1.10±0.53	0.20-2.51
SUVmean (g/ml)	0.79±0.32	0.11-1.49
ADCmean (x10^{-4}) (mm^2/s)	13.30±4.52	1.29-26.60

SUVmax: maximum standardized uptake value; SUVmean: mean standardized uptake value; ADCmean: mean apparent diffusion coefficient

protein expressed 100-1000-fold higher in prostate cancer cells than in normal tissues and provides metabolic information about prostate cancer cells [17]. SUV is a semi-quantitative parameter reflecting PSMA uptake of tissues. PSMA PET was shown to have positive correlation with Gleason scores [18]. Also, ADC values were shown to be inversely correlated with Gleason scores [19]. We found a weak inverse correlation between SUVmax values and ADCmean values in metastatic lymph nodes. Inverse correlation was also reported previously for bone lesions and primary prostate lesions in prostate cancer [20, 21]. Wetter et al found moderately significant inverse correlation between SUVmax and ADC values of metastatic bone lesions of prostate cancer [22]. Also, Uslu-Besli et al found an inverse relationship between SUVmax and ADC values of primary prostate lesions detected by PSMA PET/MRI [11]. Wang et al showed that ADC values had significant negative correlation with Gleason score and SUVmax in primary prostate lesions [23]. Wu et al found that minimum ADC values inversely correlated with the Gleason score in prostate lesions [24].

Most scientific articles compared SUVmax values obtained by PET/CT with MRI ADC values, however in our study we used hybrid PET/MR machine for determining SUVmax and ADC values. Contrary to sequential PET/CT imaging, hybrid PET/MR involves simultaneous acquisition of PET and MRI images which enables excellent PET and MRI fusion, reducing the fusion-related artifacts. Also, as MRI has better soft-tissue resolution compared to CT, detection and characterization of lymph nodes is better with PET/MR compared to PET/CT.

The main limitation of our study is its small sample size. We have evaluated 120 lymph nodes in 20 patients. Lack of histopathological diagnosis of lymph nodes is another limitation of our study.

Conclusion

PET/MR, which combines both advantages of PET and MRI, is an important tool for prostate cancer diagnosis and management. ADCmean values of metastatic lymph nodes were found to be significantly lower than those of reactive lymph nodes. Also, SUVmax values and ADCmean values of metastatic lymph nodes were found to be inversely correlated. Combination of both SUVmax values and ADCmean values may reinforce each other

and increase the diagnostic accuracy of Ga-68 PSMA PET/MR in the detection of lymph node metastases.

Ethics Committee Approval: This study was approved by Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (Approval number, and registration number: 01/14/2019-6927).
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.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – F.A., A.K., R.L.U.B.; Design – F.A., A.K., R.L.U.B.; Supervision – F.A., K.S.; Resources – M.S.S., H.B.S.; Materials – M.S.S., H.B.S.; Data Collection and/or Processing – R.L.U.B., M.S.S., H.B.S.; Analysis and/or Interpretation – F.A., R.L.U.B., K.S.; Literature Search – M.S.S., H.B.S.; Writing Manuscript – F.A., A.K., R.L.U.B.; Critical Review – F.A., K.S.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Chang SS. Overview of prostate-specific membrane antigen. Rev Urol 2004;6:13-8. https://pubmed.ncbi.nlm.nih.gov/16985927/.

[2] Wester HJ, Schottelius M. PSMA-Targeted radiopharmaceuticals for imaging and therapy. Semin Nucl Med 2019;49:302-12. https://doi.org/10.1053/j.semnuclmed.2019.02.008.

[3] Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer 1998;82:2256-61. https://doi.org/10.1002/(sici)1097-0142(19980601)82:11<2256::aid-cncr22>3.0.co;2-s.

[4] Bravaccini S, Puccetti M, Bocchini M, Ravaioli S, Celli M, Scarpi E, et al. PSMA expression: a potential ally for the pathologist in prostate cancer diagnosis. Sci Rep 2018;8:4254. https://doi.org/10.1038/s41598-018-22594-1.

[5] Perera M, Papa N, Christidis D, Wetherell D, Hofman M S, Murphy D G, et al. Sensitivity, specificity, and predictors of positive Ga-68-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70:926-37. https://doi.org/10.1016/j.eururo.2016.06.021.

[6] Eiber, M, Weirich, G, Holzapfel, K., Souvatzoglou, M., Haller, B, Rauscher I, et al. Simultaneous 68Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. Euro Urol 2016;70:829-36. https://doi.org/10.1016/j.eururo.2015.12.053.

[7] Bernstein AN, Shoag JE, Golan R, Halpern JA, Schaeffer EM, Hsu, WC. et al. Contemporary Incidence and Outcomes of Prostate Cancer Lymph Node Metastases. J Urol 2018;199:1510-7. https://doi.org/10.1016/j.juro.2017.12.048.

[8] Chen M, Qiu X, Zhang Q, Zhang C, Zhou Y, Zhao X, et al. PSMA uptake on [68Ga]-PSMA-11-PET/CT positively corrects with prostate cancer aggressiveness. Q J Nucl Med Mol Imaging 2019;Suppl. https://doi.org/10.23736/S1824-4785.19.03172-8.

[9] Uprimny C, Kroiss AS, Decristoforo C, Fritz J, von Guggenberg E, Kendler D, et al. 68Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. Eur J Nucl Med Mol Imaging 2017;44;941-9. https://doi.org/10.1007/s00259-017-3631-6.

[10] Surov A, Meyer HJ, Wienke A. Correlations between apparent diffusion coefficient and Gleason score in prostate cancer: A Systematic Review. Eur Urol Oncol 2020;3:489-97. https://doi.org/10.1016/j.euo.2018.12.006.

[11] Uslu-Beşli L, Bakır B, Asa S, Güner E, Demirdağ Ç, Şahin OE, et al. Correlation of SUVmax and apparent diffusion coefficient values detected by Ga-68 PSMA PET/MRI in primary prostate lesions and their significance in lymph node metastasis: Preliminary results of an on-going study. Mol Imaging Radionucl Ther. 2019;28:104-11. https://doi.org/10.4274/mirt.galenos.2019.63825.

[12] Vag T, Heck MM, Beer AJ, Souvatzoglou M, Weirich G, Holzapfel K, et al. Preoperative lymph node staging in patients with primary prostate cancer: comparison and correlation of quantitative imaging parameters in diffusion-weighted imaging and 11C-choline PET/CT. Eur Radiol 2014;24:1821-6. https://doi.org/10.1007/s00330-014-3240-8.

[13] Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic efficacy of (68) Gallium-PSMA positron emission tomography compared to conventional 'maging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol 2016;195:1436-43. https://doi.org/10.1016/j.juro.2015.12.025.

[14] Hope TA, Aggarwal R, Chee B, Tao D, Greene KL, Cooperberg MR, et al. Impact of 68Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. J Nucl Med 2017;58:1956-61. https://doi.org/10.2967/jnumed.117.192476.

[15] Han S, Woo S, Kim YJ, Suh CH. Impact of 68Ga-PSMA PET on the Management of patients with prostate cancer: A Systematic Review and Meta-analysis. Eur Urol 2018;74:179-90. https://doi.org/10.1016/j.eururo.2018.03.030.

[16] Abdel Razek AAK, Soliman NY, Elkhamary S, Alsharaway MK, Tawfik A. Role of diffusion-weighted MR imaging in cervical lymphadenopathy. Euro Radiol 2006;16:1468-77. https://doi.org/10.1007/s00330-005-0133-x.

[17] Afshar-Oromieh A, Babich JW, Kratochwil C, Giesel FL, Eisenhut M, Kopka K, et al. The Rise of PSMA Ligands for Diagnosis and Therapy of Prostate Cancer. J Nucl Med 2016;57:79S-89S. https://doi.org/10.2967/jnumed.115.170720.

[18] Bravaccini S, Puccetti M, Bocchini M, Ravaioli S, Celli M, Scarpi E, et al. PSMA expression: a potential ally for the pathologist in prostate cancer diagnosis. Sci Rep 2018;8:4254. https://doi.org/10.1038/s41598-018-22594-1.

[19] Park SY, Kim CK, Park BK, Lee HM, Lee KS. Prediction of biochemical recurrence following radical prostatectomy in men with prostate cancer by diffusion-weighted magnetic resonance imaging: initial results. Eur Radiol 2011;21:1111-8. https://doi.org/10.1007/s00330-010-1999-9.

[20] Sokmen BK, Sokmen D, Ucar N, Ozkurt H, Simsek A. The correlation between biological activity and diffusion-weighted MR imaging and ADC value in cases with prostate cancer. Arch Ital Urol Androl 2017;89:277-81. https://doi.org/10.4081/aiua.2017.4.277.

[21] Jena A, Taneja R, Taneja S, Singh A, Kumar V, Agarwal A, et al. Improving diagnosis of primary prostate cancer with combined 68Ga-Prostate-Specific Membrane Antigen-HBED-CC simultaneous PET and multiparametric MRI and clinical parameters. AJR Am J Roentgenol 2018;211:1246-53. https://doi.org/10.2214/AJR.18.19585.

[22] Wetter A, Lipponer C, Nensa F, Heusch P, Rübben H, Schlosser TW, et al. Quantitative evaluation of bone metastases from prostate cancer with simultaneous [18F] choline PET/MRI: combined SUV and ADC analysis. Ann Nucl Med 2014;28:405-10. https://doi.org/10.1007/s12149-014-0825-x.

[23] Wang L, Yu F, Yang L, Zang S, Xue H, Yin X, et al. 68Ga-PSMA-11 PET/CT combining ADC value of MRI in the diagnosis of naive prostate cancer: Perspective of radiologist. Medicine (Baltimore) 2020;99:e20755. https://doi.org/10.1097/MD.0000000000020755.

[24] Wu X, Reinikainen P, Vanhanen A, Kapanen M, Vierikko T, Ryymin P, et al. Correlation between apparent diffusion coefficient value on diffusion-weighted MR imaging and Gleason score in prostate cancer. Diagn Interv Imaging 2017;98:63-71. https://doi.org/10.1016/j.diii.2016.08.009.

Original Article – General Urology

Grand J Urol 2022;2(1):21-5
DOI: 10.5505/GJU.2022.36035

How did The COVID-19 Pandemic Affect Urology Publications?

COVID-19 Pandemisi Üroloji Yayınlarını Nasıl Etkiledi?

Tumay Ipekci[1], Ahmet Asfuroglu[2], Ali Yildiz[3], Muhammet Murat Dincer[4], Emrah Yuruk[5], Murat Bozlu[6], Ates Kadioglu[7]

[1]Department of Urology, Bahcesehir University Faculty of Medicine, VM Medical Park Maltepe Hospital, Istanbul, Turkey
[2]Department of Urology, Etimesgut State Hospital, Ankara, Turkey
[3]Department of Urology, Okan University Faculty of Medicine, Istanbul, Turkey
[4]Department of Urology, University of Health Sciences, Bagcilar Training and Research Hospital, Istanbul, Turkey
[5]Department of Urology, BHT Clinic Istanbul Tema Hospital, Istanbul, Turkey
[6]Department of Urology, Mersin University Faculty of Medicine, Mersin, Turkey
[7]Department of Urology, Istanbul University Faculty of Medicine, Istanbul, Turkey

Cite as: Ipekci T, Asfuroglu A, Yildiz A, Dincer MM, Yuruk E, Bozlu M, Kadioglu A. How did the COVID-19 pandemic affect urology publications? Grand J Urol 2022;2(1):21-5.

Submission date: 29 September 2021 **Acceptance date:** 13 December 2021 **Online First:** 25 December 2021 **Publication date:** 20 January 2022

Corresponding Author: Ahmet Asfuroglu / Etimesgut State Hospital, Department of Urology, Ankara, Turkey / ahmetasfur@hotmail.com / ORCID ID: 0000-0002-4310-7444

Abstract

Objective: To evaluate the effect of the pandemic on the publications related to urology.
Materials and Methods: All publications about urology in the PubMed database between 2016 and 2020 were reviewed. The number and the rate of change in the number of these publications issued between the years 2016-2019, and in 2020 were recorded. The publications about urology and COVID-19 in the pandemic period were identified, their publication rates among them were examined.
Results: There was a reduction of 24.33% in the rates of publications on urology during the pandemic period compared to the time interval between the years 2016, and 2019, but without any statistically significant difference (p=0.122). A statistically significant difference was found only in the number of publications related to urological surgery between 2016-2019 and 2020 (p=0.045), but without any statistically significant difference in the number of publications on other subdiciplines of urology (p>0.05). The ratio of publications on COVID-19 and urology to all publications on COVID-19 was 1.33 percent. The ratio of publications on COVID-19 and urology to all publications on urology in 2020 was found to be 1.98 percent.
Conclusion: The COVID-19 pandemic did not make a significant difference in the number of publications on urology. Although disasters such as pandemics may not affect the number of publications, they can change the types of publications to which scientists are directed to.

Keywords: COVID-19, pandemic, publication, article, urology

Öz

Amaç: COVID-19 pandemisinin üroloji ile ilgili yayınlara etkisinin değerlendirilmesi amaçlandı.
Gereçler ve Yöntemler: 2016-2020 yılları arasında PubMed veri tabanında üroloji ile ilgili tüm yayınlar incelendi. 2016-2019 ve 2020 yılları arasındaki yayın sayıları ve sayılarındaki değişim oranı kaydedildi. Pandemi döneminde üroloji ve COVID-19 ile ilgili yayınlar tespit edildi, tüm yayınlarla oranı incelendi.
Bulgular: Pandemi döneminde 2016-2019 yılına göre üroloji ile ilgili yayınlarda %24,33 azalma oldu ancak istatistiksel olarak anlamlı fark yoktu (p=0,122). Sadece ürolojik cerrahi ile ilgili yayın sayısında 2016-2019 ve 2020 yılları arasında istatistiksel olarak anlamlı fark bulundu (p=0.045), ancak üroloji ile ilgili diğer başlıklara sahip yayın sayısında istatistiksel olarak anlamlı bir fark yoktu (p>0,05). COVID-19 ve üroloji ile ilgili yayınların toplam COVID-19 yayınlarına oranı %1,33 oldu. 2020 yılında COVID-19 ve üroloji ile ilgili yayınların toplam üroloji yayınlarına oranı %1,98 olarak bulundu.
Sonuç: COVID-19 pandemisi üroloji ile ilgili yayın sayısında anlamlı bir fark yaratmadı. Pandemi gibi afetler yayın sayısını etkilemese de bilim insanlarının yöneldiği yayın türlerini değiştirebilir.

Anahtar kelimeler: COVID-19, pandemi, yayın, makale, üroloji

ORCID ID: **T. Ipekci** 0000-0002-2755-0526 **M.M. Dincer** 0000-0001-7110-4155 **M. Bozlu** 0000-0002-8624-0149
A. Yildiz 0000-0003-0293-9989 **E. Yuruk** 0000-0002-2343-8828 **A. Kadioglu** 0000-0002-5767-4837

Introduction

The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it has a worldwide impact on healthcare systems. During the pandemic period, there has been a significant alteration in the health care procedures in many medical establishments [1]. All routine non-oncological and certain oncological surgical procedures were canceled, and some patient interviews were conducted by the telephone or as video consultations [2,3]. Besides, full-scale restrictions were implemented by the governments of many countries to put an end to the pandemic [4]. In addition to the risk of healthcare workers getting the disease, there is also a risk of developing adverse psychological consequences such as anxiety, burnout, depression, fear of infection, a sense of incompatibility, and post-traumatic stress disorder [5].

The pandemic also negatively affected the publication process from the preparation and submission of the studies to their acceptance. Due to the pressure to publish highly acclaimed information on COVID-19, concerns about the quality of the data and peer reviews by editors were raised. The urgency of publicising available data on the pandemic seems to justify the basic limitations of the studies, such as their small sample size, lack of randomization or blinding, and invalidated results [6].

Although the negative effect of the pandemic on the process and quality of the publications is taken into consideration, to the best of our knowledge, its effect on the publications in any subspecialty of medicine has not been specifically investigated. Therefore, we aimed to evaluate the impact of the pandemic on urology publications.

Materials and Methods

This retrospective study reviewed all publications on urology included in the PubMed database between 2016 and 2020. All publications related to COVID-19 released between December 31, 2019 where the first case was declared by the World Health Organization and January 1, 2021 were evaluated.

The publications were reviewed and grouped according to the mostly searched inclusive titles as urology, endourology, urooncology, pediatric urology, andrology, urogynecology, robotic urology, neuro-urology and urinary incontinence, kidney transplantation, urology, and infectious diseases, prostatic diseases, bladder diseases, urinary stone disease, urologic surgery, and urological emergency. The number of publications retrieved was recorded. The number of publications released between the years 2016-2019 and in the year 2020 was compared and the rate of change in their numbers was recorded. The publications were compared according to the titles sought between 2016- 2019 and in the year 2020.

All publications on urology were grouped and quantitatively evaluated in terms of clinical trials, meta-analyses, randomized controlled trials, review articles, and systematic reviews. Letters to the editor, book chapters, oral presentations, and moderated posters were excluded in this study. The number of all types of publications released between 2016- 2019 and in 2020 was compared and the rate of change in their numbers was recorded.

Besides, the publications on urology and COVID-19 in the pandemic period (2020) were identified, grouped using the same titles and types, and their numbers were recorded. The ratio of all publications and all individual types of publications on COVID-19 and urology, to all, and individual types of publications on COVID-19 was noted. The ratio of all and individual types of publications on COVID-19 and urology to all, and individual types of publications on urology in 2020 was also noted. The study was approved by the Ethics Committee of University of Health Sciences Dr. Sadi Konuk Training and Research Hospital (Approval number: 2021/577).

Statistical Analysis

In the statistical analysis of this study, Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 27.0 program was used. For descriptive statistics, categorical variables were expressed as absolute numbers and percentages, and continuous variables as means ± standard deviations. The percentage difference between two dependent variables was calculated. For comparisons between two dependent variables, the Wilcoxon test was used for non-normally distributed data. A value of $p< 0.05$ was considered statistically significant.

Results

In the current study, it was found that between 2016 and 2019 and in 2020 a total of 45,018, and 8,516 publications related to urology were published, respectively. During the pandemic period in the year 2020, the number of urology-related publications decreased, albeit not statistically significantly by 24.33% compared to the average of the previous four years ($p=0.122$).

In the detailed evaluation, the total number of publications on subspecialties of urology released between 2016- 2019 is shown in **Table 1**.

Considering the titles of the publications, there was a statistically significant difference only in the number of publications related to urological surgery between 2016- 2019 and in 2020 ($p=0.045$). Any statistically significant difference in the number of publications related to other subspecialties of urology was not noted ($p>0.05$). The average number of publications related to urology between 2016- 2019 and during the pandemic period is shown in **Table 2**.

Between 2016, and 2019, 7,729 clinical trials, 3,740 meta-analyses, 4988 randomized controlled trials, 23,703 review articles, and 4,858 systematic reviews were published. When the 2016-2019 and 2020 data were compared, it was observed that the highest reduction among the types of publications related to urology was in clinical trials, the lowest reduction was in reviews, as well as an increase in systematic reviews. The number, and rate of change in publication types related to urology are shown in **Table 3**.

The andrology publications increased by 30.22% in 2020 compared to the average number of publications particularly including review articles and systematic reviews released between 2016, and 2019. Especially in 2020, 70 articles were published on Peyronie's disease, with an important increase of 105.9% among andrology publications. Compared to the average number of publications released between 2016, and 2019, an increase of

Table 1. Total number of publications on urology subbranches between 2016-2019

Urology subbranches	Total number (n)
Endourology	114
Urooncology	294
Pediatric urology	1103
Andrology	1284
Urogynecology	445
Robotic urology	863
Neuro-urology and urinary incontinence	79
Kidney transplantation	4836
Urology and infectious diseases	185
Prostate diseases	7668
Bladder diseases	3694
Urinary stone diseases	433
Urologic surgery	7875
Urologic emergency	1217

26.32% in endourology, 2.63% in pediatric urology, 1.51% in robotic urology, 23.24% in urological infections, and 29.17% in urological emergencies were observed in 2020.

The ratio of publications on COVID-19 and urology to total publications on COVID-19 was found to be 1.33 percent. This ratio was 0.26% in clinical trials, 1.21% in meta-analysis, 1.36% in review articles, and 1.55% in systematic reviews. The ratio of publications on COVID-19 and urology to total number of publications on urology in 2020 was found to be 1.98 percent. This ratio was 0.14% in clinical trials, 1.45% in meta-analysis, 2.66% in review articles, and 1.45% in systematic reviews. During the pandemic period, randomized clinical trials on urology were not conducted.

Discussion

The COVID-19 pandemic did not make a significant difference in the number of publications on urology. It was observed that the number of systematic reviews increased, but the number of clinical trials, meta-analyses, randomized controlled trials, and reviews decreased. It has been predicted that scientists are still continuing their scientific studies during the pandemic.

In the study published by Palayew et al. [7], 93% of the publications on COVID-19 released in the first 12 weeks were accepted by the relevant journals within the first 30 days. It was observed that the acceptance rates of publications on COVID-19 and the pandemic increased, and the time to acceptance of the publications shortened due to the urgent need for medical information concerning the pandemic. The number of peer-reviewed publications decreased with the onset of the pandemic and the number of preprint publications increased significantly due to the pressure created by the urgent need for medical information related to the pandemic [8]. One reason for this may be that large-scale randomized controlled trials may not be feasible or ethical in critical and emergency situations [5]. However, these preprint publications could not reach the quality of peer-reviewed publications [8]. In our study, the PubMed database research was conducted using peer-reviewed publications that were considered to be of high quality, not released as a result of the pressure caused by urgent need for relevant medical information. A non-significant decrease in the number of relevant publications was observed which revealed that the pandemic period had not significantly affected the number of publications.

In a study by Myers et al. [9] on the effect of the pandemic on the working time of the scientists, it was found that before the pandemic the weekly average working time of the scientists was 61 hours, and it decreased to 54 hours after the pandemic with an average decrease of 11% in all scientific fields. Working hours of a scientist working in the field of health sciences also decreased by 12 percent [9]. In the guideline prepared by the European Association of Urology Guidelines Office Rapid Reaction Group, surgical priorities were classified as a low priority, intermediate priority, high priority, and emergency in the pandemic, and a roadmap was drawn for situations related to the decrease in the number of patients receiving the treatment in clinics. However, elective surgery plans were noticeably interrupted due to the changes in the duties of healthcare professionals, work stoppages, and loss of workforce due to COVID-19 infection [10]. The decrease in publications on neuro-urology and urinary incontinence should be evaluated within this scope. Postponing elective surgical procedures to reduce exposure to COVID-19 may have led to a reduction in the number of patients admitted to clinics [2,10]. The decrease in the number of patients may also have led to a decrease in publications [2]. Considering the effect of working time spent on the preparation and publishing of the manuscripts, the decrease in the number of publications by scientists can be associated with the decrease both in the weekly working hours and in the number of patients evaluated in outpatient clinics. It can be predicted that prospective studies may have been prematurely terminated or canceled due to the decrease in the number of patients. However, as can be seen based on the results of this study, during the pandemic period there may be an increase in the number of the review articles and systematic reviews published, because they do not require patient follow-up with potentially reduced patient burden and the prevalent tendency to release such publications.

The limitations of this study can be indicated as errors that may arise from search engine filtering and the fact that the data in the PubMed database has not been compared with the data of other reputable scientific databases such as Web of Science and Scopus.

Table 2. The publications related to urology in both 2016-2019 and 2020

Topics	2016-2019		2020		Rate of change (%)	p
	Average number (n)	Mean of subtypes (mean±SD)	Number (n)	Mean of subtypes (mean±SD)		
Urology	3,732	746.40±682.64	3,623	724.60±845.71	-2.92	0.883
Endourology	28.5	5.70±7.18	36	7.20±10.01	26.32	0.333
Urooncology	73.5	14.70±14.99	69	13.80±18.38	-6.12	0.778
Pediatric urology	275.8	55.15±61.82	283	56.60±74.73	2.63	0.888
Andrology	321	64.20±50.00	418	83.60±103.52	30.22	0.497
Urogynecology	111.3	22.25±13.81	81	16.20±18.21	-27.19	0.366
Robotic urology	215.8	43.15±42.23	219	43.80±55.45	1.51	0.940
Neuro-urology and urinary incontinence	19.8	3.95±4.53	3	0.60±1.34	-85	0.080
Kidney transplantation	1,209	241.80±276.85	869	173.80±249.95	-28.12	0.100
Urology and infectious diseases	46.3	9.25±8.60	57	11.40±13.65	23.24	0.438
Prostate diseases	1917	383.40±328.69	860	172.00±152.65	-55.14	0.060
Bladder diseases	923.5	184.70±178.86	472	94.40±97.63	-48.89	0.071
Urinary stone diseases	108.3	21.65±30.34	80	16.00±20.26	-26.10	0.281
Urologic surgery	1,968.8	393.75±313.88	884	176.80±154.86	-55.10	**0.045**
Urologic emergency	304.3	60.85±83.69	393	78.60±127.30	29.17	0.423
COVID-19 and urology	0	0.00±0.00	169	33.80±58.49	100	0.266
TOTAL	11,254.5	2250.90±2086.83	8,516	1,703.20±1,984.94	-24.33	0.122

Table 3. Number and rate of change of publication types related to urology

	2016-2019 Average number (n)	2020 Number (n)	Rate of change (%)
Clinical trials	1,932.3	720	-62.74
Meta-analysis	935	484	-48.24
Randomized controlled trials	1,247	492	-60.55
Reviews	5,925.8	5,144	-13.19
Systematic reviews	1,214.5	1,676	38.00

Conclusion

In conclusion, disasters such as pandemics affect the functioning of every field, especially healthcare field, COVID 19 pandemic did not significantly affect the number of publications on urology but can change the types of publications to which scientists are especially interested in.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital (Approval date, and registration number: 20.12.2021/577).
Informed Consent: This study does not require informed consent.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – T.I., A.K.; Design – T.I., A.A., A.Y., A.K.; Supervision – A.K., M.M.D., M.B.; Resources – T.I., A.A., A.Y., A.K.; Materials – A.A.; Data Collection and/or Processing – T.I., A.A., A.Y., A.K.; Analysis and/or Interpretation – T.I., A.A., A.Y., M.M.D., M.B., E.Y., A.K.; Literature Search – T.I., A.A., A.Y., E.Y, A.K.; Writing Manuscript – T.I., A.A., A.Y., M.M.D., E.Y, A.K., M.B.; Critical Review – T.I., M.M.D., E.Y., A.K., M.B.
Conflict of Interest: All authors have no conflict of interest.
Financial Disclosure: This study received no financial support.

References

[1] Carenzo L, Costantini E, Greco M, Barra FL, Rendiniello V, Mainetti M, et al. Hospital surge capacity in a tertiary emergency referral centre during the COVID-19 outbreak in Italy. Anaesthesia 2020;75:928-34. https://doi.org/10.1111/anae.15072.

[2] Spinelli A, Pellino G. COVID-19 pandemic: perspectives on an unfolding crisis. Br J Surg 2020;107:785-7. https://doi.org/10.1002/bjs.11627.

[3] Ho HC, Hughes T, Bozlu M, Kadioglu A, Somani BK. What do urologists need to know: Diagnosis, treatment, and follow-up during COVID-19 pandemic. Turk J Urol 2020;46:169-77. https://doi.org/10.5152/tud.2020.20119.

[4] Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. J Travel Med 2020;27:taaa020. https://doi.org/10.1093/jtm/taaa020.

[5] Dubey S, Biswas P, Ghosh R, Chatterjee S, Dubey MJ, Chatterjee S, et al. Psychosocial impact of COVID-19. Diabetes Metab Syndr 2020;14:779-88. https://doi.org/10.1016/j.dsx.2020.05.035.

[6] London AJ, Kimmelman J. Against pandemic research exceptionalism. Science 2020;368:476-7. https://doi.org/10.1126/science.abc1731.

[7] Palayew A, Norgaard O, Safreed-Harmon K, Andersen TH, Rasmussen LN, Lazarus JV. Pandemic publishing poses a new COVID-19 challenge. Nat Hum Behav 2020;4:666-9. https://doi.org/10.1038/s41562-020-0911-0.

[8] Smart P. Publishing during pandemic: innovation, collaboration, and change. Learn Publ 2020;33:194-7. https://doi.org/10.1002/leap.1314.

[9] Myers KR, Tham WY, Yin Y, Cohodes N, Thursby JG, Thursby MC, et al. Unequal effects of the COVID-19 pandemic on scientists. Nat Hum Behav 2020;4:880-3. https://doi.org/10.1038/s41562-020-0921-y.

[10] Ribal MJ, Cornford P, Briganti A, Knoll T, Gravas S, Babjuk M, et al. European Association of Urology Guidelines Office Rapid Reaction Group: An Organisation-wide Collaborative Effort to Adapt the European Association of Urology Guidelines Recommendations to the Coronavirus Disease 2019 Era. Eur Urol 2020;78:21-8. https://doi.org/10.1016/j.eururo.2020.04.056.

Original Article – General Urology

Grand J Urol 2022;2(1):26-32
DOI: 10.5505/GJU.2022.02886

How did The COVID-19 Pandemic Affect Urology Outpatient Clinic Applications?

COVID-19 Pandemisi Üroloji Poliklinik Başvurularını Nasıl Etkiledi?

Ahmet Emre Cinislioglu[1], Nazan Cinislioglu[2], Saban Oguz Demirdogen[1], Fatih Kursat Yilmazel[1], Sibel Guclu Utlu[3], Ibrahim Karabulut[1], Senol Adanur[4], Ozkan Polat[4]

[1]Department of Urology, University of Health Sciences, Regional Training and Research Hospital, Erzurum, Turkey
[2]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Regional Training and Research Hospital, Erzurum, Turkey
[3]Department of Emergency Medicine, University of Health Sciences, Regional Training and Research Hospital, Erzurum, Turkey
[4]Department of Urology, Ataturk University Faculty of Medicine, Erzurum, Turkey

Cite as: Cinislioglu AE, Cinislioglu N, Demirdogen SO, Yilmazel FK, Guclu Utlu S, Karabulut I, Adanur S, Polat O. How did the COVID-19 pandemic affect urology outpatient clinic applications? Grand J Urol 2022;2(1):26-32.

Submission date: 24 October 2021 **Acceptance date:** 08 January 2022 **Online First:** 12 January 2022 **Publication date:** 20 January 2022

Corresponding Author: Ahmet Emre Cinislioglu / University of Health Sciences, Regional Training and Research Hospital, Department of Urology, Erzurum, Turkey / emrecinisli@hotmail.com / ORCID ID: 0000-0002-1037-815X

Abstract

Objective: The Coronavirus Disease-2019 (COVID-19) is particularly more common and deadly among older men who also constitute a significant portion of urology patients. In this study, we aimed to evaluate the change in the diagnostic spectrum in urology outpatient applications after the declaration of pandemic compared to the pre- pandemic period.
Materials and Methods: All patients were enrolled between February 12 and May 6, 2020. Demographic, and clinical data of the patients were analyzed pertaining to the period of 4 weeks before, and the first, and second 4 weeks after declaration of the pandemic. Data obtained from the database such as age, gender, diagnoses were anonymized. Recurrent applications with the same diagnosis within ten days after the first presentation were excluded from the analysis.
Results: Compared to the pre-pandemic period a significant decrease in the number of patients applied to the urology outpatient clinics after declaration of the pandemic, and in the frequency of diagnoses of prostate diseases, and urine transport, storage and emptying disorders and a significant increase in the frequency of diagnoses of urinary system stone disease, benign or malignant bladder diseases, upper urinary system tumors, and sexual dysfunction were observed after declaration of the pandemic.
Conclusion: The risk perception of COVID-19 disease may cause changes in the diagnostic distribution of patients applied to the urology outpatient clinics. During periods of outbreak, the health system must be redesigned by focusing on outpatients.

Keywords: COVID-19, outpatient, urological diseases, diagnostic distribution, epidemiology

Öz

Amaç: Tüm dünyayı hızla etkisi altına alan Coronavirüs Hastalığı-2019 (COVID-19), özellikle üroloji hastalarının önemli bir bölümünün içinde yer aldığı yaşlı erkeklerde daha sık görülen ölümcül bir hastalıktır. Bu çalışmada, pandemi ilanından sonra üroloji poliklinik başvurularının tanı spektrumundaki değişimi pandemi öncesine göre değerlendirmeyi amaçladık.
Gereçler ve Yöntemler: 12 Şubat ile 6 Mayıs 2020 tarihleri arasında kayıt yaptıran tüm hastalar, pandemi ilanı öncesi 4 hafta ve sonrası 8 hafta olmak üzere 4 haftadan oluşan 3 bölümde (pandemi ilanı öncesi, sonrası ilk ve ikinci 4 hafta) analiz edildi. Veri tabanından elde edilen yaş, cinsiyet, tanı gibi veriler anonim hale getirildi. İlk başvurudan sonraki on gün içinde aynı tanı ile tekrarlayan başvurular dışlandı.
Bulgular: Pandemi ilanı sonrası üroloji polikliniklerine başvuran hasta sayısında pandemi öncesine göre anlamlı bir azalma izlendi. Pandemi ilanı sonrası, prostat hastalıkları ve idrar taşıma, depolama ve boşaltma bozuklukları ile ilişkili hastalıkların tanı sıklığında pandemi öncesine göre anlamlı azalma ve üriner sistem taş hastalığı, benign veya malign mesane hastalıkları, üst üriner sistem tümörleri ve cinsel işlev bozukluğu tanı sıklığında pandemi öncesine göre anlamlı bir artış saptandı.
Sonuç: COVID-19 risk algısı, üroloji polikliniğine başvuran hastaların tanısal dağılımında değişikliklere neden olabilir. Pandemi dönemlerinde sağlık sistemi ayaktan hastalara odaklanılarak yeniden tasarlanmalıdır.

Anahtar kelimeler: COVID-19, poliklinik, ürolojik hastalıklar, tanısal dağılım, epidemiyoloji

ORCID ID: **N. Cinislioglu** 0000-0002-6865-5551 **S. Guclu Utlu** 0000-0001-8635-1562 **O. Polat** 0000-0001-9961-662X
S.O. Demirdogen 0000-0002-8697-8995 **I. Karabulut** 0000-0001-6766-0191
F.K. Yilmazel 0000-0001-8744-5317 **S. Adanur** 0000-0002-2508-199X

Introduction

Cases of pneumonia caused by a newly identified virus began to be reported in the Wuhan Province of China on 31 December 2019 [1]. The clinical spectrum of the disease has ranged from asymptomatic infection to severe pneumonia. The disease has been defined as coronavirus disease-2019 (COVID-19) on 20 February 2020 by the World Health Organization (WHO) [2].

Although COVID-19 affects both genders and all age groups, it is particularly more common and more severe in the elderly, in men and in those with comorbidities [3-5]. In a China-based study involving 55924 COVID-19 patients, most patients were between the ages of 30-69 (77.8%), and only 2.4% of the patients were 18 years or younger, and the average age was reported as 51 years [6]. The male/female ratio of confirmed cases 1.06:1.00 in China [7]. On the other hand, the male population had a higher incidence rate than the female population in South Korea and Iceland [8,9]. Furthermore, men had experienced second incident of Covid-19 disease twice more frequently than women [10].

Initially emerging in China, COVID-19 has spread to many countries around the world. In Turkey, the first cases were recorded on 11 March 2020 on the date the WHO declared the disease as a pandemic [11]. After the first official cases, the government has started to implement gradually several social isolation measures to prevent regional spread. The curfew has been the first step of these measures to ensure social isolation. As another precaution, face-to-face education has been terminated in schools, and a distance education protocol was implemented. Venues such as worship areas, shopping centers, cinemas, etc., where people congregate have been closed indefinitely. While land, air and sea transportations through all borders of the country have been suspended, travels within the country were also limited. In the last week of March, a full-time curfew has been imposed on individuals under 20 and over 65 years of age. To limit social life in major cities of the country, a curfew has been declared on weekends. All over the country, citizens have been called to 'stay at home' via visual and social media. Despite all these measures, according to the website Worldometer, which provides real-time statistics from all over the world, as of 12 October 2020, there were more than 5,306,690 verified cases of COVID-19 patients in Turkey, and 48,428 of these patients had lost their lives [12].

In order to prevent the spread of the COVID-19, according to sanctions implemented by the government, the number of medical services provided in outpatient clinics of hospitals and elective surgical procedures were restricted until the pandemic was brought under control [13]. This approach may have affected the applications to the urology outpatient clinics, especially for elderly and male patients in the high-risk group. In this study, we aimed to investigate the effects of COVID-19 pandemic on the number of patient presentations and the distribution of diagnoses at the outpatient clinics of urology.

Materials and Methods

Study Design

The study was planned as a single-center cross-sectional retrospective study. Approval was obtained from the local ethics committee (2021/17-254). Outpatients who had applied to the urology outpatient clinics between February 2020 and May 2020 were included in the study. Demographic, and clinical data of the patients were analyzed pertaining to the period of 4 weeks before, and the first, and second 4 weeks after declaration of the pandemic. We found it appropriate to evaluate the first 4th weeks after declaration of the pandemic that lacked legal restrictions as a transition period. While evaluating the change in frequency distributions, we interpreted the results between "the last 4 weeks before the pandemic" and "the first and second 4th weeks after declaration of the pandemic" to reveal the differences in incidence rates more precisely.

Data Collection

The age, gender, presentation date and the ICD-10 (International Classification of Diseases-10) diagnostic codes were accessed from the electronic database. The presentation of the same patient within 10 days of the first presentation was regarded as a control visit. Patients with repetitive presentations for control or follow-up and their diseases were identified. However, repetitive presentations with the same diagnosis within ten days of the first visit were not included in the study.

In our retrospective study, since ICD-10 disease classification codes cannot designate some of the diseases encountered in the urology practice and the unique style of each urologist, standardization of the data was required. For this reason, the ICD-10 diagnosis codes of the patients recorded in the system were reconsidered. The diagnoses had been made based on diagnostic classification of diseases indicated in the 12th edition of Campbell-Walsh Wein Urology (2020) to achieve standardization [14]. A single diagnostic code was used for separate diagnoses that attempted to designate the diseases (for example, acute cystitis, pyelonephritis= infectious diseases of the urinary system; renal stone, bladder stone, renal colic= urinary system stone diseases; varicocele, orchitis= genital diseases, and overactive bladder, neurogenic bladder= urine transport, storage and emptying disorders, etc.). In patients with more than one unrelated diagnosis, the first diagnostic code was taken as reference. Consequently, more than 300 ICD-10 codes were simplified and organized under nine subheadings. Since the data processing staff anonymized the data of the patients, no individual consent was obtained.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics® 21.0 and MSExcel® 2010. Kolmogorov-Smirnov test was used for normality analysis, and Pearson's chi-square test for the analysis of categorical variables. Independent samples for normally distributed continuous variables were compared using Kruskal-Wallis H test or Mann-Whitney U test, when appropriate. A p value of <0.05 was considered statistically significant. After Kruskal -Wallis H and chi-square tests, Bonferroni correction was applied as post -hoc analysis.

Results

A total of 104142 visits had been made to outpatient clinics except for the COVID-19 outpatient clinics, and the urology

outpatient clinics were consulted for 5380 (5.1%) times during the 12-week period from February 12 to May 6, 2020. Among them 197 (3.6%) patients made more than one visit to the urology outpatient clinics. The change in the number of applications to urology outpatient clinics before and after the declaration of pandemic is shown in Figure 1. A significant decrease in the number of patients applied to the hospital and urology outpatient clinics within the first and second 4th weeks after declaration of the pandemic compared to the pre-pandemic period (25.5% and 10.8% vs 63.8%, p=0.001 for all outpatient clinics of the hospital, 14.7% and 7.9% vs 77.3%, p=0.001 for urology outpatient clinic).

The changes in the frequency of application and distribution of age and gender are summarized in **Table 1**. While mostly male (71%), and less frequently female (29%) patients had applied to the urology outpatient clinics before the pandemic, this difference between genders decreased after declaration of the pandemic (p<0.001). Compared to the pre-pandemic period, the mean age of female and male patients applied to the urology outpatient clinics decreased significantly after declaration of the pandemic (p=0.028, and p=0.032, respectively).

The distribution of the diagnoses of the patients who had applied to the urology outpatient clinic before and after declaration of the pandemic is shown in **Table 2**. Compared to the pre-pandemic period, there was a significant decrease in the frequency of diagnoses of prostate diseases and urine transport, storage and emptying disorders (p=0.003, p=0.001, respectively) and significant increase in the frequency of diagnoses of urinary system stone disease, benign or malignant bladder diseases, upper urinary system tumors (UUST), and sexual dysfunction after declaration of the pandemic (p=0.001, p=0.001, p=0.001, p=0.001, respectively). No significant difference was observed in the frequency of the diagnoses of genital disease, urinary infections and urinary system trauma after declaration of the pandemic relative to the pre-pandemic period (p=0.180, p=0.220, p=0.350, respectively).

Discussion

Countries around the world have taken a number of measures to delay the spread of the COVID-19 disease and prevent the increase in the number of COVID-19 patients [15,16]. First of all, some countries have begun screening travellers coming from China and/or endemic regions for fever [17]. Moreover, mass meeting events, including religious, sporting, musical and even medical conferences (European Association of Urology, American Society of Clinical Oncology, and American Urological Association annual meetings, etc.) were canceled or postponed [17-20]. After these measures, quarantine practices were implemented with the prohibition of entering or exiting metropolitan cities, international travels, face-to-face education, and ensuring that individuals over 65 years of age stayed at home. Some countries declared a national state of emergency [21,22]. Stricter health measures such as postponing all non-urgent elective surgeries [15] and the provision of inpatient and outpatient treatment services only for critically ill patients were also implemented [23,24].

The COVID-19 pandemic is a disease that is particularly

Table 1. Evaluation of age, gender and frequency of application before and after the declaration of the pandemic

Last 4-weeks		Before Pandemic	After Declaration of Pandemic		p-value
		1st 4-weeks	2nd 4-weeks		
Number of applications to all departments† (n=104142)		66418 (63.8%)	26518 (25.5%)	11206 (10.8%)	**<0.001**[a,b,c]
Number of applications to the urology (n=5380)		4160 (77.3%)	793 (14.7%)	427 (7.9%)	**<0.001**[a,b,c]
Age (year)	Male	50,95±15,03	37,44±14,9	32,2±10,2	**<0.028**[b,c]
	Female	39,08±15,6	33,2±10,5	32,8±12,1	**<0.032**[b,c]
Gender	Male	2988 (71.8%)	450 (56.7%)	230 (53.9%)	**<0.001**[a,b]
	Female	1172 (28.2%)	343 (43.2%)	197 (46.1%)	

Data are expressed as the number of applications to the outpatient clinic (percentage)

Kruskal-Wallis H and Pearson's chi-squared tests were used. Bonferroni correction was applied as post-hoc (Mann Whitney-U and z-test, respectively) after Kruskal Wallis-H and chi-square tests. Significant values were shown in bold.

† Other than COVID-19 outpatient clinics,

a: adjusted p value<0.05 for the difference between "last 4-weeks before the pandemic" and "1st 4-weeks after the declaration of pandemic"

b: adjusted p value<0.05 for the difference between "last 4-weeks before the pandemic" and "2nd 4-weeks after the declaration of pandemic"

c: adjusted p value<0.05 for the difference between "1st 4-weeks after the declaration of pandemic"; and "2nd 4-weeks after the declaration of pandemic"

Table 2. Comparison of the diagnosis frequencies of outpatients admitted to urology outpatient clinics before and after the declaration of the pandemic

Diseases	Before Pandemic	After Declaration of Pandemic		p-value
	Last 4-weeks (n=4160)	1st 4-weeks (n=793)	2nd 4-weeks (n=427)	
Prostate diseases	1305 (31.4%)	243 (30.6%)	100 (23.4%)	**0.003**[b,c]
Urinary system stone diseases	1252 (30.1%)	308 (38.8%)	155 (36.3%)	**<0.001**[a,b]
Genital diseases	206 (5.0%)	43 (5.4%)	13 (4.9%)	0.180
Benign and malignant bladder diseases	75 (1.8%)	26 (3.2%)	20 (4.7%)	**<0.001**[a,b]
Upper urinary tract tumors	21 (0.5%)	20 (2.5%)	21 (4.9%)	**<0.001**[a,b]
Urinary system infectious diseases	700 (16.8%)	41 (5.1%)	65 (15.2%)	**<0.001**[a,c]
Urine transport, storage and emptying disorders	412 (9.9%)	69 (8.7%)	20 (4.7%)	**0.001**[b,c]
Trauma	48 (1.2%)	7 (0.8%)	2 (0.5%)	0.350
Sexual dysfunction	141 (3.4%)	36 (4.5%)	31 (7.3%)	**<0.001**[b,c]

Data are expressed as the number of applications to the outpatient clinic (column percentage) Pearson's chi-square test was used. Bonferroni correction was applied as post-hoc (z-test) after chi-square tests. Significant values were shown in bold
a: adjusted p value<0.05 for the difference between "last 4-weeks before the pandemic" and "1st 4-weeks after the declaration of the pandemic"
b: adjusted p value<0.05 for the difference between "last 4-weeks before the pandemic" and "2nd 4-weeks after the declaration of the pandemic"
c: adjusted p value<0.05 for the difference between "1st 4-weeks after COVID-19"; and "2nd 4-weeks after the declaration of the pandemic"

more common and deadly among older men who also constitute a significant portion of urology patients. In this study, we aimed to examine the effects of the measures taken, bans imposed, and the effective "stay at home" calls broadcasted on local or national media during the COVID-19 pandemic, on the number of patient visits to the urology polyclinic, and the distribution of diagnoses in this patient population.

The first decrease in the number of patients presenting to the hospital occurred when news about refugees from Iran being quarantined spread. Furthermore, it was determined that the number of patients applied to the hospital increased rapidly with the announcement of positive updates. We observed a logarithmic decrease in the frequency of presentations to our outpatient clinics approximately two weeks after the announcement of the first confirmed case **(Figure 1)**. Compared with the pre-pandemic period a 5.1-fold decrease in urology outpatient clinic visits in the first 4th (the transition period) and a 9.7-fold decrease in the second 4th weeks were observed with corresponding 2.5- and 5.9-fold decreases in general hospital visits. Compared to hospital-wide patient flow, a significantly higher decrease in the urology outpatient clinic visits was observed. We believe that this marked decrease in urology outpatient clinic visits is due to relatively more pronounced perception of COVID-19 risk among men of advanced age. We think that compared to the pre-pandemic period this significant drop in hospital visits during the transition period when legal restrictions were not imposed, is due to the effective role of awareness campaigns running on visual and social media.

The decrease in the mean ages of both male and female patients who applied to the urology outpatient clinics after declaration of the pandemic was also noteworthy compared to the pre-pandemic period. We believe that the curfew imposed on individuals over the age of 65 in the early period after declaration of the pandemic, and especially the news in the media that men over 65 were more frequently affected by COVID-19 was effective.

Additionally, increase in the frequency of diagnosis of urinary system stone disease may be due to the severity of the symptoms of the disease being superior to the perception of the pandemic risk, and that the effective curfew applied in this period negatively affected the spontaneous fall of stones due to limited mobilization. We believe that the increase in diagnoses of benign or malignant bladder diseases is related to hematuria, which is one of the most common alarming symptoms of this disease group, and is a driving force for patients despite the "stay at home" calls. The fact that patients with diagnosed bladder tumors do not miss their control cystoscopy appointments may have also been effective in this increase. In addition, it should be emphasized that the decrease in the rates of less serious diseases after declaration of the pandemic may have caused a relative increase in the incidence of serious diseases.

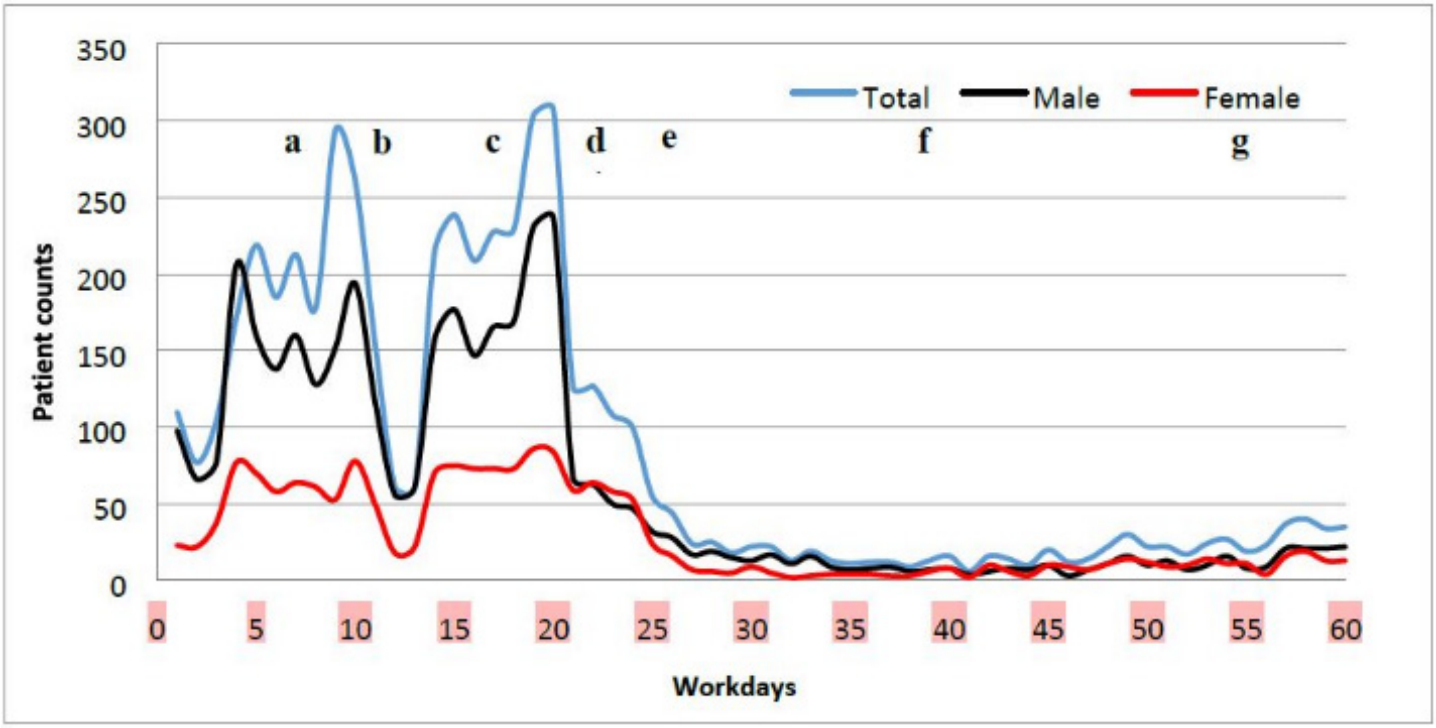


Figure 1. Change in daily patient frequency before and after COVID-19 outbreak
February 24: The period when refugees from the neighboring country Iran were quarantined in our city (**a**), February 28: It was announced that the PCR test (polymerase chain reaction) results of the refugees were negative (**b**), March 11: The first COVID-19 case was confirmed in Turkey, and the World Health Organization declared a pandemic (**c**), March 17: The first death due to COVID-19 was reported in Turkey (**d**), March 22: Curfew was declared indefinitely for individuals over the age of 65 (**e**), April 4: Curfew was declared indefinitely for individuals under the age of 20 (**f**), May 11: The normalization process has begun in Turkey (**g**).

Studies have shown an increase in the frequency of psychological diseases such as anxiety and depression in the community during the COVID-19 pandemic [25]. It is known that sexual dysfunction is accompanied by anxiety, depression, lack of self-confidence, a negative attitude towards life and emotional stress [26,27]. While there was no significant change in the diagnostic frequency of sexual dysfunction in the transition period compared to the pre-pandemic period, we observed a significant increase in the diagnostic frequency of sexual dysfunction after declaration of the pandemic relative to the pre- pandemic period. We believe that this is due to the patients' need for medical advice due to the stress factors outweighing the perception of the COVID-19 pandemic risk.

Prostate diseases can be accompanied by chronic diseases (chronic obstructive pulmonary disease (COPD), obesity, and metabolic syndrome, etc.) that are common among older men [28-30]. Although COVID-19 causes severe illnesses in healthy individuals of all ages, it is more common and more deadly in adult men with advanced age or medical comorbidities. During the pandemic, the media consistently published news that the COVID-19 had a worse course among the elderly and the government implemented an effective curfew for individuals older than 65 years of age. We believe that both the curfew imposed on individuals over 65 years of age and the effective use of the media may have led to the decrease in the number of patients diagnosed as prostate diseases by making the perception of the pandemic risk among elderly males outweigh the symptoms related to the disease.

Studies have reported that urine transport, storage, and emptying disorders negatively affect social life and reduce the quality of life of the patients. Although a presumptive rise in the number of diagnoses due to the increased stress factors after declaration of the pandemic was anticipated, we identified a decrease in the frequency of diagnoses of this disease group compared to the pre-pandemic period. We believe that the patients' perception of the pandemic risk outweighing the symptoms of the disease may have been effective in the decreased number of diagnoses made during prepandemic period. We think that the fact that effective calls to "stay at home," mainly broadcasted on the media increased the time spent at home and made the symptoms of the disease (such as urgency, and urinary incontinence) more tolerable, and also contributed to this decrease in the number of diagnoses made during pre-pandemic period.

There was no significant difference in the frequency of diagnoses of urinary system infections before and after declaration of the pandemic. However, in our analysis, we did identify a fluctuation in the frequency of diagnoses in this patient group before, and at the first and second 4th weeks after declaration of the pandemic (16.8%, 5.1%, and 15.2%, respectively). We believe that the referral of patients diagnosed with urinary tract infections to urology outpatient clinics from the outpatient clinics of infectious diseases, which had a primary role in managing the pandemic, may have been effective in this fluctuation.

In the literature scan we performed with regard to urological patients during the COVID-19 pandemic, we observed that research and guideline recommendations have focused on urological emergencies. This study was carried out to gain a better understanding of the reason why patients with urological diseases

presented to the hospital during a period of a deadly global pandemic, and we included all patient groups in our survey which constituted the strength of our study. Many factors that affect the quality of life, the perception of risk depending on the age and gender of individuals, and the increased burden of stress, have changed the diagnostic distribution of urology practices during the pandemic.

Considering lack of any reliable prediction assessment criteria about the duration, economic and social consequences of the pandemic, we believe that a fundamental issue in the practice of urology that needs to be addressed is how to prioritize outpatients without coronavirus disease who require treatment and how to manage these patients. We consider that telemedicine applications defined by the World Health Organization (WHO) as "The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies" can fill this gap for the management of patients who cannot make applications to the outpatient clinics for any reason [31]. In the light of the data, we obtained as a result of this study, the pilot study that we initiated to evaluate the effectiveness of telemedicine applications recommended by the WHO in the pandemic period continues.

The limitations of our study are its retrospective design, failure to make detailed clinical examinations, and the lack of data relating to the quality of life, anxiety levels, treatments applied, and individual risk perception of COVID-19 by the patients. The patients often had unrelated complaints and symptoms and sharing patient complaints and symptoms without triaging can alter the prioritization of diagnoses in the database. Furthermore, due to the extreme variety of urological diseases, urologists work within a narrow diagnostic framework in clinical practice, depending on the ICD-10 diagnostic classification unable to cover all diagnostic entities in urology.

Conclusion

Males at an advanced age in whom the COVID-19 is more severe and mortal comprise a significant portion of patients applied to the urology outpatient clinics. The risk perception of COVID-19 may cause changes in the diagnostic distribution of patients applied to the urology outpatient clinics. During pandemic periods, the health system must be redesigned by focusing on outpatients.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences, Erzurum Regional Training and Research Hospital (Approval date, and number: 2021/17-254).
Informed Consent: This study does not require informed consent.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – A.E.C, N.C., I.K.; Design – A.E.C, N.C., S.A., O.P.; Supervision – I.K. S.A., O.P.; Resources – S.O.D, F.K.Y, S.G.U.; Materials – S.O.D, F.K.Y, S.G.U.; Data Collection and/or Processing – N.C., S.O.D., F.K.Y., S.G.U.; Analysis and/or Interpretation – A.E.C., I.K., S.A., O.P.; Literature Search – A.E.C., S.O.D., F.K.Y.; Writing Manuscript – A.E.C., N.C., I.K.; Critical Review – A.E.C., N.C., I.K., S.A., O.P.
Conflict of Interest: All authors have no conflict of interest.
Financial Disclosure: This study received no financial support.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33. https://doi.org/10.1056/NEJMoa2001017.

[2] World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020. (accessed June 4, 2020).

[3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[4] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13. https://doi.org/10.1016/S0140-6736(20)30211-7.

[5] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9. https://doi.org/10.1001/jama.2020.1585.

[6] Xie Y, Wang Z, Liao H, Marley G, Wu D, Tang W. Epidemiologic, clinical, and laboratory findings of the COVID-19 in the current pandemic: Systematic review and meta-analysis. BMC Infect Dis 2020;20:640. https://doi.org/10.1186/s12879-020-05371-2.

[7] Response EWG for NE, And Prevention CC for DC. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 2020;41:145-51. https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.003.

[8] Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic population. N Engl J Med 2020;382:2302-15. https://doi.org/10.1056/NEJMoa2006100.

[9] COVID-19 National Emergency Response Center, Epidemiology and Case Management Team. Coronavirus disease-19: The first 7,755 cases in the Republic of Korea. Osong Public Heal Res Perspect 2020;11:85-90. https://doi.org/10.24171/j.phrp.2020.11.2.05.

[10] COVID-19 National Emergency Response Center, Epidemiology and Case Management Team. Coronavirus disease-19: Summary of 2,370 contact investigations of the first 30 cases in the Republic of Korea. Osong Public Heal Res Perspect 2020;11:81-4. https://doi.org/10.24171/j.phrp.2020.11.2.04.

[11] Republic of Turkey Ministry of Health, General Directorate of Public Health. COVID19 (SARS-CoV2 Infection) Guide (Science Board Study): General information, epidemiology and diagnosis 2020. https://covid19bilgi.saglik.gov.tr/depo/rehberler/covid-19-rehberi/ covid19_rehberi_genel_bilgiler_epidemiyoloji_ve_tani.pdf. (accessed June 4, 2020).

[12] COVID-19 coronavirus pandemic. Worldometers website 2020. https://www.worldometers.info/coronavirus/country/turkey/ (accessed June 9, 2021).

[13] Amparore D, Campi R, Checcucci E, Sessa F, Pecoraro A, Minervini A, et al. Forecasting the Future of Urology Practice: A Comprehensive Review of the Recommendations by International and European Associations on Priority Procedures During the COVID-19 Pandemic. Eur Urol Focus 2020;6:1032-48. https://doi.org/10.1016/j.euf.2020.05.007.

[14] Partin AW, Dmochowski RR, Kavoussi LR, Peters CA. Campbell-Walsh-Wein Urology. 12th Edition Review. Elsevier Health Sciences; 2021.

[15] Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three months in England. BMJ 2020;368:m1106. https://doi.org/10.1136/bmj.m1106.

[16] Chan MC, Yeo SEK, Chong YL, Lee YM. Stepping Forward: Urologists' Efforts During the COVID-19 Outbreak in Singapore. Eur Urol 2020;78:e38-9. https://doi.org/10.1016/j.eururo.2020.03.004.

[17] Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. JAMA 2020;323:709-10. https://doi.org/10.1001/jama.2020.1097.

[18] McCloskey B, Zumla A, Ippolito G, Blumberg L, Arbon P, Cicero A, et al. Mass gathering events and reducing further global spread of COVID-19: a political and public health dilemma. Lancet 2020;395:1096-9. https://doi.org/10.1016/S0140-6736(20)30681-4.

[19] Gostin LO, Hodge JG, Wiley LF. Presidential Powers and Response to COVID-19. JAMA 2020;323:1547-8. https://doi.org/10.1001/jama.2020.4335.

[20] Rimmer A. Covid-19: Medical conferences around the world are cancelled after US cases are linked to Massachusetts meeting. BMJ 2020;368:m1054. https://doi.org/10.1136/bmj.m1054.

[21] Yang Y, Peng F, Wang R, Guan K, Jiang T, Xu G, et al. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J Autoimmun 2020;109:102434. https://doi.org/10.1016/j.jaut.2020.102434.

[22] Kupferschmidt K, Cohen J. Can China's COVID-19 strategy work elsewhere? Science (80-) 2020;367:1061-2. https://doi.org/10.1126/science.367.6482.1061.

[23] Naspro R, Da Pozzo LF. Urology in the time of corona. Nat Rev Urol 2020;17:251-3. https://doi.org/10.1038/s41585-020-0312-1.

[24] Adanur S, Al S, Polat O. Coronavirus (COVID-19) pandemic and radical cystectomy. Eurasian J Med 2020;52:106-7. https://doi.org/10.5152/eurasianjmed.2020.010620.

[25] Xiang YT, Jin Y, Cheung T. Joint International Collaboration to Combat Mental Health Challenges during the Coronavirus Disease 2019 Pandemic. JAMA Psychiatry 2020;77:989-90. https://doi.org/10.1001/jamapsychiatry.2020.1057.

[26] Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol 1994;151:54-61. https://doi.org/10.1016/S0022-5347(17)34871-1.

[27] Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: Prevalence and predictors. JAMA 1999;281:537-44. https://doi.org/10.1001/jama.281.6.537.

[28] Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984;132:474-9. https://doi.org/10.1016/S0022-5347(17)49698-4.

[29] Peng YH, Huang CW, Liao WC, Chen HJ, Yin MC, Huang YM, et al. Association between chronic obstructive pulmonary disease and increased risk of benign prostatic hyperplasia: A retrospective nationwide cohort study. BMJ Open 2017;7:e015581. https://doi.org/10.1136/bmjopen-2016-015581.

[30] Hammarsten J, Högstedt B. Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. Eur Urol 2001;39:151-8. https://doi.org/10.1159/000052430.

[31] World Health Organization. Telemedicine: opportunities and developments in member states. 2010. https://www.who.int/goe/publications/goe_telemedicine_2010.pdf (accessed January 6, 2021).

Case Report – Urological Oncology

Grand J Urol 2022;2(1):33-7
DOI: 10.5505/GJU.2022.69775

Sertoli Cell Nodule with Histomorphological and Immunohistochemical Features and its Differential Diagnosis: A Case Report

Histomorfolojik ve İmmunhistokimyasal Özellikleri ile Sertoli Hücreli Nodül ve Ayırıcı Tanısı: Bir Olgu Sunumu

Oyku Dila Gemci[1], Halil Firat Baytekin[1], Ismail Evren[2], Omer Yildiz[3]

[1]Department of Pathology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[2]Department of Urology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[3]Department of Radiology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

Cite as: Dila Gemci O, Baytekin HF, Evren I, Yildiz O. Sertoli cell nodule with histomorphological and immunohistochemical features and its differential diagnosis: a case report. Grand J Urol 2022;2(1):33-7.

Submission date: 26 March 2021 **Acceptance date:** 25 August 2021 **Online First:** 19 September 2021 **Publication date:** 20 January 2022

Corresponding Author: Oyku Dila Gemci / University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Department of Pathology, Istanbul, Turkey / oykudilagemci@gmail.com / ORCID ID: 0000-0002-6558-7258

Abstract

Non-germ cell testicular tumors are rarely seen. Sex-cord stromal tumors, which make up the majority of testicular tumors other than germ cell tumors, share common immunohistochemical and histomorphological features. Our aim in presenting this case is to define the Sertoli cell nodule (SCN), which is one of the relatively rare primary testicular pathologies that can be detected in half of adult undescended testes, with its histomorphological and immunohistochemical features, and to make its differential diagnosis.

Keywords: Sertoli cell nodule, testicular dysgenesis syndrome, testicular nodule, testicular pathology, testicular tumor

Öz

Germ hücreli dışı testis tümörleri nadir görülürler. Germ hücreli tümörler dışında kalan testis tümörlerinin çoğunluğunu oluşturan seks-kord stromal tümörler ortak immunhistokimyasal ve histomorfolojik özellikler paylaşırlar. Bu olgunun sunulmasındaki hedefimiz, erişkin inmemiş testislerin yarısında saptanabilen, görece olarak nadir primer testiküler patolojilerden biri olan Sertoli hücreli nodülün (SCN), histomorfolojik ve immunhistokimyasal özellikleri ile tanımlanması ve ayırıcı tanısının yapılmasıdır.

Anahtar kelimeler: Sertoli hücreli nodül, testiküler disgenezi sendromu, testiküler nodül, testiküler patoloji, testis tümörü

ORCID ID: H.F. Baytekin 0000-0002-7086-4758 **I. Evren** 0000-0003-4008-8038 **O. Yildiz** 0000-0003-4774-9281

Introduction

Tumors of the testicles other than germ cell neoplasms are extremely rare and the majority of testicular neoplasms in this group are sex cord stromal tumors. This class of tumors, mostly with a benign course, are more common in childhood. It constitutes 25%, and 2-5% of all testicular neoplasms in prepubertal ages and in adults, respectively [1].

Leydig cell tumors are the most common sex cord stromal tumors, followed by Sertoli cell tumors, granulosa cell tumors and myoid gonadal tumors in order of decreasing frequency [1]. Sertoli cell neoplasia group, which is the second most common testicular tumors after Leydig cell tumors among sex-cord stromal tumors, constitutes 1% of all testicular tumors [2].

Sertoli cell nodule (SCN) is defined as embryo-like nodular structures consisting of seminiferous tubules with a smaller diameter than the surrounding parenchyma. They can be detected as single or several separate nodules with diameters ranging from submillimeter up to one centimeter. They are rarely detected in normal testicles. The Sertoli cell nodule, which can be detected in half of the undescended testicles in adulthood, can be found in the normal testicular parenchyma in the peripheral part of germ cell tumors and in infertile patients.

Case

Clinical history; It was learned that a 31-year-old male patient admitted to the urology clinic with a complaint of right inguinal pain lasting for a month had limited range of motion due to intermittent pain and pain. Physical examination revealed that the right testicle was not in the scrotum, but in the inguinal canal. Examination of the genitourinary system was normal, except for the inguinal right testis. The patient's hemogram values and biochemical parameters were within normal limits. Oligoastenospermia was detected in the semen analysis of the patient.

In the scrotal color Doppler USG examination, the left testicle was of normal size, and structure, while the right testicle was in the inguinal canal and its size was smaller than the left testicle. Testicular contours were smooth, testicular parenchyma was homogeneously isoechoic, intratesticular vascularization was physiologic. Intratesticular space-occupying lesion was not detected. While the left epididymis was in natural appearance, the right epididymis was heterogeneously expanded compared to its normal size, and hypervascularization was detected. Right inguinal orchiectomy together with repair of right direct ingunal hernia detected during the operation was performed.

Pathological Findings

Macroscopic examination; A 5 cm-long spermatic cord with a diameter of 2.5 cm at its widest part and an adjacent 4x3x2.5 cm testis in its normal structural appearance were observed. In the sections performed, solid millimetric nodules of off-white color with a smooth border with the surrounding testicular tissue, were found in several patchy areas in the normal-appearing testicular parenchyma.

Microscopic examination; In most areas, seminiferous tubules

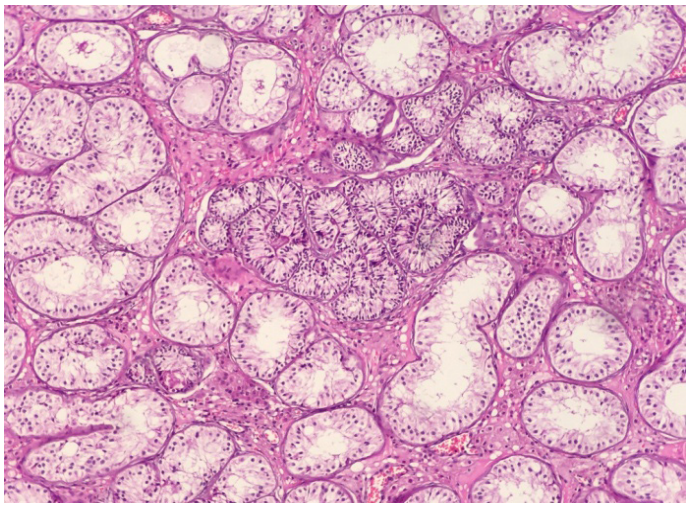


Figure 1. Submillimetric SCN consisting of large-diameter seminiferous tubules in the periphery and conglomerated infantile-looking tubules in the central area

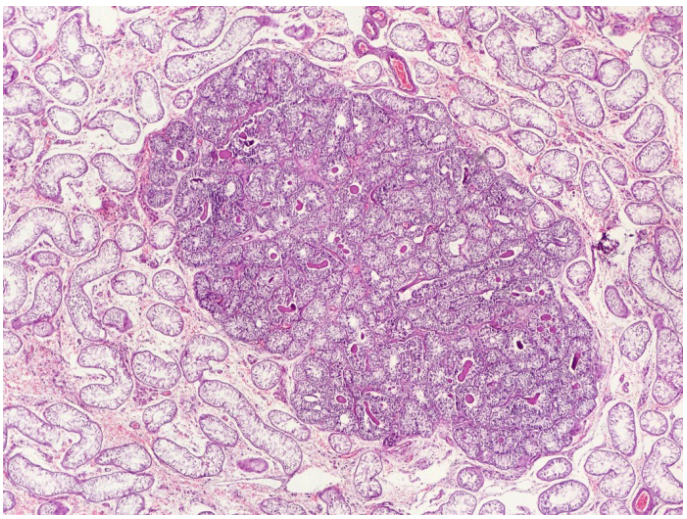


Figure 2. Fetal-looking tubules with narrow diameter and containing greater number of cells (x100 magnification), decreased amount of stroma when compared with the surrounding parenchyma

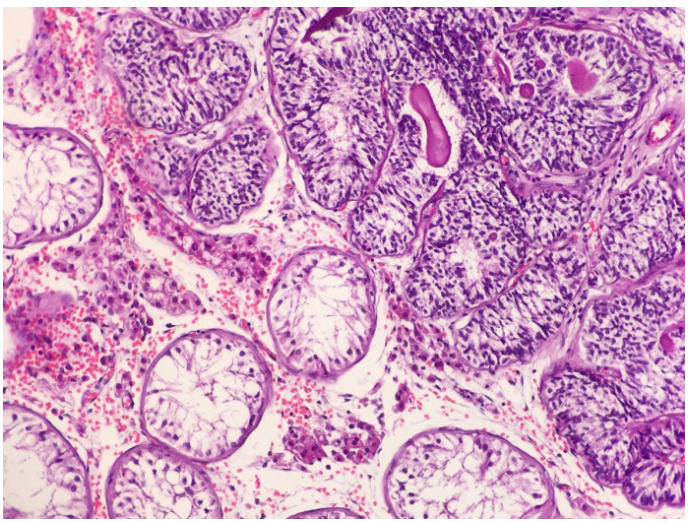


Figure 3. Stratified Sertoli cells, and intertubular Leydig cell clusters (x200 magnification)

with open lumen, usually lined by a single layer of Sertoli cells with small round nuclei were observed **(Figure 1)**. Although a small number of germ cells were observed in these seminiferous tubules, which can be demonstrated by SALL-4 immunohistochemical staining, it was observed that spermatogenesis stopped in the whole testicle.

In the testicular parenchyma, a few noncapsulated dispersed millimetric nodules separated from the environment by their smooth contours were observed. These nodules contained minimally wide interstitium, and adjacent seminiferous tubules denser than the surrounding parenchyma **(Figure 2)**. Tubules in this nodular area were observed to be lined with only pseudostratified Sertoli cells with elongated hyperchromatic nuclei. Sertoli cell nuclei were hyperchromatic, elongated and contained one or two small peripheral nucleoli **(Figure 3)**. Germ cells were detected in the conglomerated tubules in the nodular area by immunohistochemical methods at histomorphological level **(Figure 4)**.

In immunohistochemical studies, Sertoli cells in nodular areas showed weaker reactivity with CD99, androgen receptor (AR) and inhibin than Sertoli cells in the surrounding tubules. In addition, while areas stained with desmin showed myoid cells around the seminiferous tubules outside the nodular areas, myoid cells were not detected in the nodular areas. The Ki-67 proliferation index was estimated as 1-2% in the densest area, higher than that of the surrounding parenchyma **(Figure 5)**.

A few seminiferous tubules without stratified Sertoli cells, sharing similar features with non-nodular tubules surrounded by myoid cells, were detected in scarce number of peripheral tubules within the nodule **(Figure 6)**. Although the nodular seminiferous tubules were lined with pseudostratified Sertoli cells, their fetal appearance was remarkable with their diameters narrower than those of the surrounding tubules. Basement membrane-like material densified in an amphophilic appearance in the tubule lumens was detected in all areas. With the histomorphological and immunohistochemical features described above, the case was reported as a Sertoli cell nodule.

Discussion

Sertoli cell nodule is defined as the presence of one or more separate foci in the testicular tissue, consisting of infantile-looking seminiferous tubules. Although the term Sertoli cell nodule was first reported in 1973, it was described as a “Pick adenoma” by Pick in 1905 and it was also reported as a lesion with similar features [3,4]. This lesion has also been termed in different reports with different names such as Sertoli cell hyperplasia, tubular dysgenesis or hypoplastic seminiferous tubule areas [5-7].

In the Sertoli cell nodule, each cluster of seminiferous tubules is observed as noncapsulated but well-defined nodules. Nodules can be single or multiple, millimetric or submillimetric. In a few published cases on macronodular Sertoli cell nodules, it has been reported that the nodules reached up to 1,7 cm in diameter [8]. Except for the rare presence of a palpable mass in large nodules at presentation, most of the time, any remarkable signs, and symptoms are not detected on clinical examination. Ultrasonographic findings may suggest a testicular tumor. Nodules can be single or multiple. Each nodule in the cross section can be

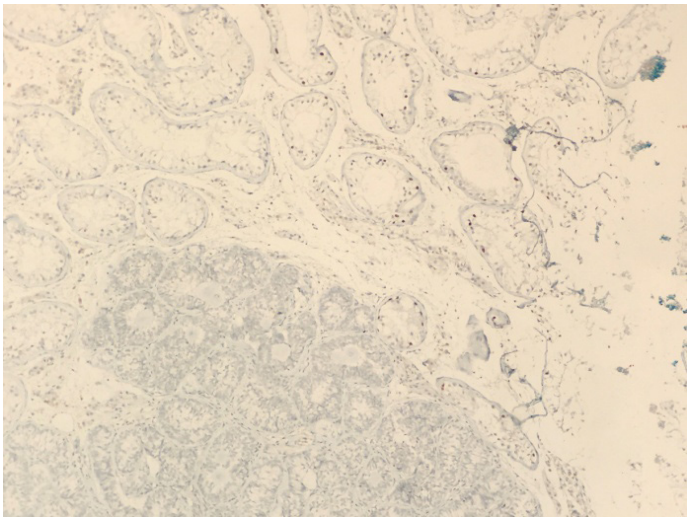


Figure 4. In immunohistochemical staining with SALL 4 while no germ cells are detected in SCN, a small number of germ cells are observed in the surrounding tubules

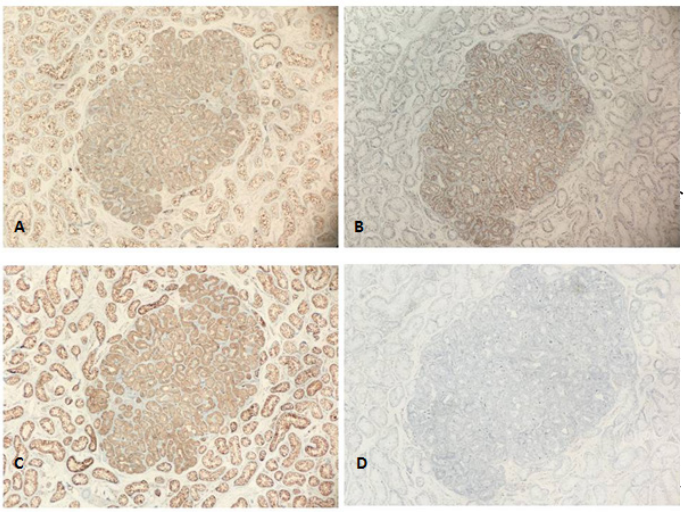


Figure 5. SCN immunohistochemical staining patterns; A- CD99, B- Androgen receptor, C- Inhibin, D- Ki-67

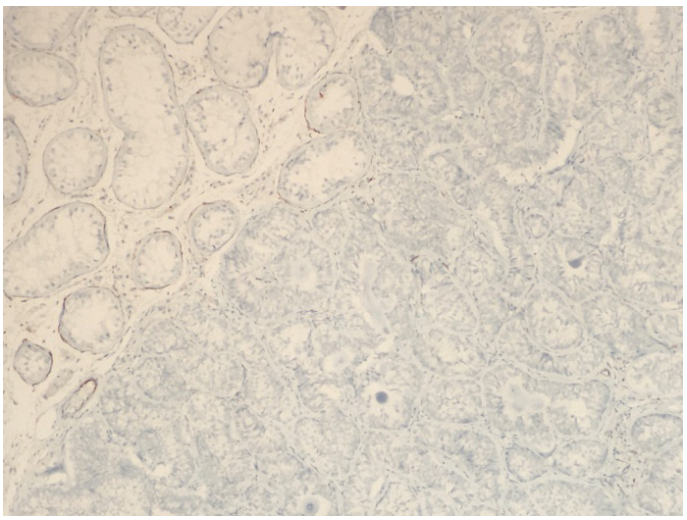


Figure 6. Parenchymal peritubular myoid cells were stained positively with desmin while myoid cells were not detected in the tubules forming the nodule

differentiation, to clarify the microanatomy, or to show the presence and distribution of a particular cell type. Identification of the small numbers of germ cells was possible with SALL-4 immunohistochemistry. CD99, AR and inhibin were used for sex cord stromal differentiation, and desmin was used to demonstrate the presence of peritubular myoid cells. If the maturation of Sertoli cells cannot be determined histomorphologically, cytokeratin 8 and cytokeratin 18 expressions can be evaluated. These two types of keratin are used to identify immature Sertoli cells [10]. Differential diagnosis of Sertoli cell nodule include intratubular large cell hyalinizing Sertoli cell neoplasia, Sertoli cell adenoma, tubular hamartoma in androgen insensitivity syndrome (AIS), testicular areas containing focal Sertoli cell-only tubules, Sertoli cell tumor and gonodoblastoma.

In intratubular large cell hyalinizing Sertoli cell neoplasia (ITLCHSCN), multiple nodules are detected as in SCN, however, tubules do not anastomose in ITLCHSCN and are distinguished by their larger diameter. In addition, unlike the Sertoli cells observed in SCN, in ITLCHSCN the Sertoli cells with vesicular nuclei, central single nucleoli and eosinophilic cytoplasm, progress to the more advanced stages of maturation [11].

Though rarely, when SCN contains only a few germ cells, it is important to distinguish it from gonodoblastoma. Gonodoblastoma is almost always detected in gonadal dysgenesis or malformed testis, and it contains greater number of germ cells than SCN. Nodules consist of large clusters of Sertoli cells and germ cells surrounding the eosinophilic material rather than in the form of conglomerated tubules.

Macroscopically, Sertoli cell adenoma and tubular hamartoma in androgen insensitivity syndrome (AIS) are in the form of larger nodules, and the Sertoli cells lining the tubules are distinguished by having round nuclei rather than elongated ones.

In Sertoli cell- only tubules, nodular organization defined in SCN is not detected. They are found as tubules that consist entirely of Sertoli cells that do not tend to cluster. In the Sertoli cell nodule, the Sertoli cells and peritubular myoid cells, unlike the surrounding testicular parenchyma, do not respond to hormonal stimuli or respond irregularly and poorly. As a result, the prepubertal Sertoli cells lining the tubules and forming the lesion acquire a fetal-looking nodular structure consisting of conglomerated tubules. Different factors are thought to have an effect on the incomplete maturation of Sertoli cells in cryptorchidism. The main etiologic factors are exposure of the undescended testis to high temperature and congenital hormonal insensitivity [12].

It is important to distinguish SCN from Sertoli cell neoplasms. Sertoli cell nodules are mostly microscopic, rarely as single or multiple macroscopic nodules. Although mitosis was not detected in our case, it is thought-provoking that the Ki-67 proliferation index is 1% higher than the environment, but today there is no evidence that these are precancerous lesions.

Ethics Committee Approval: N / A.
Informed Consent: An informed consent was obtained from the patient.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – O.D.G.; Design – O.D.G.; Supervision – O.D.G.; Resources – H.F.B.; Materials – O.D.G., I.E.; Data Collection and/or Processing – O.Y.; Analysis and/or Interpretation – O.D.G, I.E.; Literature Search – O.D.G., H.F.B.; Writing – O.D.G., H.F.B., I.E.; Critical Review – O.D.G., H.F.B., I.E.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Moch H, Humphrey PA, Ulbright TM, Reuter VE. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th Edition, Volume 8. Lyon, France: International Agency for Research on Cancer; 2016.

[2] Nagata M, Kurimoto S, Takeuchi T, Ohta N, Minowada S, Kitamura T. Tiny Nodule in the Testicle: Case Report of a Sertoli Cell Tumor. Int J Urol 2004;11:61-2. https://doi.org/10.1111/j.1442-2042.2004.00727.x.

[3] Mostofi FK, Price EB. Tumors of the Male Genital System [Atlas of Tumor Pathology]. 2nd series, fascicle 8. Washington DC: Armed Forces Institute of Pathology; 1973.

[4] Pick L. Ueber Neubildungen am genitale bei Zwittern (nebst beiträ gen zur Lehre von den Adenomen des Hodens und Eierstockes). Archiv für Gynäkologie 1905;76:191–281. https://link.springer.com/article/10.1007/BF01834723.

[5] Stalker AL, Hendry WT. Hyperplasia and Neoplasia of the Sertoli Cell. J Pathol Bacteriol 1952;64:161-8. https://doi.org/10.1002/path.1700640116.

[6] Halley JB. The Growth of Sertoli Cell Tumors: A Possible Index of Differential Gonadotrophin Activity in the Male. J Urol 1963;90:220-9. https://doi.org/10.1016/s0022-5347(17)64394-5.

[7] Hedinger CE, Huber R, Weber E. Frequency of So-called Hypoplastic or Dysgenetic Zones in Scrotal and Otherwise Normal Human Tests. Virchows Arch Pathol Anat Physiol Klin Med 1967;342:165-8. https://doi.org/10.1007/BF00960585.

[8] Roth LM, Czernobilsky B. Macroscopic Sertoli Cell Nodule of the Testis Containing Numerous Spermatogonia. Pathol Res Pract 2016;212:943-5. https://doi.org/10.1016/j.prp.2016.07.006.

[9] Wohlfahrt-Veje C, Main KM, Skakkebaek NE. Testicular Dysgenesis Syndrome: Foetal Origin of Adult Reproductive Problems. Clin Endocrinol (Oxf) 2009;71:459-65. https://doi.org/10.1111/j.1365-2265.2009.03545.x.

[10] Manisha B, Narayani J, Nag BP, Yadav ML. Sertoli Cell Nodule of the Testis: An Incidental Finding. IAIM 2017;4:64-7. http://oaji.net/articles/2017/1398-1493351876.pdf.

[11] Ulbright TM, Amin MB, Young RH. Intratubular Large Cell Hyalinizing Sertoli Cell Neoplasia of the Testis: A Report of 8 Cases of a Distinctive Lesion of the Peutz-Jeghers Syndrome. Am J Surg Pathol 2007;31:827-35. https://doi.org/10.1097/PAS.0b013e3180309e33.

[12] Govender D, Sing Y, Chetty R. Sertoli Cell Nodules in the Undescended Testis: A Histochemical, Immunohistochemical, and Ultrastructural Study of Hyaline Deposits. J Clin Pathol 2004;57:802–6. https://doi.org/10.1136/jcp.2004.015982.

Case Report – Urological Oncology

Grand J Urol 2022;2(1):38-41
DOI: 10.5505/GJU.2022.70299

Distant Metastases from a Small Renal Cell Carcinoma in a Renal Allograft Recipient with Prostate Carcinoma: A Case Report

Prostat Kanserli Bir Renal Allogreft Alıcısında Küçük Renal Hücreli Karsinomdan Uzak Metastazlar: Bir Olgu Sunumu

Yunus Colakoglu[1], Deniz Noyan Ozlu[1], Serdar Karadag[1], Zehra Sibel Kahraman[2], Oznur Dilek Ciftci[3], Mehmet Dikec[4], Suheyla Apaydin[5], Ali Ihsan Tasci[1]

[1]Department of Urology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul,Turkey
[2]Department of Pathology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul,Turkey
[3]Department of Nuclear Medicine, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital,Istanbul,Turkey
[4]Department of Nephrology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul,Turkey
[5]Department of Nephrology, Yeditepe University Faculty of Medicine, Istanbul, Turkey

Cite as: Colakoglu Y, Ozlu DN, Karadag S, Sibel Kahraman Z, Dilek Ciftci O, Dikec M, Apaydin S, Tasci AI. Distant metastases from a small renal cell carcinoma in a renal allograft recipient with prostate carcinoma: a case report. Grand J Urol 2022;2(1):38-41.

Submission date: 25 March 2021 **Acceptance date:** 27 August 2021 **Online First:** 27 September 2021 **Publication date:** 20 January 2022

Corresponding Author: Deniz Noyan Ozlu / University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey / noyanozlu@hotmail.com / ORCID ID: 0000-0003-2435-5482

Abstract

Immunosuppressive therapy is related to the increasing frequency of malignancies after transplantation. A small percentage (4.6%) of malignancies seen in kidney transplant patients are renal cell carcinomas (RCC) which occur almost exclusively in native kidneys. The prognosis of RCC largely depends on the presence of metastasis. Metastatic disease is very rare in small renal masses. In this case report, we aimed to present our case of approximately 4 cm-mass of metastatic RCC in our kidney transplant patient. During the examination due to exhaustion and weight loss, multiple suspicious metastatic lesions were observed in non-contrast computed tomography. In the patient who had multiple bone metastases on the whole-body bone scintigraphy, prostate cancer metastasis was considered in the first plan due to a history of prostate cancer before transplantation. This diagnosis could not be supported with prostate-specific membrane antigen-positron emission tomography/computed tomography (PSMA-PET/CT) scan. Whole body 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) was performed. A hypermetabolic mass lesion in the left kidney, multiple hypermetabolic lesions in the liver, in the left aortorenal junction, and in the skeletal system were observed. A biopsy was performed from the metastatic mass in the right lobe of the liver and the result was reported as renal cell carcinoma metastasis. Immunohistochemistry evaluation demonstrated positive staining for PAX-8, CK19, CD10 and negative staining for CK7, CK20, GATA-3, NAPSIN A, TTF-1, PSAP, glutamine synthetase and arginase. With all these findings, it was thought that the primary of metastases was the 4-cm mass in the left native kidney.

Keywords: kidney transplant, distant metastasis, small renal mass, renal cell carcinoma, immunosuppression

Öz

İmmünosüpresif tedavi, transplantasyon sonrası malignitelerin görülme sıklığının artmasıyla ilişkilidir. Böbrek nakilli hastalarda görülen malignitilerin %4,6'sı renal hücreli karsinom (RHK)'dur ve neredeyse sadece nativ böbreklerde ortaya çıkar. RHK'un prognozu büyük ölçüde metastaz mevcudiyetine bağlıdır. Küçük böbrek kitlelerinde metastatik hastalık çok nadir görülmektedir. Biz bu olgu sunumunda, böbrek nakilli hastamızda nativ böbrekte ortaya çıkan yaklaşık 4 santimetrelik metastatik RHK vakamızı sunmayı amaçladık. Genel durum bozukluğu ve kilo kaybı olması nedenli tetkik edilirken çekilen kontratsız bilgisayarlı tomografide multipl, metastaz şüpheli lezyonlar izlendi. Tüm vücut kemik sintigrafisinde multipl kemik metastazları izlenen hastada, nakil öncesi prostat kanseri öyküsü olması nedenli ilk planda prostat kanseri metastazı düşünüldü. Çekilen PSMA-PET/CT'de bu tanı desteklenemedi. Bunun üzerine çekilen tüm vucut FDG-PET/CT'de sol böbrekte hipermetabolik kitle lezyonu, karaciğerde multiple hipermetabolik lezyonlar, sol aorta-renal mesafede multiple hipermetabolik lenf nodları, iskelet sisteminde multiple hipermetabolik lezyonlar izlendi. Karaciğer sağ lobdaki metastatik kitleden biyopsi yapıldı ve patoloji sonucu renal hücreli karsinom metastazı olarak geldi. İmmünohistokimya değerlendirmesi PAX-8, CK19, CD10 için pozitif boyama ve CK7, CK20, GATA-3, NAPSIN A, TTF-1, PSAP, glutamin sentetaz ve arginaz için negatif boyama gösterdi. Tüm bu bulgular eşliğinde, metastazların primer odağının sol nativ böbrekteki 4 santimetrelik kitle olduğu düşünüldü.

Anahtar kelimeler: böbrek nakli, uzak metastaz, küçük renal kitle, renal hücreli karsinom, immünosupresyon

ORCID ID:	**Y. Colakoglu**	0000-0001-6432-765X	**O.D. Ciftci**	0000-0002-7715-5276	**A.I. Tasci**	0000-0002-6943-6676
	S. Karadag	0000-0002-1420-4536	**M. Dikec**	0000-0003-1318-6556		
	Z.S. Kahraman	0000-0003-3902-8265	**S. Apaydin**	0000-0001-6224-405X		

Introduction

Kidney transplantation is one of the best treatment options for end-stage renal disease (ESRD) patients. As the survival of the graft after transplantation prolongs, life expectancy increases. However, patients face late-term complications as they live longer. Malignancies, which are among the most important of these complications, are the second most common cause of death in renal transplantation recipients after cardiovascular diseases [1].

Case

A 62-year-old male patient became a preemptive renal transplant candidate due to ESRD secondary to hypertensive nephropathy. He was also suffering from lower urinary system symptoms and his prostate-specific antigen (PSA) level was 2.36 ng/mL (range: 0-4 ng/ml) during the transplant preparations. Upon monitoring bilateral contour irregularity in the prostate on digital rectal examination, the patient underwent transrectal ultrasound-guided prostate biopsy and the result was prostatic adenocarcinoma with Gleason pattern 6 (3+3) at 1/10 foci. A total of 6720 cGy primary radiotherapy was applied on the patient's prostate in 28 fractions at daily doses of 240 cGy per fraction dose with volumetric modulated arc therapy (VMAT) technique using a linear accelerator device. PSA value was 0.24 ng/mL in the fifth month following radiotherapy.

The patient underwent a robot-assisted living donor kidney transplantion using the kidney donated by his wife. As immunosuppressive treatment, he was given methylprednisolone in the induction period and the maintenance was provided with mycophenolic acid, tacrolimus, and prednisolone.

The patient was followed up with routine annual ultrasonography (US). Two years after surgery, based on the non-contrast computed tomography taken while examining the patient for exhaustion and weight loss, lesions were detected in the left kidney. The largest having dimensions of 38x27 mm which were evaluated as complicated hemorrhagic cysts. There was a lymph node in the left aortorenal junction and hyperdense lesions were noticed on the right iliac bone, right femoral neck, and left pubic bone. There was no evidence of malignancy in the endoscopy and colonoscopy of the patient who also had microcytic iron deficiency anemia. Multiple suspicious metastatic lesions were detected in the liver in the contrast-enhanced magnetic resonance imaging (MR) of the patient, the biggest of them was in segment 8 and had a diameter of 12 mm. Multiple simple and complicated hemorrhagic cortical cysts were noticed in both kidneys. There were multiple lymph nodes around the left renal vein, the biggest of them had the dimensions of 25x16 mm and a mass suggesting renal malignancy in the first place with a size of 39.5x24.5 mm in the upper-middle zone of the left kidney were observed **(Figure 1)**. Multiple metastatic nodules were noticed in all bones in the sections covered in the abdomen MR imaging area.

Whole-body bone scintigraphy of the patient was compatible with multiple bone metastases and prostate cancer metastasis were first considered since the patient had prostate cancer diagnosis before transplantation. The latest PSA level of the patient was 0.28 ng/mL and heterogeneous foci of low-level gallium-68

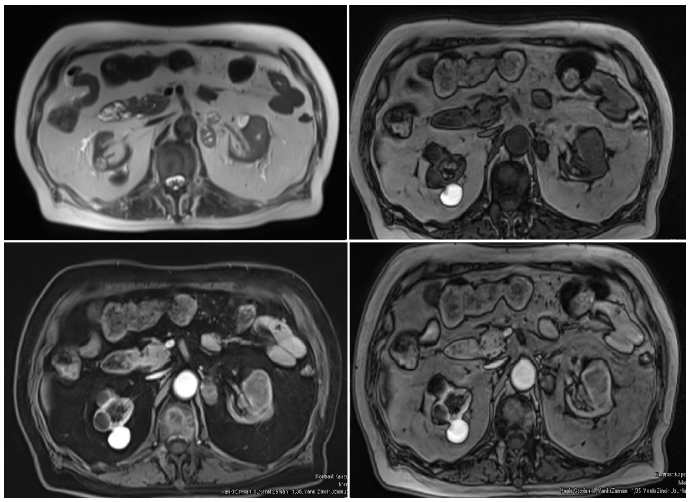


Figure 1. Contrast-enhanced magnetic resonance imaging showing a mass with a size of 39.5x24.5 mm in the upper-middle zone lateral of the left kidney

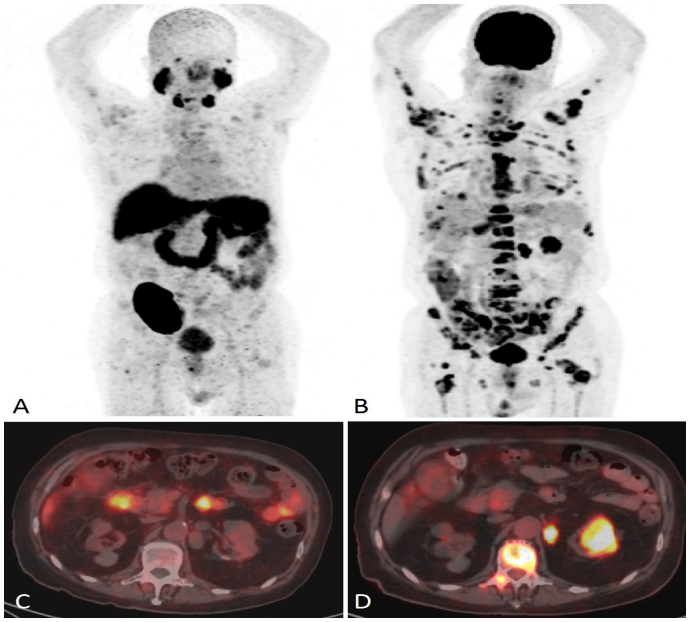


Figure 2A- Coronal image of PSMA-PET/CT: Heterogeneous mild Ga-68 PSMA uptake in the skeletal system and slightly increased heterogeneous Ga-68 PSMA uptake in the prostate gland, B- Coronal image of 18F-FDG PET/CT: A hypermetabolic mass lesion in the left kidney, multiple hypermetabolic lesions in the liver and multiple hypermetabolic lesions in the skeletal system, C- Axial image of PSMA-PET/CT: No pathological Ga-68 PSMA involvement was detected in the 40x32 mm lesion in the left kidney, D- Axial image of 18F-FDG PET/CT: Increased FDG uptake is observed in the 40x32 mm lesion in the left kidney (Suv Max: 18.82)

uptake were observed in the skeletal system in prostate-specific membrane antigen-positron emission tomography/computed tomography (PSMA-PET/CT) and Ga-68 PSMA uptake was not observed in other metastatic lesions. Ga-68 PSMA uptake was detected in the lesion in the left kidney. Since diagnosis of prostate cancer metastasis was not quite possiblly made based on these findings, whole body 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) was performed. A hypermetabolic mass lesion in the left

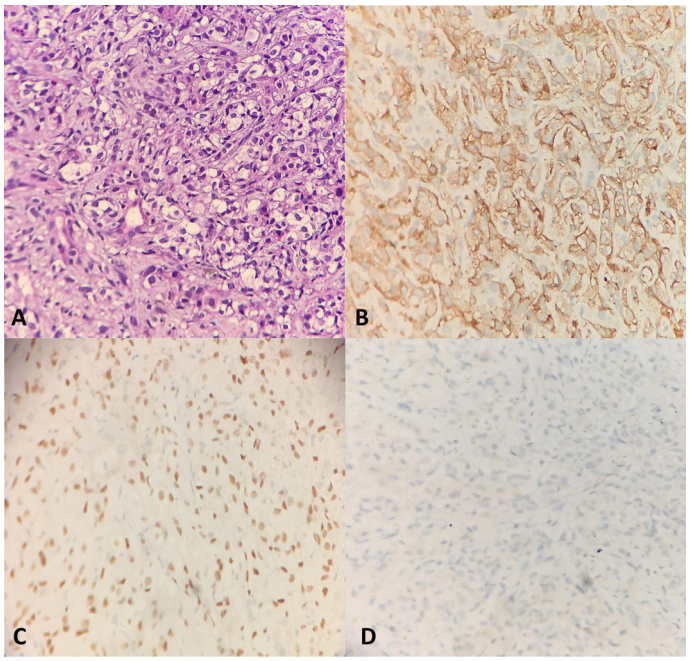


Figure 3. Core needle biopsy from the metastatic mass in the right lobe of the liver; diffuse tumoral infiltration that makes nesting locally, with large hyperchromatic nucleus and clear cytoplasm A- Hematoxylin & Eosin x400, B- Positive staining for CD10, C- Positive staining for PAX-8, D- Negative staining for PSAP

kidney, multiple parenchymal and subpleural millimetric nodules in both lung parenchymas, multiple hypermetabolic lesions in the liver, and the skeletal system multiple hypermetabolic lymph nodes in the left aortorenal junction, and increased uptake of contrast material in the area of mural induration in the distal part of the duodenum were observed **(Figure 2)**.

A core needle biopsy was performed from the metastatic mass in the right lobe of the liver, and the result was renal cell carcinoma (RCC) metastasis **(Figure 3)**. Immunohistochemistry evaluation demonstrated positive staining for PAX-8, CK19, CD10 and negative staining for CK7, CK20, GATA-3, NAPSIN A, TTF-1, PSAP, glutamine synthetase and arginase. All these findings suggested that the primary focus of these metastases was the 4-cm mass in the left native kidney. The patient was started on sunitinib therapy and palliative radiotherapy was planned for bone metastases.

Discussion

At the present time, renal transplantation has become one of the primary treatment options in ESRD patients because of its superiority to dialysis in terms of cost-efficiency and quality of life [2]. Malignancies constitute one of the most important complications limiting survival in these patients, and 4.6% of malignancies seen in kidney transplant patients are metastases from RCC [3]. Renal malignancies are the third most common cause of death associated with malignancy at a rate of 9.8% [4].

The mechanism of RCC development in kidney transplant patients is still not fully elucidated. As is known, the best-defined risk factors for RCC are smoking, hypertension, obesity and family history [5]. In addition to the well-known general risk factors, in transplant kidney recipients; the type of immunosuppression, primary disease of the native kidney, recipient/donor age, duration of dialysis before transplantation, and presence of microscopic hematuria are other risk factors for the development of RCC [6].

To maintain long-term allograft function, use of potent immunosuppressive agents is imperative to prevent acute and chronic allograft rejection. Immunosuppressive treatment is related to the increase in the prevalence of malignancies after transplantation [3]. It is also well known that RCC is an immunogenic phenotype that is sensitive to immunotherapy by inducing a potential immune response. It has been shown that RCC cells could escape from the immune cells such as T-cells by down-regulating HLA molecules in immunosuppressed recipients [7].

As in our patient, RCC occurs almost only in native kidneys in transplant recipients [3]. The risk of RCC in native kidneys in the acquired cystic disease of the kidney and end-stage renal failure is 3-7%, which is nearly 100 times its incidence in the general population [8]. In the recent study performed by Eggers et al., prevalence of RCC was found to be 1.2% in native kidneys and 0.4% in allografts [9]. In the study of Moris et al., the average time until the diagnosis of RCC in native kidneys after transplant was 151 months. Most of these patients were diagnosed incidentally. Compared to other malignancies (stomach, lung, colorectal, prostate, and breast cancers), RCC was observed at a later stage of the disease in these patients. However, its prognosis was better compared to other malignancies, except for breast cancer [10].

The prognosis of RCC largely depends on the presence or absence of metastatic disease. The most appropriate treatment for the non-metastatic disease is surgery, and the associated survival is prolonged, while 5-year survival rate in metastatic disease decreases to 10% [11]. The incidence of metastatic disease is directly proportional to the size of the primary mass. Metastasis is less likely in masses smaller than 5 cm in diameter [12].

Most RCCs detected in transplant recipients are asymptomatic, usually incidentally diagnosed, and have a good prognosis because they are mostly low grade and stage. However, the prognosis of metastatic RCC is poor [10]. Metastatic disease is quite rare in small renal masses and thus active surveillance can also be an option for these lesions. The primary mass of our patient can also be defined as a small renal mass since it was only 4 cm in diameter. In the retrospective study conducted by Thompson et al., among 781 patients with a tumor mass less than 3 cm in diameter, only one patient had metastatic disease at diagnosis [13].

RCC, which makes up about 2% of all cancers, has been seen more frequently in the last 50 years with the development of imaging techniques [12]. Most transplant units do not take a specific approach to screening for RCC in native kidneys or renal allografts of renal transplant recipients due to its low incidence. Studies for modeling the performance of US scanning has shown that its cost-effectiveness is low. According to Wong et al., with routine annual US screening for RCC, survival can increase by 25%. However, there is no evidence of its cost-effectiveness, even for kidney recipients at high risk for disease [14].

Studies contrary to this view are also present. Klein et al. recommended US once in every two years for the early detection of RCC [5]. Eggers et al. supported this approach and even

recommended annual screening for patients getting ready for a kidney transplant and ESRD patients receiving dialysis treatment [9]. Moris et al. also defended the necessity of routine ultrasound scanning for renal transplant patients during the first five years after transplantation for early stage detection of a malignancy [10]. In our institute, we also perform screening with US annually after renal transplantation.

In kidney transplant patients, immunosuppressive agents constitute a risk factor for the development of malignancy. Renal malignancies are an important cause of morbidity and mortality in these patients. Survival in RCC is significantly associated with the presence of metastases, which can be rarely seen in small renal masses. In this respect, the early diagnosis of RCC provides an advantage in terms of survival. Because of the risk of RCC, regular US scanning of the native kidneys of kidney recipients should be considered.

Ethics Committee Approval: N / A.
Informed Consent: An informed consent was obtained from the patient.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – Y.C., D.N.O.; Design – S.K., Z.S.K.; Supervision – Y.C., D.N.O.; Resources – S.K., Z.S.K.; Materials – Y.C., S.K.; Data Collection and/or Processing – Z.S.K., D.N.O.; Analysis and/or Interpretation – Y.C., S.A.; Literature Search – Y.C., S.A.; Writing – Y.C., D.N.O.; Critical Review – Y.C.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Végsö G, Toronyi E, Hajdu M, Piros L, Görög D, Deák PA, et al. Renal Cell Carcinoma of the Native Kidney: A Frequent Tumor After Kidney Transplantation with Favorable Prognosis in Case of Early Diagnosis. Transplant Proc 2011;43:1261-3. https://doi.org/10.1016/j.transproceed.2011.03.068.

[2] Moris D, Lu L, Qian S. Mechanisms of Liver-induced Tolerance. Curr Opin Organ Transplant 2017;22:71-8. https://doi.org/10.1097/MOT.0000000000000380.

[3] Penn I. Primary Kidney Tumours Before and After Renal Transplantation. Transplantation 1995;59:480-5. https://pubmed.ncbi.nlm.nih.gov/7878750/.

[4] Farrugia D, Mahboob S, Cheshire J, Begaj I, Khosla S, Ray D, et al. Malignancy-related Mortality Following Kidney Transplantation is Common. Kidney Int 2014;85:1395-403. https://doi.org/10.1038/ki.2013.458.

[5] Klein JA, Gonzalez SA, Fischbach BV, Yango AF, Rajagopal A, Rice KM, et al. Routine Ultrasonography Surveillance of Native Kidneys for Renal Cell Carcinoma in Kidney Transplant Candidates. Clin Transplant 2016;30:946-53. https://doi.org/10.1111/ctr.12769.

[6] Filocamo MT, Zanazzi M, Li Marzi V, Guidoni L, Villari D, Dattolo E, et al. Renal Cell Carcinoma of Native Kidney After Renal Transplantation: Clinical Relevance of Early Detection. Transplant Proc 2009;41:4197-201. https://doi.org/10.1016/j.transproceed.2009.08.082.

[7] Tomita Y, Nishiyama T, Fujiwara M, Sato S. Immunohistochemical Detection of Major Histocompatibility Complex Antigens and Quantitative Analysis of Tumour-infiltrating Mononuclear Cells in Renal Cell Cancer. Br J Cancer 1990;62:354-9. https://doi.org/10.1038/bjc.1990.296.

[8] Tickoo SK, dePeralta-Venturina MN, Harik LR, Worcester HD, Salama ME, Young AN, et al. Spectrum of Epithelial Neoplasms in End-stage Renal Disease: An Experience from 66 Tumor-bearing Kidneys with Emphasis on Histologic Patterns Distinct from Those in Sporadic Adult Renal Neoplasia. Am J Surg Pathol 2006;30:141-53. https://doi.org/10.1097/01.pas.0000185382.80844.b1.

[9] Eggers H, Güler F, Ehlers U, Ivanyi P, Peters I, Grünwald V. Renal Cell Carcinoma in Kidney Transplant Recipients: Descriptive Analysis and Overview of a Major German Transplant Center. Future Oncol 2019;15:3739-50. https://doi.org/10.2217/fon-2019-0397.

[10] Moris D, Kakavia K, Argyrou C, Garmpis N, Bokos J, Vernadakis S, et al. De Novo Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients: A Single-center Experience. Anticancer Res 2017;37:773-9. https://doi.org/10.21873/anticanres.11376.

[11] Tosoian JJ, Cameron JL, Allaf ME, Hruban RH, Nahime CB, Pawlik TM, et al. Resection of Isolated Renal Cell Carcinoma Metastases of the Pancreas: Outcomes from the Johns Hopkins Hospital. J Gastrointest Surg 2014;18:542-8. https://doi.org/10.1007/s11605-013-2278-2.

[12] Mai KT, Landry DC, Robertson SJ, Commons AS, Burns BF, Thijssen A, et al. A Comparative Study of Metastatic Renal Cell Carcinoma with Correlation to Subtype and Primary Tumor. Pathol Res Pract 2001;197:671-5. https://doi.org/10.1078/0344-0338-00144.

[13] Thompson RH, Hill JR, Babayev Y, Cronin A, Kaag M, Kundu S, et al. Metastatic Renal Cell Carcinoma Risk According to Tumor Size. J Urol 2009;182:41-5. https://doi.org/10.1016/j.juro.2009.02.128.

[14] Wong G, Howard K, Webster AC, Chapman JR, Craig JC. Screening for Renal Cancer in Recipients of Kidney Transplants. Nephrol Dial Transplant 2011;26:1729-39. https://doi.org/10.1093/ndt/gfq627.

Case Report – Andrology

Grand J Urol 2022;2(1):42-4
DOI: 10.5505/GJU.2022.44153

Inguinal Fistula by Suture Granuloma Post Microsurgical Varicocelectomy: A Rare Entity

Mikrocerrahi Varikoselektomi Sonrası Sütür Granülomu ile Oluşan İnguinal Fistül: Nadir Bir Olgu

Ayhan Karakose, Yasin Yitgin

Department of Urology, Istinye University Faculty of Medicine, Istanbul, Turkey

Cite as: Karakose A, Yitgin Y. Inguinal fistula by suture granuloma post microsurgical varicocelectomy: a rare entity. Grand J Urol 2022;2(1):42-4.

Submission date: 16 July 2021 **Acceptance date:** 09 October 2021 **Online First:** 20 October 2021 **Publication date:** 20 January 2022

Corresponding Author: Yasin Yitgin / Istinye University Faculty of Medicine, Department of Urology, Istanbul, Turkey / yasinyitgin@hotmail.com / ORCID ID: 0000-0003-1111-6941

Abstract

Varicocele is dilatation and tortuosity of the vessels in the pampiniform plexus of spermatic cord and occurs in 11.7% of adult men. Varicocelectomy may lead to various complications such as hydrocele, testicular atrophy, haematoma, infection, damage of nerves and recurrence. A 22-year-old man presented after varicocelectomy with a rare postoperative complication of a fistula. The fistula tract was removed en bloc. The patient had a history of varicocelectomy, suggesting suture reaction. The fact that it is a rare complication of varicocelectomy makes our case interesting.

Keywords: varicocele, inguinal fistula, suture foreign body, suture granuloma, varicocele surgery

Öz

Varikosel, spermatik kord damarlarının anormal genişlemesi ve kıvrımlaşması olup yetişkin erkeklerin %11.7'sinde görülür. Varikoselektomi ameliyatı hidrosel, testis atrofisi, hematom, enfeksiyon, sinir hasarı ve nüks gibi çeşitli komplikasyonlara yol açabilir. 22 yaşında erkek hasta varikoselektomi sonrası kasık fistülü gelişmesi sonrası varikoselektominin nadir bir komplikasyonu ile başvurdu. Fistül traktı en blok halinde çıkarıldı. Hastanın sütür reaksiyonunu düşündüren varikoselektomi öyküsü vardı. Olgumuz varikoselektomi sonrası nadir görülen bir komplikasyon olması nedeniyle ilginçtir.

Anahtar kelimeler: varikosel, inguinal fistül, sütür yabancı cisim, sütür granülomu, varikosel cerrahisi

ORCID ID: A. Karakose 0000-0003-3905-1772

Introduction

Varicocele is dilatation and tortuosity of the vessels in the pampiniform plexus of spermatic cord, while 11.7% of adult men and 25.4% of men with abnormal semen analysis have varicocele. Also, the most common correctable cause of male infertility is varicocele. It affects 19 to 41% of men with primary, and 45 to 81% of men with secondary infertility [1].

Treatment of varicocele has been the subject of discussion in recent years. Many studies have shown that surgical varicocelectomy significantly improves semen parameters not only in men with clinical varicoceles, but also in men with non-obstructive azoospermia [2].

Inguinal varicocelectomy may lead to several complications including hydrocele which is the most frequent adverse postoperative outcome occurring in 3% of patients followed by testicular atrophy, recurrence, haematoma and infection. Other complications include damage to the ilioinguinal, genitofemoral, or obturator nerves. These complications are significantly more common in non-microsurgical methods [3,4].

In this report, we present a rare case of fistula occurring after microsurgical varicocelectomy and extending from the spermatic canal up to the skin of inguinal area and led to persistent wound formation. We aimed to emphasize the risk of fistula formation after varicocelectomy and to share our experience in the treatment of this complication.

Case

A 22-year-old male patient presented to urology department of our hospital with a rare surgical complication developed one year after bilateral varicocelectomy. The patient complained of a persistent subcutaneous inguinal swelling that intermittently discharged fluid through the skin. Varicocelectomy had been performed by a different surgeon with open microsurgery in the subinguinal region on both sides.

During physical examination, we detected bilateral subinguinal incision scar, a stiff palpable fistula tract extending from the inguinal canal to skin and an oozing purulent discharge. Ultrasonography (US) demonstrated a 17-mm long 5-mm thick hypoechoic tract extending from the spermatic canal to the skin **(Figure 1A)**. Blood levels of acute phase reactants were within normal ranges.

The operation was started using the previous incision line. A catheter was placed into the fistula tract which was freed from surrounding tissues by dissections **(Figures 1B-C).** At the junction of the spermatic cord and the fistula tract, silk suture materials causing granulomatous inflammatory reaction were detected. The fistula tract was removed en bloc. After complete excision of the fistula tract, and 2 pre-tied silk sutures were removed **(Figure 1D)**. Pathological examination showed inflammatory granuloma characterised by giant-cell reaction **(Figure 2)**. There was no recurrence of the fistula or the presence of additional findings during the 6-month postoperative follow-up.

Discussion

Varicocele can be treated using methods such as macroscopic or microscopic open surgery, laparoscopic surgery, embolization and sclerotherapy. It has been reported that complications such as recurrence and hydrocele are the least common after microsurgical varicocelectomy among varicocele treatment methods. However, it was stated that there was no significant difference in hematoma and infection rates between varicocele treatment methods [5].

There is no available data in the literature regarding the incidence of inguinal fistula after varicocele surgery. In our case, the patient developed inguinal fistula caused by suture granuloma

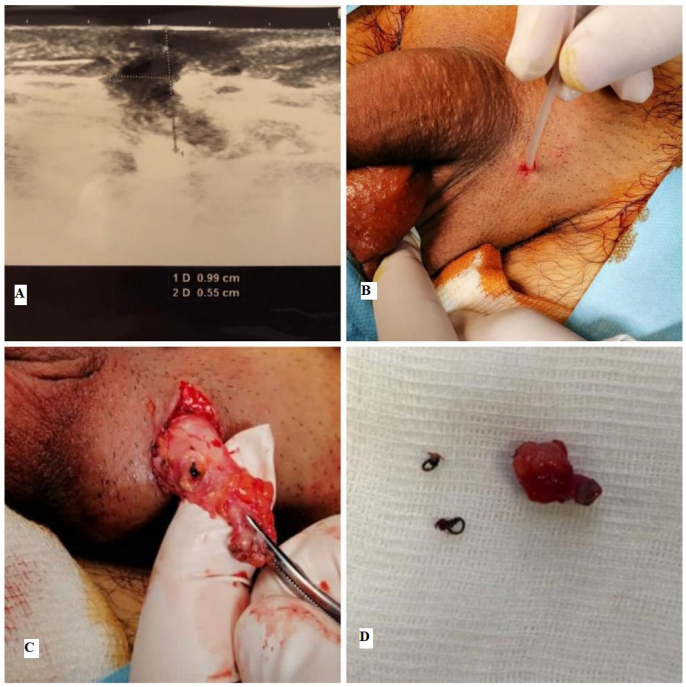


Figure 1.A- Ultrasound image of the fistula tract B- A catheter was placed into the fistula C- Silk sutures and granuloma D- En-block fistula tract and total sutures removed

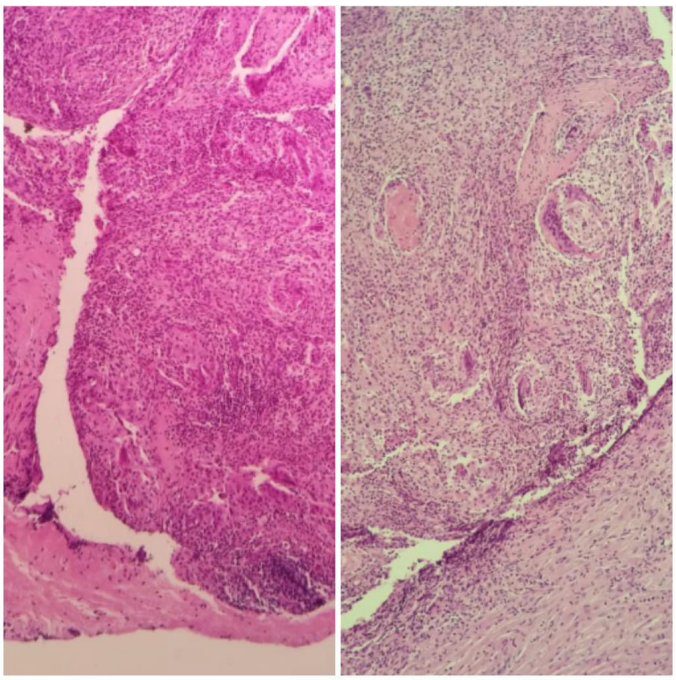


Figure 2. Microscopic view of fistula and inflammatory giant cells (H-E x100)

which occurred after microsurgical inguinal varicocelectomy.

A suture granuloma is a rare surgical complication. It is an inflammatory, benign and granulomatous lesion that develops as a foreign body reaction to non-absorbable suture material at the surgery site. It may manifest as erythema, swelling, pain and leakage from the incision line. Silk suture, which is produced from silkworm larva and consists of protein fibers, is the most common non-absorbable suture material used. This silk suture is slowly degraded in the tissue over 2 years [6]. In the early postoperative period, an inflammation along the suture line can cause suppuration and sinus formation. However, a delayed inflammatory reaction of the suture is rare [7]. The variable time interval between the postoperative development of suture granuloma and subsequent formation of fistula has been reported by different authors as 2 years or few months to years [8,9]. In our case, this time interval was one year.

The pathogenesis of suture granuloma involves development of two succesive reactions. Initial reaction in the tissue reflects the severity of injury caused by the passage of the needle, and then after the initial reaction has subsided, the suture material causes a specific inflammatory reaction [8].

To our knowledge, we are presenting the first case of suture granuloma with inguinal fistula developed after microsurgical inguinal varicocelectomy, which therefore makes our case interesting.

In conclusion, we recommend the use of absorbable sutures or metallic surgical clips in varicocele surgeries to avoid such complications.

Ethics Committee Approval: N / A.
Informed Consent: An informed consent was obtained from the patient.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – YY.; Design – YY.; Supervision – AK.; Resources – AK.; Materials – AK.; Data Collection and/or Processing – AK.; Analysis and/or Interpretation – YY.; Literature Search – YY.; Writing – YY.; Critical Review – AK.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors have declared that they did not receive any financial support for the realization of this study.

References

[1] Agarwal A, Deepinder F, Cocuzza M, Agarwal R, Short RA, Sabanegh E, et al. Efficacy of varicocelectomy in improving semen parameters: new meta-analytical approach. Urology 2007;70:532-8. https://doi.org/10.1016/j.urology.2007.04.011.

[2] Esteves SC, Miyaoka R, Roque M, Agarwal A. Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and meta-analysis. Asian J Androl 2016;18:246-53. https://doi.org/10.4103/1008-682X.169562.

[3] Amelar RD. Early and late complications of inguinal varicocelectomy. J Urol 2003;170:366-9. https://doi.org/10.1097/01.ju.0000074975.79734.17.

[4] Wang J, Xia SJ, Liu ZH, Tao L, Ge JF, Xu CM, et al. Inguinal and subinguinal micro-varicocelectomy, the optimal surgical management of varicocele: a meta-analysis. Asian J Androl 2015;17:74-80. https://doi.org/10.4103/1008-682X.136443.

[5] Çayan S, Orhan I, Akbay E, Kadıoğlu A. Systematic review of treatment methods for recurrent varicoceles to compare post-treatment sperm parameters, pregnancy and complication rates. Andrologia 2019;51:e13419. https://doi.org/10.1111/and.13419.

[6] Eryilmaz R, Demir M, Aslan R. Rare complication of varicocelectomy: Suture granuloma. Andrologia 2019;51;e13256. https://doi.org/10.1111/and.13256.

[7] Javalgi AP, Arakeri SU. Post thyroidectomy suture granuloma: a cytological diagnosis. J Clin Diagn Res 2013;7:715-7. https://doi.org/10.7860/JCDR/2013/5366.2890.

[8] Chung YE, Kim EK, Kim MJ, Yun M, Hong SW. Suture granuloma mimicking recurrent thyroid carcinoma on ultrasonography. Yonsei Med J 2006;47:748-51. https://doi.org/10.3349/ymj.2006.47.5.748.

[9] Karaköse A, Alp T, Güner ND, Çıtlak MB, Aydın S. The place of andrological cases in our general urology practice. Turk J Urol 2010;36:49-54. https://turkishjournalofurology.com/EN/march-2010-002.

Letter to the Editor – Endourology

Grand J Urol 2022;2(1):45-6
DOI: 10.5505/GJU.2022.08208

Re: Huseynov et al.: The Effects of Previous Renal Stone Surgery on Percutaneous Nephrolithotomy Outcomes (Grand J Urol 2021;1:18-21)

Re: Huseynov ve ark.: Geçirilmiş Böbrek Taşı Cerrahisinin Perkütan Nefrolitotomi Sonuçları Üzerine Etkileri (Grand J Urol 2021;1:18-21)

Emrullah Sogutdelen, Mustafa Kucukyangoz

Department of Urology, Abant Izzet Baysal University Faculty of Medicine, Bolu, Turkey

Cite as: Sogutdelen E, Kucukyangoz M. Re: Huseynov et al.: The effects of previous renal stone surgery on percutaneous nephrolithotomy outcomes (Grand J Urol 2021;1:18-21). Grand J Urol 2022;2(1):45-6.

Submission date: 21 April 2021 **Acceptance date:** 28 April 2021 **Online First:** 30 April 2021 **Publication date:** 20 January 2022

Corresponding Author: Emrullah Sogutdelen / Abant Izzet Baysal University Faculty of Medicine, Department of Urology, Bolu, Turkey / esdelen@gmail.com / ORCID ID: 0000-0002-1454-5672

Dear Editor,

I read the article by Huseynov et al., [1] in which they examined the effects of previous renal stone surgery on percutaneous nephrolithotomy outcomes with great interest. They concluded that previous renal stone surgery increases the risk of residual stone with a similar complication rate. However, I would like to highlight some issues regarding the methodology and the results of this study.

Using the method of percutaneous nephrolithotomy (PNL) in the treatment of renal stones 2 cm and greater is a gold standard according to European Association of Urology guidelines [2]. By increasing surgeon experience and technological development of tools using in PNL surgery increase the success of the surgery and decrease the complication rate. However, it is known that the success of PNL is also affected by some other influencers such as hydronephrosis, stone location, and as well as Hounsfield unit (HU) [3]. Gucuk et al. [4] showed that the higher HU values increase the stone-free rate and HU is an independent predictive factor affecting the success of PNL. In the study by Huseynov et al., the higher HU may influence the stone-free rate of patients in primary PNL. Therefore, we thought that it must be mentioned in the discussion.

Another issue that we have to be clear about is estimated blood loss and stone size. In addition to the decrease in hemoglobin level, the estimated blood loss during the surgery was analyzed but not mentioned how was calculated in the relevant section. Furthermore, calculation of stone size was also mentioned as it was multiplying two dimensions but in the result section, it was expressed the volume of stone in mm^3 which means multiplying the three dimensions. For this reason, we are curious about your method of calculating the estimated blood loss during the operation and the technique of preoperative stone size calculation.

As a result, we think that other factors including stone location in the kidney affects the success PNL. Hence, it should be examined in the study, otherwise, mentioned in the limitations of this study.

Ethics Committee Approval: This article does not contain any studies with human participants performed by the author.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.S., M.K.; Design – E.S., M.K.; Supervision – E.S., M.K.; Resources – E.S., M.K.; Materials – E.S., M.K.; Data Collection and/or Processing – E.S., M.K.; Analysis and/or Interpretation – E.S., M.K.; Literature Search – E.S., M.K.; Writing – E.S., M.K.; Critical Review – E.S., M.K.

Conflict of Interest: The author declares that he has no conflict of interest.

Financial Disclosure: No grants or funding was provided for this study.

ORCID ID: M. Kucukyangoz 0000-0003-4766-7454

References

[1] Huseynov J, Kalfazde N, Guner E. The Effects of Previous Renal Stone Surgery on Percutaneous Nephrolithotomy Outcomes. Grand J Urol 2021;1(1):18-21. https://doi.org/10.5222/gju.2021.47966.

[2] Türk C, Neisius A, Petřík A, Seitz C, Skolarikos A, Somani B, et al. EAU Guidelines on Urolithiasis. Eur Assoc Urol 2016;69:475–82. https://uroweb.org/guideline/urolithiasis/.

[3] Jabrayilov H, Koparal M, Gürocak S, Küpeli B, Tan M. Factors Affecting the Success Rate of Percutaneous Nephrolithotomy in Paediatric Patients. J Clin Med 2018;7:43. https://doi.org/10.3390/jcm7030043.

[4] Gücük A, Üyetürk U, Öztürk U, Kemahli E, Yildiz M, Metin A. Does the hounsfield unit value determined by computed tomography predict the outcome of percutaneous nephrolithotomy? J Endourol 2012;26:792–6. https://doi.org/10.1089/end.2011.0518.