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Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR,

editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study KidneyInt: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktivitelerive Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. SağlıkBilimleriEnstitüsü, DoktoraTezi. 2007.

Manuscripts accepted for publication, not published yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub ahead of print articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. DiagnIntervRadiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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RESEARCH ARTICLE

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RESEARCH / ARAŞTIRMA
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THE EFFECT OF INTRAOPERATIVE URETERAL CATHETER USAGE ON BACTERIURIA AND COMPLICATIONS IN DECEASED DONOR RENAL TRANSPLANTATION*

KADAVERİK BÖBREK NAKLİNDE İNTRAOPERATİF ÜRETERAL KATETER KULLANIMININ BAKTERİÜRİ VE KOMPLİKASYON OLUŞUMUNA ETKİSİ

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ABSTRACT

Objective: The use of ureteral catheters in renal transplantation is controversial. We aimed to investigate the effect of intraoperative catheter use on bacteriuria and urological complications in deceased donor renal transplantation.

Material and Method: Study design is cross sectional study. A total of 150 patients who underwent deceased donor renal transplantation in the Istanbul University Istanbul Faculty of Medicine Transplantation Unit were included in the study. Ureteral catheters were used in 72 patients but not in the remaining 78. The two patient groups were compared in terms of the incidence of early postoperative urological complications and bacteriuria in the first month after transplantation.

Result: Ureteral catheter usage significantly reduced the frequency of early postoperative urological complications (p=0.004). The frequency of bacteriuria in the first month after transplantation was significantly lower in patients using ureteral catheters (p<0.001). In patients with ureteral catheters, the duration of anti-thymocyte globulin administration (p=0.003) and Foley catheter usage (p<0.001) was found to be significantly shorter than in the group without ureteral catheters.

Conclusion: The routine use of ureteral catheters results in fewer urological complications in patients with deceased donor renal transplantation. Catheter use does not increase, and even lowers, the risk of early bacteriuria. The significant reduction in early

ÖZET

Amaç: Kadaverik böbrek naklinde, intraoperatif üreteral kateter kullanımının bakteriüri ve ürolojik komplikasyonlara olan etkisini incelemeyi amaçladık.

Gereç ve Yöntem: Bu kesitsel çalışmada İstanbul Üniversitesi, İstanbul Tıp Fakültesi Transplantasyon Ünitesi'nde kadavradan böbrek nakli yapılan 150 hasta çalışmaya alındı. Üreteral kateter kullanılmayan 78 hasta ve üreteral kateter kullanılan 72 hasta olduğu tespit edildi. Bu iki hasta grubu postoperatif erken dönem ürolojik komplikasyonlar, nakil sonrası 1. ayda görülen bakteriüri varlığı açısından karşılaştırıldı.

Bulgular: Üreteral kateter kullanılan olgularda, postoperatif erken dönem ürolojik komplikasyon sıklığı anlamlı düzeyde azalmıştır (p=0,004). İlginç bir şekilde üreteral kateter kullanılan hastalarda, nakil sonrası birinci ayda görülen bakteriüri sıklığı da anlamlı düzeyde azalmıştır (p<0,001). Üreteral kateter kullanılan hastalarda, anti-timosit globulin kullanım süresi (p=0,003) ve foley kateter kullanım süresi (p<0,001) üreteral kateter kullanılmayan gruba göre anlamlı düzeyde kısa saptanmıştır.

Sonuç: Kadaverik böbrek nakli olgularında rutin üreteral kateter kullanımında ürolojik komplikasyonlar daha az görülmektedir. Kateter kullanılan grupta erken bakteriüri görülme riskinin artmadığı hatta azalmış olduğu saptanmıştır. Bu anlamlı düzeyde azalmanın, üreteral kateterli hasta grubunda anti-timosit glo-

*This study was derived from the General Surgery Thesis of the corresponding author.

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bacteriuria in patients with ureteral catheters is associated with significantly shorter durations of anti-thymocyte globulin and Foley catheter usage. Therefore, the routine use of intraoperative ureteral catheters is recommended in deceased donor renal transplantation.

Keywords: Bacteriuria, complications, deceased donor renal transplantation, ureteral catheter

bulin kullanım süresi ve foley kateter kullanım süresinin anlamlı düzeyde kısa olması ile ilşkili olduğu düşünülmüştür. Bu nedenle kadaverik böbrek naklinde rutin intraoperatif üreteral kateter kullanımı önerilmektedir.

Anahtar Kelimeler: Bakteriüri, komplikasyonlar, kadaverik böbrek nakli, üreteral kateter

INTRODUCTION

End-stage renal disease is an important health issue that requires resolution in both socioeconomic and medical terms. The gold standard in renal replacement therapy is renal transplantation. Renal transplantation can be performed from a deceased or living donor.

Urological complications such as urinary obstructions, urinary leakage, and urinomas may occur after renal transplantation. The frequency of these complications is 4-8% and resulting mortality is very rare (1,2). Major urological complications after renal transplantation are usually seen in the early period (first three months) after transplantation and are usually caused by vesicoureteral anastomosis (3). These complications may cause morbidity and graft loss in patients (4). Ureteral ischemia is thought to be mainly responsible for early ureteral complications in cases when there are no technical complications (5).

The use of ureteral catheters in renal transplantation, although its therapeutic benefit is controversial, is thought to be advantageous in facilitating the creation of a waterproof anastomosis between the ureter and bladder, and reducing anatomical folding (3,6). There are studies showing that the use of prophylactic intra-operative ureteral catheters positively affects the graft function by reducing urological complications in patients with deceased donor renal transplantation (7). There are reports suggesting that good vascularization and a non-tense anastomosis are effective in preventing both early and late ureteral complications. They recommend ureteral catheter usage only in difficult anastomoses or in situations where the vesicoureteral anastomotic blood supply may be compromised (8).

The most serious complication of catheter use is the possibility of an increase in the frequency and severity of UTIs. In one study, the use of ureteral catheters was associated with an increase in UTIs (9). On the other hand, there are studies arguing that the use of ureteral catheters is not associated with bacteriuria (10).

Other complications that may be caused by ureteral catheters include permanent hematuria, bladder discomfort, migration of the catheter, broken catheter, calcification of the catheter, and complications seen during removal of the catheter (7).

The aim of this study is to investigate the effect of ureteral catheter use in terms of early urinary complications, bacteriuria after renal transplantation in order to evaluate the decision to use ureteral catheters in renal transplantation due to controversial results.

MATERIAL and METHODS

A total of 151 patients who underwent deceased donor renal transplantation in the Istanbul University Istanbul Faculty of Medicine Transplantation Unit between 2006 and 2016 were retrospectively analyzed after approval of the Ethical Committee of Istanbul Faculty of Medicine was obtained (Date: 10.08.2018, No:13). Since most of the data of one of the patients were unavailable, this patient was excluded from the statistical analysis. The remaining 150 patients were included in the study.

Ureteral catheters were not used in patients with deceased donor renal transplantation in our clinic between 2006 and 2011, but have been routinely used since 2011, due to the change of the decision of the surgical team. Patients were divided into two groups depending on the use of ureteral catheters. Seventy-eight patients without ureteral catheter were defined as Group 1, and 72 patients with ureteral catheter were defined as Group 2.

All the clinical findings and laboratory results of the patients, both pre- and postoperative data, were obtained from our hospital's computer registry system, patient epicrisis, patient follow-up files, and pre-transplant patient preparation forms.

The collected data included the sex of the patients, the pre-transplant dialysis method (hemodialysis or peritoneal dialysis) used, the use of anti-thymocyte globulin (ATG) after transplantation, the length of ATG administration (days) and total dose (mg) used, the use of basiliximab, the type of calcineurin inhibitor used (cyclosporine or tacrolimus), the use of antibiotherapy, delayed graft function in the early period (whether dialysis was required in the first postoperative week), urological complications (urinary leak or urinary stenosis) in the early (first three months) postoperative period, the use of ureteral catheters, duration of Foley catheter use, whether bacteriuria was seen in the first month (early period) after transplantation, the time of bacteriuria detection (postoperative day), whether the urine culture was positive at the time

the positive urine sample was given (day), and the deceased donor kidney cold ischemia time.

Surgical procedures

All of the cadaver donor renal transplantations included in the study were performed by the same surgical team. All kidneys were transplanted extraperitoneally and heterotopically into the iliac fossa. Arterial anastomosis was performed between the renal artery and the external iliac artery; vein anastomosis was performed between renal vein and the external iliac vein as an end-to-side anastomosis. In the use of right kidneys, the renal vein was anastomosed after tubular lengthening by using the inferior vena cava. Ureteral anastomosis was performed in the form of ureteroneocystostomy using the Lich-Gregoir technique to create a submucosal anti-reflux mechanism.

The two groups were compared in terms of the immunosuppressive treatments they received after transplantation, the duration of Foley catheter usage, the rate of urological complications in the postoperative period, the rate of bacteriuria (positive urine culture), the time when bacteriuria started, the duration of deceased donor kidney cold ischemia, and postoperative delayed graft function.

Statistical analysis

Mean and standard deviation values, and minimum and maximum values were calculated for the descriptive statistics of continuous variables. Frequency distributions and ratios were calculated for the descriptive statistics of categorical variables.

The Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) program was used for statistical analysis. While evaluating the data of the study, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio), the Shapiro Wilks test and box plot graphics were used to evaluate the suitability of variables to normal distribution.

Normally distributed variables were compared between the two groups using the t-test for independent groups. The Mann Whitney U test was used for non-normally distributed data. The chi-square test and Fisher's Exact test were used for the comparison of qualitative data. The results were evaluated at the 95% confidence interval, and $p<0.05$ was considered to be statistically significant.

RESULTS

Of the 150 patients included in the study, 55.3% (n=83) were female and, 44.7% (n=67) were male.

When the type of dialysis used before transplantation was examined, 80% of the patients (n=120) had hemodialysis, 12.7% (n=19) had peritoneal dialysis, and 7.3% (n=11) had hemodialysis and peritoneal dialysis at different times.

It was found that 98% of the patients (n=147) received ATG after the deceased donor renal transplantation. The duration of ATG use ranged from 2 to 23 days, with an average of 10.32±6.07 days, while the doses ranged from 50 to 3.236 mg with an average dose of 974.09±6,174.52 mg. Basiliximab was used in 38.7% (n=58) of the patients, while 146 patients received calcineurin inhibitors after transplantation. Of the latter 146 patients, tacrolimus was used in 42.5% (n=62) and cyclosporine in 57.5% (n=84).

Seventy-eight patients without ureteral catheters were defined as group 1, and 72 patients in whom ureteral catheters were used were defined as group 2. When the immunosuppressive treatment received by the patients after deceased donor renal transplantation was compared according to the patient group (use and non-use of ureteral catheters), no statistically significant difference was found between the two groups in terms of the rate of use or dose of ATG ($p>0.05$). The duration of ATG use was found to be significantly shorter in group 2 patients compared to group 1 ($p=0.003$) (Table 1).

Table 1: Immunosuppressive treatments received by patients according to use of ureteral catheters

		UC (-)	UC (+)	Test value	p-value
ATG usage	No	2 (2.6)	1 (1.4)	0.264	[c]**0.999**
	Yes	76 (97.4)	71 (98.6)		
Duration of ATG use (day)	Median (Q1-Q3)	9 (6-19)	7 (5-13)	-2.944	[b]**0.003****
ATG dose (mg)	Median (Q1-Q3)	780 (485-1460)	740 (500-1290)	-0.322	[b]**0.748**
Basiliximab	No	55 (70.5)	37 (51.4)	5.774	[a]**0.016***
	Yes	23 (29.5)	35 (48.6)		
Tacrolimus/Cyclosporine	Tacrolimus	1 (1.4)	61 (84.7)	103.819	[a]**<0.001****
	Cyclosporine	73 (98.6)	11 (15.3)		

[a]: Pearson chi-square test, [b]: Mann-Whitney U test, [c]: Fisher exact test, AGT: Anti-thymocyte globulin, Q1: First quartile, Q3: Third quartile, UC: Ureteral catheter, *: p<0.05, **: p<0.01

It was found that the rate of basiliximab use in group 2 was significantly higher than in group 1 patients (p=0.016), as was the use of tacrolimus/cyclosporine (p<0.001) (Table 1).

It was found that the rate of urological complications in the postoperative period between the groups was statistically significantly lower in group 2 patients compared to group 1 (p=0.004).

A statistically significant difference was found between the groups in terms of the Foley catheter removal time (p<0.001). The Foley catheter was removed in a shorter time in cases with ureteral catheters than in cases without ureteral catheters (Table 2).

It was observed that both groups received intravenous antibiotic prophylaxis for the first seven postoperative days. It was determined that the early period bacteriuria rate was statistically significantly lower in group 2 than in group 1 patients (p<0.001). There was no statistically significant difference between the groups in terms of the day of detection of bacteriuria (p>0.05) (Table 2).

It was determined that the duration of cold ischemia of the donor kidney groups was significantly shorter in the group 2 patients compared to group 1 (p=0.003) (Table 3).

No statistically significant difference was found between the groups in terms of delayed graft function in the early postoperative period (needing hemodialysis in the first week) (p>0.05) (Table 3).

Patients with postoperative urological complications, medical comorbidities (acute myocardial infarction, sepsis), early rejection, a second surgical intervention in the early period, early explantation, or postponed ureteral catheter intake due to positive urine culture were excluded from the statistical analyses. The catheter removal time ranged from 17 to 76 days with an average of 44.45±13.38 days.

DISCUSSION

Complications associated with ureteral-bladder anastomosis such as ureteral obstruction due to edema or stricture in the anastomosis and urinary leakage are usually seen in the first three months after renal transplantation and threaten graft survival (7).

In a Cochrane Systematic Review published in 2013 that recommends the use of prophylactic intraoperative ureteral catheters, the basis of this recommendation is the randomized controlled studies that demonstrate the use of intraoperative ureteral catheters in reducing the incidence of major urological complications. Urinary tract infections (UTI) were more common in the catheter group; however, the incidence was equivalent between the two groups if 480 mg of cotrimoxazole was used (11).

There are centers that routinely use catheters to prevent urological complications. However, the use of ureteral catheters may lead to an increase in other catheter-related complications, such as infection, persistent hematuria,

Table 2: Comparison of the two groups in terms of specified parameters

		Group 1	Group 2	Test value	p-value
Urological complication rate in the postoperative period	No	61 (78.2%)	68 (94.4%)	8.201	[a]**0.004****
	Yes	17 (21.8%)	4 (5.6%)		
The duration of Foley catheter usage (day)	Median (Q1-Q3)	10.5 (3-14.75)	8 (7-10)	-5.016	[b]**<0.001****
Bacteriuria in the early period	No	17 (21.8%)	36 (50%)	13.035	[a]**<0.001****
	Yes	61 (78.2%)	36 (50%)		
Bacteriuria detection time (day)	Median (Q1-Q3)	11 (8-15)	12 (9-16)	-0.419	[b]**0.675**

[a]: Pearson chi-square test, [b]: Mann-Whitney U test, [c]: Fisher exact test, Q1: First quartile, Q3: Third quartile, *: p<0.05, **: p<0.01

Table 3: Comparison of the two groups in terms of the duration of cold ischemia and postoperative delayed graft function in the early period

		UC (-)	UC (+)	Test value	p-value
The duration of cold ischemia	Mean±sd	17.81±5.18	15.52±3.92	3.011	[b]**0.003****
Postoperative delayed graft function in the early period	Yes	28 (35.9)	19 (26.4)	1.573	[a]**0.210**
	No	50 (64.1)	53 (73.6)		

[a]: Pearson chi-square test, [b]: Independent groups t test, [c]: Mann-Whitney U test, Q1: First quartile, Q3: Third quartile, UC: Ureteral catheter, sd: Standard deviation, **: p<0.01

bladder irritation, catheter migration, catheter break, catheter calcification, and complications during removal. There are also publications showing that the use of ureteral catheters increases the rate of urinary tract infection while decreasing that of urological complications (7). Urinary tract infections may also adversely affect graft function as a catheter-related complication. In contrast, Chordia et al. showed that the use of ureteral catheters was not associated with an increase in bacteriuria in renal transplant patients (10). It is also probable that in the presence of the ureteral catheter, the lack of resistance in the flow of urine prevents stasis and may prevent urinary infection. Our findings indicate that using a ureteral catheter did not increase the rate of bacteriuria in deceased donor renal transplantation, with the infection rate even decreasing in the catheter group. The role of antibiotic prophylaxis in preventing infection has not been evaluated, since both groups used prophylactic antibiotics.

In our study, it was determined that the routine use of ureteral catheters in renal transplantation significantly decreased postoperative urological complications. This finding is consistent with other reports. Interestingly, we found the rate of positive urine culture to be lower in patients with ureteral catheters. While this result is consistent with several reports, others have described an association between ureteral catheter usage and an increased risk of UTI (9).

In our study, we have shown that the use of ureteral catheters reduces both urological complications and bacteriuria. Consequently, the period of hospitalization after transplantation of patients with ureteral catheters was significantly shortened compared to the group in which ureteral catheters were not used. This shortening of the hospitalization period also helps to protect renal transplant recipients receiving immunosuppressive therapy from nosocomial infections, particularly those by antibiotic-resistant microorganisms. In addition, the shortening of the hospitalization periods and the significant decrease in the rate of urological complications requiring additional intervention help to reduce the burden on the health system.

Catheter insertion during renal transplantation is easily performed and does not require instrumentation or imaging. However, removal of the catheter requires an additional endoscopic procedure, which adds to additional cost and burden. Occasionally, delay or forgetting to remove the catheter can cause increased health expenses (7). Numerous centers have adopted the approach of using prophylactic ureteral catheters and endoscopic removal at a specified time after transplantation (12). Generally, ureteral catheters are removed 2-12 weeks post-renal transplantation (13).

In a prospective randomized controlled study, removal of the ureteral catheter in the first week after living-donor renal transplantation was found to reduce the risk of UTI compared to its removal at the routine fourth week; however, the complication rates were similar (14).

In a study investigating the optimal time for post-transplant prophylactic ureteral catheter removal, patients were divided into two groups in which the catheter was removed early (day 5) or late (week 6). It was found that catheter-related complications such as hematuria, migration, fragmentation, and UTIs in the first three months were less and the quality of life was improved in patients with early catheter removal (15).

In our patients, while the targeted time for ureteral catheter removal was four weeks, we found that the actual time of removal tended to be later than this due to patients not keeping appointments or delays due to non-clinical reasons. Despite this, there was no increase in the bacteriuria rate as expected.

Considering the benefit of ureteral catheters in preventing urinary complications, despite our recommendation for removing them as soon as possible, our study demonstrated that the duration of ureteral catheter use could be as long as 44.45±13.38 days. However, this prolonged duration of catheter use did not cause a significant increase in bacteriuria. Removing ureteral catheters before complete tissue healing can result in a higher risk for urinary complications.

The significantly shorter removal time for the Foley catheter in the ureteral catheter group was attributed to two reasons. First, there was a decrease in urological complications due to the application of a ureteral catheter to the ureteroneocystostomy anastomosis area. Second, the surgical team may have felt safer with using the ureteral catheter which may have led to the earlier removal of the Foley catheter and also to reduce the risk of UTIs. Publications showing that prolonged bladder catheterization is a risk factor for UTI in renal transplant recipients (16) and early removal of the Foley catheter in renal transplant patients reduces the risk of UTI (17) support this view.

The observation that the duration of ATG use was shorter in the second group and in terms of tacrolimus/cyclosporine use, tacrolimus was used predominantly in the second group with less bacteriuria, suggests that using a potent immunosuppressive such as ATG for a longer period may play a role in the development of bacteriuria.

While cyclosporine was used more frequently in the first group, tacrolimus was used predominantly in the second group. The bacteriuria rate was found to be lower in this group in which tacrolimus, a potent immunosuppressive, was used. In our opinion, however, while there are many factors responsible for the formation of infection, the use of a more potent immunosuppressive drug or prolonging the duration of ATG use (on average nine days in the first

group and seven days in the second group), although statistically significantly shorter, cannot be considered sufficient to reach a conclusion about the susceptibility to infection. In addition, it was thought that the shorter cold ischemia time in group 2 may have contributed to the a lower incidence of UTI by reducing the possibility of acute tubular necrosis. The shorter cold ischemia duration in group 2 is thought to be related to change in organ distribution system in May 2008 and fewer double transplants in group 2. Cold ischemia duration is not related to the usage of ureteral catheter.

The strengths of our study include well-matched numbers of patients with and without ureteral catheters, consistency in the surgical procedures where a team experienced in kidney transplantation performed the transplantations procedures using the same surgical technique, and the provision of detailed data on the early follow-up after transplantation.

This retrospective study showed that the routine use of ureteral catheters in deceased donor renal transplantation reduces urinary complications and shortens the time of Foley catheter removal. Although we recommend that the routine ureteral catheter used in deceased donor kidney transplantation cases be removed as soon as possible, there was no increase in the risk of bacteriuria in cases where catheter removal was delayed for non-medical reasons.

In conclusion, we recommend that the ureteral catheter should be used routinely in all deceased renal transplantations since we did not observe any adverse effects of ureteral catheterization on the incidence of infection.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 10.08.2018, No:13).

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THE EFFECT OF INTRAVESICAL ONABOTULINUM TOXIN A TREATMENT ON QUALITY OF LIFE IN PATIENTS WITH OVERACTIVE BLADDER

İNTRAVEZİKAL ONABOTULİNUM TOKSİN A TEDAVİSİNİN AŞIRI AKTİF MESANE HASTALARINDA YAŞAM KALİTESİ ÜZERİNE ETKİSİ

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ABSTRACT

Objective: Overactive bladder (OAB) syndrome is common in women and negatively affects their quality of life. Our study aimed to evaluate the effect of intravesical onabotulinum toxin A injection on quality of life and urinary symptoms in patients with treatment resistant OAB syndrome.

Material and Method: The treatment records of 20 patients with treatment-resistant OAB were reviewed. The patients were injected with a 1:1 solution of saline and 100 units of onabotulinum toxin A at 20 different points on the body, avoiding the bladder trigon. The following survey instruments were used to determine the patient's quality of life before and after treatment: the King's Health Questionnaire (KHQ), the short-form Urodistress Inventory (UDI 6), the short-form Incontinence Impact Questionnaire (IIQ 7), the International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules (ICIQ FLUTS), the Female Sexual Function Index (FSFI), and the Pelvic Organ Prolapse/Urinary Incontinence Inquiry form (PISQ-12). The pre-and post-treatment results of the questionnaires were then evaluated.

Result: The uroflowmetry parameters indicated that the patients' maximum urine flow rate decreased significantly after treatment, as did their KHQ scores on all but one item. Evaluation of their FSFI scores indicated no significant change after treatment; however, the other quality of life questionnaires used (UDI-6, IIQ-7, ICIQ-FLUTS, and PISQ-12) revealed significant decreases, indicating an improvement in quality of life.

ÖZET

Amaç: Aşırı aktif mesane (AAM), kadınlarda oldukça sık görülen ve hayat kalitesini olumsuz etkileyen bir sendromdur. Çalışmamızın amacı; tedaviye dirençli AAM sendromu olan hastalarda intravezikal onabotulinum toksin A enjeksiyonunun hastaların hayat kalitesine ve üriner semptomlarına olan etkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya medikal tedaviye dirençli toplam 20 hasta dahil edildi. Hastalara 1:1 oranda salin ile sulandırılıp 100 Ünite onabotulinum toksin A kullanılarak 20 farklı noktaya, mesane trigonundan kaçınılarak enjeksiyon yapılmıştır. Hastaların yaşam kalitelerini belirlemek için kullanılan "King Sağlık Anketi (KHQ), Ürogenital Distres Envanteri kısa formu (UDI 6), İnkontinans Etki Anketi kısa formu (IIQ 7), ICIQ-FLUTS, Kadın Cinsel Fonksiyon Endeksi formu (FSFI), Pelvik Organ Prolapsusu/Üriner İnkontinans Sorgulama formu (PISQ-12)" anketlerin tedavi öncesi ve tedavi sonrası sonuçları değerlendirilmiştir.

Bulgular: Tedavi öncesi ve sonrası üroflowmetri parametrelerinden maksimum idrar akım hızında anlamlı azalma izlendi. Tedavi öncesi ve sonrası yapılan KHQ skorlarının değerlendirilmesinde kişiler arası ilişkiler dışında tüm skorlarda anlamlı azalma izlendi. Tedavi öncesi ve sonrası FSFI skorları değerlendirildiğinde anlamlı bir değişiklik olmadığı izlendi. Ancak, diğer yaşam kalite anketleri olan UDI-6, IIQ-7, ICIQ-FLUTS ve PISQ-12'de anlamlı bir azalma olduğu ve yaşam kalitesinde olumlu değişim olduğu izlendi.

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Conclusion: When the patients' short-term results were evaluated, it was found that this therapy reduced their symptoms and complaints, thus improving their quality of life. Although none of the patients in the sample group experienced complications, in some cases catheterization is necessary due to infection and increased residual urine. Intravesical onabotulinum toxin A injection is a cheap and easy-to-administer treatment for OAB that has not responded to other treatments and does not cause serious side effects.

Keywords: Overactive bladder, onabotulinum toxin A, urinary retention, urgency

Sonuç: Medikal tedaviye dirençli aşırı aktif mesane sendromu olan hastalarda; intravezikal onabotulinum toksin A enjeksiyonunun kısa dönem sonuçları değerlendirildiğinde hastaların semptom, şikayetlerini azaltmış ve hastaların hayat kalitelerini olumlu yönde arttırmıştır. Bizim hasta grubumuzda komplikasyon gelişmemiş olsa da enfeksiyon ve rezidü idrar artışına bağlı kateterizasyon görülebilmektedir. Medikal tedaviye yanıt alınmayan AAM tedavisinde intravezikal onabotulinum toksin A enjeksiyonu ucuz, kolay uygulanabilir ve ciddi yan etkisi olmayan bir tedavi seçeneği olduğu düşünmekteyiz.

Anahtar Kelimeler: Aşırı aktif mesane, onabotulinum toksin A, üriner retansiyon, aciliyet hissi

INTRODUCTION

The International Continence Society defines overactive bladder (OAB) as a chronic urgency with or without urge incontinence, usually with increased frequency of urination and nocturia. The prevalence of OAB increases with age, and it is estimated to affect 16.6% of all women (1). Risk factors include age, overweight, metabolic syndrome, smoking, neurological diseases, and menopause (2,3).

A detailed anamnesis, followed by a complete physical and systemic examination, is required to diagnose OAB. If a patient has one or more neurological and/or orthopedic diseases that may cause incontinence, that should be noted. A urogynecological examination begins with a physical examination and patients undergo a stress test, a Q-tip test, a Marshall–Bonney test, a pad test, and a tampon test; they are also asked to keep a bladder diary (4-8). Patient's symptoms and quality of life assessment scales were also evaluated. In addition to the physical examination, which includes a pelvic floor muscle strength assessment, urodynamic assessment tests (cystometry, uroflowmetry, and a urethral pressure profile) are conducted. Diagnoses can be made clinically or urodynamically. Symptoms are specific and sensitive as urodynamic studies in diagnosis (9).

OAB symptoms significantly reduce these patients' quality of life (10). This condition negatively affects many physical and social activities of daily and professional life and can be detrimental to mental health (11). The loss of workforce and treatment costs caused by the disease causes serious economic problems. Decreased self-confidence, embarrassment, and helplessness generally affect social relations negatively; 44% of women diagnosed with OAB report experiencing depression, and 80% report a reduced quality of life due to limitations on their social life or physical activity (12,13).

The low efficacy and poor tolerance of the available therapies reduce these patients' compliance with their treatment. Side effects such as dry mouth, constipation, and blurred vision caused by antimuscarinic agents lead to the discontinuation of these drug treatments (14). Alternative treatment options such as magnetic and sacral nerve stimulation are not always suitable for patients because they require frequent hospital visits and are less successful (15,16).

Onabotulinum toxin A, a third-stage overactive bladder treatment, relaxes the patient's muscles by inhibiting neurotransmitter release from presynaptic nerve terminals such as motor and parasympathetic nerves (17). It inhibits the release of acetylcholine from presynaptic terminals in the detrusor muscle, thus reducing the involuntary contraction of the muscle (17). It also suppresses urgency by affecting the afferent pathway, which is thought to block the release of neurotransmitters such as the substance P and adenosine triphosphate and inhibits the expression of the P2X3 receptor and TRPV1 (18).

Our study aimed to evaluate the effect of intravesical injection of onabotulinum toxin A on the quality of life and urinary symptoms of patients with treatment resistant OAB syndrome. The literature supports the use of onabotulinum toxin A to treat OAB and reduce patients' urinary symptoms (19). In our study, we assessed not only urinary symptoms but also the patient's quality of life and sexual function.

MATERIALS and METHOD

Patient selection and data collection

Patients treated at our clinic presenting with frequent urination, sense of urgency, nocturia, and/or urgent urinary incontinence between April 2014 and March 2018 were retrospectively assessed. In our study, 20 patients were included. All patients included in the study sample were over 18 years of age, diagnosed with treatment-resistant OAB syndrome following a urogynecological evaluation, had received at least two anticholinergic treatments over at least three months, and had been treated with onabotulinum toxin A. The patients in our sample discontinued their use of oral anticholinergic and ß receptor agonist drugs seven days before receiving the onabotulinum

toxin A injections. Patients who were under 18 years of age and those who had a history of neurological disease, stress urinary incontinence predominant mixed urinary incontinence, pregnancy, urinary retention, and/or with a postvoiding residue above 100 cc were excluded from the study. The study was approved by the Ethics Committee of the Istanbul Faculty of Medicine (Date: 21.10. 2022, No: 19).

Preoperative evaluation and postoperative period

During the patients' urogynecological follow-ups, their urological symptoms, gynecological examination findings, stress tests, Q-tip tests, pelvic floor muscle strength evaluations, four-day bladder diaries, 24-hour pad tests, and urodynamic examinations before and after treatment were assessed. The urodynamic examination data included the maximum urine flow rate (Qmax), flow time, micturition volume, postvoiding residual urine volume, and maximum bladder capacity.

The pre-and post-treatment results of a series of instruments (the King's Health Questionnaire [KHQ], the short-form Urodistress Inventory [UDI6], the short-form Incontinence Impact Questionnaire [IIQ7], the International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules [ICIQFLUTS], the Female Sexual Function Index [FSFI], and the Pelvic Organ Prolapse/Urinary Incontinence Inquiry form [PISQ-12]) were used to determine the patient's quality of life. The patients' demographic data, urological symptoms, urogynecological evaluations, bladder diaries, pad tests, urodynamic examination data, treatments, and treatment results were recorded. Their cystometry, uroflowmetry, pad test, Q-tip test, stress test, and physical examination results were recorded before treatment; following treatment, they again underwent a uroflowmetry test and physical examination on the 15th day, and at postoperative 1st month a physical examination was conducted and the surveys were administered and a final physical examination at postoperative six months. The control results were recorded.

Treatment procedure

Intravesical onabotulinum toxin A treatment was administered to patients over 18 years of age with idiopathic resistant OAB and whose symptoms persisted despite the use of two different anticholinergic treatments for at least three months in our clinic between April 2014 and March 2018. These patients were sedated, given local anesthesia, and injected with 100 units of onabotulinum toxin A diluted with saline at a ratio of 1:1 at 20 different points. These 20 points were randomly selected on the body of the bladder. Trigon and ureteral orifices were not injected. The procedures were performed with a rigid cystoscopy using a 22 G injection needle. Prophylactic antibiotic treatment was administered pre-and postoperatively to avoid the patients from developing a urinary tract infection (UTI).

The primary outcome of our study was the finding that onabotilinum toxin A was effective in treating OAB syndrome. The secondary result was the finding that this treatment positively affected the patients' social lives.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 15.0 software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Number and percentage distributions were used to evaluate the discrete data obtained from the patients. In our evaluation of the continuous data, we first used the Kolmogorov–Smirnov test to determine whether it had a normal distribution. The data obtained from the same individuals before and after the procedure were evaluated using the Wilcoxon signed-rank test. P values below 0.01 were considered statistically significant.

RESULTS

Twenty patients were included in the study. The patients' mean age was 56.8±11.03 years (max: 73 years; min: 32 years). The patient's symptoms were frequent urination, sense of urgency, nocturia, and/or urgent urinary incontinence and/or stress urinary incontinence (Table 1). The mean number of births was 4.1±2.1 (2-9). One patient (5%) had never given birth; 17 (85%) had only vaginal deliveries; and 2 (10%) had both vaginal and cesarean section deliveries. The patients' mean body mass index (BMI) was 33.7±7.4. Fourteen patients (70%) were sexually active, while 6 (30%) were not. Four patients (20%) had no comorbidities while 16 (80%) had one or more, including hypertension (2 patients; 10%); only diabetes mellitus (DM; 1

Table 1: Patients' symptoms

Patients' symptoms	Frequency	Percentage
Stress incontinence + urgent urinary incontinence	3	15
Stress incontinence + urgent urinary incontinence + nocturia	3	15
Stress incontinence + urgent urinary incontinence + frequent urination	4	20
Frequent urination+ sense of urgency + urgent urinary incontinence	5	25
Nocturia + urgent urinary incontinence	2	10
Frequent urination + sense of urgency + nocturia	3	15
Total	20	100

patient; 5%); both hypertension and DM (5 patients; 25%); only depression (1 patient; 5%); DM, hypertension, and a goiter (2 patients; 10%); DM, hypertension, and asthma (1 patient; 5%); endometrial cancer, depression, and a goiter (1 patient; 5%); DM, hypertension, a goiter, and asthma (1 patient; 5%); only bipolar disorder (1 patient; 5%); and DM and osteoporosis (1 patient; 5%) (Table 2). Three patients (15%) were smokers, while 17 (85%) were non-smokers. All but four patients had a history of at least one gynecological operation: 8 patients (40%) had undergone an abdominal hysterectomy, 1 (5%) patient had undergone a Lefort Colpocleisis and perineoplasty, 5 patients (25%) had undergone a repair of the anterior vaginal wall, 1 patient (5%) had undergone a transoburator tape procedure, and 1 patient (5%) had undergone a transoburator tape procedure, cystoscopy, and other abdominal operations. Ten patients (50%) had been diagnosed with urgent urinary incontinence, and 10 (50%) had been diagnosed with mixed urinary incontinence. The mean duration of incontinence was 3.4±0.8 years (2-4 years).

The mean weight of the 24-hour pad tests before the treatment was 306±605 g. The mean value of the Q-tip test before treatment was 46±23.4°. Seventeen patients (85%) had performed pelvic floor exercises for at least three months before their procedure. The remaining three patients (15%) did not want to exercise. In the pre-treatment cystometric analysis, the patients' mean maximum bladder capacity, abdominal pressure, and detrusor pressure were found to be 250±123 mL, 118±45.7 cmH_2O, and 61±34 cmH_2O, respectively. Among all patients, the first urine sensation was observed at 109±65.4 cmH_2O pressure and the compression sensation was felt at 161±94.5 cmH_2O pressure (Table 3).

Table 2: Patients' comorbidities

	Frequency	Percentage
Comorbidities		
No comorbidities	4	20
Hypertension	2	10
Diabetes Mellitus	1	5
Hypertension + Diabetes Mellitus	5	25
Hypertension + Diabetes Mellitus + Goiter	2	10
Hypertension + Diabetes Mellitus + Asthma	1	5
Hypertension + Diabetes Mellitus + Asthma + Goiter	1	5
Depression	1	5
Depression+ Goiter+Endometrial Cancer	1	5
Bipolar Disorder	1	5
Diabetes Mellitus + Osteoporosis	1	5
Total	20	100

Table 3: Patients' pre-treatment cystometry values

Cystometric results	Mean
Bladder capacity	250.6±123.3 (95–507) mL
Maximum abdominal pressure	118.2±45.7 (20–187) cmH_2O
Maximum detrusor pressure	61.7±34 (21–148) cmH_2O
First sensation of need to urinate	109±65.4 (17–288) cmH_2O
First sensation of urgency	161.3±94.5 (31–376) cmH_2O

The maximum total dose used in each application was 100 units. Five patients (25%) were re-injected with intravesical onabotulinum toxin A after their first procedure; 3 (15%) underwent two re-injections; and 2 (10%) underwent three re-injections. A comparison of the patients' daily bladder data before and after treatment revealed a significant decrease in the mean diuretic fluid intake and urinary incontinence frequency ($p<0.05$). Although the patients' sense of urgency, the number of nocturia incidents, and urination decreased after treatment, there were no statistically significant differences in these symptoms (Table 4, Figure 1).

Table 4: Data from patients' four-week bladder diaries before and after treatment

	Pre-treatment	Post-treatment	p
Bladder diary item	**Mean**	**Mean**	
Average fluid intake (mL)	1842.6±714.2	1671±476.5	0.387
Diuretic fluid intake (mL)	777.2±444.8	515.2±215.6	0.013
Number of incidents of sense of urgency (n)	6.6±4. 8	5.3±3.8	0.204
Number of incidents of urination	11±5.4	8.4±3.3	0.089
Number of incidents of nocturia	1.9±1.8	1.73±1.1	0.687
Number of incidents of urinary incontinence	3.4±2.8	1.4±1.3	0.009

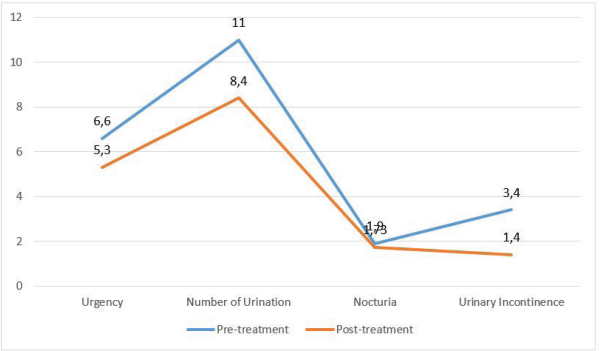

Figure 1: Changes in the patients' urinary diaries

Uroflowmetric examination revealed no significant difference before and after the procedure, except for the maximum urine flow rate (p>0.05). The maximum urine flow rate was observed to be statistically significantly lower after the procedure (p<0.05). There was no significant increase in residual urine volume (Table 5). The KHQ revealed a statistically significant decrease in the patient's total scores before and after the procedure, and significant improvement was observed in all subgroups except interpersonal relationships (p<0.05, Table 6). There was no significant change in the patients' pre- and post-treatment FSFI scores, indicating that they did not experience any improvement in quality of life; however, their scores on the other quality of life questionnaires (UDI6, IIQ7, ICIQFLUTS, and PISQ-12) demonstrated that their quality of life did improve (p<0.05; Table 7, Figure 2).

Table 5: Patients' pre- and post-treatment uroflowmetry values

	Pre-treatment	Post-treatment	p
Uroflowmetry	**Mean**	**Mean**	
Maximum flow rate (mL/sec)	30.1±14.4	23.5±11	0.001
Average flow rate (mL/sec)	12.5±5.2	10.7±5.6	0.176
Residual urine volume (mL)	44.2±65. 6	33±32	0.896

Table 6: Patients' King's Health Questionnaire results before and after treatment

	Pre-treatment	Post-treatment	p
Questionnaire item	**Mean**	**Mean**	
Detection of general health	72.5±26.8	35.4±25	0.002
Incontinence effect	86.7±29.5	48.2±36.7	0.005
Role restrictions	80.8±35.0	40±37.6	0.002
Physical restrictions	72.5±34.7	42.4±40	0.005
Social restrictions	63.3±35.5	44.3±35	0.05
Interpersonal relations	20.8±31	22.5±34	0.575
Feelings	75.5±36.8	40.5±30.4	0.001
Sleep/energy	64.1±30.7	40.8±31.2	0.008
Intensity measurements	74.6±23.0	40.3±32.8	<0.001
Total score	611±161.8	369±235.4	0.002

Table 7: Patients' results for other questionnaires before and after treatment

	Pre-treatment	Post-treatment	p
FSFI			
Total	26.0±5.2	24.5±5.9	0.277
UDI-6			
Irritation/Urgency	48.8±13	32.5±13.5	0.02
Stress symptoms	35.9±10.6	31.2±14	0.013
Obstructive/ disturbing symptoms	27.3±14	19.1±15	0.021
Total	37.3±9.08	27.6±10.6	0.108
IIQ-7			
Total	32±13	23±15.4	0.04
PISQ-12			
Emotional	7.3±3	6.9±3.5	0.36
Physical	17±3.5	19±1.65	0.07
Partner-dependent	8.3±2	7.8±2.3	0.98
Total	32.6±5.3	33.6±5.8	0.24
ICIQ-FLUTS			
Total	4.56±3.3	2.4±2.3	0.04

FSFI: Female Sexual Function Index, ICIQ-FLUTS: International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules, IIQ-7: Incontinence Impact Questionnaire, PISQ-12: Pelvic Organ Prolapse/Urinary

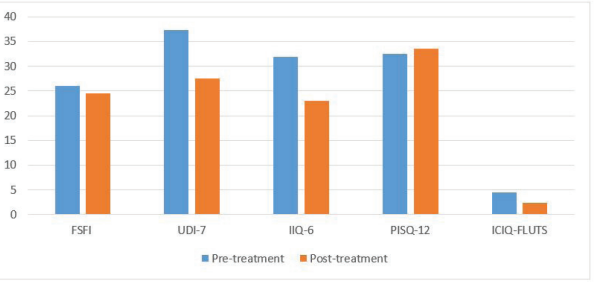

Figure 2: Patients' quality of life survey results before and after treatment

FSFI: Female Sexual Function Inde, ICIQ-FLUTS: International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules, IIQ-7: Incontinence Impact Questionnaire, PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Inquiry; UDI-6: Urodistress Inventory

DISCUSSION

Although OAB syndrome is a disease that entails serious financial and psychogenic losses for patients, the side effects of current medical treatments are detrimental to treatment compliance and reduce treatment success. Developments in the use of onabotulinum toxin A treatment and its positive results are promising for these patients.

Increasing age is a risk factor for OAB. In a meta-analysis of 13 studies on OAB, it was found that the prevalence of urinary incontinence peaked in the fifth and eighth decades of life (18). In our study, the ages of the patients ranged from 32 to 73 years, with an average of 56.08±11.03 years, which is similar to the data reported in the literature. Smoking is one of the preventable risk factors for OAB. In a study of 11,678 patients conducted in Japan, 21.2% of the patients were smokers, and OAB was found to be significantly more common among smoking women (19). However, in another study conducted in the United States, the effect of smoking on OAB was not found to be significant (20). In our study, 17 (85%) of the patients did not smoke. Although we did not identify smoking as a definite predisposing factor, we think that spasms and the cholinergic effects of smoking in triggering conditions such as frequent coughing cause urinary leakage and play a role in OAB.

Vaginal birth is another risk factor for OAB. Although the rate of OAB and stress urinary incontinence after vaginal delivery is more common than delivery by cesarean section, this difference decreases as time and the number of births increases (21). Parazzini et al. found that vaginal delivery increased stress and mixed-type urinary incontinence, but did not significantly increase detrusor overactivity (22). In our study, all but one patient (5%) had given birth at least once, and all of the patients who had given birth had a history of at least one vaginal delivery. The fact that the majority of the patients we reviewed had given birth suggests that it may be a risk factor for OAB syndrome.

Diuresis is a risk factor for urinary incontinence in diseases such as DM, chronic obstructive pulmonary disease, and some neurological diseases. In patients with DM in particular, the duration of the disease and treatment and the presence of vascular complications is important. Brown et al. found an increase in the frequency of urinary incontinence in patients with impaired fasting glucose (33.4%) compared to the normal population (16.8%) (23). Eleven (55%) of the patients we reviewed had been diagnosed with DM. Neuropathy, which is one of the advanced complications of DM, may worsen OAB patients' symptoms.

Obesity, OAB, stress, urinary incontinence, and pelvic organ prolapse cause many urogynecological problems. In their study of 1,050 cases, Palma et al. compared patients with a normal BMI of 18.5–24.9 to those with high BMIs and found that nocturia, sense of urgency, and urgent urinary incontinence were significantly more common in patients with a BMI>25 (24). The patients we reviewed had BMIs in the range of 33.7±7.4. We believe that increased intra-abdominal and intravesical pressure due to obesity exacerbates OAB symptoms.

We evaluated the patients' four-day bladder diaries and found no significant increase in the amount of fluid taken before and after the treatment ($p>0.05$). A significant decrease was observed in the number of reports of urinary incontinence compared to the period before treatment. The patients' diuretic fluid intake also decreased significantly after treatment. However, the sense of urgency was not significant, although the incidents of urination and nocturia decreased. These findings are not consistent with the literature (25,26). Although we think that this may be caused by genetic factors in response to Botox treatment and the experience of the practicing clinician, studies of larger sample populations are needed to draw definitive conclusions.

Hsieh et al. found that the effect of residual urine volume was a dose-dependent drug effect and that doses of >150 U were more common (27). They also emphasized that it was a temporary side effect, arguing that it peaked two weeks after injection with onabotulinum toxin A and then gradually decreased (27). Although increased residual urine volume after intravesical onabotulinum toxin A injection is a common complication, we did not find an increase in the post-treatment uroflowmetry results. When we compared the pre-and post-treatment uroflowmetry parameters, we found no significant change except for a decrease in the maximum flow rate, which we considered to be a natural result of onabotulinum toxin A treatment.

Some studies conducted on patients who did not benefit from intravesical onabotulinum toxin A injection have reported that patients develop antibodies against onabotulinum toxin A in their serum, possibly due to frequent urinary infections (28). We routinely administer prophylactic antibiotic therapy to prevent pre- and postoperative UTIs, and we believe that this will both reduce the development of antibodies against onabotulinum toxin A and protect against UTIs.

There are studies in the literature showing an improvement in quality of life after intravesical onabotulinum toxin A injection (29,30). Twenty patients who received intravesical onabotulinum toxin A injections were included in our study. Of these, 5 (25%) required one subsequent re-injection, three required two subsequent re-injections, and two required three subsequent re-injections. When we reviewed the questionnaires administered to evaluate the patient's quality of life before and after treatment, we found a significant decrease in parameters other than interpersonal relationships in the KHQ. We found no signif-

icant change in the patients' FSFI responses before and after treatment, but we did observe a significant decrease in scores for the UDI-6, IIQ-7, ICIQ-FLUTS, and PISQ-12, indicating a positive change in the patient's quality of life.

The fact that our study is retrospective is a limitation. Studies with larger sample populations, longer-term follow-up, and multicenter studies are needed to draw more precise conclusions about onabotulinum toxin A.

CONCLUSION

In examining the short-term results of intravesical onabotulinum toxin A injection in patients with treatment-resistance OAB syndrome, we found that this therapy reduced the patient's symptoms and complaints and positively increased their quality of life. Although none of the patients in our sample population developed complications, catheterization may be needed in the event of infection and residual urine increase. We think that intravesical onabotulinum toxin A injection is an inexpensive alternative treatment for treatment-resistant OAB syndrome that is easy to administer and has no serious side effects.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 21.10.2022, No: 19).

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SURVIVAL EFFECT OF PALLIATIVE RADIOTHERAPY IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER DEVELOPING OLIGO-PROGRESSION UNDER ANTIANDROGEN TREATMENT

ANTİANDROJEN TEDAVİSİ ALTINDA OLİGO-PROGRESYON GELİŞEN METASTATİK KASTRASYONA DİRENÇLİ PROSTAT KANSERLİ HASTALARDA METASTAZA YÖNELİK VÜCUT RADYOTERAPİSİNİN SAĞKALIM ETKİSİ

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ABSTRACT

Objective: Androgen pathway inhibitors have a significant impact on the treatment of prostate cancer. The treatment approach is controversial in patients who develop oligo-progression under anti-androgen therapy. This study aimed to investigate the effects of metastasis-directed stereotactic body radiotherapy (SBRT) on survival in the first-line setting of patients with metastatic castration-resistant prostate cancer who continued the antiandrogen therapy after oligo-progression.

Materials and Methods: Fifty-seven metastatic castration-resistant (serum testosterone <50 ng/dl) prostate cancer patients treated with abiraterone or enzalutamide in the first-line setting were analysed retrospectively. Thirty-nine of the patients with the oligo-progressive disease, which was defined as ≤3 lesions on imaging, received SBRT by continuing the same antiandrogen therapy.

Results: The median age was 70 (range 40-85). In the castration-sensitive setting, 27 (47.4%) patients received docetaxel. The oligo-progressive metastatic sites were as follows: bone in 21 (52.3%), lymph node in 6 (15.3%) and visceral metastasis in 12

ÖZET

Amaç: Androjen yolağı inhibitörleri prostat kanserinin tedavisinde önemli etkiye sahiptir. Anti-androjen tedavisi altında oligo-progresyon gelişen hastalarda tedavi yaklaşımı tartışmalıdır. Bu çalışma, metastaza yönelik stereotaktik vücut radyoterapisinin (SBRT) oligo-ilerlemeden sonra antiandrojen tedavisine devam eden metastatik kastrasyona dirençli prostat kanserli hastalarda birinci basamakta sağkalım üzerindeki etkilerini araştırmayı amaçladı.

Gereç ve yöntem: Birinci basamakta abirateron veya enzalutamid ile tedavi edilen 57 metastatik kastrasyon dirençli (serum testosteron <50 ng/dl) prostat kanseri hastası retrospektif olarak analiz edildi. Görüntülemede ≤3 lezyon olarak tanımlanan oligo-progresif hastalığı olan 39 hasta aynı antiandrojen tedavisine devam edilerek SBRT aldı.

Bulgular: Medyan yaş 70 (dağılım 40-85) idi. Kastrasyona duyarlı ortamda, hastaların 27'si (%47,4) dosetaksel almıştır. Oligo-progresif metastatik bölgeler 21 (%52,3) hastada kemik, 6 (%15,3) hastada lenf nodu ve 12 (%30,9) hastada visseral metastaz olarak saptandı. Abirateron ve enzalutamid sırasıyla %47,4, %52,6

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(30.9%) patients. Abiraterone and enzalutamide were preferred in 47.4% and 52.6% of patients, respectively. The 12-month progression-free survival (PFS) was 79.0% and 88.9% in patients who received or did not receive SBRT (p<0.001). SBRT-related grade 1-2 toxicity was observed in 35 (61.4%) patients. SBRT was also an independent risk factor for PFS (p=0.007, HR:15.7; 95% CI 2.05-118.7). The presence of visceral metastases, isolated bone metastases, the choice of anti-androgen therapy, and Eastern Cooperative Oncology Group Scale Performance Status (ECOG PS) were not significantly associated with PFS. SBRT had no impact on overall survival.

Conclusion: Patients treated with metastasis-directed SBRT without changing treatment in the oligo-progression setting had worse survival outcomes. Thus, metastasis-directed SBRT with continuation of the same antiandrogen therapy should be prioritised only in selected cases.

Keywords: Stereotactic body radiotherapy, abiraterone, enzalutamide, castration-resistant prostate cancer

hastada tercih edildi. SBRT alan ve almayan hastalarda 12 aylık progresyonsuz sağkalım (PFS) %79,0 ve %88,9 idi (p<0,001). Otuz beş (%61,4) hastada SBRT ile ilişkili derece 1-2 toksisite gözlendi. SBRT ayrıca PFS için bağımsız bir risk faktörüydü (p=0,007, HR:15,7; %95 GA 2,05-118,7). Visseral metastazlar, izole kemik metastazları, anti-androjen tedavi seçimi ve Eastern Cooperative Oncology Group (ECOG) performans skalası varlığı, PFS ile istatistiksel olarak anlamlı değildi. SBRT'nin genel sağkalım üzerinde hiçbir etkisi olmamıştır.

Sonuç: Oligo-progresyon durumunda tedaviyi değiştirmeden metastaza yönelik SBRT ile tedavi edilen hastalarda sağkalım sonuçları daha kötüydü. Bu nedenle, aynı antiandrojen tedavisine devam edilerek metastaza yönelik SBRT'ye sadece seçilmiş vakalarda öncelik verilmelidir.

Anahtar Kelimeler: Stereotaktik vücut radyoterapisi, abiraterone, enzalutamide, kastrasyona dirençli prostat kanseri

INTRODUCTION

Prostate cancer is the most common cancer in men worldwide, and up to 60% of cases are diagnosed in metastatic settings (1). Castration-resistant prostate cancer (CRPC) is defined as having evidence of disease progression (an increase in serum prostate-specific antigen (PSA), new metastases, or progression of existing metastases), under castrate levels of serum testosterone (<50 ng/dL) (2).

The androgen pathway inhibitors such as enzalutamide, abiraterone etc. have less toxicity than chemotherapy, and are additionally related to a better quality of life (3,4). However, CRPC is still a life-limiting illness, and the median progression-free survival (PFS) under enzalutamide or abiraterone is 15-17 months (5,6). A subgroup of these patients shows oligo-progression, which was defined as the progression of only a limited number of metastatic lesions (≤3 metastasis). Meanwhile, all other lesions remain controlled by systemic therapy. Several trials showed the efficacy and safety of metastasis-directed therapy as surgery or stereotactic body radiotherapy (SBRT) in prostate cancer and many cancer types (7-10). Eliminating these oligo-progressed lesions with SBRT, which is thought to be the resistant clone to ongoing therapy, may allow continuing the same systemic therapy and may delay the following progression time. The benefit of SBRT with systemic treatment prolonged survival and was related to favourable outcomes in patients with metastatic CRPC (11-13). The phase II trial showed the benefit of SBRT by delaying the androgen deprivation therapy-free survival (14). In the CRPC setting, few studies with small sample sizes have shown the benefit of metastasis-directed SBRT (15,16). In the literature, the use of single or multiple fractions (3–4–5–8) has been described, with no current standardisation of the dose fractionation (17-19).

This study aimed to enhance the data in current literature on the benefit of metastasis-directed SBRT by continuing the same antiandrogen therapy in the oligo-progression setting of the metastatic CRPC.

MATERIAL and METHODS

Fifty-seven men diagnosed with oligo-progressive metastatic castration-resistant (serum testosterone <50 ng/dl) prostate cancer (CRPC) between 2015-2021 were included in this study. Oligo-progressive disease was defined as ≤3 lesions on conventional imaging. Androgen deprivation therapy was continued in all patients. Thirty-nine of the patients received metastasis-directed therapy continued by the same antiandrogen therapy; the remaining patients were treated with the subsequent line of treatment. The physician's choice antiandrogen therapy was enzalutamide 160 mg once daily or abiraterone 1,000 mg once daily (in combination with prednisone 5 mg twice daily). Leuprolide acetate 22.5 mg every three months was continued in all patients. Patients' data were retrospectively obtained from patients' charts. Patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 3 and 4, who could not continue to active follow-up, were excluded from data analysis.

SBRT was performed to all oligo-progressive lesions (≤3). SBRT was linac-based in all cases, and daily image-guided radiotherapy was performed for each patient. The planning target volume was defined as the gross tumour volume plus a 5–8 mm isotropic margin, depending on tumour location. 48 Gy per five fractions and 60 Gy per three fractions were used for lung metastasis. SBRT of lymph node metastasis was performed in a single fraction. For bone lesions the fraction of SBRT was 35 Gy in five fractions or 30 Gy in three fractions.

The treatment response, including partial response (PR), complete response (CR), stable disease (SD) and progressive disease (PD), as well as objective response rates (PR and CR), were evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 by conventional thorax and abdomen computerized tomography (CT) scan and prostate-specific membrane antigen/positron emission tomography (PSMA/PET) CT. However, biochemical response to treatment was not assessed.

Written informed consent was obtained from patients, and the Local Ethics Committee of Istanbul Medipol University approved the study (Date: 26.10.2022, No: 904).

Statistical analysis

SPSS 24.0 (SPSS Inc., IBM Corp, ARMONK, NY, USA) software was used for all statistical analyses. Parameters were described with their median values, and due to non-normal distribution, nonparametric tests were used. PFS was defined as the allocation date of enzalutamide or abiraterone to the radiological progression date. Overall survival (OS) was defined as the time from CRPC diagnosis to the death or last seen date or loss to follow-up. Survival analysis and curves were performed using the Kaplan-Meier method and compared with the log-rank test. The multivariate COX regression analysis was performed to evaluate independent prognostic factors. Toxicity was defined according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests, and p values less than or equal to 0.05 were considered statistically significant.

RESULTS

The median age was 70 (range 40-85). The number of patients with ECOG PS of 0.1 and 2 was 29 (50.9%), 23 (40.4%) and 5 (8.8%), respectively. Most of the patients were Gleason grade 4 and 5 (25.5% and 56%). The number of patients who received docetaxel chemotherapy in the castration-sensitive setting was 27 (47.4%). Eight (14.0%) patients had visceral metastases, and 23 (40.4%) patients had isolated bone metastases. Abiraterone was preferred in 47.4% and enzalutamide in 52.6% of patients. Thirty-nine patients (68.4%) had oligo-progression and were treated with palliative radiotherapy, continued by the same antiandrogen therapy. The oligo-progressive metastatic sites were as follows: bone in 21 (52.3%), lymph node in 6 (15.3%) and visceral metastasis in 12 (30.9%) patients. SBRT-related grade 1-2 toxicity was observed in 35 (61.4%) patients. The most seen grade1/2 side effects were fatigue (21.0%), nausea (14.0%), skin irritation (7.0%) and thrombocytopenia (8.7%). Only one patient had grade 3 cytopenia after SBRT. Of the 57 patients, 32 had CR or PR (56.1%), 13 (22.8%) had SD, 12 had (20.1%) PD, and death occurred in 29 (50.9%) patients (Table 1). The rate of local control in irradiated sites were 85.9% (n=49).

Table 1: Patients and tumour characteristics

Characteristics	Number of patients
	n (%)
Median age (range)	70 (40-85)
Median PSA (before treatment)	7 (0.50-90.2)
Gleason grade grup	
2	3 (5.5)
3	7 (12.7)
4	14 (24.5)
5	31 (54.3)
Unknown	2 (3.0)
ECOG PS	
0	29 (50.9)
1	23 (40.4)
2	5 (8.8)
Pre-docetaxel treatment	27 (47.4)
Metastatic sites	
Visceral metastasis	8 (14.0)
Only bone metastatic disease	23 (40.4)
Multiple metastases	26 (45.6)
Choice of antiandrogen therapy	
Abiraterone	27 (47.4)
Enzalutamide	30 (52.6)
Metastasis-directed SBRT	
Present	39 (68.4)
Absent	21 (31.6)
Oligo-progressive metastatic site	
Bone	21 (53.8)
Lymph-node	6 (15.3)
Visceral	12 (30.9)
Toxicity related to SBRT	
Grade 1-2	35 (61.4)
Grade 3-4	1 (1.7)
Treatment response	
Complete/partial response	32 (56.1)
Stable disease	13 (22.8)
Progressive disease	12 (20.1)

PSA: Prostate-specific antigen, ECOG PS: Eastern Cooperative Oncology Group Performance status, SBRT: Stereotactic body radiotherapy

At a median follow-up of 19.2 months (range: 1.7-55.2 months), the median PFS was 12.8 months, and the median OS was 25.6 months in the total cohort. The median PFS in patients who received SBRT was 11.1 months, and the median OS was 25.7 months.

Twelve month PFS was 79.0% in the group that received SBRT, while it was 88.9% in the group that did not ($p<0.001$) (Figure 1). The oligometastatic site, Gleason

grade group (p=0.4), pre-docetaxel treatment (p=0.2), the choice of antiandrogen therapy (p=0.8), and ECOG PS (p=0.08) were not significantly associated with PFS. SBRT was also a significant independent risk factor for PFS (p=0.007, HR: 15.7; 95% CI 2.05-118.7) in multivariate analysis. Changing systemic treatment in the oligo-progression setting was significantly correlated with better PFS rates (Table 2).

The 24-month OS rate in patients treated with metastasis-directed SBRT was 85.9%, while the 24-month OS rate in patients whose systemic treatment changed without SBRT was 73.4% (Figure 2). Thus, metastasis-directed SBRT did not significantly affect OS in this study (p=0.2). The univariate analysis revealed that there was no significant correlation between OS and Gleason grade group (p=0.6), pre-docetaxel treatment (p=0.3), oligo-progression in bone, lymph node and visceral metastatic sites

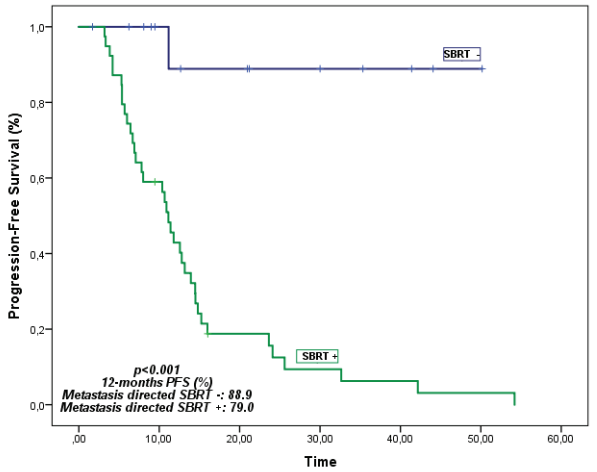

Figure 1: Progression-free survival in patients treated with metastasis-directed Stereotactic body radiotherapy

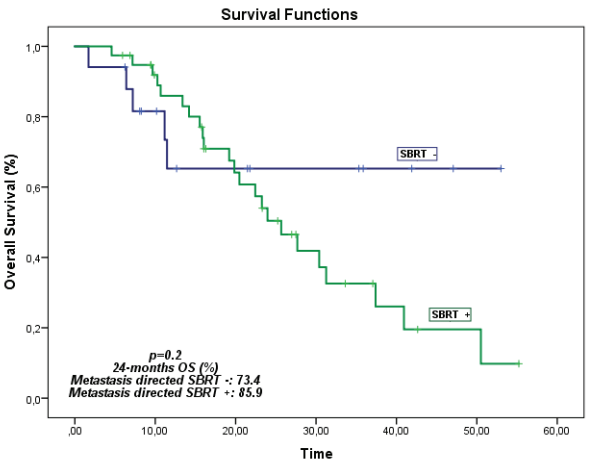

Figure 2: Overall survival in patients treated with metastasis-directed Stereotactic body radiotherapy

Table 2: The prognostic factors for PFS and OS

Factors	Progression-free survival		Overall survival	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	p	P (HR 95% CI)	P	P (HR 95% CI)
Gleason score (Risk group*) High/very high risk versus intermediate/low risk	0.4		0.6	
ECOG PS	0.08	0.6 (1.1; 0.70-1.77)	**0.04**	**0.03 (1.7; 1.05-2.75)**
Pre-docetaxel treatment	0.2	0.2 (0.6; 0.28-1.36)	0.3	
Site of oligo-progression				
Bone	0.2	0.3 (1.7; 0.55-5.18)	0.5	0.4 (0.6; 0.29-1.59)
Lymph-node	0.6		0.06	
Visceral	0.09		0.4	
Choice of enzalutamide or abiraterone	0.8		0.9	
Metastasis-Directed SBRT	**<0.001**	**0.007 (15.7; 2.05-118.7)**	0.2	0.6 (1.2; 0.41-3.93)

*Risk Groups are defined by the Grade Group of the cancer and other measures, including PSA, clinical tumour stage (T stage), PSA density, and number of positive biopsy cores,*CI: Confidence interval, *SBRT: Stereotactic body radiotherapy,* ECOG PS: Eastern Cooperative Oncology Group Performance Status

(p=0.5, p=0.06, p=0.4 respectively) and the choice of antiandrogen therapy (p=0.9). In multivariate analysis, ECOG PS was the only statistically significant factor on OS (p=0.03, HR:1.7; 95%CI 1.05-2.75).

DISCUSSION

Oligometastatic disease in CRPC is common, and the metastasis-directed SBRT ought to eradicate resistant clones and delay progression. There is no optimal consensus on the oligometastatic setting, and each decision has several risks and benefits. Several retrospective studies have shown the benefit of SBRT in oligometastatic settings in small cohorts. Thus, we aimed to contribute to the literature with our single-centre experience with SBRT in patients treated with abiraterone or enzalutamide in the first line of CRPC.

Berghen et al. examined 30 metastatic CRPC patients who experienced oligo-progression under any systemic treatment, including antiandrogen therapies. All patients received SBRT to the oligo-progressive lesions while ongoing systemic treatment was continued. The median time for next-line systemic treatment (NEST) was 16 months (95% CI: 10–22), and the median progression-free survival was ten months (95% CI 6–15) (15). Similarly, SBRT to all oligo-progressive lesions in 34 CRPC patients led to a median NEST-free survival of 16.9 months and a median PFS of 13.47 months in a retrospective study by Ingrosso et al. (16). Another study compared SBRT with a cohort of patients treated with a change in systemic treatment alone. SBRT was associated with favourable outcomes and improved cancer control (13). Despite these retrospective trials in our study, we could not demonstrate a significant benefit of SBRT. Moreover, SBRT was significantly related to worse PFS rates. A possible reason might be the inclusion of patients (47.4%) treated with docetaxel chemotherapy in metastatic castration-sensitive settings.

Sixty-two prostate cancer patients had a biochemical recurrence after primary curative intent treatment, had oligo-progression and had serum testosterone levels > 50 ng/mL. We were enrolled in a phase II trial. They compared active surveillance and metastasis-directed SBRT, which showed the survival benefit of SBRT (13 months (80% CI, 12 to 17 months) vs 21 months (80% CI, 14 to 29 months) respectively) (14). We found that 12-month PFS was 79.0% in the group that received SBRT, while it was 88.9% in the group that did not (p<0.001). These controversial results are related to the design of our study. We enrolled patients who had oligo-progression under first-line CRPC treatment; 12 of the patients (30.9%) had progression on visceral sites, and the majority of the patients were in Gleason grade groups 4 and 5 (25.5% and 56%).

Another study demonstrated the survival benefit of SBRT compared to treatment change in 30 patients with oligo-progression, mostly in bone (17). A multicentre retrospective study by Detti et al. demonstrated a median PFS of 9.6 months in an oligo-progression setting of metastatic CRPC patients treated with abiraterone (20). Another multicentre study by Triggiani et al. included 86 patients with bone or lymph node oligo-progressive lesions treated with SBRT and revealed that the median new metastasis-free survival was 12.3 months, with a majority of the patients receiving further SBRT (10). In our study, the median PFS in the SBRT group was 11.1 months, and the median OS was 25.6 months. The median PFS of our study was similar to these previous studies (10,17,19).

We acknowledge that the limitation of our study was the retrospective design and enrolling the high-risk featured patients, which may affect the results. And we should have analysed the progression after SBRT. Thus, we cannot comment on the additional benefit of SBRT over changing the systemic treatment. However, this study reflects real-world practice and highlights characteristics within a cohort of patients who oligo-progressed on antiandrogen therapy. We contribute to the literature by demonstrating that the high-risk featured metastatic CRPC patients who had oligo-progressed under antiandrogen therapy may not be eligible for metastasis-directed SBRT. Progression under enzalutamide or abiraterone may relate to systemic resistance; thus, next-line treatment would be the best option in these patients.

CONCLUSION

In our single-centre study, we could not demonstrate any survival benefit with metastasis-directed SBRT. Additionally, the PFS was poorer in the metastasis-directed SBRT group than in patients who received next-line systemic treatment. However, it is difficult to draw any conclusions due to this study's small number of patients. Metastasis-directed SBRT with continuing the same antiandrogen therapy should be prioritised only in selected cases.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Istanbul Medipol University (Date: 26.10.2022, No: 904).

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THE EFFECT ON OVARIAN RESERVE IN THE EARLY POSTOPERATIVE PERIOD IN HYSTERECTOMY ACCORDING TO THE TYPE OF SURGERY

CERRAHİ METODUN TÜRÜNE GÖRE HİSTEREKTOMİNİN AMELİYAT SONRASI ERKEN DÖNEMDE OVER REZERVİNE ETKİSİ

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ABSTRACT

Objective: The aim of this study was to estimate the possible differential levels of influence of the applied hysterectomy type on ovarian reserve.

Materials and Methods: Our study is a single-center prospective cross-sectional study. We included 82 patients who underwent benign hysterectomies between July 2021 and March 2022. There were two groups, abdominal hysterectomy (n=54) and laparoscopic (L/S) hysterectomy (n=28). Transvaginal ultrasonography and hormone status were evaluated before and after the hysterectomy. Patients with a preoperative anti-Mullerian hormone (AMH) value greater than 0.01 ng/dl and a follicle stimulating hormone (FSH) value less than 15 IU/L were included in the study.

Results: There was a significant difference between the groups regarding age, parity, duration, and bleeding. There was no significant difference in the percent decrease in AMH value between abdominal and laparoscopic hysterectomies. There was no difference in the comparison regarding the amount of decrease in ovarian volume and antral follicle count (AFS) parameters. In the analysis of serum estradiol values, an increase in 33 patients and a decrease in 49 patients were observed. While serum estradiol values decreased in 33 of 54 patients who underwent abdominal hysterectomy, this rate was 67.3% among patients with decreased estradiol. The difference in estradiol values was not statistically significant. There was a difference between the two groups in the comparative analysis regarding the amount and rate of increase in FSH parameters (p=0.03).

ÖZET

Amaç: Bu çalışmada yapılan histerektomi tipine göre over rezervinin ne kadar etkilendiğini tahmin etmeyi amaçladık.

Gereç ve yöntem: Çalışmamız tek merkezli prospektif kesitsel bir çalışmadır. Temmuz 2021 ile Mart 2022 arasında benign histerektomi yapılan 82 hastayı dahil ettik. Abdominal histerektomi (n=54) ve laparoskopik (L/S) histerektomi (n=28) olmak üzere iki grup vardı. Histerektomi öncesi ve sonrası transvajinal ultrasonografi ve hormon durumu değerlendirildi. Ameliyat öncesi anti-Müllerian hormon (AMH) değeri 0,01 ng/dl'nin üzerinde ve folikül uyarıcı hormon (FSH) değeri 15 IU/L'nin altında olan hastalar çalışmaya alındı.

Bulgular: Gruplar arasında yaş, parite, süre ve kanama açısından anlamlı fark vardı. Abdominal ve laparoskopik histerektomiler arasında AMH değerindeki azalma yüzdesi açısından anlamlı bir fark yoktu. Over hacmindeki azalma miktarı ve antral folikül sayısı (AFS) parametreleri açısından karşılaştırmada fark yoktu. Serum estradiol değerlerinin analizinde 33 hastada artış, 49 hastada düşüş gözlendi. Artanların %63,7'si, azalanların ise %67,3'ü abdominal histerektomi geçirenlerdi. Estradiol değerleri arasındaki fark istatistiksel olarak anlamlı değildi. FSH parametrelerindeki artış miktarı ve hızı açısından karşılaştırmalı analizde iki grup arasında fark vardı (p=0,03).

Sonuç: Her iki grupta da ameliyat öncesi ve sonrası over rezervinde azalma gözlendi. Aralarında yapılan analizlerde anlamlı bir fark gözlenmedi. FSH düzeylerindeki artış L/S lehine daha anlamlıydı. Elektrotermal enerji kullanımına bağlı olarak over foliküllerinde inhibin-B düzeylerinin araştırılması da dahil olmak

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Conclusion: In both groups a decrease in ovarian reserve before and after surgery was observed. No significant difference was observed in the analyses performed between them. The increase in FSH levels was more significantly in favor of L/S. Prospective large-scale studies are needed to investigate the effect of L/S hysterectomy on ovarian reserve compared to abdominal surgery, including investigating inhibin-B levels in ovarian follicles due to electrothermal energy use.

Keywords: Hysterectomy, ovarian reserve, anti-mullerian hormone, follicle stimulating hormone, estradiol

üzere, karın cerrahisine kıyasla L/S histerektominin yumurtalık rezervi üzerindeki etkisini araştırmak için prospektif büyük ölçekli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Histerektomi, yumurtalık rezervi, anti-mullerian hormon, folikül uyarıcı hormon, estradiol

INTRODUCTION

Hysterectomy is the second most common type of operation after cesarean section performed by gynecologists in women of reproductive age. Uterine leiomyomas remain the most common indication for hysterectomy. Other benign causes are abnormal bleeding, adenomyosis, endometriosis, pelvic organ prolapse, pelvic inflammatory disease, chronic pelvic pain, and pregnancy-related conditions (1). In the retrospective study of Moawad G. et al. in 2017 on 527,964 women who had undergone hysterectomy for benign reasons, the most common indication for all types of surgery (abdominal, vaginal, laparoscopic, robotic) was fibroids (leiomyoma, benign neoplasms) and the other indications were endometriosis, pelvic prolapse (2).

Today, there are various operative approaches to hysterectomy. The uterus can be removed abdominally, transvaginally, or laparoscopically. However, abdominal hysterectomy is still the most frequently used method for benign reasons; vaginal and laparoscopic operations are considered minimally invasive surgical approaches in terms of short hospital stays and postoperative recovery times (2,3).

The Cochrane Database, which included 47 studies with 5,102 women who had undergone laparoscopic, abdominal, vaginal, and robot-assisted hysterectomy methods, were analyzed comperatively regarding postoperative results. It was stated that a vaginal hysterectomy should be performed as much as possible. In cases where vaginal hysterectomy is not possible, the pros and cons of both laparoscopic and abdominal hysterectomy should be discussed with the patient during the decision-making process (4).

Ovarian reserve represents a woman's reproductive potential as a function of the number and quality of oocytes. Many factors affect ovarian reserves, such as advanced female age (>40 years old is the most critical parameter that determines ovarian reserve), conditions that damage the ovaries, such as endometriosis and pelvic infection, and previous ovarian surgery. In the study of Wang Y. et al., the effects of environmental, social, and surgical factors on ovarian reserve were examined (5). They stated the importance of a significant inverse relationship between early menarche, previous adnexal surgery, intense exercise, alcohol use, sleep quality, and female fertility.

It is known that the use of medical agents, certain radiotherapeutic trials and surgical interventions that damage the ovarian parenchyma significantly damage the ovarian reserve. Surgery that cuts off blood flow to the ovaries or directly damages the ovarian parenchyma can be expected to result in a reduction in the ovarian follicle pool. Many studies have also stated the relationship between surgical interventions and decreased ovarian reserve (6). In the study conducted by Chun S. and Y IJ. in 2020, the ovarian reserve was investigated in short term by evaluating the anti-Mullerian hormone (AMH) levels on preoperative and postoperative 3rd day in women who had undergone laparoscopic and non-laparoscopic hysterectomy. In the results of the research, a significant decrease was observed in both groups. The authors suggested that the electro-thermal energy from laparoscopic surgical devices can cause additional damage to the ovarian reserve. (7).

To our knowledge, there is limited literature comparing the change in ovarian reserve after laparoscopic hysterectomy and non-laparoscopic hysterectomy performed for benign gynecological reasons. In our study, we investigated the early effects on postoperative ovarian reserve in patients undergoing laparoscopic and non-laparoscopic hysterectomy for benign gynecological reasons.

MATERIAL and METHODS

Our study is a single-center, prospective cross-sectional study comparing the effects of hysterectomy performed for benign gynecological reasons with the types of operations on early ovarian reserve. We included a total of 82 patients who were scheduled for benign uterine hysterectomy at to the Health Sciences University Bursa Yüksek Ihtisas Training and Research Hospital, Department of Obstetrics and Gynecology, between July 2021 and March 2022. The Clinical Research Ethics Committee

of the University of Health Sciences Bursa Yüksek Ihtisas Training and Research Hospital approved the research (Date: 23.06.2021, No: 2011-KAEK-25 2021/06-10). The patients were given detailed information about our study and the operation, and informed consent was obtained. Preoperative care of each patient and control one month after the operation was planned. Patients who agreed to come for this follow-up and volunteered to participate in the study were included.

Patients' age, height, weight, body mass index, parity, previous operation history, hysterectomy indication, and type of hysterectomy performed were recorded. In addition, ovarian volume, number of antral follicles, AMH, FSH, and estradiol (E2) values were evaluated and recorded by transvaginal ultrasonography performed on the third day of menstruation and in the first month postoperatively.

The same gynecologist also performed a total laparoscopic hysterectomy and bilateral salpingectomy. In this process, round and utero-ovarian ligaments were sealed and cut by Ligature 10 (Covedian 1037 with a blunt tip as a bipolar vessel sealing device, used with a force trial generator to provide a permanent fusion for the vessels up to 7 mm diameter and heat spread depending on the tip and the duration of activation). The uterine artery was sealed (cutting mood, power 40 W) and cut by bipolar cautery (Günter Bissinger Medizintechnik 's Powergrip bipolar), and the bladder was separated by sharp dissection. Finally, the vaginal cuff was cut by monopolar cautery and sutured. During both processes, if present, adhesion of the bowel and omentum to the anterior wall of the abdomen was released.

Patients who had a history of using drugs that would affect ovarian reserve, any surgical procedure to the ovaries during the operation, patients who had no menstrual bleeding in the past year, and patients with malignancy were excluded from the study. Preoperative blood samples were taken from the patients on the third day of their menstruation for the hormone profile. Blood samples were studied in the central laboratory of Bursa Yüksek Ihtisas Training and Research Hospital. AMH was measured by the ELISA method (Beckman Coulter-Inc). Reference ranges were taken for AMH as 0.01-6.2 ng/ml (8). Preoperative transvaginal ultrasonography (TVUSG) (GE Voluson 730 4D MHZ) was used to calculate ovarian volume and antral follicle count. The volume of each ovary was calculated by taking measurements perpendicular to each other (length × width × depth × 0.52 = volume). We measured and averaged the diameters of both ovaries. In TVUSG, follicles with a diameter of 2-10 mm were counted as antral follicles. The antral follicles in both ovaries were counted, and the largest antral follicles were sampled. Ultrasonographic measurements were performed by the same specialist doctor. Patients were called in for follow-up in the first month after surgery, and serum hormone levels were evaluated. The average of both ovarian volumes or the ovarian tissue left in after the operation was measured with TVUSG, and the antral follicle numbers were calculated.

Statistical analysis

The conformity of the data to the normal distribution was examined using the Shapiro Wilk test. Normally distributed continuous data are defined by mean and standard deviation, and non-normally distributed continuous data are defined by median and minimum-maximum values. Normally distributed continuous data between the two groups were compared with the Student's t test and non-normally distributed continuous data were compared with the Mann-Whitney U test. The comparison of categorical data between the two groups was made with chi-square and Fisher's exact chi-square test, and descriptive statistics were given as frequency and percentage. The Fisher-Freeman Halton test was used to compare categorical data for more than two groups. SPSS v23 (SPSS, IBM, USA) package programs were used in the analysis of the data. In the statistical analyses, α=0.05 was taken as the level of significance.

RESULTS

Eighty-two patients were included in the study. Patients were classified into 2 groups abdominal (n=54) and laparoscopic (n=28) hysterectomy. Patients with a preoperative AMH value greater than 0.01 ng/ml and an FSH value less than 15 IU/L were included in the study. After the hysterectomy, two patients whose laboratory derived FSH value could not be measured, six patients whose AMH value could not be measured, and two patients due to the inability to visualize the ovaries on USG were excluded in the comparison according to the types of surgery.

The number of patients who underwent abdominal hysterectomy was 54, and the mean age was 44. The body mass index (BMI) median value was 28.3; parity was calculated as 2. The mean surgical time was 119 minutes (95% confidence level, mean between 108.80 and 129.60 minutes), and the mean amount of bleeding was 206 ml (95% confidence level, mean between 161.72 and 250.28 ml). The number of patients who underwent L/S hysterectomy was 28. The average age was also 46. Median values were calculated as BMI 28.8, parity 3. The mean operative time was 122 minutes (95% confidence level, mean between 105.54 and 139.66 minutes), and the mean amount of bleeding was 134 ml (95% confidence level, mean between 70.03 and 198.77 ml) in this group. When the two groups were compared statistically, there was no difference in terms of BMI. Age, parity, amount of bleeding, and mean operative time values were found to be statistically significant. The sociodemographic and operative data of the patients are summarized in Table 1.

Table 1: Comparison of demographic characteristics, surgical findings and preoperative and postoperative AMH and FSH values of the study groups

	Abdominal hysterectomy (n=54)	Laparoscopic hysterectomy (n=28)	p-value
	Mean±SD; Median (Min-Max)	Mean±SD; Median (Min-Max)	
Age (years) β	44 (21-49)	46 (38-49)	0.025
Body Mass Index (kg/m2) β	28.3 (18.3-48.9)	28.8 (23.4-37.1)	0.89
Parity β	2 (0-7)	3 (2-9)	0.01
Duration (min) *	119.2±3.9	122.6±4.4	0.01
Bleeding (ml) *	206±16.6	134.4±16.6	0.01
Preoperative AMHβ (ng/ml)	0.37 (0.02-3.48)	0.11 (0.02-2.45)	0.021
Preoperative FSH (IU/l) β	4.9 (0.14-14.5)	9 (1.28-15)	0.013
Postoperative AMHβ (ng/ml)	0.14 (0.01-1.5)	0.01 (0.01-2.2)	0.02
Postoperative FSH (IU/l)β	**10.1 (3-89)**	**20 (5-87)**	**0.013**

AMH: Anti Mullerian Hormone, FSH: Follicle Stimulating Hormone, SD: Standard deviation, Min: Minimum, Max: Maximum, *: Student t test, β: Mann Whitney U test

The hormone profile data of the patients were compared according to the type of operation. When the pre- and post-operative values were compared, it was observed that the AMH value decreased in both operation types, and the FSH value increased in both operation types. Table 1 presents the analysis of the data.

In the analysis comparing E2 values in both hysterectomy types, it was found that the E2 value of 21 patients who underwent abdominal hysterectomy and 12 patients who underwent L/S hysterectomy was increased; E2 values of 33 patients who underwent abdominal hysterectomy and 16 patients who underwent L/S hysterectomy were decreased. When the data of both groups were compared, no significant difference was found (p=0.72). Statistical data comparing E2 values are given in Table 2.

The percentage of reduction in AMH levels between the two types of hysterectomy performed was evaluated (Table 3). Six laboratory-derived patients were not included in the evaluation. In the assessment made on 76 patients, the median percent decrease in AMH was 49.4±28.7; in L/S hysterectomy, it was calculated as 37.5±34.4. When the two groups were compared with each other, no significant difference was found (p=0.13).

Preoperative and postoperative 1st-month FSH was measured in each patient. However, two patients of laboratory origin could not be included. In the FSH samples taken

Table 2: Analysis table of serum estradiol values according to hysterectomy types

	Abdominal hysterectomy n (%)	Laparoscopic hysterectomy n (%)	n (%)	X^2	p*
Increased E2	**21 (63.6%)**	**12 (36.4%)**	**33 (100%)**	**0.121**	0.72
Decreased E2	**33 (67,3%)**	**16 (32,7%)**	**49 (100%)**		

E2: Estradiol, *: Pearson Chi-Square, p<0.05 was considered significant

Table 3: Comparative analysis of percent decrease in anti-mullerian hormone parameters between groups

	Abdominal hysterectomy (n=49)	Laparoscopic hysterectomy (n=27)	p-value*
	Mean±SD	Mean±SD	
Anti-müllerian hormone reduction percentage	49.4±28.7	37.5±34.4	0.13

SD: Standard deviation, * Student-t test, p<0.05 was considered significant

from 80 patients, an increase was observed in both types of operation compared to the preoperative period. In the statistical evaluation based on the FSH change value and increase rate between the groups, a significant increase was observed in the L/S type compared to the abdominal type (FSH change value p:0.03 and FSH increase rate p=0.03) (Table 4).

Evaluation of ovarian reserve was performed ultrasonographically in all patients. Still, one patient who had undergone an abdominal hysterectomy and another who had undergone an L/S hysterectomy were excluded for reasons such as postoperative mobility of the ovaries and obesity. By taking the width, height, and depth measurements of both ovaries in three dimensions, volume calculations were made with the formula D1xD2xD3x0.523, and the average of the sum of the volumes of both ovaries was taken. Follicles between 2-10 mm in the ovaries were accepted as antral follicles, and AFS was examined. The change in preoperative and postoperative ovarian volume and AFS were inspected. When the changes in preoperative and postoperative ovarian volume and AFS were examined in both types of operation, both types of ovarian volume and AFS were decreased. When the two operation types were compared, no significant difference was observed (p=0.59, p=0.57, respectively). Ovarian volume and AFS of both types of hysterectomy are evaluated in Table 5.

DISCUSSION

Hysterectomy is the second most common type of surgery performed by gynecologists after cesarean section in the reproductive age. The total number of hysterectomies performed for benign reasons in our gynecology clinic last year was 470; 260 were done abdominally, 136 laparoscopically, and 74 vaginally. In 103 abdominal cases and 42 laparoscopic cases, only hysterectomy was performed, while oophorectomy was not performed. The abdominal/laparoscopic hysterectomy rate in our study was consistent with the annual total abdominal/laparoscopic hysterectomy rates in our department. Salpingoopherectomy was performed in 53% of these hysterectomies. Salpingoopherectomy was performed in 53% of these hysterectomies. The number of patients in the study was also distributed into groups in proportion to the number of surgeries in our department, following the literature examples (9).

This study aimed to evaluate the early period ovarian reserve according to the operation type of hysterectomy performed for benign reasons. As a result, AMH levels, ovarian volume, and the number of antral follicles decreased significantly in the first month postoperatively for all participants when compared before and after surgery; it was observed that FSH levels increased significantly. There was no significant variation in E2 levels. The second aim of our study was to evaluate whether the early postoperative changes of ovarian reserve differ according to the type of surgery. As a result of the study, we observed a decrease in serum AMH values in the early period in both types of operation. The percentage of reduction in AMH parameters was not significant in both types of operation. Also, the decrease in mean ovarian volume and AFS in the ultrasonographic examination

Table 4: Comparison analysis table in terms of the amount and rate of increase in FSH parameters between groups

	Abdominal hysterectomy (n=52)	Laparoscopic hysterectomy (n=28)	p-value *
	Mean±SD; Median (Min-max)	Mean±SD; Median (Min-max)	
FSH exchange value (IU/L)	3.9 (0.2-85.3)	12.3 (0.4-72.8)	**0.03**
FSH increase rate (%)	1.8 (0.3-24.4)	3.2 (1.1-10)	**0.03**

FSH: Follicle Stimulating Hormone, SD: Standard deviation, *: Mann Whitney-U test, p<0.05 was considered significant

Table 5: Comparison analysis table in terms of decrease in Ovarian Volume and Antral Follicle Count parameters between the groups

	Abdominal hysterectomy (n=52)	Laparoscopic hysterectomy (n=28)	p-value*
	Mean±SD; Median (Min-max)	Mean±SD; Median (Min-max)	
Ovarian volume change (ml)	2.5 (0.5-10.7)	3.2 (0.0-7.5)	0.59
Change in the number of antral follicles	2 (0.0-6)	2 (0-7)	0.57

SD: Standard deviation, *: Mann Whitney-U test, p<0.05 was considered significant

were insignificant in both operation types. We found that serum FSH values after surgery increased significantly in the L/S type compared to the abdominal type.

The main difference between laparoscopic hysterectomy and non-laparoscopic hysterectomy is that electrothermal vessel ligation is used more frequently in laparoscopy. Usually, vessel sealing is accomplished with sutures using Vicryl or Silk during vaginal or abdominal hysterectomy. Electrothermal vessel ligation may damage ovarian flows, thereby accelerating follicular depletion and premature menopause (10). However, to our knowledge, there is limited literature comparing changes in ovarian reserve after laparoscopic and abdominal hysterectomy. In the results of a study conducted with the participation of 50 patients examining the change in ovarian reserve markers after laparoscopic ovarian cystectomy (LOC), it was found that ovarian reserve decreased after LOC, independent of the presence of endometrioma, which can be distinguished by serum AMH levels (11). In another study examining the effects of total salpingectomy performed during abdominal hysterectomy on ovarian reserve and ovarian stromal blood flow, it has been reported that mean FSH, LH, estradiol values and ovarian volume did not change, but mean pulsatility index, resistance index and systole/diastole (S/D) ratio decreased significantly compared to the initial values (12). In another study on 30 premenopausal women evaluating the short-term effects of salpingectomy performed during laparoscopic hysterectomy on ovarian reserve, in which the ovaries were planned to be preserved, the mean serum AMH values measured before and after the operation were compared; it was reported that salpingectomy does not have short-term harmful effects on ovarian reserve (13).

In our study, FSH values increased more significantly in L/S type hysterectomies in the early postoperative period compared to the abdominal method. We think that the negative feedback effect on FSH disappears due to the decrease in inhibin-B secreted from the granulosa cells, which is caused by the destruction of the granulosa cells in the follicles, in addition to the thermal heat used in L/S surgery, and this is the reason for the early increase in FSH. In a study in which ovarian reserve tests were evaluated to determine the histologically defined follicle pool, a post-oophorectomy specimen and serum ovarian reserve tests were compared, and it was mentioned that the first change in the early perimenopausal period was the suppression of serum E2 values with the increase in FSH due to the decrease in inhibin-B (14). The decrease in ovarian volume and the decrease in AFS, which we analyzed in our study's early postoperative ultrasonographic examination, are other reasons for the increased FSH levels.

It is controversial that only the infundibulopelvic ligament can provide perfusion of the ovaries in a hysterectomy performed as an ovarian-sparing surgery. In the literature, various studies compare ischemia due to perfusion damage in the ovaries between cutting and burning the uterine artery with electrothermal effect and ligating it with sutures. In our study, we observed that ovarian volume was higher in the L/S type between the two groups in which ovarian volume and AFS decreased in all patient groups in the early postoperative ultrasonographic imaging.

The critical aspect of our study is that in the early postoperative period, serum AMH, FSH, and E2 values should be evaluated together with inhibin-B, and the correlation of high FSH and variable E2 values with inhibin-B might be necessary. There need to be more studies on inhibin-B in the literature. In addition, increasing the total number of volunteers and working with different populations are other study limitations.

It is obvious that the ovarian reserve decreases after ovarian-sparing hysterectomy. Our study also supports this. There was no significant difference in AMH levels, ovarian volume and AFS reduction levels when compared according to hysterectomy types.

CONCLUSION

As a result, there is evidence in the literature that ovarian-sparing surgery when performed in women who do not carry the risk of ovarian cancer is life-long. It is still discussed whether L/S type hysterectomy causes more damage to the ovary with electrothermal effect. With the development of new surgical devices and techniques, minimally invasive surgery indications are expanding. Electrothermal devices with the least power should be used whenever possible. Electrothermal energy used in laparoscopic hysterectomy may cause additional damage to ovarian reserve. Prospective large-scale studies are needed to investigate its effect on ovarian reserve compared to abdominal surgery.

Ethics Committee Approval: This study was approved by University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Date: 23.06.2021, No: 2011-KAEK-25 2021/06-10).

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SURGICAL MANAGEMENT OF ENDOSCOPICALLY UNRESECTABLE COLORECTAL POLYPS

ENDOSKOPİK OLARAK ÇIKARILAMAYAN KOLOREKTAL POLİPLERE CERRAHİ YAKLAŞIM

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ABSTRACT

Objective: To define the management of colorectal polyps that were technically unsuitable for endoscopic removal.

Materials and Methods: Between May 2010 and January 2019, 4886 polyps from 3822 of 16,996 colorectal endoscopies were analyzed. Of the total colorectal polyps, 135 (2.8%) were identified as endoscopically unresectable single polyps and examined in detail.

Result: The rate of invasive colorectal cancer (CRC) in unresectable and resectable polyps was 26.7% and 1.7%, respectively (p<0.001). Unresectable polyps were more common in the ascending colon and cecum (p<0.001), but the potential to contain invasive CRC was greater in the sigmoid colon and rectum-located polyps (p=0.001). In addition, advancing age (p=0.014), increased polyp size (p=0.012), deep submucosal invasion (p<0.001), and the presence of lymphovascular invasion (p<0.001) were associated with the development of CRC. Unresectable polyps requiring surgery after non-curative endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) were found to have a significantly higher risk of containing CRC compared with polyps that underwent surgical resection primarily (p=0.002). In the multivariate model, advancing age (p=0.010) and detected deep submucosal invasion (p=0.002) were more associated with the development of CRC.

Conclusion: The study suggests that oncologic surgery for polyps with deep submucosal invasion (particularly by EMR or ESD) that cannot be endoscopically resected in older patients should be considered carefully and, perhaps, without delay,

ÖZET

Amaç: Bu çalışma, endoskopik olarak çıkarılması teknik olarak uygun olmayan kolorektal poliplerin tedavisini tanımlamayı amaçladı.

Gereç ve Yöntem: Mayıs 2010 ile Ocak 2019 tarihleri arasında 16,996 kolorektal endoskopiden 3,822'sinde 4,886 polip analiz edildi. Total kolorektal poliplerin 135'i (%2,8) endoskopik olarak çıkarılamayan tekli polip olarak tanımlandı ve detaylı olarak incelendi.

Bulgular: Rezeke edilemeyen bir polipte invaziv kolorektal kanser (KRK) oranı %26,7 iken, rezeke edilebilir bir polipte bu oran %1,7 idi (p<0,001). Rezeke edilemeyen polipler çıkan kolon ve çekumda daha yaygındı (p<0,001), ancak invaziv KRK içerme potansiyeli sigmoid kolon ve rektum yerleşimli poliplerde daha fazlaydı (p=0,001). Ayrıca ilerleyen yaş (p=0,014), artmış polip boyutu (p=0,012), derin submukozal invazyon (p<0,001) ve lenfovasküler invazyon varlığı (p<0,001) KRK gelişimi ile ilişkiliydi. Küratif olmayan endoskopik mukozal rezeksiyon (EMR) veya endoskopik submukozal diseksiyon (ESD) sonrası ameliyat gerektiren rezeke edilemeyen poliplerin, primer olarak cerrahi rezeksiyon uygulanan poliplere kıyasla anlamlı derecede daha yüksek KRK içerme riskine sahip olduğu bulundu (p=0,002). Çok değişkenli modelde ilerleyen yaş (p=0,010) ve saptanan derin submukozal invazyon (p=0,002) KRK gelişimi ile daha fazla ilişkiliydi.

Sonuç: Çalışma, yaşlı hastalarda endoskopik olarak rezeke edilemeyen derin submukozal invazyonlu (özellikle EMR veya ESD ile) polipler için onkolojik cerrahinin dikkatli bir şekilde düşünülmesi gerektiğini ve belki de gecikmeden, öncelikle tekrarlanan

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primarily by abandoning repeated endoscopic resection attempts.

Keywords: Colorectal neoplasms, polyps, endoscopy, endoscopic mucosal resection, endoscopic submucosal dissection

endoskopik rezeksiyon girişimlerinden vazgeçilmesi gerektiğini önermektedir.

Anahtar Kelimeler: Kolorektal neoplaziler, polipler, endoskopi, endoskopik mukozal rezeksiyon, endoskopik submukozal diseksiyon

INTRODUCTION

Colorectal cancer (CRC) is the third most common and the second leading cause of cancer-related deaths worldwide (1). Colorectal polyps are well-known precursor lesions of invasive carcinomas. Successful removal of these polyps through screening programs provided reduced incidence of CRCs (2,3). Screening colonoscopy identifies benign adenomatous polyps in approximately 20% of individuals, advanced adenomatous polyps in approximately 6%, and colorectal cancer in just over 1% (4).

Prediction of the presence of carcinoma in a polyp and the carcinoma invasion depth is challenging in endoscopy. Risk modeling can be performed according to pathologic examination or/and endoscopic appearance. The Haggitt level system and Kikuchi classification have been based on pathologic features to reveal the carcinoma invasion depth into colonic layers. The endoscopic appearance of an unresectable polyp can vary from benign appearance to high suspicion of malignancy. The Kudo pit pattern and Paris classifications are based on the endoscopic view in predicting carcinoma invasion depth, supported with dye assistance or image-enhanced methods, according to morphologic features (5). Likewise, assessments of surface and vascular patterns can be used to predict lesion histology and, in particular, assess for areas of early invasion (6).

Furthermore, difficult access, the presence of scarring, and location close to the dentate line, appendical orifice, ileocaecal valve, or diverticula can make resection very challenging, and resection of these difficult polyps requires techniques beyond simple polypectomy and also poses new risks of complications. Irrespective of the experience of the endoscopist, up to 15% of polyps cannot be resected completely due to polyp size, location, features, and patient-specific conditions and it requires surgical resection (7-9).

The present study aimed to investigate colorectal polyps that were technically unsuitable for endoscopic removal, reveal potential risk factors to predict invasive CRC and define the management of these unresectable polyps.

MATERIAL and METHODS

Study design and study population

This retrospective case-control study of patients with polyps was conducted at Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, Surgical Endoscopy Unit between May 2010 and January 2019. Four thousand eight hundred eighty-six polyps from 3822 of 16,996 colorectal endoscopies were analyzed.

The evaluation of polyps was performed according to the following methods:

- Polyp size
- Polyp morphology
  - Paris classification (protruding, flat elevated, flat lesions)
  - Lateral spreading (granular, non-granular)
- Polyp surface pattern (Kudo neoplastic polyp classification)
- Non-lifting sign
- Endosonography (EUS)

The above methods were preferred based on the endoscopists' decision; not all were used in the evaluation of the same polyp. EUS was used to examine the polypectomy margin of suspicious polypectomies in the assessment of invasion depth in incompletely resected pedunculated or sessile polyps. In addition, EUS was used to evaluate the invasion depth of flat lesions with suspicious other lesion features, especially in the distal colon and rectum.

Histopathologically, the Japan NBI Expert Team (JNET) classification, which has a range from carcinoma-free or intramucosal neoplasia to carcinoma with deep submucosal invasion, and which also examines vessel patterns, was used to evaluate polyps.

Submucosal invasion was evaluated according to EUS findings, and through histopathologic examinations, if possible, in incomplete polypectomy specimens of pedunculated or sessile lesions, or non-curative endoscopic mucosal resection/endoscopic submucosal dissection (EMR/ESD) specimens (1,2).

After the initial evaluation, standard polypectomy procedures were performed in line with the surgical endoscopy unit algorithm of our center, including hot biopsy for polyps ≤5 mm, and snare polypectomy for polyps >5 mm. Snare polypectomy was performed with additional submucosal injections for large and sessile polyps.

EMR has been preferred for <30 mm pedicle polyps, <20 mm non-granular/non-depressed flat lesions, or granular lesions since 2012. Generally, EMR was skipped in the ulcerated, depressed, or deep submucosa-infiltrated (by EUS) lesions. ESD has been initiated to be performed as of 2015, in cases where polyps have these features above-mentioned that would not be preferred for EMR and also if the polyp sizes are relatively larger.

Although based on physicians' experience, surgical resection was considered primarily because of the following characteristics of a polyp;

- for laterally (around) more than two-thirds of the intestine covering polyps,
- laterally (around) more than two-thirds of the intestine covering polyps,
- polyps extending longitudinally on two consecutive haustral folds,
- polyps extending to the appendix, diverticulum, through the ileocecal valve,
- lifting-sign negative polyps,
- polyps highly suspected of invasive CRC based on their morphological features of surface pattern,
- according to EUS findings, polyps with deep submucosal invasion especially located in the distal colon and rectum.

In addition, histopathologically, surgical resection was performed under the following conditions;

- cancer at the polypectomy resection margin of <2mm,
- if deep submucosal invasion is present in polyps that cannot be completely resected by polypectomy,
- if deep submucosal invasion is present in non-curative EMR/ESD specimen.

The flow chart of the approach to colorectal polyps is summarized in Figure 1.

In the study, endoscopically resectable (n=4751) and unresectable single polyps (n=135) that could be surgically resected were examined separately. Unresectable polyps were evaluated in two groups. In the first group, some polyps could not be curatively resected through EMR or ESD (n=47). The second group consisted of polyps that were incompletely resected with standard polypectomy that were decided to undergo surgical resection, and polyps that were determined to be unsuitable for any endoscopic removal by endoscopic evaluation and were decided for surgical resection (n=88).

Invasive CRC (T1-T2) was defined as residual T1-T2 cancer in the surgical resection specimens of patients who underwent surgical resection after incomplete polypectomy or non-curative EMR/ESD, or T1-T2 cancer in the surgical resection specimens of patients who underwent surgery primarily.

All patients were informed about the diagnostic and therapeutic procedures, and written informed consent was obtained. The study protocol was approved by the Istanbul Faculty of Medicine Ethics Committee (Date: 17.12.2010, No: 09).

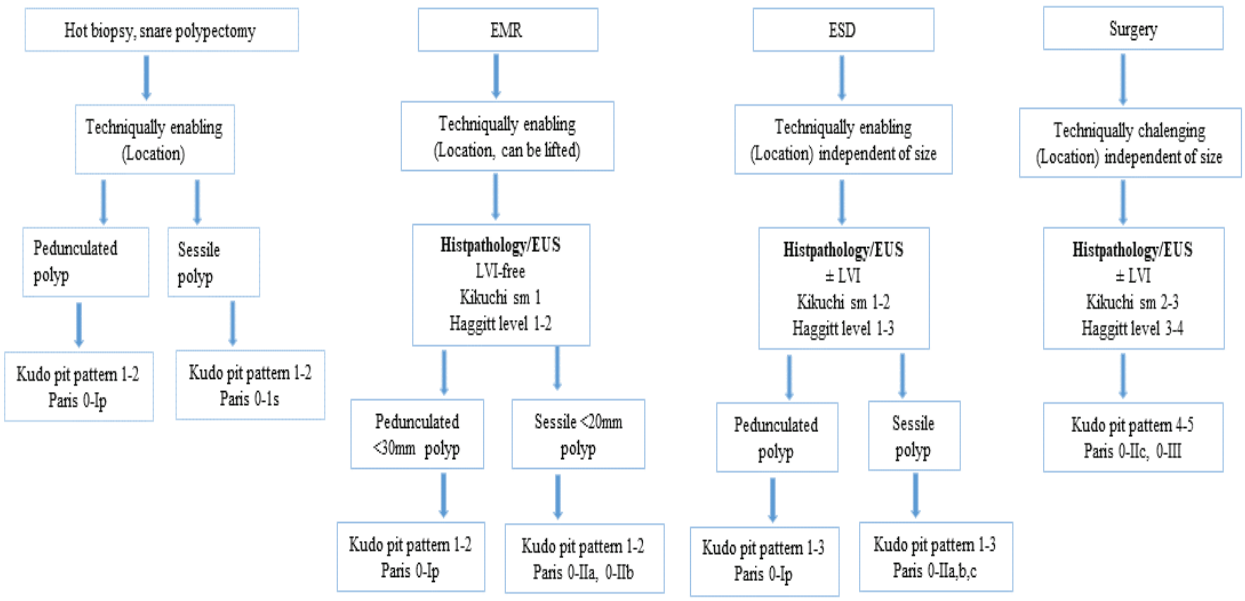

Figure 1: Flow-chart of the study.
EMR: Endoscopic mucosal resection, ESD: Endoscopic submucosal dissection, EUS: Endosonography, LVI: Lymphovascular invasion

Statistics

Descriptive statistics of the quantitative variables in the study are given as numbers and percentages. Pearson's Chi-square test was used for comparisons between groups in terms of the incidence of categories of the relevant qualitative variable. The conformity of the numerical variables to normal distribution was examined using the Shapiro-Wilk test. Student's t-test (independent sample t-test) was used to compare the mean values of two independent groups, and the Mann-Whitney U test was used to compare the median values of two independent groups. Variables that were significant as a result of univariate analyses were included in multivariate analyses, and binary logistic regression analysis was performed. Model explanatory power was examined using the Nagelkerke R square value, and the fit of the model was examined using the Hosmer and Lemeshow test. The agreement between the predicted values obtained as a result of binary logistic regression, and the observed values was examined using the kappa coefficient and accuracy rates were obtained. The statistical significance level was taken as 0.05. The SPSS (version 28) package program was used in the calculations.

RESULTS

Unresectable polyps were usually larger than resectable polyps (p<0.001). Localization of colorectal polyps in the ascending colon and the cecum made endoscopic resection more complicated than in the other parts of the colon (p<0.001). The resectability was independent of the presence of villous features in a polyp (p=0.315). Dysplasia (low/high-grade) was detected in preoperative biopsies with a higher frequency in unresectable polyps than in resectable polyps (p<0.001). Invasive cancer rates of unresectable and resectable polyps were 26.7% and 1.7%, respectively (p<0.001). Table 1 presents the factors affecting the resectability of colorectal polyps and the detected in-situ invasive cancer rates in colorectal polyps.

The frequency of invasive CRC in unresectable colorectal polyps increased with the increase of the age of patients (p=0.014), but it was independent of the patient's sex (p=0.846). The mean size of invasive CRC-infiltrated polyps was significantly larger than invasive cancer-free polyps (p=0.012). The potential to contain invasive CRC was greater in the sigmoid colon and rectum-located polyps (p=0.001). Underlying villous features (p=0.331) and dysplasia (p=0.057) were not effective in developing invasive CRC. Deep submucosal invasion was detected in the pathologic examinations of incomplete polypectomy specimens of two patients and non-curative EMR or ESD specimens of 14 patients. In addition, deep submucosal invasion was demonstrated in EUS examinations of eight patients with distal colon and rectum-located polyps. Deep submucosal invasion (p<0.001) and current LVI (p<0.001) were predictive factors for invasive CRC involvement. Unresectable polyps requiring surgery after non-curative EMR or ESD were found to have a significantly higher risk of invasive CRC involvement compared with polyps that underwent surgical resection primarily (p=0.002). Lymph node spread was detected in the surgical specimens of 6 of all unresectable polyps. Two of these were polyps with cancer invading the deep submucosa, but in which the cancer invasion was limited in the submucosa. Factors associated with invasive CRC involvement are given in Table 2.

The significant associations and potential risk factors in predicting invasive CRC are summarized in Table 3. Overall, polyp size, location, the presence of lymphovascular invasion, and management path were not associated with the development of invasive CRC. However, advancing age (p=0.010) and deep submu-

Table 1: Technical and histological factors affecting resectability and detected cancer frequency

Total=4886		**Resectable polyps n (%)=4751**	**Unresectable polyps n (%)=135**	**p**
Size, mm (mean, std. deviation) *		18.8 (6.3)	50.2 (6.7)	<0.001
Location of the polyp	Rectum, sigmoid colon	1963 (42.3)	30 (22.2)	<0.001
	Descending, transverse colon	1481 (31.2)	36 (26.7)	
	Ascending colon, cecum	1307 (27.5)	69 (51.1)	
Underlying villous features	Absence	3757 (79.1)	104 (77.0)	0.315
	Presence	994 (20.9)	31 (23.0)	
Dysplasia		661 (13.9)	97 (71.9)	<0.001
Invasive cancer-free		4499 (94.7)	99 (73.3)	<0.001
T1-2		82 (1.7)	36 (26.7)	

* Mann Whitney U test, Chi-square test (Pearson Chi-square, continuity correction, Fisher's exact test)

Table 2: Preoperative potential risk factors to predict invasive cancer in an unresectable colorectal polyp

		Invasive cancer-free n (%)=99	T1-2 n (%)=36	p
Age (mean, std. deviation) *		52.1 (7.0)	55.7 (7.9)	0.014
Female, n (%)		50 (50.5)	17 (47.2)	0.846
Male, n (%)		49 (49.5)	19 (52.8)	
Size mm (mean, std. deviation) **		49.0 (7.6)	53.3 (10.7)	0.012
Polyp location	Rectum, sigmoid colon	18 (18.2)	18 (50.0)	0.001
	Descending, transverse colon	32 (32.3)	8 (22.2)	
	Ascending colon, cecum	49 (49.5)	10 (27.8)	
Underlying villous features	Absence	52 (52.5)	15 (41.7)	0.331
	Presence	47 (47.5)	21 (58.3)	
Dysplasia	No	32 (32.3)	6 (16.7)	0.057
	Low-grade	38 (38.4)	12 (33.3)	
	High-grade	29 (29.3)	18 (50.0)	
Deep submucosal invasion		2 (2.0)	22 (61.1)	<0.001
LVI		9 (9.1)	17 (47.2)	<0.001
Non-curative EMR/ESD > SR		27 (27.3)	20 (55.6)	0.002
Primary surgery		72 (72.7)	16 (44.4)	

* Independent sample t-test, ** Mann Whitney U test, Chi-square test (Pearson chi-square, continuity correction, Fisher's exact test), LVI: Lymphovascular invasion, SR: Surgical resection

Table 3: Multivariate logistic regression analysis

	OR	Signature	95% C.I. for EXP(B)	
			Lower	Upper
Age	6.68	0.010	1.03	12.5
Size	0.87	0.722	0.82	1.12
Polyp location	0.78	0.676		
Polyp location *	0.80	0.841	0.74	0.96
Polyp location **	0.49	0.483	0.045	0.88
Deep submucosal invasion (1)	9.68	0.002	4.37	66.78
LVI (1)	2.08	0.149	1.86	2.19
Primary surgery (1)	0.57	0.447	0.396	0.82
Nagelkerke R Square		0.643		
Hosmer and Lemeshow Test		0.944		

* Rectum, sigmoid colon and descending, transverse colon, ** Descending, transverse colon and ascending colon, cecum, LVI: Lymphovascular invasion

cosal invasion (p=0.002) were significantly associated with invasive CRC. It was determined that the established binary logistics model had a good fit (p=0.944) for Hosmer and Lemeshow, and the model was determined to be significant according to Nagelkerke R square (p=0.643). The accuracy rate of the model was 89.6% ((97+24)/135). The kappa coefficient value for the agreement between the predicted value and the observed values was calculated as 0.71.

DISCUSSION

Colonoscopy is the current standard procedure in the screening of possible premalignant lesions located in the

colon and rectum. Colonoscopy could allow diagnosis of these colorectal lesions with a biopsy as well as total excision of suspicious lesions. Although total excision of large polyps is possible through colonoscopy, removal of sessile polyps with lateral extension, very large polyps, or polyps located in the right colon may be more complicated. (10,11).

In previous literature, CRC frequency has been estimated to range from 4.6% for polyps larger than 1 cm, and up to 56% for polyps larger than 2 cm (12). Muto et al. reported that 17% of total polyps were larger than 2 cm, and CRC was detected in 46% of these polyps in their study. The study concluded that large polyp size, polyps containing villous histology, and cellular atypia were effective in developing invasive CRC (13).

Another study from Shinya et al. reported a 10.8% CRC frequency in excised large polyps. This study also revealed similar risk factors for CRC involvement in polyps larger than 2 cm. In addition, they determined that polyps located in the distal colon were associated with an increased risk of CRC (14). These opinions are supported by our similar findings of increased CRC risk with large polyp size and with distal colon polyp location; however, they conflict with the increased risk of malignancy with the presence of villous formation. McDonald et al. examined the cancer risk in 100 surgically-removed endoscopically unresectable colorectal polyps, and again, large polyp size was associated with CRC, which is in line with our present study (15).

Alder et al. reported a CRC frequency of 16%. In their study, they found that unresectable polyps were more often located in the right colon, but localization in the distal colon might probably increase the risk of CRC in a polyp. However, as a counter-opinion to our study, they claimed that polyp size was an independent factor in the occurrence of CRC (16). Despite the known relationship between left-sided lesions and increased CRC rate, our overall low rate of cancer might be explained by the fact that more than 75% of unresectable polyps were in the other parts of the colon.

In light of these reported different invasive cancer frequencies, in our study, the rate of invasive CRC in unresectable polyps was estimated as 36/135 (26.7%). Ninety-seven (97.7%) polyps were identified as containing dysplasia and 24 (17.8%) had deep submucosal invasion identified in preoperative evaluations. As is known, the malignancy risk of CRC increases with increased age, and, in line with this, the risk of malignancy in an unresectable polyp also increases with increased age. Possible factors that may predict the development of CRC in an unresectable polyp were also examined in the study. Accordingly, villous features and dysplasia were found not to be effective in CRC development in unresectable polyps, and deep submucosal invasion was determined as an independent risk factor.

Worldwide, EMR/ESD has become the recent standard practice in managing early-stage CRC. Although EMR is easier and more reliable, it may cause more recurrence or provide less en-bloc or curative resection when compared with ESD. Many studies reported that these endoscopic advanced polyp removal methods were feasible, and reported endoscopic resection results with less morbidity when compared with surgical resection (17). The present study also aimed to investigate the potential of residual invasive CRC after unsuccessful endoscopic resections. CRC was detected more frequently in surgical resection specimens after non-curative advanced endoscopic resection attempts than in specimens of patients who underwent surgery primarily. This finding has been interpreted in a way that avoiding further next endoscopic resection attempts would be a more appropriate approach in this issue.

LVI describes the detection of tumor cells in the lymphatic system within the tissue. Al-Sukhni et al. and Huh et al. reported that LVI was significantly associated with the depth of cancer invasion (18-20). Several studies tried to determine the role of the presence of LVI or perineural invasion in adjuvant therapy (21,22). The present study revealed that LVI had an important role in predicting invasive carcinoma in unresectable polyps; however, although the study did not aim to investigate the effect of LVI in adjuvant therapy, it still revealed a significant association with the prediction of CRC.

It has long been thought that infiltration of tumor cells into the lower third of the submucosa is associated with an increased risk of a lymphatic spread rather than only mild penetration (23). According to evidence from previous patient series, a lymph node metastasis rate of up to 23% has been reported in polyps with deep submucosal invasion by cancer (24). In this study, lymph node spread was detected in the surgical specimens of 6 of all unresectable polyps. Two of these were polyps with cancer invading the deep submucosa, but in which the cancer invasion was limited in the submucosa. Although 2 lymph node spread was detected in the histopathologic examination of cancers with submucosa-limited invasion, no significant association between submucosal invasion and lymph node metastasis was revealed.

The presence of a stalk and the location of the polyp are the main determinants of a successful polypectomy. The polyp location should be tattooed according to the local protocol with a specific reagent containing carbon particles if surgery is considered (25). If a polyp is unsuitable for polypectomy, a biopsy provides no scientific value to the endoscopist. Of note, biopsy results may lead to suboptimal management in 8% of patients (26).

There are some limitations in the study that should be addressed. First, due to being a retrospective case-control study, it does not offer exact prospective standardized criteria for further treatment, but only recommendations. For example, right-sided polyps can be considered technically more difficult to remove, leading to a change in selection criteria. In addition, the differences between the size of the polyp determined by the endoscopic appearance and the size in the definitive pathologic examination may cause confusing interpretations in predicting invasive carcinoma. Furthermore, the level of experience in interventional endoscopy may differ in all institutions. Also, more advanced endoscopic or microinvasive techniques that have been used in the clinic have not been included in the study due to the relatively small number of applications. As another limitation of the study, the rate of colorectal cancer in complex colon polyps has been found as 10-15% in the literature, but there are no polyps that can be resected with advanced endoscopic techniques in these studies (27,28). In our study, the rate of invasive CRC was found in unresectable polyps with a high rate of 26.7%. However, in our study, analyses of polyps that could be resected with advanced techniques were not included, and when these outcomes were added, CRC rates in complex polyps were determined to be similar to the ones in the literature.

CONCLUSION

It may be extrapolated that EMR/ESD is a safe and feasible method to remove early-stage CRC-containing polyps or for resection of benign polyps that have been decided to be endoscopically unresectable. However, after non-curative EMR/ESD procedures, more attention should be paid due to the relatively high risk of CRC.

Unresectable polyps are more prone to CRC involvement than resectable polyps. The presence of LVI and deep submucosal invasion should be considered carefully to predict CRC. However, more importantly, oncologic surgery for polyps with deep submucosal invasion (particularly by EMR or ESD) that cannot be endoscopically resected in older patients should be considered carefully and, perhaps, without delay, primarily by abandoning repeated endoscopic resection attempts.

Ethics Committee Approval: This study was approved by Istanbul University, Istanbul Faculty of medicine Clinical Research Ethics Committee (Date: 17.12.2010, No: 09).

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COMPARING THE TRAJECTORY ACCURACY OF PEDICLE SCREWS PLACED WITH A FREE-HAND TECHNIQUE AND A THREE-DIMENSIONAL COMPUTED TOMOGRAPHY-ASSISTED NAVIGATION SYSTEM IN SPINE SURGERY: A RETROSPECTIVE STUDY

OMURGA CERRAHİSİNDE SERBEST EL TEKNİĞİ VE ÜÇ BOYUTLU BİLGİSAYARLI TOMOGRAFİ DESTEKLİ NAVİGASYON SİSTEMİYLE YERLEŞTİRİLEN PEDİKÜL VİDALARININ YÖNELİM DOĞRULUĞUNUN KARŞILAŞTIRILMASI: RETROSPEKTİF ÇALIŞMA

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ABSTRACT

Objective: We evaluated a free-hand technique and a three-dimensional computerized tomography (3D-CT)-assisted navigation technique, which are pedicle screw placement techniques used in spinal surgery, regarding screw placement and reliability.

Materials and Methods: A total of 1664 screws in 73 patients with spinal deformities who underwent spinal instrumentation using pedicle screws were evaluated in this study. Forty patients were in the free-hand technique group, and 33 patients were in the 3D-CT-assisted navigation technique group. The placement and reliability of pedicle screws in all patients were evaluated using the Gertzbein–Robbins classification using CT images taken in the postoperative period.

Result: There were no significant differences found regarding age, body mass index (BMI), sex (female or male), or deformity (scoliosis or kyphosis) (p>0.05). When the pedicle screws were evaluated in terms of transverse penetration, the 3D-CT-assisted navigation technique was determined Grade A (89.6%), as was the free-hand technique (76.5%), but the 3D-CT-assisted navi-

ÖZET

Amaç: Spinal cerrahide kullanılan pedikül vida yerleştirme tekniklerinden serbest el tekniği ve üç boyutlu bilgisayarlı tomografi (3D-BT) destekli navigasyon tekniği, vida yerleştirme ve güvenilirlik açısından karşılaştırıldı.

Gereç ve Yöntem: Pedikül vidası ile spinal enstrümantasyon uygulanan 73 spinal deformiteli hastanın toplam 1664 vidası çalışmada değerlendirildi. Serbest el tekniği grubunda 40 hasta ve 3D-BT destekli navigasyon tekniği grubunda 33 hasta vardı. Pedikül vidalarının tüm hastalarda yerleştirilmesi ve güvenilirliği, ameliyat sonrası dönemde çekilen BT görüntüleri kullanılarak Gertzbein-Robbins sınıflaması kullanılarak değerlendirildi.

Bulgular: Yaş, vücut kitle indeksi (VKİ), cinsiyet (kadın veya erkek) ve deformite (skolyoz veya kifoz) açısından gruplar arası anlamlı fark bulunmadı (p>0,05). Pedikül vidaları transvers penetrasyon açısından değerlendirildiğinde, 3D-BT destekli navigasyon tekniğinde Grade A (%89,6), serbest el tekniğinde Grade A (%76,5) olarak belirlendi. 3D-BT destekli navigasyon tekniği trasvers penetrasyon açısından istatistiksel olarak daha güvenilir tespit edil-

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gation technique was statistically more reliable (p<0.001). When the pedicle screws were evaluated in terms of anterior penetration, both the 3D-CT-assisted navigation technique (92.5%) and the free-hand technique (82.9%) were determined Grade A, but the 3D-CT-assisted navigation technique was statistically more reliable (p<0.001).

Conclusion: According to our study's results, the 3D-CT-assisted navigation technique is more reliable than the free-hand technique in surgeries involving spine deformities for pedicle screw insertion.

Keywords: Spine deformity, navigation, posterior instrumentation

di (p<0,001). Pedikül vidaları anterior penetrasyon açısından değerlendirildiğinde, hem 3D-BT yardımlı navigasyon tekniğinde Grade A (%92,5) ve serbest el tekniğine Grade A (%82,9) olarak belirlendi. 3D-BT yardımlı navigasyon tekniği anterior penetrasyon açısından istatistiksel olarak daha güvenilir tespit edildi (p<0,001).

Sonuç: Çalışmamızın sonuçlarına göre, omurga deformitelerini içeren ameliyatlarda pedikül vidası yerleştirmede 3D-BT destekli navigasyon tekniği serbest el tekniği ile karşılaştırıldığında daha güvenilirdir.

Anahtar Kelimeler: Omurga deformitesi, navigasyon, posterior enstrümantasyon

INTRODUCTION

The first posterior spinal fusion surgery was performed by Hibbs in 1911 (1). In the 1950s, Harrington started a new period in posterior spinal instrumentation by developing a hook and rod system that could perform traction and compression (2). By the 1990s, pedicle screws were being used in posterior spinal instrumentation.

Pedicle screw placement techniques are divided into free-hand techniques and imaging-guided techniques. In the free-hand technique, pedicle screws are placed using the pedicle probe, taking into account the spine anatomy and various anatomical landmarks. The freehand technique requires detailed preoperative planning. This technique has a higher learning curve that can be achieved with higher practice (3). There are two types of imaging-guided techniques: fluoroscopy-guided and navigation-guided. In the fluoroscopy-guided technique, the most important advantages are the control of the screw entry site and the screw delivery axis. However, it is a disadvantage that the imaging can be done in 2 plans. 3D imaging and cross-sectional imaging provide additional advantages in the navigation-guided technique. Ughwanogho et al. evaluated the placement accuracy of 485 thoracic pedicle screws and found significantly less unsafe screw placement with the navigation technique compared to the free-hand technique (4).

In this study, we aimed to compare the accuracy of pedicle screw insertion using both a free-hand technique and an intraoperative 3D-CT-assisted navigation system in patients undergoing posterior spinal instrumentation due to deformity.

MATERIALS and METHODS

Patient selection

In inclusion criteria for the study, it was determined that the patient had been operated on for scoliosis or kyphosis, the main curvature was 40 degrees and above in scoliosis patients, the cobb angle was 70 degrees and above in kyphosis patients, the patient had a CT scan taken for fusion control in the postoperative one year, and the patient consented to participate in the study. In exclusion criteria from the study, it was determined that the patient had been operated on with diagnoses other than kyphosis or scoliosis, surgeries performed for cosmetic purposes, and the patient did not consent to participate in the study. Seventy-three patients who underwent surgery in our clinic to correct a spinal deformity (scoliosis or kyphosis) between January 2017 and December 2018 were retrospectively included in the study. Informed consent was obtained from all participants. The ethics committee approved the study (Date:15.01.2019, No:2019-1/34), which was conducted as a thesis of specialization in medicine (Number: 536843). The patients were grouped according to their surgeries' pedicle screw placement technique: 33 patients were in the 3D-CT-assisted navigation technique group (the Nav group), and 40 patients were in the free-hand technique group (the F-H group). As an adjunct, all patients' sensory- and motor-evoked potentials were monitored.

Methods

The patients' postoperative 1-year CT images were evaluated using a picture archiving and communication system (PACS). The evaluation was performed separately for cases of transverse penetration of the pedicle (medial or lateral) and penetration of the vertebral corpus (anterior). Screw penetration was graded according to the Gertzbein–Robbins classification (Figure 1a, b, c, d, e) (5-6). The thoracolumbar spine was divided into 4 regions: upper thoracic, mid-thoracic, lower thoracic, and lumbosacral regions. The thoracic spine was divided into three anatomical regions and examined. It was defined as the upper thoracic region between the T1-T4 vertebrae, the mid-thoracic region between the T5-T8 vertebrae, and the lower thoracic region between the T9-T12 vertebrae. All CT scan evaluations were performed by a single orthopedic surgeon. In addition, age, body mass index (BMI), and gender data were recorded from epidemiological data.

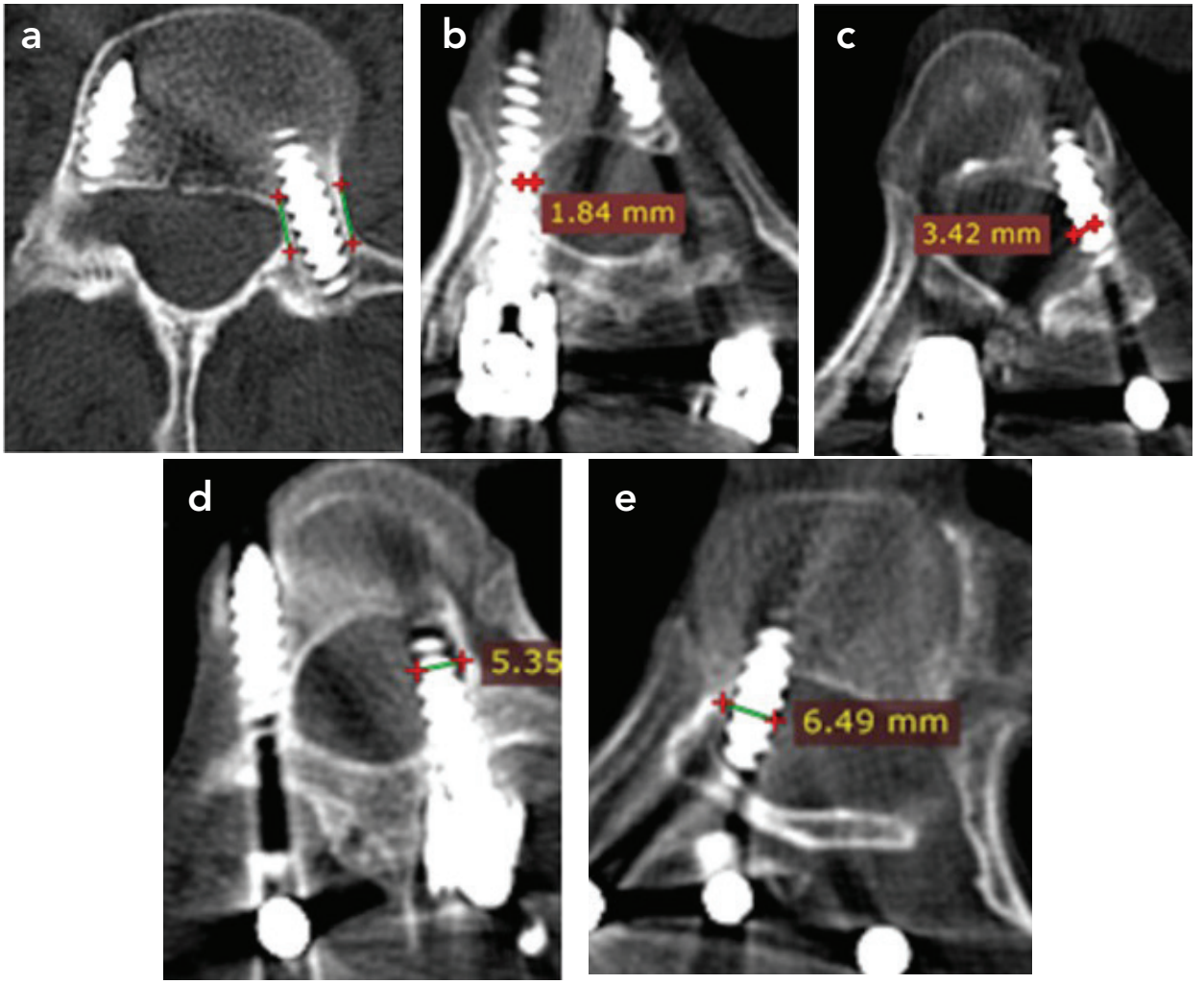

Figure 1: a) Gertzbein ve Robins classification Grade A: any penetration **b)** Gertzbein ve Robins classification Grade B: <2 mm. **c)** Gertzbein ve Robins classification Grade C: 2-4 mm **d)** Gertzbein ve Robins classification Grade D: 4-6 mm **e)** Gertzbein ve Robins classification Grade E>6 mm

Surgical techniques

During spinal surgery, all patients lay in the prone position on radiolucent operating tables. Soft pads were placed under their chests and shoulders. All patients had undergone prophylaxes for infection and venous thromboembolism. Intravenous tranexamic acid and intracutaneous and subcutaneous epinephrine were used to reduce blood loss in patients without contraindication (7-8). A midline incision was used in all patients (8).

In the Nav group, a reference frame was placed in one of the spinous processes for spinal navigation after opening. Then, a CT scan was acquired, and intraoperative CT images were processed and transferred to the navigation system. Screw length, diameter, entry point, and trajectory were dictated by the navigation system. After the screw entry point was determined, it was pierced using a straight awl. With the assistance of navigation, pedicle screws of appropriate length and diameter were inserted, the placement of which was checked on the navigation monitor (Figure 2).

In the F-H group, pedicle screw placement was performed according to Roy-Camille et al.'s technique (9). After the screw entry point was determined, it was pierced with a straight awl. The depth was checked using a probe. Then, pedicle screws of appropriate length and diameter were placed. After all screws had been inserted, fluoroscopy was used to adjust the position of the screws.

Postoperative management

Respiratory physiotherapy was started immediately after surgery. On the 1st postoperative day, the drains of all patients were removed, the patients were mobilized, and physiotherapy was started. Antibiotic prophylaxis was administered to the patients for 24 hours postoperatively (Cefazolin sodium). Deep vein thrombosis prophylax-

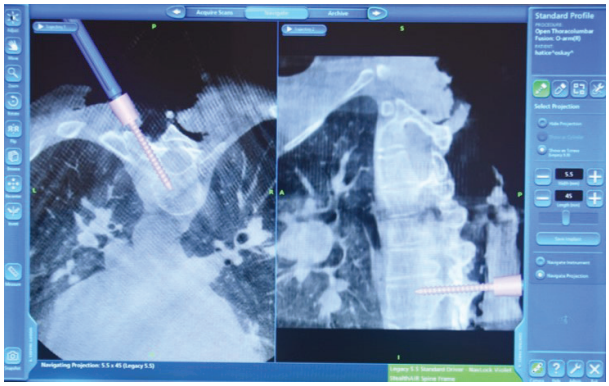

Figure 2: The insertion of pedicle screw under the navigation guidance

is was applied to the patients for 21 days (Antiembolic stockings and enoxoparin sodium 4000IU 1x1). A dressing was applied to the patients every two days, and sutures were removed on the 14th postoperative day. The patients were followed up with x-rays on the 15th day, 1st month, 3rd month, 6th month, and 1st year, and a CT scan was performed for fusion control in all patients in the postoperative 1st year.

Statistical analysis

Statistical analysis was performed using SPSS ver. 22.0 (IBM Corp., Armonk, NY). Number and percentage values from the descriptive data were used. Whether the data fit the normal distribution was checked with the Kolmogorov-Smirnov test. An independent sample T-test was used to compare parametric data. Pearson's chi-squared and Yate's corrected chi-squared tests were used to compare categorical data. The accepted degree of statistical significance was $p<0.05$.

RESULTS

The differences in characteristics between the two groups were compared. There were no significant differences found regarding age, body mass index (BMI), sex (female or male), or deformity (scoliosis or kyphosis) ($p>0.05$) (Table 1). No decrease in sensory- and motor-evoked potentials was observed in all patients in both groups on peroperative neuromonitoring.

At the T1–S1 vertebral level, 962 screws in the F-H group and 702 screws in the Nav group were inserted. Both groups used the least number of screws, 2, in T1. The largest number of screws inserted in one place was 56 in the F-H group (T3) and 72 in the Nav group (T12).

Tranverse penetration

According to the Gertzbein–Robbins classification for transverse penetration, 1365 screws were Grade A, and 299 were non-Grade A (Grade B, C, D, E) (Table 2). The Nav group showed more accuracy (Grade A: 89.6%) than the F-H group did (Grade A: 76.5%), a finding that was statistically significant ($p<0.05$). There were 299 screws with transverse penetration (not Grade A): 179 were medial (59.9%), and 120 were lateral (40.1%). There were no significant differences found in either group regarding screw direction ($p>0.05$) (Table 3).

Three regions make up the thoracic vertebrae, depending on pedicle size: upper, mid, and lower. The Nav group showed more accuracy than the F-H group in each thoracic region, as well as the lumbosacral region ($p<0.05$). In the F-H group, screws placed in the lumbosacral region were the most accurate ($p<0.05$). In the Nav group, no significant differences were found ($p>0.05$) (Table 4).

Anterior penetration

According to the Gertzbein–Robbins classification for anterior penetration, 1495 screws were Grade A, and 169 were non-Grade A (Grade B, C, D ,E) (Table 5). The Nav group had more accuracy (Grade A: 92.5%) than the F-H group did (Grade A: 87.9%), a finding that was statistically significant ($p<0.05$). The Nav group showed more accuracy than the F-H group in the upper thoracic region, but there were no differences in the other regions ($p<0.05$). In the F-H group, screws placed in the lower thoracic region were the most accurate ($p<0.05$). In the Nav group, the lower thoracic and lumbosacral regions had more accurate placements than the other regions ($p>0.05$) (Table 6).

DISCUSSION

Several studies in the literature have compared the 3D-CT-assisted navigation technique with various other techniques (fluoroscopy, 2D navigation, preop BT navigation, and robotics), while others have evaluated the penetration rates of this technique directly (5). Most of those involved in the research have been trauma patients, but some were patients with lumbar degeneration. Publications that compare free-hand and 3D-CT-assisted navigation techniques in patients with spinal deformities are limited; therefore, the difference between the two techniques is not clear (10).

Jin et al. compared screw placements performed with the free-hand and 3D-CT-assisted navigation techniques in patients with neurofibromatosis type I scoliosis at the apical regions of the deformity (11). Screw positions were evaluated according to the Gertzbein–Robbins classification. Penetration of Grades C, D, and E was accepted. In the free-hand group, transverse penetration was 32% (14% medial and 18% lateral), and anterior penetration was 1%. In the 3D-CT-assisted navigation group, transverse penetration was 18% (2% medial and 16% lateral), and anterior penetration was 3%. In our study, the anterior penetration rates were higher. Also, while Jin et al. documented more lateral than medial penetrations, we

Table 1: Group demographics and deformities

		F-H Group n (%)	Nav Group n (%)	p value
Gender	Male	19 (47.5)	12 (36.4)	0.471
	Female	21 (52.5)	21 (63.6)	
Deformity	Kyphosis	9 (22.5)	4 (12.1)	0.397
	Scoliosis	31 (77.5)	29 (87.9)	
BMI	<25 kg/m^2	24 (60)	22 (66.7)	0.731
	>25 kg/m^2	16 (40)	11 (33.3)	
Age	<18	19 (47.5)	19 (57.6)	0.534
	>18	21 (52.5)	14 (42.4)	

BMI: Body mass index, F-H: Free-hand, Nav: Navigation

Table 2: Quantity of screws with transverse penetration and penetration rates in each group

	F-H Group n (%)	Nav Group n (%)	p value
A	736 (76.5)	629 (89.6)	0.000
B	116 (12.1)	39 (5.6)	
C	59 (6.1)	14 (2)	
D	39 (4.1)	11 (1.6)	
E	12 (1.2)	9 (1.3)	
Total	**962**	**702**	

F-H: Free-hand, Nav: Navigation

Table 3: Quantity of screws with transverse penetration and penetration rates in each group, categorized by direction

	F-H Group n (%)	Nav Group n (%)	p value
Medial	134 (59.3)	45 (61.6)	0.722
Lateral	92 (40.7)	28 (38.4)	

F-H: Free-hand, Nav: Navigation

Table 5: Quantity of screws with anterior penetration and penetration rates in each group

	F-H Group n (%)	Nav Group n (%)	p value
A	846 (87.9)	649 (92.5)	0.000
B	89 (9.3)	21 (3.4)	
C	17 (1.8)	15 (2.1)	
D	6 (0.6)	7 (1)	
E	4 (0.4)	7 (1)	
Total	962	702	

F-H: Free-hand, Nav: Navigation

found no significant difference regarding penetration orientation in our study (11).

Although Zhao et al. used a different classification system when evaluating scoliosis patients' screw positions (i.e., Grade 0: no penetration, Grade 1: <1 mm penetration, Grade 2: 1–3 mm penetration, and Grade 3: >3 mm penetration), they did compare the free-hand and 3D-CT-assisted navigation techniques (12). Allowing Grades 2 and 3 to be accepted as penetration, the penetration rate

Table 4: Quantity of screws with transverse penetration and penetration rates, categorized by vertebral region

Region	Group	Grade A n (%)	Grade B,C,D,E n (%)	p value
Upper Thoracic	F-H Group	91 (71.1)	37 (28.9)	0.002
	Nav Group	122 (87)	18 (12.9)	
Mid Thoracic	F-H Group	179 (69.1)	80 (30.9)	0.000
	Nav Group	156 (87.2)	23 (12.8)	
Lower Thoracic	F-H Group	210 (76.6)	64 (23.4)	0.000
	Nav Group	160 (92)	14 (8)	
Lumbosacral	F-H Group	256 (85)	45 (15)	0.045
	Nav Group	191 (91.4)	18 (8.6)	

F-H: Free-hand, Nav: Navigation

Table 6: Quantity of screws with anterior penetration and penetration rates, categorized by vertebral region

Region	Group	Grade A n (%)	Grade B, C, D, E n (%)	p value
Upper Thoracic	F-H Group	90 (70.3)	38 (29.7)	0.002
	Nav Group	121 (86.4)	19 (13.6)	
Mid Thoracic	F-H Group	220 (84.9)	39 (15.1)	0.080
	Nav Group	163 (91.1)	16 (8.9)	
Lower Thoracic	F-H Group	260 (94.9)	14 (5.1)	0.763
	Nav Group	167 (96)	7 (4)	
Lumbosacral	F-H Group	276 (91.7)	25 (8.3)	0.116
	Nav Group	198 (95.7)	9 (4.3)	

F-H: Free-hand, Nav: Navigation

was 18.4% using the free-hand technique and 12.1% using 3D-CT-assisted navigation. Zhao et al. also reported that the rate of pulmonary effusion was higher in the free-hand technique group (12).

Qiao et al. compared free-hand and 3D-CT-assisted navigation techniques when placing screws in patients with scoliosis due to Marfan syndrome (13). Pedicle screw placements were categorized according to the Gertzbein–Robbins classification. Unlike our and others' studies, Qiao et al. reported that, regarding all screws, penetration rates in the thoracic vertebrae were lower than in the lumbar vertebrae (22.3% and 34.1%, respectively) (13). They hypothesized that this difference could be explained by the fact that those with Marfan syndrome have thinner pedicles in the lumbar vertebrae. When comparing surgical techniques, the study's results showed that 3D-CT-assisted navigation (11.4%) was more successful than free-hand (30.8%).

Urbanski et al. researched screw placement in patients with idiopathic scoliosis and found no significant difference between the penetration rates of the 3D-CT-assisted navigation technique group (17.97%) and the free-hand technique group (17.08%) (10). They also found that in both groups, the highest penetration rate was in the upper thoracic region.

Mobile CT device is used in 3D-CT-assisted navigation systems. These devices can never reach the resolutions of conventional CT devices. Therefore, malpositions can be seen even in pedicle screws placed with a 3D-CT-assisted navigation system. Therefore, in our study group, all patients were examined in terms of screw malposition using postoperative conventional CT methods. Screw malpositions that could not be detected in peroperative CT were detected with conventional CT.

There are some limitations to our study. First, a radiologist was not involved in the study; all radiological evaluations were performed by an orthopedic surgeon specializing in spine surgery. In addition, interobserver and intraobserver reliability were not evaluated in the study. Second, only anatomical evaluations were performed (i.e., the effects of the surgeries on the patients were not evaluated), and pedicle screw malposition does not always cause problems in the clinic. In addition, the small number of samples and the lack of power analysis are other limitations of the study.

CONCLUSION

In our study, the 3D-CT-assisted navigation technique demonstrated lower transverse and anterior penetration rates compared to the free-hand technique at all levels. Also, no significant difference was found between medial and lateral transverse penetration orientations.

Ethics Committee Approval: This study was approved by Uludag University Faculty of Medicine Clinical Research Ethics Committee (Date:15.01.2019, No:2019-1/34).

Peer Review: Externally peer-reviewed.

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THE DIAGNOSTIC ROLE OF 18F-FDG-PET/CT IN PATIENTS WITH CONSTITUTIONAL SYMPTOMS

KONSTİTÜSYONEL SEMPTOMLARI OLAN HASTALARDA 18F-FDG-PET/BT'NİN TANIYA KATKISININ ARAŞTIRILMASI

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ABSTRACT

Objective: The contribution of 18F-FDG-PET/CT to diagnosis and its role in differential diagnosis were investigated in patients examined for constitutional symptoms.

Materials and Methods: The 18F-FDG-PET/CT scan results and clinical data were analyzed retrospectively in 144 patients with constitutional symptoms examined between January 2017 and December 2019 in our outpatient and inpatient clinics in Istanbul University Istanbul Faculty of Medicine Internal Medicine Department. The FDG uptake other than physiological FDG uptake was considered as PET-positive. Clinical, laboratory data, and 18F-FDG-PET/CT scan results were evaluated retrospectively from records. All patients were classified into four categories as malignancies, infectious diseases, rheumatic diseases and other diseases based on their definitive diagnoses. The contribution of 18F-FDG-PET/CT in establishing a definitive diagnosis was investigated.

Results: The 144 patients comprised 85 (59.0%) men and 59 (41.0%) women with a mean age of 58.0±17.2 years. The mean duration of symptoms was 4.01±4.46 months. A definitive diagnosis was established in 95.1% (n=137) of the patients based on physical examination, imaging methods, laboratory tests, and other diagnostic tests. In comparison, no definitive diagnosis was established in the remaining 4.9% (n=7) of the patients. 18F-FDG-PET/CT contributed to diagnosis in 86.8% (n=119) of patients. The patients were classified into four categories based on their diagnoses: (i) malignancies (n=79; 57.7%), (ii) rheumatic diseases (n=22; 16.1%), (iii) infectious diseases (n=19; 13.9%), and (iv) other diseases (n=17; 12.4%). The sensitivity, specificity, and positive and negative predictive values of 18F-FDG-PET/CT in the diag-

ÖZET

Amaç: Konstitüsyonel semptomları nedeniyle tetkik edilen hastalarda 18F-FDG-PET/BT'nin tanıya katkısı ve ayırıcı tanıdaki rolü araştırıldı.

Gereç ve Yöntem: Ocak 2017 ile Aralık 2019 tarihleri arasında İstanbul Tıp Fakültesi'nde konstitüsyonel semptomlarla tetkik edilen ve 18F-FDG-PET/BT çekilen 144 hasta retrospektif olarak incelendi. Görüntülerin değerlendirilmesinde FDG'nin vücuttaki fizyolojik tutulum bölgeleri dışında saptanan tutulumlar pozitif kabul edildi. Tüm hastaların klinik, laboratuvar ve PET/BT görüntüleme sonuçları geriye dönük incelendi. Hastaların son tanıları malignite, enfeksiyon, romatizmal hastalıklar ve diğer olmak üzere 4 grupta toplandı. Hastalarda PET/BT pozitifliğinin tanıya katkısı araştırıldı.

Bulgular: Çalışmaya 59'u (%41) kadın 85'i (%59) erkek olmak üzere 144 hasta dahil edildi. Toplam yaş ortalamaları 58,0±17,2 idi. Hastaların semptom süresi ortalama 4,01±4,46 ay olarak saptandı ve %95,1'inde (n=137) hastalık teşhisi saptanmasına rağmen, %4,9'unda (n=7) herhangi bir hastalık teşhis edilemedi. 18F-FDG-PET/BT bu hastaların %86.8'inde tanıya katkı sağladı. Hastalık teşhis edilebilen olgu grubu incelendiğinde %57,7 (n=79) oranı ile en sık maligniteler; %16,1 (n=22) oranı ile romatizmal hastalıklar, %13,9 (n=19) enfeksiyonlar ve %12,4 (n=17) diğer hastalık gruplarının yer aldığı görüldü. 18F-FDG-PET/BT'nin hastalık teşhisinde %97,5 sensitivite, %31,8 spesifite, %88,8 pozitif prediktif değer ve %70 negatif prediktif değere sahip olduğu görüldü.

Sonuç: Konsitüsyonel semptomları olan hastaların tanısında 18F-FDG-PET/BT, duyarlılığının ve pozitif prediktif değerinin

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nosis of constitutional symptoms were 97.5%, 31.8%, 88.8%, and 70%, respectively.

Conclusion: We found that 18F-FDG-PET/CT is a valuable diagnostic tool in diagnosing patients with constitutional symptoms and provides high sensitivity and positive predictive value.

Keywords: 18F-FDG-PET/CT, constitutional symptoms, diagnosis, malignancy

yüksek olması nedeniyle değerli bir görüntüleme yöntemidir ve tanısal süreçte kullanılması gereken önemli görüntüleme protokollerden biridir.

Anahtar Kelimeler: 18F-FDG-PET/BT, konstitüsyonel semptomlar, tanı, malignite

INTRODUCTION

Constitutional symptoms such as fever, night sweats, weight loss, and loss of appetite can be encountered in numerous malignant diseases as well as infections and inflammatory rheumatic diseases (1,2). Despite the advancements and the easy accessibility of diagnostic methods, diagnostic delay and failure remain to be severe problems. It is essential to consider the diagnostic role of tests and procedures in evaluating patients with constitutional symptoms and suspected malignancy.

The advantage of F18 FDG-PET/CT over other imaging methods is that it allows the whole body to be examined reasonably. In addition, it can be used in staging most cancers, evaluating the response to treatment, and identifying foci of infection (3,4). PET/CT, which is used concurrently with traditional imaging techniques like USG, CT, or MRI, can prevent the findings from being overlooked and reduce false positive and negative results (5).

Moreover, compared to conventional scintigraphic techniques, 18F-FDG-PET/CT can report results with higher resolution and higher sensitivity in chronic low-grade infections and high accuracy in the central skeleton. It also provides a relatively shorter period between the injection of radiopharmaceuticals and the imaging moment (6).

In the studies conducted so far, it has been documented that 18F-FDG-PET/CT contributes to the diagnosis at a rate of 42-67% in patients followed up with a fever of unknown origin (FUO) (7). The purpose of this study was to evaluate the contribution of 18F-FDG-PET/CT in establishing a definitive diagnosis in cases presenting with constitutional symptoms when other diagnostic tests and imaging approaches have failed.

MATERIALS and METHODS

Patients

The study included 144 patients with constitutional symptoms who were examined in Istanbul University Istanbul Faculty of Medicine, Internal Medicine Department. All patients who could not get a diagnosis with conventional imaging techniques, and underwent 18F-FDG-PET/BT imaging were included in the study. Clinical, laboratory data and 18F-FDG-PET/CT results were evaluated retrospectively from patient records.

Basic diagnostic evaluation

Laboratory, imaging, and physical examination findings of all patients were recorded through hospital records (a detailed clinical history including business, travel, and previous partners, and tests for FUO, along with a complete blood test, creatinin and transaminase levels, lactate dehydrogenase, electrolyte levels, C-reactive protein (CRP), sedimentation rate of erythrocytes (ESR), urine tests, abdominal ultrasonography, and chest radiography).

In addition to these, if performed, blood and urine cultures, serological tests for Salmonella, cytomegalovirus IgM, Brucellosis, Epstein-Barr virus, and viral hepatitis A, B, and C, Echocardiography, CT, MRI, and histopathological examinations were recorded.

18F-FDG-PET/CT imaging

All scans were performed using a 16-slice multi-detector CT integrated PET scanner (Biograph TruePoint TrueV PET/CT; Siemens Healthcare). Patients fasted for at least six hours before 18F FDG injection, blood glucose levels were less than 150 mg/dL, and they had good hydration before the scan. 260-550 MBq (7-14,8 mCi) FDG was given intravenously. After the injection, the patients were kept in a quiet environment for approximately one hour to allow for whole-body biodistribution of FDG uptake. After the patients were positioned, an initial scout image was acquired to define the examination range for the PET/ CT image acquisition. First, a low-dose CT was performed. Emission scans of 18F-FDG-PET/CT were acquired in 3D mode; the scanning from the top of the skull through the upper thighs was performed. If it was clinically required, a scan including the lower extremities, was also done.

All patients with non-physiological FDG uptake were classified as PET-positive. Disease-related and unrelated FDG involvement was evaluated separately according to the definitive diagnosis of PET-positive patients.

Study protocol

The clinical course of the disease was followed up using 18F-FDG-PET/CT, diagnostic tests, other imaging methods, and interventional procedures. Definitive diagnosis was established based on histopathological, microbiological, and serologic investigations and/or long-term clinical and imaging follow-up records. The contribution

of 18F-FDG-PET/CT to the proven diagnosis and its role in differential diagnosis were investigated.

Istanbul Faculty of Medicine Ethics Committee approved the study protocol (Date: 20.12.2019, No: 21).

Statistical analysis

Data were analyzed using SPSS for Windows version 21.0 (Armonk, NY: IBM Corp.). Descriptive statistics were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies (n) and percentages (%). Cross-table statistics (Chi-square and Fisher's exact tests) were used to compare categorical variables. Normally distributed parametric data were compared using Student's t-test and ANOVA, and non-parametric data that did not conform to normal distribution were compared using Kruskal-Wallis tests. The post hoc test was used to compare multiple groups. A p-value of <0.05 was considered significant.

RESULTS

The 144 patients comprised 85 (59.0%) men and 59 (41.0%) women with a mean age of 58±17.2 years (56.4±17.7 years in men and 60.3±16.3 in females). No significant difference was found between male and female patients with regard to age (p=0.195). A definitive diagnosis was established in 95.1% (n=137) of the patients based on physical examination, imaging methods, laboratory tests, and other diagnostic tests. In comparison, no definitive diagnosis was established in the remaining 4.9% (n=7) of the patients.

The mean duration of constitutional symptoms was 4.0±4.4 months. Hepatosplenomegaly was the most common presenting physical examination finding (26.4%, n=38), followed by cardiac findings (18.1%; pathological murmur, swollen neck veins, detection of third and fourth heart sounds, and edema), superficial lymphadenopathy (14.6%), joint findings (9.0%, arthritis, arthralgia), skin findings (8.3%; rash, discoloration), and palpable masses (2.8%) (Table 1).

The LDH level was significantly higher in the malignancy group compared to other groups (p=0.024) (Figure 1). ESR was non significantly higher in the rheumatic diseases group compared to other groups (p=0.051). No significant

Table 1: Distribution of presenting physical examination finding

	n	%
Hepatosplenomegaly	38	26.4
Cardiac findings	26	18.1
Superficial lymphadenopathy	21	14.6
Joint findings	16	9
Skin findings	12	8.3
Palpable masses	4	2.8

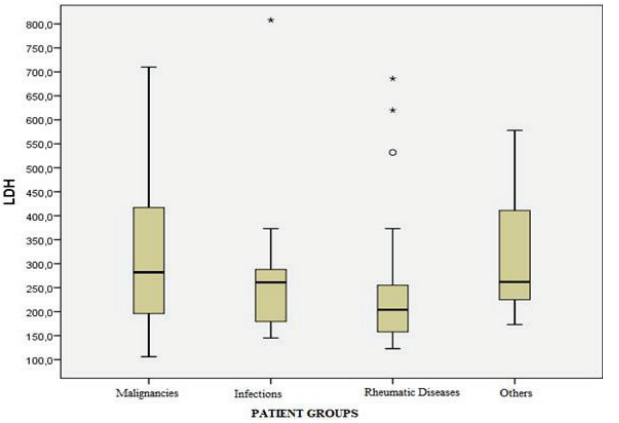

Figure 1: Distribution of LDH in patient groups

difference was found among the groups with regard to the levels of leukocytes, lymphocytes, hemoglobin, hematocrit, mean platelet volume, thrombocytes, C-reactive protein (CRP), albumin, gamma-glutamyl transferase, alkaline phosphatase, iron, total iron-binding capacity, ferritin, calcium, uric acid, and transferrin saturation (p>0.05 for all).

The patients were classified into four categories based on their definitive diagnoses: (i) malignancies (n=79; 57.7%), (ii) infectious diseases (n=19; 13.9%), (iii) rheumatic diseases (n=22; 16.1%), and (iv) other diseases (n=17; 12.4%) (Table 2). Additionally, four patients were found to have two different primary diseases concurrently; one patient had both ovarian cancer and colon cancer, one patient had both Castleman disease and Kaposi's sarcoma, one patient had both lung cancer and gastrointestinal stromal tumor, and the remaining one patient had a graft inflammation associated with nickel allergy.

On PET/CT, non-physiological FDG uptake was detected in 93.1% (n=134) of the patients, and FDG uptake was unrelated to definitive disease involvement in 15 patients. PET-negative patients accounted for 6.9% (n=10) of all patients. The definitive diagnosis was obtained by tissue biopsy in 74 patients, while a laboratory, imaging, and clinical course could diagnose the others.

Moreover, PET had a sensitivity of 97.5%, a specificity of 31.8%, a positive predictive value of 88.8%, and a negative predictive value of 70% (Table 3).

At the end of the study, 94.9% (n=75) of patients with malignancies, 78.9% (n=15) of patients with infectious diseases, 86.3% (n=19) of patients with rheumatic diseases, and 58.8% (n=10) of patients with other diseases showed FDG uptake on 18F-FDG-PET/BT (Figure 2).

DISCUSSION

In internal medicine, diagnosing constitutional symptoms can be challenging since various clinical conditions

Table 2: Distribution of etiologies

	n		n		n		n
Infections	**19**	**Neoplasia**	**79**	**Inflammatory and rheumatic diseases**	**22**	**Others**	**17**
Tuberculosis	10	Non-Hodgkin lymphoma	21	Large vessel vasculitis	6	Primary sclerosing cholangitis, hemolytic anemia, Oncocytoma, Autoimmune Polyglandular Syndrome, Myelodysplastic Syndrome, Subacute Thyroiditis, Macrophage Activation Syndrome (CMV associated), Common Variable Immune Deficiency, Immune Thrombocytopenic Purpura, Primary Myelofibrosis, postinfection polyserositis, Lymphomatoid Granulomatosis, chronic fibrinous pleuritis, nickel allergy, amyloidosis, sarcoidosis, Hypereosinophilic Syndrome	1
Infective endocarditis	3	Lung carcinoma	12	Adult-onset Still's disease, Polymyalgia rheumatica	5		
Mesenteric Panniculitis, graft infection	2	Gastric carcinoma	6	Systemic lupus erythematosus	3		
Prostatic abscess, Bartonella infection	1	Malignant mesothelioma	5	Mixed connective tissue disease, Temporal arteritis, Behcet's disease, Microscopic polyangiitis	1		
		Hodgkin Lymphoma, Multipl Myeloma	4				
		Adenocarcinoma of unknown origin, colon carcinoma, pancreatic carcinoma, renal cell carcinoma, leukemia	3				
		Gastrointestinal stromal tumor, ovarian carcinoma	2				
		Breast carcinoma, gallbladder carcinoma, Warthin Tumor, cholangiocarcinoma, Castleman Disease, Malignant Melanoma, esophageal carcinoma, Kaposi Sarcoma	1				

can cause them. Infections, cancer, metabolic or endocrine disorders, and mood disorders are all possible causes of constitutional symptoms (8). There are still no guidelines in evaluation for the etiology of constitutional symptoms. Metalidis et al. observed that major organic disease and malignancy are extremely uncommon in patients with extensive unexplained weight loss when a baseline screening is completely normal (9). We assessed the contribution of PET/CT to the diagnosis. Our study is the first to evaluate the use of PET/CT as a diagnostic tool in patients with constitutional symptoms.

Table 3: Distribution of PET results

Clinical variable	**Definitive disease**		**Total**
	+	**-**	
PET-positive n (%)	119	15*	134
PET-negative n (%)	3	7	10
Total	122	22	144

* FDG uptake was unrelated to definitive disease involvement in 15 patients

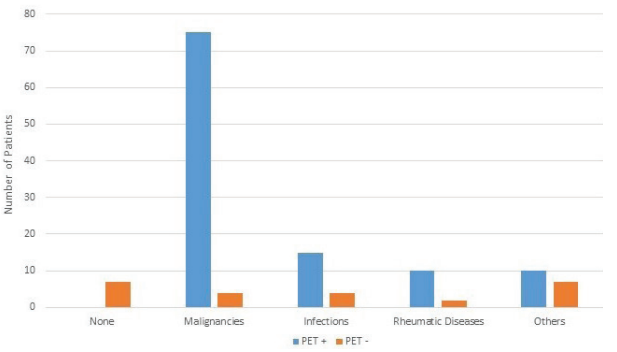

Figure 2: Comparison of PET results among patient groups

Previous studies have shown that high ESR and CRP levels can predict PET/CT positivity, particularly in detecting FUO and inflammatory foci (10,11). In our study, ESR was non significantly higher in the rheumatic diseases group compared to other groups, while CRP level showed no significant difference.

Inflammatory and infectious diseases can be diagnosed using USG, CT, and MRI. Still, these methods cannot diagnose the early stages of the diseases or post-operative pathologies unless a mass has formed (7). On the other hand, patients who cannot be diagnosed using laboratory tests performed concomitantly with physical examination and basic imaging procedures like USG, CT, and MRI require advanced imaging techniques (12).

Nuclear medicine techniques (labeled leukocyte, labeled immunoglobulin, gallium-67 scintigraphy, and PET-CT) showing functional and metabolic changes can often be used as a second-line diagnostic test in diagnosing patients with FUO. Labeled leukocyte, labeled immunoglobulin, and gallium-67 scintigraphy can be used in selected cases due to prolonged processing times, high radiation doses, poor accessibility, and image quality (7). 18F-FDG-PET/CT scintigraphy has recently emerged as an important tool in the detection of inflammatory and infectious foci and in the diagnosis, staging, prognosis, and response to the treatment of malignancies (13-16).

The urinary system, brain, and gastrointestinal tract cannot all be evaluated with 18F-FDG-PET/CT due to urine excretion, increased accumulation, and variable absorption of FDG with peristalsis, respectively (7). Insulin-induced hypoglycemia increases the absorption of FDG in muscle and adipose tissue while decreasing the uptake by the tumor, and the overall tumor-to-background ratio is reduced (17). A study examining 18F-FDG-PET/CT results showed that the diagnostic errors were relatively infrequent (around 2%) but non-negligible (18). The literature indicates that some tumors, including a subset of liposarcomas, diffuse gastric adenocarcinomas, and signet cell colonic adenocarcinomas use substances other than glucose for growth and proliferation, such as glutamine or fatty acids. Thus, their FDG uptake is relatively lower (19). Additionally, some aggressive sarcomas and mucinous tumors might be interpreted as PET-negative when the signal from tumor cells is predominated by low FDG uptake in the surrounding extracellular matrix or mucin production (20). On the other hand, despite having a low proliferation rate, some tumors, including benign oncocytomas (parotid, thyroid, or renal), pheochromocytomas, and hereditary paragangliomas, show a higher FDG uptake on 18F-FDG-PET/CT (21).

In a meta-analysis that investigated 823 individuals with FUO, the contribution of 18F-FDG-PET/CT to the diagnosis ranged from 42% to 67% (7, 22). Schönau et al. observed that 18F-FDG-PET/CT was useful in the diagnosis of 136 out of 240 (71.6%) patients with FUO or inflammation of unknown origin (11). Sonoda et al. reported that the contribution of 18F-FDG-PET/CT to the diagnosis was 79% in 231 patients (23). In comparison to the previous studies, our study indicated that the contribution of 18F-FDG-PET/CT to the diagnosis was remarkably higher (86.8%), while this rate was 78.9% (15/19) in the detection of infectious diseases.

It is known that 18F-FDG-PET/CT can detect tissues with high FDG uptake in individuals with suspected malignancy. Therefore, it has a wide variety of uses in the diagnosis, staging, prognosis, and evaluation of the effectiveness of treatment for malignancies (24). In a study by Cengiz et al., 121 patients with an unknown primary malignancy underwent diagnostic PET/CT scanning, and primary malignancy focus was detected in 59 (49%) of the patients (25). A previous review reported that PET/CT had a sensitivity of 88% and a specificity of 84% for diagnosing oncological diseases (26). In our study, 18F-FDG-PET/CT contributed to the diagnosis in 75 out of 79 patients diagnosed with malignancies, and thus provided a sensitivity of 95%. Including patients with FUO and constitutional symptoms may have led to the increased prevalence.

The effectiveness of 18F-FDG-PET/CT in detecting rheumatic diseases and its superiority to other imaging techniques have been shown in numerous studies (27,28). In a study by Bleeker-Rovers et al., high FDG uptake was observed in periaortitis caused by Takayasu's arteritis, Wegener's granulomatosis, polymyalgia rheumatica, giant cell arteritis, and infectious vasculitis. The study also noted that 18F-FDG-PET/CT had a specificity of 89% and a sensitivity of 77-100% for identifying vasculitis (29). In contrast, it has also been reported that if the giant cell artery is restricted to the temporal arteries alone, the sensitivity of 18F-FDG-PET/BT may remain low due to the small arterial diameter and significant background FDG retention in the brain (30). In a study by Umekita et al., 18F-FDG-PET/CT was shown to be more effective than CT and MRI for the diagnosis of Takayasu's arteritis, particularly in early-stage lesions (29). In our study, 18F-FDG-PET/CT contributed to the diagnosis in 19 out of 22 rheumatic diseases (86.4%) and all eight vasculitis patients (100%). These findings indicate that 18F-FDG-PET/CT is highly effective in identifying vasculitis.

Previous studies have primarily focused on the diagnostic effect of 18F-FDG-PET/CT in FUO patients (31). In contrast, the present study included patients with constitutional symptoms other than fever, which makes our study different from other studies. It is considered that malignancies are observed to be much higher than in other patient groups as a result of FUO and/or constitutional symptoms. A 2022 review indicated that 18F-FDG-PET/CT is superior

to conventional CT or other nuclear imaging techniques in individuals examined for FUO (32). In our study, the contribution of 18F-FDG-PET/CT in diagnosis was highlighted in patients with constitutional symptoms.

On the other hand, we also found that diseases other than vasculitis in the rheumatic diseases group and particularly benign disorders in the other diseases group did not show FDG uptake, which explains our study's low negative predictive value.

In conclusion, constitutional symptoms are not specific to any disease and may be the only findings of a serious underlying disease. Regardless of the presence of FUO, using 18F-FDG-PET/CT in such patient groups contributes significantly to the diagnosis.

Ethics Committee Approval: This study was approved by Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 20.12.2019, No: 21).

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HOW DO THE GENETIC VARIANTS OF *MMP 9* AND *TIMP 1* AND VITAMIN D AFFECT CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS?*

MMP 9 VE *TIMP 1* GENETİK VARYANTLARI VE VİTAMİN D NAZAL POLİPOZİSLİ KRONİK SİNÜZİTTE NASIL ETKİLİDİR?

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ABSTRACT

Objective: Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a multifactorial disease in which the sinus and nasal mucosa are affected. We investigated the relationship between the genetic polymorphism of *MMP9* (rs17576) and *TIMP1* (rs48498) and serum levels, and we wanted to investigate the effect of *MMP9* and *TIMP1* genotypes on Vitamin serum levels in CRSwNP with and without Aspirin-Exacerbated Respiratory Disease (AERD).

Materials and Methods: This study consisted of 99 patients with CRSwNP with AERD and CRSwNP without AERD. The RT-PCR method and ELISA were used in this study. ELISA was used for MMP9 and TIMP1 serum levels and Vitamin D levels.

Results: Serum levels of MMP9 were markedly higher in AG genotype than GG genotype in CRSwNP with AERD. Serum levels of MMP9 were statistically higher in carrying of A (+) allele in CRSwNP with AERD than in not carrying of A (+) allele. In addition, serum levels of Vitamin D were discovered significantly lower in TIMP1 CT genotype in comparison to CC and TT genotypes in all of CRSwNP.

Conclusion: The rising of MMP9 serum levels may be a marker of chronic inflammation or they may be a significant factor in the

ÖZET

Amaç: Nazal polipli kronik rinosinüzit sinüs ve nazal mukozanın etkilendiği multifaktöriyel bir hastalıktır. *MMP9* (rs17576) ve *TIMP1* (rs 4898) genetik polimorfizmleri ile serum düzeyi arasındaki ilişki ve *MMP9* ve *TIMP1* genotipleri ve Vitamin D arasındaki bağlantının gösterilmesini araştırdık.

Gereç ve Yöntem: Bu çalışma, aspirinle alevlenen solunum hastalığı olan veya olmayan nazal polipozisli kronik rinosinüzitli 99 hastadan oluşmaktadır. RT-PCR ve ELISA metodu kullanılmıştır. MMP9, TIMP1 ve Vitamin D serum seviyeleri için ELISA metodu kullanılmıştır.

Bulgular: Aspirinle alevlenen solunum hastalığı eşlik eden nazal polipozisli kronik sinüzit hastalarında MMP9 serum seviyesi, *AG* genotipli hastalarda *GG* genotipli hastalara kıyasla daha yüksek seviyededir. Aynı zamanda bu hasta grubunda MMP9 serum seviyesi, A (+) alleli taşıyan grupta A (+) alleli taşımayan gruba göre daha yüksek seviyededir. Buna ek olarak *TIMP1* CT genotipine sahip olanlar, *TIMP1* CC ve TT genotipleri ile kıyaslandığında Vitamin D serum seviyesinin anlamlı olarak düşük olduğu gösterilmiştir.

*This study was presented as an oral presentation at the 7th International Congress of Molecular Medicine (5-7 September 2019)

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resistance to diseases. This study may lead to a further understanding of disease severity in CRSwNP with AERD.

Keywords: Nasal polyposis, *MMP9, TIMP1*, genetic polymorphism, chronic rhinosinusitis

Sonuç: MMP9 serum düzeylerinin yükselmesi, kronik inflamasyonun bir belirteci olabilir veya hastalık direncinde önemli bir faktör olabilir. Bu çalışma, aspirinle alevlenen solunum hastalığı olan nazal polipozisli kronik rinosinüzitte hastalık şiddetinin daha iyi anlaşılmasına yardımcı olabilir.

Anahtar Kelimeler: Nazal polip, *MMP9, TIMP1*, genetik polimorfizm, kronik sinüzit

INTRODUCTION

Nasal polyposis is identified as a subgroup of chronic rhinosinusitis in European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 (1). Nasal polyposis is an inflammatory circumstance in which the sinus and nasal mucosa are affected. There are many factors in the etiology of nasal polyposis, and many theories are mentioned in the pathophysiology of nasal polyposis. A theory that covers all patients has not been defined yet (2). Matrix metalloproteinase (MMP) that has a significant effect in extracellular matrix remodeling is an endopeptidase. MMP7 and MMP9 that were discovered in many tissues have a natural inhibitor named TIMP1. Extracellular matrix deposition occurs due to the instability between MMP and TIMP (3).

Vitamin D has antiproliferative, anti-inflammatory, and immunomodulatory effects. The deficiency of Vitamin D was associated with the severity of disease in CRSwNP (4). The mechanism of how Vitamin D affects the secretion of MMP was not explained fully (5). There are no studies on how genetic polymorphism of *MMP9* and *TIMP1* affects serum levels. In our study, we aimed to research the correlation between genetic polymorphism of MMP9, TIMP1, and their serum levels. Also, the relationship between Vitamin D levels and genotypes of *MMP9* and *TIMP1* was described.

MATERIAL and METHOD

Patients and study design

Ninety nine patients (61 male and 38 female) with chronic rhinosinusitis with nasal polyposis applied to Istanbul University, Istanbul Faculty of Medicine, Otorhinolaryngology-Head, and Neck Surgery Department between August 2018 and April 2019. Their complaints at the time of admission were rhinorrhea, anosmia, nasal obstruction and altered taste perception. Forty one patients were categorized as CRSwNP with AERD, and 58 patients were categorized as CRSwNP without AERD. None of the patients had any history of ciliary dyskinesia or antrochoanal polyp.

According to EPOS 2012 guidelines, the diagnosis of sinus diseases was based on nasal endoscopy, clinical examination, and history. Endoscopic examination was performed with 4 mm 0 and 30-degree rigid endoscopes. To evaluate the endoscopic grading, Meltzer's endoscopic nasal polyp grading was used. Atopy evaluation was performed according to diagnosis of allergic rhinitis, asthma and urticaria. The patients with CRSwNP diagnosis at the time of their visit to asthma and allergic clinic were recruited for the evaluation of AERD. Oral aspirin challenge was used to detect ASA hypersensitivity. The ratio of eosinophil (%) and the level of Vitamin D (ng/ml) were evaluated between these two groups. Vitamin D serum levels examined via ELISA in the routine examinations of patients' files were also evaluated. The quality of life was evaluated with the SNOT-22 questionnaire. The samples were taken into a gel tube for serum analyses and into an EDTA tube for DNA analyses. The study was approved by the Ethics Committee on Istanbul University, Istanbul Faculty of Medicine (Date: 10.08.2018, No: 13). Before sampling and experimental studies, a voluntary informed consent form was taken from all patients.

Real-time PCR analysis

Samples were collected from the peripheral blood, and DNA extraction was performed. TaqMan System (Applied Biosystems, 45 Life Technologies) PrimerProbMix, and qPCR ProbesMaster (Jena Bioscience, Germany, PCR-360) were used for genotyping according to the manufacturer's protocols. A total of two SNPs, i.e. matrix metalloproteinase *MMP9 (*rs17576*)* and tissue inhibitor of metalloproteinase *TIMP1 (*rs4898*)* were selected for this study (Table 1). *TIMP1* rs4898 (372T>C) polymorphism

Table 1: Detailed information on the studied SNPs Sequels

SNP ID	rs17576	rs4898
Gene name	MMP matrix metallopeptidase 9	TIMP metallopeptidase inhibitor 1
Polymorphism	A/G, Transition Substitution	C/T, Transition Substitution
Context Sequence [VIC/FAM]	*CTCCTCGCCCCAGGACTCTACACCC[A/G]GGACGGCAATGCTGATGGGAAACC*	*TCTTGCACATCACTACCTGCAGTTT[C/T]GTGGCTCCCTGGAACAGCCTGAGT*

and *MMP9* rs17576 (Gln279Arg) polymorphism were investigated. Allelic discrimination of two SNPs was performed with ABI StepOne RT PCR System (Applied Biosystems, 45 Life Technologies). The TaqMan assay was used. The total reaction mix volume was 20 µL. 2 µL of DNA, 10 µL of qPCR ProbesMaster, 7 µL PCR Grade water, and 1 µL of TaqMan probe mix. For real-time PCR reaction, a 2-minute cycle was used performed as the first denaturation step at 95 °C. Immediately followed were 40 cycles of 15 seconds at 95 °C and 1 minute at 60 °C each. After fluorescence level measurement, allele frequencies were evaluated with the TaqMan assay with the aid of SDS v 3.0 (Applied Biosystems). All experimental studies, including PCR analysis and determination of serum protein levels, were carried out in the laboratory of Aziz Sancar Experimental Medicine Research Institute, Molecular Medicine Department.

ELISA test

MMP9 and TIMP1 serum levels were determined in supernatants of patients with each nasal polyposis using the MMP-9 Human ELISA Kit (Invitrogen, Vienna, Austria) and the TIMP1 Human ELISA Kit (ENZO LIFE, Farmingdale, NY, USA). The plate was incubated for 2 hours at room temperature. After washing, 100 µL of the streptoavidin-HRP solution was added and incubated for 30 minutes at room temperature. After the second washing step, 100 µL of chromogen was added to each well. After 30 minutes of incubation at room temperature, enzymatic activity was stopped with a stop solution. Optical density (OD) was measured with a Tecan ELISA plate reader (Tecan, Switzerland). After the standard graph was created, MMP9 and TIMP1 concentrations were calculated.

Statistical analysis

SPSS ver.22.0 (IBM Corp., Armonk, NY, USA) program was used for data analysis. The statistical significance limit was taken as $p<0.05$. Student's t-test and Chi-square, Fischer and Annova tests were chosen to evaluate the effects of genes on activity.

RESULTS

Fifty eight patients (58.6%) were included in CRSwNP without AERD, and forty one patients (41.4%) were included in CRSwNP with AERD. Concerning the eosinophil ratio, it was found to be higher in CRSwNP with AERD. The presence of atopy was 82.9% in CRSwNP with AERD, and 10.3% in CRSwNP without AERD. It was observed that the presence of atopy increased 42-fold in CRSwNP with AERD. When smoking was evaluated in the overall study group, it was statistically lower in CRSwNP with AERD ($p=0.033$) (Table 2).

According to the genotypes and alleles of *MMP9* and *TIMP1*, no statistical difference was found between CRSwNP with AERD and without AERD ($p>0.05$) (Tables 3 and 4).

There was no statistical difference in serum levels of MMP9 according to genotypes and alleles in CRSwNP without AERD. When serum levels of MMP9 were compared in CRSwNP with AERD, they were statistically higher in AG genotype than GG genotype ($p=0.012$). In addition, they were statistically higher in carrying of A (+) allele than in not carrying of A (+) allele in CRSwNP with AERD ($p=0.028$) (Table 5).

According to genotypes and alleles of *TIMP1*, serum levels of TIMP1 were compared between CRSwNP with AERD and CRSwNP without AERD. When these parameters were examined, there was no statistical difference in this study ($p>0.05$).

The ratio is 75% for undergoing two or more surgeries, while the ratio is 58% for undergoing less than two

Table 2: Demographic and clinical characteristics in CRSwNP with AERD and without AERD

	CRSwNP without AERD	CRSwNP with AERD	P
Age (year) (mean±SD)	46.31±14.06	45.27±12.93	0.708
Gender (female/male)	16/42	22/19	0.009
BMI (kg/m²) (mean±SD)	26.80±4.93	26.72±4.0	0.927
Smoking (no/yes) (%)	60.3/39.7	80.5/19.5	0.033
Alcohol (no/yes) (%)	94.8/5.2	100/0	0.197
Right polyp grade (mean±SD)	2.64±0.85	2.32±1.15	0.114
Left polyp grade (mean±SD)	2.60±0.81	2.49±1.05	0.557
Eosinophil ratio (mean±SD)	3.75±2.93	5.41±3.53	0.012
Atopy (no/yes) (%)	89.7/10.3	17.1/82.9	0.000*
Family history (no/yes) (%)	84.5/15.5	78.0/22.0	0.414

CRSwNP without AERD: chronic rhinosinusitis with nasal polyposis without Aspirin –Exacerbated Respiratory Disease, CRSwNP with AERD: chronic rhinosinusitis with nasal polyposis with Aspirin –Exacerbated Respiratory Disease, SD: Standard deviation, BMI: Body mass index

Table 3: *MMP9* genotypes and A/G alleles relationships in CRSwNP with AERD and without AERD

	CRSwNP without AERD n=58	CRSwNP with AERD n=41	OR and CI
***MMP9* genotypes**			
AA	24 (41.4%)	18 (43.9%)	reference
GG	8 (13.8%)	6 (14.6%)	1.0 (0.295-3.395)
AG	26 (44.8%)	17 (41.5%)	0.872 (0.367-2.069)
Alleles			
A	74 (63.7%)	53 (64.6%)	reference
G	42 (36.2%)	29 (35.3%)	0.902 (0.402-2.024)

CRSwNP without AERD: chronic rhinosinusitis with nasal polyposis without Aspirin –Exacerbated Respiratory Disease, CRSwNP with AERD: chronic rhinosinusitis with nasal polyposis with Aspirin –Exacerbated Respiratory Disease, MMP9: Matrix Metalloproteinase 9 p>0.05

Table 4: *TIMP 1* genotypes and C/T alleles relationships in CRSwNP with AERD and without AERD

	CRSwNP without AERD n=58	CRSwNP with AERD n=41	OR and CI
***TIMP1* genotypes**			
CC	23 (39.7%)	13 (31.7%)	reference
TT	28 (48.3%)	17 (41.5%)	1.074 (0.433-2.665)
CT	7 (12.1%)	11 (26.8%)	2.78 (0.866-8.92)
Alleles			
C	53 (45.68%)	37 (45.12%)	reference
T	63 (54.31%)	45 (54.87%)	1.415 (0.610-3.28)

CRSwNP without AERD: chronic rhinosinusitis with nasal polyposis without Aspirin –Exacerbated Respiratory Disease, CRSwNP with AERD: chronic rhinosinusitis with nasal polyposis with Aspirin –Exacerbated Respiratory Disease, TIMP1: tissue inhibitor of metalloproteinase 1 p>0.05

Table 5: MMP9 serum levels according to AA, AG and GG genotypes and A/G alleles

	CRSwNP without AERD	P	CRSwNP with AERD	P
***MMP 9* genotypes**	MMP9 serum levels		MMP9 serum levels	
AA	858.39±382.46	ns	795.56±239.75	
GG	565.32±283.60	ns	605.00±250.72	***0.012*** *vs AG
AG	713.66±409.74	ns	908.12±241.03	
A-	760.18±400.00		605.00±250.72	
A+	565.32±283.60	ns	853.55±243.42	***0.028***
G-	858.39±382.46		795.56±239.75	
G+	669.70±377.69	ns	829.05±273.97	ns

CRSwNP without AERD: chronic rhinosinusitis with nasal polyposis without Aspirin –Exacerbated Respiratory Disease, CRSwNP with AERD: chronic rhinosinusitis with nasal polyposis with Aspirin –Exacerbated Respiratory Disease, MMP9: Matrix Metalloproteinase 9 ns: p>0.05; Serum levels are expressed as mean (±SD).

surgeries in patients who had *TIMP1* in carrying of T (+) allele in CRSwNP without AERD. Likewise, the ratio is 75% for undergoing two or more surgeries and it is 44% for undergoing less than two surgeries in patients who had *TIMP1* TT genotype. (Table 6). Although not reaching statistical significance, the risk of having more than two surgeries increased approximately 2-fold in CRSwNP without AERD with *TIMP1* in carrying of T (+) allele and approximately 4-fold in CRSwNP without AERD with the *TIMP* TT genotype. (p>0.05, OR: 2.17, 95 % CI: 0.39-11.84; p>0.05, OR: 3.81, 95 % CI: 0.70-20.79).

The ratio is 91% for undergoing two or more surgeries, while it is 77% for undergoing less than two surgeries in patients who had *MMP9* carrying of A (+) allele in CRSwNP

with AERD. Likewise, the ratio is 52.2% for undergoing two or more surgeries and it is 33% for undergoing less than two surgeries in patients who had *MMP9* AA genotype. Although not reaching statistical significance, the risk of undergoing more than two surgeries increased approximately 3 times in CRSwNP with AERD with *MMP9* in carrying of A (+) allele and approximately 2 times in CRSwNP with AERD with *MMP9 AA* genotype (p>0.05, OR: 3.00, %95 CI: 0.48-18.64 for A (+) allele; p>0.05, OR: 2.18, 95% CI: 0.60-7.81 for *MMP9* AA genotype).

The relationship between the mean of SNOT 22 scores and genotypes of *MMP9* and *TIMP1* was investigated, but no significant differences were found.

Serum levels of Vitamin D were researched concerning the genotypes of *MMP9* and *TIMP1*. When Vitamin D serum levels were evaluated according to *TIMP1* genotypes, it was observed that they were statistically lower in *TIMP1* CT genotype in CRSwNP with AERD and without AERD (p=0.030) (Table 7).

DISCUSSION

Chronic rhinosinusitis with nasal polyposis which reduces the quality of life and productivity-working capacity were examined (6) in this study. MMP9 and TIMP1 are endopeptidases that are significant factors in the pathophysiology of nasal polyposis and lower and upper respiratory tract remodeling (7). At the same time, the deficiency of Vitamin D is relevant to CRSwNP, but it is unclear how Vitamin D affects MMP secretion (5).

The atopy rate was found 85% in CRSwNP with AERD, and 66% in CRSwNP without AERD by Stevens and colleagues (8). The atopy rate was significantly different between CRSwNP with AERD and CRSwNP without AERD (8). In this study, the atopy rate was discovered at 82.9% in CRSwNP with AERD, 10.3% in CRSwNP without AERD. Furthermore, the frequency of atopy was 42-fold higher in CRSwNP with AERD.

When the literature was reviewed, we couldn't find any studies on why patients with CRSwNP with AERD don't smoke. Since respiratory system diseases such as asthma are seen in patients with CRSwNP with AERD, we think that these patients avoid smoking.

MMP9 single nucleotide polymorphism (SNP) rs3787268, rs2664538 (including rs17576), rs2274756 (including rs17577), and rs3918242 were examined in CRSwNP and the control group. According to subset decomposition, none of the SNPs had a significant p value *rs 2664538* under the recessive model in recurrent nasal polyposis. Statistical differences were not analyzed between recurrent

Table 6: The relationship between *TIMP1* TT genotype, T (+) allele and the number of surgeries in CRSwNP without AERD (P>0.05, OR:3.81, 95 % CI: 0.70-20.79 for *TIMP1* TT genotype) (p>0.05, OR: 2.17, %95 CI: 0.39-11.84 for T(+) allele)

CRSwNP without AERD	**TT-**	**TT+**	**Total**
S<2 Number (n)	28	22	50
Ratio (%)	56	44	100
S≥2 Number (n)	2	6	8
Ratio (%)	25	75	100
CRSwNP without AERD	**T -**	**T+**	**Total**
S<2 Number (n)	21	29	50
Ratio (%)	42	58	100
S≥2 Number (n)	2	6	8
Ratio (%)	25	75	100

CRSwNP without AERD: chronic rhinosinusitis with nasal polyposis without Aspirin –Exacerbated Respiratory Disease. S: surgery

Table 7: Vitamin D serum levels according to *MMP9* and *TIMP1* genotypes in the whole group

	TIMP1			**MMP9**		
	CC	**CT**	**TT**	**AA**	**AG**	**GG**
SNOT 22	47.34±16.30	46.17±17.96	43.98±18.71	46.49±18.68	45.05±18.61	43.38±10.85
D Vitamin (ng/ml)	19.51±6.61	15.40±6.44	19.19±6.35	18.40±6.28	18.67±7.26	19.09±5.53

MMP9: Matrix Metalloproteinase 9, TIMP 1: tissue inhibitor of metalloproteinase 1, SNOT: sinonasal outcome test (p=0.030 Vitamin D levels in *TIMP1* CT genotype were compared to *TIMP1* CC and TT genotype). Values are expressed as mean (±SD)

and non-recurrent CRSwNP in other genetic polymorphisms. GG, AG, and AA genotype were 56.3%, 28.1%, and 10.9% respectively in recurrent nasal polyposis (9). The distribution of genotype in our study is different from the previously mentioned study. When *MMP9* rs17576 polymorphism was checked in CRSwNP with AERD and CRSwNP without AERD, there was no significant difference according to MMP9 genotypes. GG, AG and AA genotype was 14.6%, 41.5%, and 43.9% respectively in CRSwNP with AERD. Since the dispersion of genotype differed between populations, genotypes were different in this study. The hazard of undergoing more than two operations was discovered nearly 3-fold in *MMP9* in carrying of A (+) allele; however, it was examined roughly 2-fold in the *MMP9* AA genotype in CRSwNP with AERD. This information proves that the patients with CRSwNP AERD are more resistent to treatment and necessitate recurrent surgeries in this study.

Guerra et al investigated the relationship with the concentrations of MMP2, MMP7 and MMP9, and TIMP1 and 2. In this study, increased concentrations of MMP9, MMP7 and MMP2 and decreased concentrations of TIMP1 and TIMP2 were demonstrated in nasal polypoid tissue. Also, MMP/TIMP ratio was found significantly higher in nasal polypoid tissue compared to the control group. (10) Kyung-Yeo et al. studied *MMP9* mRNA expression, Wang et al. examined *MMP9* single nucleotide polymorphism, and Mudd et al. also checked *MMP9* expression in CRSwNP (9,11,12). Wang et al. observed polymorphism of *MMP9* (9). However, the influence of these polymorphisms on serum levels was not examined. In this study, serum levels of MMP9 and TIMP1 were researched according to genotypes and alleles. According to genotypes and alleles of *TIMP1*, no significant difference was found in the comparison of TIMP1 serum levels. MMP9 serum levels were statistically higher in AG genotype compared to GG genotype in CRSwNP with AERD. Furthermore, MMP9 serum levels were higher in *MMP9* in carrying of A (+) allele compared to *MMP9* in not carrying of A (+) allele in CRSwNP with AERD. That is why the recurrence of disease increases. This study supports that the patients carrying A (+) allele in CRSwNP with AERD had an approximately 3-fold risk of having more than two surgeries.

TIMP1 genetic polymorphism was investigated in malignancies such as lung and breast cancers, vascular pathologies like intracerebral hemorrhage, senile aortic stenosis (16), and diseases such as systemic lupus erythematosus in the literature (13-17). There is no article on the examination of the genetic polymorphism of *TIMP1* in CRSwNP. We aimed to evaluate *TIMP1* rs4898 C/T polymorphism in all chronic rhinosinusitis with nasal polyposis in this study. Following genotypes and alleles, no significant difference was found between the two groups including CRSwNP with and without AERD.

Vitamin D is capable of modulating pro-inflammatory cytokines, thus having an important position in the pathogenesis of many allergic disorders (18). In addition, it inhibits the proliferation of B lymphocytes and their differentiation into anti-body secretin cells (19). Wang et al. stated MMP2 and MMP9 serum levels raised in proinflammatory with TNFα fibroblast cell cultures, and it was shown that their biological effects were significantly suppressed as a result of calcitriol administration. How Vitamin D influence the secretion of MMP9 is not known. Vitamin D may affect intracellular production, translation, or transcription (20). We aimed to evaluate how the genotypes of *MMP9* and *TIMP1* affect Vitamin D serum levels. Vitamin D serum levels were investigated according to MMP9 and TIMP1 genotypes. Serum levels of Vitamin D were significantly lower in CRSwNP who had *TIMP1* CT genotype in all patients. We did not find any articles that were about the relationship between the genotypes of *TIMP1* and *MMP9* and Vitamin D serum levels.

In this study, the influence of these polymorphisms on serum levels was studied. MMP9 serum levels were significantly higher in AG genotype and A (+) allele in CRSwNP with AERD. According to the genetic polymorphism of *MMP9* and *TIMP1*, serum levels of Vitamin D were investigated. Serum levels of Vitamin D were found statistically lower in *TIMP1* CT genotype in all CRSwNP.

Our study design has limitations. Our sample size is small, that may cause a decrease in statistical power.

We investigated the correlations between the genetic polymorphisms of *MMP9* and *TIMP1* and their serum levels. Also, the relationship between Vitamin D serum levels and genotypes of MMP9 and TIMP1 was described. The rising of MMP9 serum levels may be a marker to chronic inflammation or they may be a significant factor in the resistance of disease. It will be possible to obtain information about the prognosis of disease according to alleles and genotypes. More studies are needed to show possible differences.

CONCLUSION

We found that MMP9 serum levels were significantly higher in AG genotype than GG genotype in CRSwNP with AERD. The rising of MMP9 serum levels may be a marker to chronic inflammation or they may be a significant factor in the resistance of disease. More studies are needed to show possible differences.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 10.08.2018, No: 13).

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IMPACT OF COVID-19 QUARANTINE ON CHILD SEXUAL ABUSE: EXPERIENCE OF CHILD ADVOCACY CENTER

COVID-19 İZOLASYON DÖNEMİNDE ÇOCUK CİNSEL İSTİSMARI: ÇOCUK İZLEM MERKEZİ DENEYİMİ

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ABSTRACT

Objective: We aimed to evaluate the characteristics of child sexual abuse reports and the affecting factors during the pandemic compared to the pre-pandemic period.

Materials and Methods: The study included 506 children and adolescents admitted to the Child Advocacy Center (CAC). Case and control groups were determined according to the time of admission (first 15 months of the pandemic and 15 months before the pandemic). The data were obtained by retrospectively examining the files, forensic investigation reports, family evaluation reports, and other documents in the files of the children in the legal process.

Result: Cases applied to CAC during the pandemic decreased by 16 percent. Sexual abuse reported by teachers and professionals such as public servants decreased from 30% to 4.7%. However, abuse through online platforms doubled. Finally, recurrent domestic abuse increased significantly during quarantine ($p<0.001$).

Conclusion: The pandemic changed the way CAC is admitted and the specifics of abuse. The teachers and public servants reported fewer incidences of sexual abuse during the pandemic period. In addition, the form of abuse shifted to the online platform, and recurrent domestic abuses have increased. Professionals working in the field of sexual abuse should keep in mind that the possible effects of these changes may continue after the pandemic.

Keywords: Child abuse, COVID-19, social media

ÖZET

Amaç: Bu çalışmada, pandemi sırasında çocuk cinsel istismarı bildirim özelliklerini ve ilişkili faktörleri pandemi öncesiyle karşılaştırmalı olarak değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya Çocuk İzlem Merkezine (ÇİM) başvuran 506 çocuk ve ergen dahil edilmiştir. Çalışma ve kontrol grupları başvuru zamanına göre belirlenmiştir (pandeminin ilk 15 ayında ve pandemiden önceki 15 aylık zaman diliminde). Veriler, dosya incelemeleri, adli soruşturma raporları, aile değerlendirme raporları ve yasal süreçte çocuğun dosyasındaki diğer belgeler incelenerek retrospektif olarak toplanmıştır.

Bulgular: Pandemi döneminde ÇİM'e başvuran vakalarda %16'lık bir azalma gözlendi. Öğretmenler aracılığıyla yapılan bildirimlerin %30'dan %4,7'ye düştüğü belirlendi. Çevrimiçi platformlar üzerinden gerçekleşen istismarın iki kat arttığı tespit edildi. Karantina döneminde tekrarlayan aile içi istismarda anlamlı bir artış görüldü ($p<0,001$).

Sonuç: Pandemi, ÇİM'e başvuru türünü ve istismarın spesifik özelliklerini değiştirmiştir. Öğretmenler ve kamu çalışanları gibi profesyoneller aracılığıyla yapılan bildirimlerde azalmaya yol açmıştır. Ayrıca, istismar türünde çevrimiçi platforma doğru bir kaymaya ve aile içi gerçekleştirilen tekrarlayan istismarlarda artışa yol açmıştır. Bu değişikliklerin etkilerinin pandemi sonrasında da devam edebileceği düşünülmektedir.

Anahtar Kelimeler: Çocuk istismarı, COVID 19, sosyal medya

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INTRODUCTION

Child sexual abuse (CSA) is a broad term that covers any completed or attempted sexual harassment of children, including sexual contact, penetration, incest, and commercial sexual exploitation of children (1). It is a significant public health problem with an estimated prevalence of 4-9% in males and 12-35% in females (2). Despite the devastating long-term effects on abuse victims' physical and psychological health, only a small proportion of cases are reported to judicial authorities. Child Advocacy Centers (CAC) are multidisciplinary specialized units that aim to facilitate and optimize reports of child sexual abuse incidents and prevent secondary traumatization of children in judicial processes (3). The first CAC in Turkiye was opened in 2010, and currently, there are 62 CACs across the country.

Since the onset of the COVID-19 pandemic, radical changes have occurred in different areas of children's activities of daily living, including the increased use of digital technologies on academic and social platforms, increased time spent at home, and suspension of extracurricular activities. While the literature on the effects of extreme life events such as disasters and conflicts are scarce, a few studies have reported increased violence and all forms of abusive acts against vulnerable groups, including children (5,6). Studies have suggested that during the COVID-19 pandemic, cases of sexual abuse increased, and patterns and locations of abuse changed (7,8). During the COVID-19 pandemic, the increasing use of digital media in different areas of life, including work and educational settings, as well as socialization and leisure activities, has increased (9,10). The characteristics and patterns of CSA events may change with the increased use of social media and gaming platforms.

On the other hand, not only CSA patterns but also reporting of CSA events can be affected by school closures, suspension and/or slowdown of legal processes, and limited availability of medical departments and other child protection facilities (11). Some factors such as age, gender, type of CSA, and relativity of perpetrator to the child affect disclosure status, to whom, and when to disclosure (12). There are few studies reporting an increase in CSA events during the COVID-19 pandemic (11,13,14). Data collection sources and study methods (emergency services, online surveys, etc.), the time period selected during the pandemic, and the cultural/regional characteristics of the studies may partly explain these controversial findings.

In this cross-sectional study, we aimed to evaluate the characteristics and associated factors of CSA events during the pandemic compared to the pre-pandemic period.

MATERIALS and METHODS

A total of 506 children and adolescents admitted to CAC with suspected CSA were included in the study. Cases applying to CAC within the first 15 months of the pandemic (April 2020-May 2021) were accepted as the study group, and cases applying to CAC in the 15 months before the pandemic (January 2019-March 2020) were selected as the control group. Data were obtained from file reviews, forensic investigation reports, and family assessment reports. During the data collection process, care was taken to keep the subjects' personal information confidential and not violate the individuals' privacy and confidentiality. This study was approved by Sakarya University, Faculty of Medicine Ethics Committee (Date: 29.05.2021, No: 302).

An assessment form was developed in order to obtain the subjects' information about age, gender, socioeconomic status, legal domicile, family support, any given psychiatric diagnoses, the reporter of the event, type of CSA, the relation of the perpetrator to the child, the number of perpetrators, the effect of social media, reoccurrence of CSA, and first and last dates of the CSA incident.

Statistical analysis

The SPSS 22.0 program was used for statistical analysis. Descriptive statistics were applied to determine the minimum, maximum, mean, standard deviation, and frequency of the data. The distribution of variables was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney U test and independent-sample t-test were used in the analysis of quantitative data. The chi-square test and Fisher's precision test were used in the analysis of qualitative data. A p-value of 0.05 was considered statistically significant.

RESULTS

A total of 506 children and adolescents referred to our CAC between January 2019 and December 2020 were included in the study. The study group included 213 (42.1%) cases admitted during the pandemic. The control group included 293 (57.9%) cases before the pandemic. There was no difference between the two groups in terms of age (12.62±SD and 12.49±SD, respectively, (p=0.665)) and gender (p=0.268). The socioeconomic status was significantly different between the two groups (p<0.001). The sociodemographic information is summarized in Table 1.

In the study, it was found that there was a difference between the periods (p<0.05). Regarding the source of information, there was a significant increase in parental reporting during the pandemic (54.9% in the study group and 39.2% in the control group, p<0.001) and disclosure of CSA by teachers, who made almost one-third (30%) of the declaration of abuse events before the pandemic, decreased more than six-fold (4.7%) during the pandemic (p<0.001). While the frequency of CSA through online

Table 1: Sociodemographic information on child victims of abuse

Demographic characteristics of the abuse victim		Admission period			
		Before pandemic		During pandemic	
Average age		**12.49**		**12.62**	
Data		**n**	**%**	**n**	**%**
Age group	Before adolescence	64	21.8	50	23.5
	Adolescence	229	78.2	163	76.5
Gender	Female	229	78.2	175	82.2
	Male	64	21.8	38	17.8
Socio-economic status	High	29	9.9	55	25.8
	Middle	138	47.1	150	70.4
	Low	126	43	8	3.8
Place of resident	Province	166	56.7	96	45.1
	District	126	43	92	43.2
	Village	1	0.3	25	11.7
Family support	No	50	17.1	37	17.4
	Yes	243	82.9	176	82.6
Total		293	100	213	100

platforms (social media, telephone, internet, etc.) was 12.6% in the pre-pandemic period, this almost doubled (23.5%) during the pandemic ($p<0.05$). A significant difference was observed between the periods in the transactions with the stakeholder institution (Directorate of Family and Social Policies) ($p<0.05$). Accordingly, it was determined that the rate of children for whom no action was taken (such as requesting a pregnancy test, placing under protection, requesting a social investigation, changing schools, etc.) before the pandemic was 68.9%, while this rate increased to 83.1% during the pandemic. It was determined that the rate of children for whom social investigation was requested decreased from 22.5% to 9.9%, and the rate of children taken into institutional care decreased from 5.1% to 2.8% (Table 2).

The pandemic has been evaluated as a factor that may affect the reporting time for recurrent abuses. Only the files containing reporting time information of recurrent abuse (n=206) were included in this comparison from among the files that experienced recurrent abuse (n=235). Conversely, 29 recurrent abuse files were excluded due to missing data. The chi-square analysis showed a significant relationship between the duration of reporting of recurrent abuse and pandemic periods ($p<0.05$). Accordingly, it was found that the rate of reporting between 0-7 days before the pandemic (25.7%) almost doubled during the pandemic (47.6%). No significant difference was found in single-time abuse cases ($p>0.05$) (Table 3).

Table 2: Information about abuse

Information about abuse		Admission period			
		Before pandemic		During pandemic	
Data		**n**	**%**	**n**	**%**
Reporting by (p<0.001)	Parent	115	39.2	117	54.9
	Self-reports	22	7.5	36	16.9
	Teacher	88	30	10	4.7
	Public employee	21	7.2	14	6.6
	Other	47	16	36	16.6
Abuse recurrence (p<0.02)	Yes	123	42	112	52.6
	No	170	58	101	47.4
Type of abuse (p>0.05)	Non-penetrating contact	81	27.6	70	32.9
	Contact with penetration	183	62.5	117	54.9
	Non-contact	29	9.9	26	12.2
Online abuse (p<0.001)	Yes	37	12.6	50	23.5
	No	256	87.4	163	76.5
Closeness to the perpetrator (p>0.05)	Relatives living in the same house	58	19.8	38	17.8
	Relatives living in separate households	63	21.5	38	17.8
	Acquaintance	137	46.8	112	52.6
	Foreigner	35	11.9	25	11.7
Psychiatric diagnosis (p>0.05)	Yes	260	88.7	187	87.8
	No	33	11.3	26	12.2
Procedure conducted at CAC (p>0.05)	No action taken	203	69.3	137	64.3
	Forensic and mental examination	86	29.4	73	34.3
	Other	4	1.4	3	1.4
Procedures with stakeholder institution (p<0.001)	No action taken	202	68.9	177	83.1
	Institutionalized	15	5.1	6	2.8
	Institutional care continues	10	3.4	9	4.2
	Social investigation demanded	66	22.5	21	9.9
Total		293	100	213	100

Table 3: Recurrent abuse reporting periods

Period		Recurrent abuse reporting period					Total
		Day 1-7	Day 8-30	Months 2-6	Month 7 -Year 1	Year 1 - Over	
Before the pandemic	n	26	30	19	16	10	101
	Period %	25.7	29.7	18.8	15.8	9.9	100.0
	Recurrent abuse %	34.2	68.2	45.2	69.6	47.6	49.0
	Total %	12.6	14.6	9.2	7.8	4.9	49.0
During the pandemic	n	50	14	23	7	11	105
	Period %	47.6	13.3	21.9	6.7	10.5	100.0
	Recurrent abuse %	65.8	31.8	54.8	30.4	52.4	51.0
	Total %	24.3	6.8	11.2	3.4	5.3	51.0
Total	n	76	44	42	23	21	206
	Period %	36.9	21.4	20.4	11.2	10.2	100.0
	Recurrent	100.0	100.0	100.0	100.0	100.0	100.0
	Abuse %	36.9	21.4	20.4	11.2	10.2	100.0

P=0.002

The study determined that recurrent abuses significantly increased statistically during the pandemic compared to the pre-pandemic period (before pandemic: 42%, during pandemic: 52.6%, p=0.018). Accordingly, while the proportion of children exposed to recurrent abuse by a relative living in the same house was 44.8% before the pandemic, this rate increased to 73.7% during the pandemic (p<0.001) (Table 4).

DISCUSSION

In this study, we aimed to evaluate the sociodemographic characteristics and abuse-related characteristics of the cases which were brought to the CAC with suspicion of abuse within 15 months during the pandemic and before the pandemic. During the pandemic period, several of the practices, such as community-wide quarantine, interruption of education, and social distancing, were implemented as preventive measures. At the same time, academic education and, at times, special education support could not be provided face-to-face. Children spent more time in the environment they lived in and with the people in that environment. Problems such as economic difficulties, difficulties in accessing shelter and food, and stress that comes with the pandemic and social isolation have created significant risk factors for child abuse (5).

Despite the slowing down of judicial proceedings during the pandemic, CACs in our country continued to accept judicial notifications for CSA. There was a 16% decrease in the total number of referments during the pandemic compared to the 15 months before the pandemic. In a cross-sectional study from a different location, there was a decrease in both forensic procedures and ongoing medical procedures in the first months of the pandemic (15). Similarly, studies conducted in Turkiye have also reported a decline in referments to CACs (16,17). In different states of the USA, there was a decrease in the rate of reports of child maltreatment in the first months of quarantine (14). Although it is stated that the number of referments to the hospital regarding child neglect and abuse has decreased, the rate of violence has increased, specifically in the cases requiring hospitalization (6,11). In addition, it has been argued that this decline does not reflect the reality due to disruptions in official notifications caused by the pandemic (6). In contrast to these data, it was assumed that there was a significant increase in the number of children admitted to the emergency room due to sexual abuse during the pandemic period in studies conducted in African countries and that this rate might be higher due to the difficulties experienced by families in accessing services during the pandemic period (7,13). It is assumed that quarantine will increase abuse and that restricted living will be a barrier to official reporting (5).

The age group and gender distribution of the children in our study were found to be similar between the groups. It was found that the adolescents (ages 12 to 18) and female gender constituted the majority of the cases. According to the literature, being adolescent and/or female is a risk factor that increases CSA (2,18). Consistent with our findings, in another study conducted with a similar design but in another province in Turkiye with a smaller number of cases, it was stated that age and gender-specific findings did not change during the pandemic period (16).

Table 4: Recurrent abuse and perpetrator closeness by period

Period			Closeness of the abuser				Total
			Relative living in the same house relative	Relative living separately	Acquainted	Foreigner	
Before the pandemic	No recurrent abuse	n	32	28	79	31	170
		Abuse %	18.8	16.5	46.5	18.2	100.0
		Abuser closeness %	55.2	44.4	57.7	88.6	58.0
		Total %	10.9	9.6	27.0	10.6	58.0
	Recurrent abuse exists	n	26	35	58	4	123
		Abuse %	21.1	28.5	47.2	3.3	100.0
		Abuser closeness %	44.8	55.6	42.3	11.4	42.0
		Total %	8.9	11.9	19.8	1.4	42.0
	Total	n	58	63	137	35	293
		Recurrent abuse %	19.8	21.5	46.8	11.9	100.0
		Abuser closeness %	100.0	100.0	100.0	100.0	100.0
		Total %	19.8	21.5	46.8	11.9	100.0
During the pandemic	No recurrent abuse	n	10	20	55	16	101
		Abuse %	9.9	19.8	54.5	15.8	100.0
		Abuser closeness %	26.3	52.6	49.1	64.0	47.4
		Total %	4.7	9.4	25.8	7.5	47.4
	Recurrent abuse exist	n	28	18	57	9	112
		Abuse %	25.0	16.1	50.9	8.0	100.0
		Abuser closeness %	73.7	47.4	50.9	36.0	52.6
		Total %	13.1	8.5	26.8	4.2	52.6
	Total	n	38	38	112	25	213
		Recurrent Abuse %	17.8	17.8	52.6	11.7	100.0
		Abuser closeness %	100.0	100.0	100.0	100.0	100.0
		Total %	17.8	17.8	52.6	11.7	100.0

It was determined that the applications of those with poor socioeconomic status decreased significantly during the pandemic period. This may be related to the fact that individuals from lower socioeconomic status may have experienced more difficulties in accessing governmental facilities and experienced more economic inadequacy during the quarantine period. Another explanation for this finding might be that the family itself might become a source of neglect and abuse toward children and adolescents. Due to the economic uncertainties during the pandemic period, employment declined, and job losses and economic difficulties emerged (14). Economic uncertainties accompanying the pandemic may negatively impact the child-parent dynamic, constitute an additional stress factor, and lead to more problems in children's mental health. Studies in the literature have emphasized that economic recession is directly related to increasing child abuse (19). In addition to forensic and medical pro-

cedures, the first steps taken in CAC are to carry out interventions to protect the child when necessary (health, care, and social examination, etc., which are foreseen to be implemented by Article 5 of the Child Protection Law). In this context, our findings suggest that the decrease in the number of social examinations and the number of children taken into institutional care during the pandemic period suggests that children with high familial risk factors have difficulties in accessing services.

Another finding of our study was that the individuals reporting the CSA events were different between the groups. While there was an increase in family reports and self-reports by children, there was a decrease in reports made by teachers and governmental employees. Social isolation, broken families, domestic violence, economic difficulties, and isolated families are reported as risk factors that facilitate child abuse (20,21). Negative familial factors may constitute a heightened risk for abuse, and family support may be a factor that facilitates disclosure of CSA events. Spending more time with parents and increased intra-familial interaction may facilitate the disclosure of abuse. Although the underlying factor cannot be predicted, in cases where there were not enough support resources, children preferred to report their own abuse in order to stop their abuse during the quarantine period. Consistent with our findings, other studies conducted during the pandemic reported a decrease in the declaration and reporting of abuse through official channels (5,22). In a study by Katz and colleagues, the researcher examined eight developed and eight developing countries worldwide. The decline in reports through school was emphasized, and it was argued that schools play a crucial role in detecting and revealing neglect (23). It can be said that the disruption of formal education and the transition to online education systems during the pandemic also affected the role of individuals reporting abuse. Moreover, the decrease in the rate of abuse reported by teachers has led to an increase in reporting by parents and the children themselves during the pandemic.

Regarding the type of CSA (face to face - non-penetrating contact/penetration with/no contact), no significant difference was observed for both periods ($p>0,05$), while online (social media, phone, internet, etc.) abuse increased significantly during the pandemic period ($p<0.05$). During the pandemic, as in most countries, students had to use digital platforms to attend classes at home and continue their education (24). This has indirectly led to an increase in the use of social media (10). U-Report's international research found that 47% of respondents in their study under the age of 19 reported increased negative experiences experienced through online platforms (exposure to inappropriate content, cyberbullying, hate speech, harassment, and unwanted contact) due to increased screen time during the COVID period (25). One study found that almost half of the online abuse participants experienced it for the first time during quarantine (9). Our findings led us to consider increased internet use as a risk factor that increases the child's vulnerability to online sexual abuse victimization. In addition, considering that children continue to use social media for various purposes in the process of adapting to everyday life today, it can be assumed that the effect of digital platforms on CSA characteristics will be permanent.

It was found that there was no significant change in the level of closeness of the abuser, both groups had similar characteristics, and the majority of the abusers were familiar people other than relatives such as lovers, friends, and neighbors. However, it was determined that the repetitive nature of the abuse caused a significant change in both the reporting process and the intimacy level of the abuser. Accordingly, it was observed that the notification period was earlier (between 1-7 days) during the pandemic period. Considering that most of the reporting individuals were family members, it can be said that the pandemic period enabled early recognition of abuse symptoms by parents at home.

Regarding the level of closeness of the abuser in repeated abuse events, it was found that the abuse perpetrated by relatives living in the same house during the pandemic period changed significantly ($p<0.001$) and increased almost two-fold compared to the pre-pandemic situation. This finding may show that the perpetrators in abuse cases shifted from strangers to acquaintances because of the pandemic, which creates a vital risk environment for recurrent abuse. In the study conducted during the pandemic period, it was stated that the majority of people in the household were the perpetrators of sexual abuse (7). In the pandemic, sharing the same house with the abuser, more time spent with the abuser, staying away from the teachers who play an active role in identifying sexual abuse, or limited contact with people who can be reached outside the family have been evaluated as factors that increase the risk of repeated abuse.

The study is limited to 506 cases. The study was planned and completed in a single center due to the pandemic period we were in, which is considered one of the limitations of the study. On the other hand, since it was a retrospective file review, no psychiatric diagnostic scale form could be used on the victims.

CONCLUSIONS

Our study showed that there was a significant decrease in child sexual abuse reported by teachers and public officials during the quarantine period. For this reason, educators can organize awareness-raising training on sexual abuse for children attending school. Furthermore, public institutions with which children interact, such as education

and health, can provide risk assessments for child abuse. Children at risk can be observed more closely and protective measures can be taken. The increasing sexual abuse of children and adolescents through social media was another result. In this regard, safe internet use training can be given to children and parents. In addition, it is recommended to provide appropriate social media access and follow-up by families according to the developmental period of the children.

Ethics Committee Approval: This study was approved by Sakarya University Medical Faculty Ethical Committee (Date: 29.05.2021, No: 302).

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THE EVALUATION OF TELEHEALTH SERVICES DURING THE COVID-19 PANDEMIC ON LEVELS OF PSYCHOLOGICAL GROWTH

COVID-19 PANDEMİSİ SIRASINDA SUNULAN TELESAĞLIK HİZMETİNİN PSİKOLOJİK GELİŞİM DÜZEYLERİ ÜZERİNE DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: The COVID-19 pandemic is considered a traumatic event. The aim of this study was to examine the effects of telehealth services offered at the Istanbul University, Istanbul Faculty of Medicine to health workers with presumed COVID-19 or close contact with a suspected/confirmed COVID-19 patient on pandemic management, vaccination, and psychological growth at one year after diagnosis.

Materials and Methods: The cohort study included 237 employees with COVID-19/risky contact who were monitored remotely via a telehealth service provided between April 6 and July 31, 2020. First, they were followed up for 21 days with the telehealth service. Second, they were invited by phone to complete an online questionnaire and 94 (39.7%) of them participated. The questionnaire included questions about pandemic-related difficulties experienced during the last year and the Posttraumatic Growth Inventory (PTGI).

Results: Of the 234 employees, 172 (73.5%) and 164 (70.1%) had the first and second doses of the COVID-19 vaccine, re-

ÖZET

Amaç: COVID-19 pandemisi travmatik bir olay olarak kabul edilmektedir. Bu çalışmanın amacı, İstanbul Tıp Fakültesi'nde COVID-19 olduğu varsayılan veya şüpheli/doğrulanmış bir COVID-19 hastası ile yakın temasta bulunan sağlık çalışanlarına sunulan telesağlık hizmetlerinin tanıdan bir yıl sonra pandemi yönetimi, aşılama ve psikolojik gelişim üzerine etkilerini incelemektir.

Gereç ve Yöntem: Kohort tipindeki bu çalışmada, 6 Nisan-31 Temmuz 2020 tarihleri arasında telesağlık hizmeti ile uzaktan izlenen COVID-19/riskli temaslı 237 çalışan dahil edildi. İlk olarak telesağlık hizmeti ile 21 gün boyunca takip edildiler. İkinci olarak, bir yıl sonra çevrimiçi bir anketi doldurmaları için telefonla arandılar. Katılımcıların 94'ü (%39,7) anketi doldurdu. Anket, son bir yılda yaşanan pandemi ile ilgili zorluklar ve Travma Sonrası Büyüme Envanteri (PTGI) ile ilgili soruları içeriyordu.

Bulgular: Çalışmada 234 çalışandan 172'si (%73,5) ve 164'ü (%70,1) sırasıyla birinci ve ikinci doz COVID-19 aşısı yaptırdı. Psikolojik desteğe ihtiyaç duymayan çalışanların benlik algısı ve

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spectively. Employees who did not need psychological support had significantly lower PTGI change in self-perception and total scores than those who did not/could not receive psychological support (p=0.007 and p=0.016, respectively). Employees who used personal protective equipment (PPE) more carefully had a significantly higher PTGI self-perception score (p=0.005), life philosophy (p=0.014), interpersonal relationships (p=0.011), and total score (p=0.004) than employees who reported that they did not change how they use PPE and were sometimes careless.

Conclusion: The results of our study suggest that health workers are showing evidence of posttraumatic growth by seeing the positives as well as the negatives caused by the pandemic.

Keywords: Cohort, COVID-19, psychological growth, telehealth service, vaccination

toplam puanlarındaki PTGI değişimi, psikolojik destek almayan/alamayanlara göre anlamlı derecede daha düşüktü (sırasıyla p=0,007 ve p=0,016). Kişisel koruyucu ekipmanı (KKD) daha dikkatli kullanan çalışanların KKD kullanma şeklini değiştirmediklerini ve bazen dikkatsiz olduklarını bildiren çalışanlara göre; PTGI benlik algısı puanı (p=0,005), yaşam felsefesi (p=0,014), kişilerarası ilişkiler (p=0,011) ve toplam puanı (p=0,004) anlamlı olarak daha yüksekti.

Sonuç: Çalışmamızın sonuçları, sağlık çalışanlarının pandeminin neden olduğu olumsuzlukların yanı sıra olumlu yönlerini de görerek, travma sonrası büyümenin gerçekleştiğini ortaya koymaktadır.

Anahtar Kelimeler: Kohort, COVID-19, psikolojik büyüme, telesağlık hizmeti, aşılama

INTRODUCTION

Due to the rapid spread of the COVID-19 worldwide, millions of people were forced to stay home to prevent its spread (1). In contrast, health workers had to be on the frontlines. The Occupational Health and Safety Administration (OSHA) declared that health workers fall in the group of high and very high-risk jobs during the COVID-19 pandemic (2,3). The adversities brought about by the COVID-19 pandemic have also led to a mental health pandemic. Therefore, as with all pandemics, the COVID-19 pandemic is considered a traumatic event (4).

Many people who have a traumatic experience or witness such an event can later develop problems severe enough to be classified as a psychological disorder (4,5). On the other hand, the alternative understanding that trauma brings about positive development and maturity in some individuals is defined as the concept of posttraumatic psychological growth (6,7). Health workers can also experience posttraumatic growth by saving lives and healing their patients (8).

Telehealth services, which are used as a tool to help provide healthcare without the need for face-to-face contact, became more important during the pandemic due to the transmission and virulence characteristics of SARS-CoV-2 (9-11). This service ensures continuity of medical care and provides psychological support, ensures that people are informed and educated during the interviews, and promotes adherence to treatment and isolation rules (9,10,12).

Although there are many studies evaluating health workers in the COVID-19 pandemic, none has presented long-term follow-up findings and evaluated the effects of the pandemic on psychological growth. The aim of this study was to examine the effects of telehealth services offered at the Istanbul University, Istanbul Faculty of Medicine (IFM) to health workers with presumed COVID-19 or close contact with a suspected/confirmed COVID-19 patient on pandemic management, vaccination, and psychological growth at one year after diagnosis.

MATERIAL and METHODS

The population of this cohort study consists of 237 employees who were diagnosed with COVID-19 and monitored from home or had close contact with a suspected/confirmed patient and received telehealth service provided by the Workplace and Employee Health Outpatient Clinic (WEHOC) of the IFM Department of Public Health between April 6 and July 31, 2020.

Inclusion criteria included being employed in the IFM, being 18 years of age or older, having contact with a patient with suspected or confirmed COVID-19 or being diagnosed with COVID-19, and being managed from home (Figure 1).

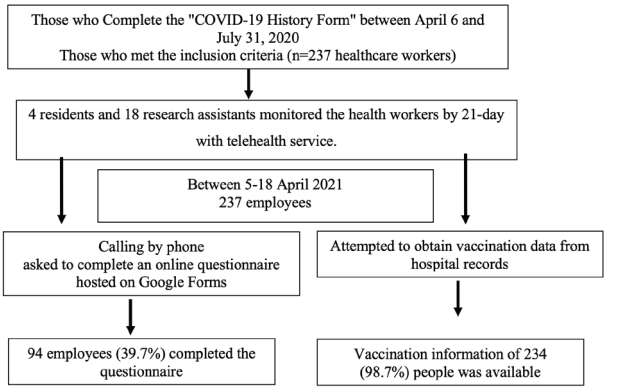

Figure 1. Flow chart of the study

In the first stage of the study, the Chief Physician sent an official letter to all departments asking IFM employees with a confirmed COVID-19 diagnosis who were monitored from home and those with close contact with a

suspected/confirmed patient to complete a COVID-19 History Form. When the IFM employee completes this form online and clicks the "send" button, a copy of the form is sent to their e-mail address and another is sent to the WEHOC institutional e-mail address. As soon as the form reached WEHOC, the IFM employees were contacted by calling the phone number given on their form from a landline phone and a 21-day remote monitoring process was initiated after obtaining their verbal consent. The remote monitoring form included questions about the participant's descriptive and contact information, profession and department, pregnancy status if applicable, COVID-19 contact history, presence of risk factors, regularly used medications, daily symptoms, and compliance with isolation rules. Patients were identified using the case definitions and case management in the "COVID-19 (SARS-CoV-2 infection) Guide" dated March 23, 2020 from the Ministry of Health General Directorate of Public Health (13).

In the second stage of the study, the 237 employees being monitored were contacted by phone between April 5 and 18, 2021 and asked to complete an online questionnaire hosted on Google Forms. Of these, 94 employees (39.7%) completed the questionnaire, which included items about the difficulties experienced during the last year of the pandemic, any loss experienced during this period, the need for psychological support, changes in their use of personal protective equipment (PPE), and the Posttraumatic Growth Inventory (PTGI). Relatives who died due to the pandemic were classified according to their relationship to the health worker as first-degree, second-degree, third-degree, and fourth-degree (14).

The PTGI was developed to measure perceived psychological growth after traumatic experiences (15). It includes 21 items rated on a 6-point Likert-type scale (0-5) and yields a total score ranging from 0 to 105. Items 5, 10-13, 15-19 assess changes in self-perception; items 1-4, 7, 14 assess changes in life philosophy; and items 6, 8, 9, 20, 21 assess changes in relationships with others. Higher scores indicate greater post-traumatic growth. The original form of the tool has five subscales. Cronbach's α coefficients of internal consistency were 0.90 for the 21-item scale and ranged from 0.77 to 0.92 for the subscales. In the Turkish validity and reliability study conducted by Kağan et al., the tool was found to be valid and reliable (16).

In addition, in the second stage of the study, we attempted to obtain vaccination data for the 237 monitored employees from hospital records. Of the 234 employees (98.7%) whose records were available, the first and second doses of COVID-19 vaccine, seasonal influenza vaccine before and during the pandemic, and pneumococcal-13 vaccine were examined.

Approval to conduct this study was obtained from the Ministry of Health, and the IFM Clinical Research Ethics Committee (Date: 17.07.2020, No: 18).

Statistical analysis

Data were evaluated using SPSS version 21.0 package software (IBM Corp, ARMONK, NY). The Kolmogorov-Smirnov test was used to determine whether numerical data were normally distributed. The non-normally distributed variables of age and Post-Traumatic Growth Inventory score also showed normal distribution after transformation to log10 base. The Chi-square test, Mann-Whitney U test, and Kruskal-Wallis test were used in the statistical analysis of the data. The level of statistical significance was accepted as $p<0.05$, with $p<0.017$ considered statistically significant if Bonferroni correction was applied.

RESULTS

The median age of the participants was 35.0 (20.0–65.0) years. After the 21-day follow-up period, 70 employees with confirmed COVID-19 diagnoses fully recovered and returned to work; 67 of those (95.7%) were called to the IFM COVID-19 Follow-up Outpatient Clinic and were placed under long-term follow-up. The sociodemographic characteristics of the employees are presented in Table 1. Neither the health workers themselves nor anyone in their households had a history of travel abroad within 14 days before presentation.

Risky contact was reported by 200 IFM employees (84.4%) at presentation, of which 53 employees (26.2%) had very close contact. Contact occurred most frequently in the Oncology Institute (n=29) and in the neonatal intensive care unit (n=24), followed by the gynecology and obstetrics (n=19), urology (n=18), COVID-19 ward (n=14), and pharmacy (n=10) departments. Although contact was most commonly with patients (n=139, 58.7%), contact with colleagues was reported by 37 employees (15.6%) and with relatives, spouses, and children by 24 employees (10.1%). Another 37 employees (15.6%) did not know who they had contacted.

The distribution of symptoms according to the day of follow-up is presented in Figure 2 and the distribution of compliance with isolation rules is presented in Figure 3.

At final follow-up on day 21, symptoms were completely resolved in 211 (89.0%) of the participants. Comparison of patients with complete recovery and those with persistent symptoms at final follow-up revealed that 33.3% of patients with Hashimoto thyroiditis and 40.0% of those with any cancer diagnosis had persistent symptoms (Table 2).

Table 1. Distribution of socio-demographic characteristics of IFM employees

Socio-demographic characteristics	Number (n=237)	%*
Gender		
Female	153	64.6
Male	84	35.4
Marital status		
Married	143	60.3
Single	94	39.7
Age groups (years)		
≤30	75	31.6
31-50	141	59.5
≥51	21	8.9
Profession		
Nurse	88	37.1
Doctor	59	24.9
Nursing staff, cleaning staff	46	19.4
Technician	16	6.8
Registration staff	10	4.2
Administrative staff	8	3.4
Pharmacist journeyman	4	1.7
Security guard	3	1.3
Other**	3	1.3
PCR result		
Negative	124	52.3
Positive	44	18.6
Not performed***	69	29.1
BT result		
No pathology (normal)	56	23.6
COVID-19 compatible	47	19.8
Not performed	134	56.6
PCR and/or CT results positive comorbidity	70	29.5
0	150	63.3
1	69	29.1
≥ 2	18	7.6
Patient follow-up status		
Working	152	64.1
Home isolation	82	34.6
Home isolation after hospitalization	3	1.3

*: column percentages, **: Midwife, pharmacist, ***: Among those who applied after a positive case of COVID-19 in their department, those who did not have any symptoms

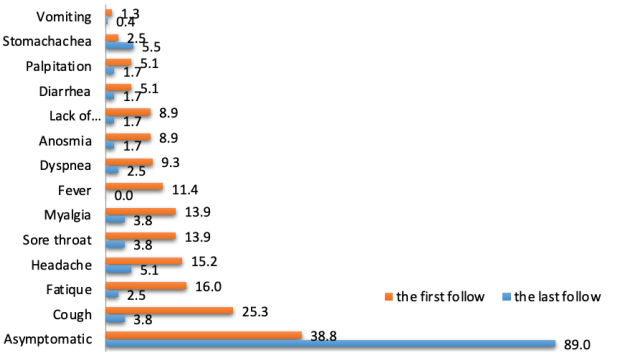

Figure 2. The distribution of symptoms according to the day of follow-up

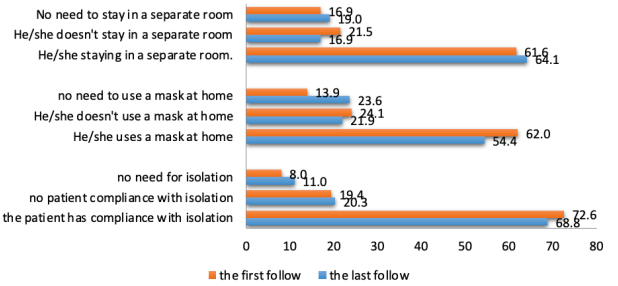

Figure 3. The distribution of compliance with isolation rules

Vaccination status could be determined for 234 of the employees. Of these, 172 (73.5%) had received the first dose of COVID-19 vaccine, 164 (70.1%) had received the second dose of COVID-19 vaccine, and 7 (3.0%) had received the pneumococcal-13 conjugate vaccine. Seasonal flu vaccination was documented in 10 employees (4.3%) before the pandemic, 41 employees (17.5%) during the pandemic, and 5 (2.1%) in both periods. The rate of seasonal influenza vaccination increased significantly during the pandemic period (χ^2=7.625; p=0.006).

After one year, a total of 94 employees (39.7%) completed the online survey. Sixty (63.8%) of the respondents were women, their median age was 36 (20-65) years, and they did not differ significantly from the population in terms of gender or age (p>0.05). Seventy (74.5%) of the participants stated that they had difficulty during the last year due to the COVID-19 pandemic, and none of them had COVID-19 again during that time. The most commonly reported problems are shown in Table 3.

Twenty-eight employees (29.8%) expressed the need for psychological support in the last year; of these, 9 (9.6%) said that they received psychological support, while 19 (20.2%) stated that they did not/could not get support even though they needed it. Barriers to getting psychological support cited in the latter group included not hav-

Table 2. Factors affecting IFM employees' persistence of symptom

		No symptoms at last follow-up (n=211)		There are symptoms at the last follow-up (n=26)		
		Number	%*	Number	%*	χ2, p
Age (year±SD) **		36.9±9.8		38.8±9.1		0.337
Gender (n,%)						
Female		135	88.2	18	11.8	0.597
Male		76	90.5	8	9.5	
Number of comorbidity						
0		137	91.3	13	8.7	
1		59	85.5	10	14.5	0.289
≥2		15	83.3	3	16.7	
Type of comorbidity (n,%)						
Smoking	Yes	38	90.5	4	9.5	0.741
	No	173	88.7	22	11.3	
Cardiovascular diseases	Yes	14	93.3	1	6.7	0.582
	No	197	88.7	25	11.3	
Respiratory	Yes	12	100.0	0	0.0	0.212
	No	199	88.4	26	11.6	
Hypertension	Yes	10	76.9	3	23.1	0.151
	No	201	89.7	23	10.3	
Hashimoto thyroid, hypothyroidism	Yes	8	66.7	4	33.3	**6.4721; 0.011**
	No	203	90.2	22	9.8	
Diabetes	Yes	4	80.0	1	20.0	0.514
	No	207	89.2	25	10.8	
Cancer	Yes	3	60.0	2	40.0	**4.4071; 0.036**
	No	208	89.7	24	10.3	
PCR result ***						
Negative		110	90.2	12	9.8	**7.9496; 0.005**
Positive		32	72.1	12	27.9	

*: Row percentage, **: Student t test, ***: PCR was not performed on 69 employees, only symptom follow-up was performed for 21 days, P values were obtained by Chi-square test.

Table 3. The most commonly reported problems during the one-year COVID-19 process

Conditions	Number (n=70)	%
Working conditions	47	67.1
Inability to support parents	31	44.3
Someone in the family has COVID19	22	31.4
Losses due to COVID-19	22	31.4
Not being with your spouse or children	20	28.6
Other *	5	7.1

* Restriction of social life, perception of health workers as a potential risk, anxiety of infecting others

ing time (n=7, 36.8%), thinking they would overcome the problem on their own (n=4, 21.1%), having a busy work schedule (n=2, 10.5%), believing the problem would resolve by itself (n=2, 10.5%), financial reasons (n=2, 10.5%), the relevant departments being closed at the start of the pandemic (n=1, 5.3%), and attempting to cope with prayer (n=1, 5.3%).

In the PTGI, the participants' median total score was 62.5 (21.0–126.0) and subscale scores were 30.5 (10.0–60.0) for change in self-perception, 19.0 (6.0–36.0) for change in life philosophy, and 13.0 (5.0–30.0) points for change in relationships with others. Comparisons of scale scores according to selected variables are shown in Table 4.

Table 4. Comparisons of scale scores according to selected variables

	Self-perception score	Life philosophy score	Interpersonal relations score	Total scale score
Gender				
Female (n=60)	33.0 (10.0-60.0)	20.0 (6.0-33.0)	13.0 (5.0-30.0)	65.5 (21.0-122.0)
Male (n=34)	26.5 (10.0-60.0)	16.5 (8.0-36.0)	10.0 (5.0-30.0)	54.0 (23.0-126.0)
p	0.073	0.058	0.098	0.059
Marital status				
Married (n=54)	29.0 (10.0-60.0)	18.0 (6.0-36.0)	12.0 (5.0-30.0)	61.0 (21.0-126.0)
Single (n=40)	33.5 (10.0-60.0)	19.5 (8.0-32.0)	14.0 (5.0-30.0)	65.0 (23.0-122.0)
p	0.320	0.448	0.263	0.242
Managing the COVID-19 process				
Forced (n=24)	29.0 (10.0-60.0)	16.0 (6.0-36.0)	10.0 (5.0-30.0)	60.0 (21.0-126.0)
Unforced (n=70)	30.5 (10.0-60.0)	19.0 (7.0-33.0)	13.0 (5.0-30.0)	63.0 (23.0-122.0)
p	0.765	0.236	0.255	0.469
Psychological support during the COVID-19 process				
Not needing (n=66)	27.5 (10.0-60.0)[1]	17.0 (6.0-36.0)	12.5 (5.0-30.0)	58.5[2] (21.0-126.0)
Receiving psychological support (n=9)	33.0 (20.0-48.0)	20.0 (8.0-24.0)	16.0 (7.0-21.0)	66.0 (35.0-85.0)
Not receiving/ unable to receive psychological support (n=19)	39.0 (15.0-60.0)[1]	22.0 (11.0-33.0)	13.0 (5.0-30.0)	76.0 (31.0-122.0)[2]
p	**0.015**	0.076	0.341	**0.041**
Change in PPE use case				
There has been no change, he always uses it carefully (n=40)	30.0 (10.0-60.0)	20.0 (8.0-36.0)	13.0 (5.0-30.0)	62.5 (26.0-126.0)
There has been no change, sometimes it can be careless (n=22)	23.5 (10.0-53.0)[3]	15.0 (8.0-26.0)[4]	10.5 (5.0-22.0)[5]	50.0 (23.0-101.0)[6]
He/She uses it more carefully (n=32)	38.5 (10.0-60.0)[3]	21.0 (6.0-32.0)[4]	14.0 (5.0-30.0)[5]	74.0 (21.0-122.0)[6]
p	**0.017**	**0.026**	**0.037**	**0.012**
1st dose of COVID-19 vaccine				
Yes (n=74)	30.5 (10.0-60.0)	20.0 (6.0-32.0)	13.0 (5.0-30.0)	63.0 (21.0-122.0)
No (n=20)	31.5 (10.0-60.0)	15.0 (8.0-36.0)	12.0 (5.0-30.0)	62.0 (23.0-126.0)
p	0.982	0.122	0.753	0.641
2nd dose of COVID-19 vaccine				
Yes (n=73)	30.0 (10.0-59.0)	20.0 (6.0-31.0)	13.0 (5.0-30.0)	63.0 (21.0-120.0)
No (n=21)	33.0 (10.0-60.0)	15,0 (8.0-36.0)	13.0 (5.0-30.0)	62.0 (23.0-126.0)
p	0.660	0.266	0.917	0.964

1, 2, 3, 4, 5, 6: statistically significant groups. . Values are expressed as median (range).

DISCUSSION

Worldwide, both diagnosis and treatment were complicated processes at the start of the COVID-19 pandemic. The gold standard for the diagnosis of SARS-CoV-2 is real-time polymerase chain reaction (RT-PCR) testing of nasopharyngeal swab samples, in clinical practice the reported sensitivity of this test has varied between 42% and 83% due to numerous factors related to symptom duration, viral load, and test sample quality (17). In

cases of COVID-19 infection, case management in line with clinical, radiological, and other laboratory findings is recommended for these patients (18). In this study, RT-PCR was performed first and computed tomography (CT) was performed in case of uncertainty. According to the RT-PCR results, 18.6% of the patients were diagnosed as confirmed COVID-19, 52.3% as not having COVID-19, and 11.4% as suspected COVID-19. When RT-PCR and/or CT were performed, the definitive diagnosis rate increased to 29.5%.

People with chronic health problems and current smokers are not only at high risk of developing clinically severe COVID-19, but also are at a higher risk of death (19,20). In this study, 33.7% of the patients had at least one comorbid condition. In a meta-analysis study examining comorbidities in COVID-19 patients in a similar age group, the most common comorbidities in 1,786 patients with a mean age of 41 years were hypertension, cardiovascular disease, and cerebrovascular diseases (21). Especially for health workers with chronic diseases, receiving diligent and attentive telehealth service and monitoring their symptoms during this follow-up process may have had a positive impact on their quality of life and coping with the disease.

Health professionals are at risk of encountering many asymptomatic infected individuals during their routine daily work. In the present study, 15.6% of the employees could not identify anyone as a contact. The most frequently reported contact was with patients (58.7%) and colleagues (15.6%), indicating that half of the employees contracted COVID-19 after contact with their patients. Moreover, 26.2% of the employees had very close contact according to the Ministry of Health criteria. This finding increases the importance of PPE use.

When we evaluated PPE use at the 1-year follow-up, 42.6% of the employees stated that there was no change and they always used PPE carefully, 23.4% stated that there was no change and they were sometimes careless about using PPE, and 34.0% stated that they used PPE more carefully since the pandemic. As the early symptoms of COVID-19 are nonspecific, it is not always possible to identify infected individuals, and standard infection measures should be applied consistently and correctly when caring for patients (22). We also determined that 15.6% of the cases in this study were diagnosed after contact with infected colleagues. This finding once again demonstrates the importance of appropriate PPE use in the workplace and compliance with standard infection prevention rules. This is also important in terms of maintaining workplace health and safety and adequate staffing.

Although the COVID-19 patients under home follow-up were health professionals, they were still reminded during phone calls of the importance of isolation measures that should be applied at home. Despite all reminders, only 38.4% of them were in separate rooms at the first follow-up and 35.9% at final follow-up; 38.0% used masks at home at the first follow-up and 45.6% at final follow-up; and 27.4% were having difficulty adapting to isolation at the first follow-up and 31.2% at final follow-up. This shows that noncompliance with infection prevention rules in the workplace continues at home. For health professionals working in real high-risk settings, the perception of infection risk may change after long working hours. A study conducted among health workers in China showed that those working at risk had lower infection anxiety (23).

COVID-19 has a wide range of symptoms and can be confused with many diseases with similar symptomatology (24). The health workers in this study most frequently presented with cough (25.3%), fatigue (16.0%), and headache (15.2%). Fever at disease onset was detected in 11.4% of cases. Similar to the results of a systematic review, a third of the COVID-19 patients in our study were asymptomatic (25). People who are asymptomatic, have atypical symptoms, and some COVID-19 patients without fever pose a risk of transmitting the disease to patients, other health workers, and the community (24). From this point of view, the protection of health workers and early diagnosis of those who are infected are vital in controlling the pandemic.

In this study, 11.0% of the patients reported persistent symptoms at the final follow-up on day 21. The most commonly reported symptoms were stomachache (5.5%) and headache (5.1%). Stomachache is a less expected symptom and its persistence is a notable finding. When we compared patients with persistent symptoms and those with complete resolution at the last follow-up, we found that persistence was significantly associated with Hashimoto thyroiditis, any cancer diagnosis, and positive RT-PCR test at disease onset. Studies show that many people with COVID-19, especially those with comorbid conditions, do not recover to their previous level of health in the long term. According to a nationally representative study by the UK Office for National Statistics, approximately 1 in 10 patients with a positive COVID-19 test result was reported to have persistence of symptoms for 12 weeks or more (26). There is still much uncertainty regarding how COVID-19 affects people over time and the impact of comorbid diseases on "long COVID."

The pandemic has further increased the importance of vaccination and of the cohort in our study, 73.5% of the employees had received the first dose and 70.1% had received the second dose of COVID-19 vaccine at one year. When evaluated according to first dose, the vaccination rate can be considered good. In a systematic review presenting an updated evaluation of COVID-19 vaccine acceptance rates based on an analysis of eight

studies, COVID-19 vaccine acceptance rates were reported to be below 60% on average, with the highest rate among doctors in Israel (78.1%) and the lowest rate among healthcare workers in the Democratic Republic of Congo (27.7%) (28). The rate of pneumococcal vaccination, which is among the routine vaccination recommendations for health workers, was only 3% among the employees in our study, suggesting a serious problem in terms of adult immunization. Although the participants' rate of seasonal influenza vaccination increased significantly during the pandemic, it is still not sufficient. We believe that interventions should be implemented to support this.

As in previous pandemics, health workers have a high risk of psychological effects associated with the COVID-19 pandemic. Health workers' exposure to COVID-19 patients in their centers, being sick and quarantined, fear of infecting themselves and their relatives, and witnessing the death of their patients, relatives, or friends results in the perception of personal danger that increased with the lethality of the virus. In addition, conditions such as sudden rises in in-patient admissions and increased workload, insufficient protection against contamination, and a negative institutional culture can also cause difficulties for health workers. All of these adversities can impair the psychological health of health workers, causing problems that may continue in both the short and long term (29,30). In this study, three quarters of the participants said they had difficulty during the last year due to the pandemic, mostly related to working conditions (67.1%). One in three employees experienced loss during the pandemic period, with 95.5% of those employees saying that losing their patients was difficult for them. These two findings support each other.

Pandemics can trigger generalized mental disorders, including anxiety and depressive disorders, and posttraumatic stress disorder requiring psychological intervention in health workers. However, further research is needed to better assess the short- and long-term psychological consequences of pandemics on healthcare workers and to minimize their impact (26).

One-third of the employees in our study reported needing psychological support during the pandemic. However, a fifth of those who needed psychological support stated that they did not or could not receive support despite being a health worker themselves. In order of frequency, the reasons cited for not getting support were lack of time, thinking they would overcome the problem on their own, heavy work schedule, thinking the problem would go away by itself, financial limitations, closure of the relevant departments at the start of the pandemic, and trying to cope through prayer. This shows that as with vaccination and PPE use, there is a need to support health workers in seeking psychological support and for intervention programs to support and empower the right people for this. As stated by the The Lancet Global Health and Kang et al., providing psychological support using face-to-face or printed resources can also help in this regard (23,31,32).

In studies conducted in other pandemics, it is stated that one-third of those affected in the long term may have permanent psychological problems, develop a tendency toward higher risk behaviors, and encounter problems while leading their daily lives (33). When faced with life-threatening events, people seem to reassess their goals and priorities, perceive improved social relationships, and appreciate life more. These changes, called posttraumatic growth, include greater psychological well-being and correspond to higher functioning in certain areas after trauma. Although many studies have investigated the negative consequences of COVID-19 on mental health, very little is known about the potential positive psychological effects of the pandemic and whether it can induce posttraumatic growth (23,33).

The results of our study suggest that health workers are showing evidence of posttraumatic growth by seeing the positives as well as the negatives caused by the pandemic. Growth is not caused by the event itself, but by the way the event is handled, leading the person to re-evaluate their personal priorities. It promotes growth in three areas: self-perception, interpersonal relationships, and life philosophy (23). In this study, we observed that the self-perception and total scale scores were significantly higher in participants who did not or could not receive the psychological support they needed during the COVID-19 pandemic when compared with those who reported not needing psychological support at all. This finding suggests that those who do not receive psychological support despite feeling the need for it emerge from the pandemic by improving themselves. Similarly, it was found that those who used PPE more carefully had higher self-perception, life philosophy, interpersonal relationships, and total PTGI scores. These last two findings also indicate that individuals with high awareness can emerge from traumatic situations such as pandemics by improving themselves. Evidence suggests that people of all ages who experience various types of traumas can identify positive ways to change their lives and that these changes are associated with improved mental health and well-being. In fact, studies have determined that half of those who experience trauma show some degree of posttraumatic growth (24). Our findings demonstrate the efforts toward areas of posttraumatic growth such as building relationships with others, greater appreciation of life, discovering and embracing new possibilities, and positive mental change. However, further studies with longer follow-up

are needed to confirm these findings, predict who may experience these changes, and determine whether these changes will persist in the future.

This study has some limitations; The most important limitation is the small number of participants who completed the online questionnaire on Google Forms. Therefore, the results cannot be generalized. The second is the lack of randomization in reaching the sample, and the results of a single-center study can not be applied to the general population.

CONCLUSION

The results of this cohort study show that health workers, like other members of the community, had some difficulties obtaining an accurate diagnosis and receiving psychological support at the beginning of the pandemic. Psychological problems due to various stressors are inevitable during and after the pandemic. To overcome these problems, protective community mental health services should be given priority.

It is a remarkable and important finding that the health workers in our study supported COVID-19 vaccination and had a high vaccination rate. However, in terms of other vaccinations, PPE use, and seeking psychological support when necessary, this study revealed an unexpected lack of self-protective behavior and even disregard for risks. These issues are relevant both in routine practice and emergencies such as the COVID-19 pandemic and should be addressed through in-service training programs.

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SEPSIS DUE TO *LISTERIA MONOCYTOGENES* IN AN IMMUNOCOMPROMISED PATIENT WITH PERITONEAL CARCINOMATOSIS: A CASE REPORT

BAĞIŞIKLIĞI BASKILANMIŞ, PERİTONEAL KARSİNOMATOZİSLİ BİR HASTADA *LISTERIA MONOCYTOGENES*'E BAĞLI SEPSİS: OLGU SUNUMU

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ABSTRACT

Listeria monocytogenes is an opportunistic infectious agent that can cause self-limiting gastroenteritis in immunocompetent individuals, usually with the consumption of contaminated foods, and fatal infections in immunocompromised individuals and newborns. Local effects of intra-abdominal tumors, immune response suppression, and operations that disrupt the integrity of the peritoneal membrane and gastrointestinal tract may increase the risk of pathogen-induced invasive infection. Although cytoreductive surgical interventions, systemic and/or hyperthermic intraperitoneal chemotherapy (HIPEC) applied in the treatment of patients with abdominal and pelvic malignancies increase disease-free survival, they may predispose to infections caused by *L. monocytogenes* through gastrointestinal and systemic complications. In this case report, a 71-year-old male patient diagnosed with sepsis due to *L. monocytogenes* after treatments with systemic chemotherapy and cytoreductive surgery combined with HIPEC is discussed. It is aimed to raise clinical and laboratory awareness that *L. monocytogenes* may cause systemic and life-threatening infections in individuals whose immune system is suppressed due to cancer, surgical procedures, and the use of chemotherapeutic agents.

Keywords: Hyperthermic intraperitoneal chemotherapy, *Listeria monocytogenes*, peritoneal carcinomatosis, systemic chemotherapy, sepsis

ÖZET

Listeria monocytogenes, immünokompetan bireylerde genellikle kontamine olmuş gıdaların tüketilmesi ile kendi kendini sınırlayan gastroenterit tablosuna, immun sistemi baskılanmış bireylerde ve yenidoğanda ise ölümcül enfeksiyonlara yol açabilen fırsatçı bir enfeksiyöz ajandır. Karın içi tümörlerin lokal etkileri, immün yanıtın baskılanması, peritoneal membran ve gastrointestinal sistemin bütünlüğünü bozan operasyonlar patojen kaynaklı invaziv enfeksiyon riskinde artışa neden olabilir. Abdominal ve pelvik maligniteleri olan hastaların tedavisinde uygulanan sitoredüktif cerrahi girişimler, sistemik ve/veya hipertermik intraperitoneal kemoterapi (HİPEK) hastalıksız sağkalımı arttırmakla birlikte gastrointestinal ve sistemik komplikasyonlar yoluyla *L. monocytogenes*'in neden olduğu enfeksiyonlara zemin hazırlayabilir. Bu olgu sunumunda, sistemik kemoterapi ve sitoredüktif cerrahi ile kombine HİPEK tedavileri sonrası *L. monocytogenes*'e bağlı sepsis tanısı alan 71 yaşında bir erkek hasta tartışılmış ve *L. monocytogenes*'in kanser, cerrahi işlem ve kematerapötik ajanların kullanımı gibi sebeplerle immün sistemi baskılanmış bireylerde sistemik ve hayatı tehdit edici enfeksiyonlara neden olabileceği konusunda klinik ve laboratuvar farkındalığı yaratmak amaçlanmıştır.

Anahtar Kelimeler: Hipertermik intraperitoneal kemoterapi, *Listeria monocytogenes*, peritoneal karsinomatozis, sistemik kemoterapi, sepsis

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INTRODUCTION

Listeria monocytogenes is a Gram-positive, catalase-positive, oxidase-negative, indole-positive, motile, and non-spore-forming intracellular rod that causes foodborne outbreaks worldwide (1). It can be found in many foods such as vegetables, fruits, seafood, meat, and dairy products and is one of the leading causes of food-related mortality (2). It is the cause of foodborne gastroenteritis in immunocompetent individuals; sepsis, and meningitis in newborns; postpartum infections, meningoencephalitis, bacteremia, and sepsis in immunocompromised individuals (3). Cases of cutaneous listeriosis, bacterial endocarditis, hepatitis, liver abscess, peritonitis, biliary tract infections, and musculoskeletal infections have also been reported (4). According to somatic and flagellar antigen-based serotyping methods, four main serotypes defined as 1/2a, 1/2b, 1/2c, and 4b are responsible for most clinical cases, while serotype 4b is responsible for food-related outbreaks and sporadic diseases (5). Sporadic cases may be seen more frequently in the spring and summer with increased consumption of high-risk food products (4). Antimicrobial therapy is the only treatment option for listeriosis and the ampicillin plus gentamicin combination is the most used treatment choice. Trimethoprim/sulfamethoxazole combination can also be used as an alternative antibiotic (6). Although it is less common than other foodborne infections, listeriosis is an important public health problem in immunocompromised individuals due to its mortality rate of 30% despite appropriate antibiotic therapy (7,8). Although hyperthermic intraperitoneal chemotherapy used in peritoneal malignancies has less toxicity than systemic administration, attention should be paid to its local effects such as inflammatory reactions in the peritoneum, intraabdominal infections, bowel obstruction, and delayed wound healing (8). We present a case report of sepsis due to *L. monocytogenes* in a 71-year-old male patient who received systemic chemotherapy and cytoreductive intra-abdominal surgery combined with HIPEC for peritoneal carcinomatosis.

CASE REPORT

A 71-year-old male patient was followed up with the diagnosis of peritoneal carcinomatosis secondary to prostate cancer applied to the emergency service of Gülhane Training and Research Hospital on 03.06.2022 with complaints of weakness, inability to walk, and confusion. In his past medical history, he had a transurethral prostatectomy in 2019 and received a total of 14 cycles of chemotherapy, and in February 2022, cytoreductive surgery (CRS) and HIPEC were applied. At the time of admission, the general condition of the patient was moderate, and he was unconscious. The Glasgow coma scale score of the patient was calculated as 10. Spontaneous movements in the bilateral lower and upper extremities were observed and in ophthalmological examination pupils were normoisochoric. The patient had a fever of 38°C with no history of antibiotic use. The patient's laboratory findings were detected as follows: WBC: $1.6x10^3$ cell/mm^3 ($3.9x10^3$-$10.9x10^3$), neutrophil ratio: 91% (41-70.7), lymphocyte ratio: 2.2% (19.1-47.9), thrombocyte: $3x10^3$ cell/mm^3 ($173x10^3$-$360x10^3$), Hb: 7.4 g/dL (13,5-16,9), Hct: 21.6 % (40-49.4), urea: 137 mg/dL (17-43), creatinine: 2.67 mg/dL (0.84-1.25), CRP: 151.7 mg/L (0-5), procalcitonin: 14.3 ng/mL (0-0.65), sedimentation rate: 118 mm/h (0-20), prothrombin time: 26.3 sec (9.7-14.3), INR: 2.32 (0.8-1.2). Pancytopenia was observed according to the results of the complete blood count and peripheral smear. He was admitted to the neurosurgery intensive care unit with clinical suspicion of disseminated intravascular coagulation (DIC) and sepsis.

Blood cultures taken from the patient were inoculated into a pair of aerobic and anaerobic blood culture bottles and incubated for five days in a blood culture instrument (Zhuhai Medical Technology, China). Both aerobic and anaerobic blood cultures gave positive signals after 24 hours and were subcultured on 5% sheep blood, eosin methylene blue (EMB), and chocolate agar. ß-hemolytic colonies were observed on blood agar after 24 hours of incubation at 37°C with 5% CO_2. In Gram staining, Gram-positive rod morphology was observed. The bacterium was catalase positive, oxidase negative, and indole positive in the biochemical tests. The isolate was identified as *L. monocytogenes* using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Germany). Antibiotic susceptibility testing was determined by the disc diffusion method according to European Committee on Antimicrobial Susceptibility Testing criteria (9). The isolate was detected as susceptible to benzylpenicillin, ampicillin, erythromycin, trimethoprim-sulfamethoxazole, and meropenem. Ampicillin (2 g IV every 4 hours) and meropenem (1 g every 12 hours) were started as treatment. Despite all treatments, the patient was deceased on 12.06.2022. Informed consent was obtained from the patient.

DISCUSSION

Listeria monocytogenes are commonly found in natural environments such as soil, surface water and groundwater, sewage, and animal feeds. It has been isolated from ruminant farm animals' meat, dairy, and poultry products and from flies and ticks. *L. monocytogenes* is considered a rare but serious intracellular infectious agent, especially for neonates, elders, and immunocompromised individuals. Listeriosis is mainly occurred in humans by digesting contaminated food (10,11). Gastrointestinal adaptation is required for entrance to the host. The virulence gene that plays an important role in this adaptation is *sigma B* (10).

The pathogen has glutamate decarboxylase (GAD), arginine deaminase (ADI), and agmantine deiminase (AgDI) systems against low pH in the gastrointestinal tract (12). Tolerance to bile salts is achieved by increasing the expression of the multi-drug efflux pump so that it can colonize the liver and gallbladder (10). After colonization, it can cross the intestinal barrier in three different ways: directly, through invasion into enterocytes, or through Peyer's patches (13). Internalization occurs by binding to the extracellular domain of E-cadherin molecule in epithelial cells with the surface proteins InlB, InlC, and InlJ belonging to the internalin family (13). The listeriolysin O (LLO) toxin allows the pathogen to escape from the phagosomes. Cell-to-cell spread is achieved by actin polymerization (13,14).

Bacterial translocation is thought to be the main mechanism responsible for *L. monocytogenes* sepsis. Invasion of enteral bacteria from the epithelial mucosa of the gastrointestinal tract to the lamina propria, mesenteric lymph nodes, and other possible organs, respectively is called a bacterial translocation (15). It is known that changes in the enterobacterial flora, damaged intestinal barrier, and decreased host immunity cause bacterial translocation (15,16). Any chemotherapeutic or radiotherapeutic administration that causes loss of gastrointestinal mucosal integrity and reduces liver, spleen, and peritoneal macrophage functions may increase the risk of invasive infections (4).

Systemic chemotherapy, intra-abdominal cytoreductive surgery combined with HIPEC, damage to the peritoneal mesothelial cells, and local effects of the tumors were thought to be risk factors in the patient with *L. monocytogenes* sepsis. It is known that topical and high-concentration application of heated chemotherapeutics to the peritoneum to target microscopic tumor fragments after cytoreductive surgery may increase recovery rates in cancer patients while causing complications such as fistula, abscess, anastomotic leakage, perforation, and post-operative sepsis (17). Studies show that HIPEC administration increases the risk of infection by 43% (17). In the presented study, the risk factors mentioned above may cause mesothelial cell and gastrointestinal mucosal barrier injury, decreased intestinal motility, and impairments in local and systemic immune responses. All of these may prepare the ground for translocation and invasive infection of *L. monocytogenes*. Implementing infection control procedures and taking precautions against bacterial translocation are essential steps to prevent invasive intestinal infections in immunosuppressive patients.

According to the European Food Safety Authority (EFSA), data, 2,183 invasive *L. monocytogenes* cases (923 hospitalizations, 196 deaths) were detected in Europe in 2021. The most common cause of the exposure was reported as foodborne transmission. Samples taken from different food categories revealed that most of the foods contaminated with *L. monocytogenes* are refrigerated ready-to-eat (RTE) and meat products (3.1%) (18). In a study including fresh meat samples sold in supermarkets, butchers, and retail shops in Turkiye, the contamination rate of meats with the bacterium was found to be 12.8% (19). Ensuring food hygiene in the manufacturing or distribution stages is one of the most important steps to be taken to prevent listeriosis cases.

In Doganay's study, which included 32 cases of *L. monocytogenes* reported in Turkiye between 1987 and 2001, it was reported that the pathogen most frequently (21-43%) caused sepsis progressing to DIC in immunocompromised hosts (20). Aktaş et al. reported a case of sepsis due to *L. monocytogenes* in a 49-year-old patient diagnosed with febrile neutropenia and pleomorphic carcinoma. They observed that the infection was successfully treated after the initiation of piperacillin/tazobactam and amikacin (21). Ağuş et al. reported a case of sepsis due to *L. monocytogenes* in a 61-year-old patient who received systemic chemotherapeutics for chronic lymphocytic leukemia. Ampicillin/sulbactam and imipenem were started but the patient was deceased on the second day of hospitalization (22). Yıldız et al. conducted a retrospective study including 9 cases of listeriosis reported in Turkiye between 1991 and 2002. The remarkable feature of this study is that all patients who developed sepsis (5/9) had an underlying malignancy and a history of immunosuppressive therapy. These patients received different treatment combinations from each other, such as oral ampicillin/sulbactam, imipenem alone, and amikacin combined with penicillin or imipenem. However, the results of the study showed that different antibiotic regimens did not affect the mortality rate (23). In treatment, penicillin G or ampicillin is used as the first choice. Aminoglycosides combined with ampicillin are known to have synergistic effects. Meropenem and trimethoprim/sulfamethoxazole can be used as alternative treatment options. Multidrug-resistant *L. monocytogenes* isolates have also been reported (6,22,23). It should be kept in mind that there is high mortality despite appropriate antibiotic treatment and the risk of progression to sepsis is higher in immunocompromised patients.

In conclusion, we encountered a case of sepsis due to *L. monocytogenes* in an immunocompromised patient who received systemic chemotherapy and cytoreductive surgery combined with HIPEC for the treatment of peritoneal carcinomatosis. Serious precautions against invasive infectious agents should be taken in immunosuppressive patients receiving systemic and local chemotherapy. In addition, we conclude that awareness among clinicians and laboratories should be raised in *L. monocytogenes* which has an increasing incidence and causes fatal out-

comes in immunosuppressive patients to help advances in treatment and reduce mortality rates.

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TRIAGE AND MANAGEMENT OF MUSCULOSKELETAL INJURIES DURING EARTHQUAKE

DEPREM DURUMUNDA KAS-İSKELET YARALANMALARININ TRİYAJ VE YÖNETİMİ

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ABSTRACT

The harm of earthquakes can be decreased with operative catastrophe planning and successful emergency assistance. First aid and triage organization are essential for the medical care of those trapped under the rubble after the earthquake. Every injury seen in orthopedics and traumatology practice can be observed with being under the rubble; these can be in a spectrum ranging from simple muscle crush to pelvis fracture with vascular injury. The main function of the orthopedist is to perform a quick diagnosis and accurate treatment to save the life and extremities. The first step in the management of limb and axial skeletal injuries is accurate immobilization of the injured region, such as a cervical collar for the cervical spinal segment. Maintaining a safe airway and large-bore intravenous access for hemodynamic stabilization are also priorities in traumatized patients. Surgical procedures related to orthopedics and traumatology can be classified as follows; emergency care, emergency surgeries, delayed surgeries, and planned surgeries. While performing all these surgical procedures, a multidisciplinary approach should be applied to monitor and treat the patient's general condition.

Keywords: Disaster, trauma, crush injury, amputation, extremity salvage

ÖZET

Etkin afet planlaması ve başarılı acil durum yardımı ile depremin zararı azaltılabilir. Deprem sonrası enkaz altında kalanların tıbbi bakımı için ilk yardım ve triyaj organizasyonu şarttır. Ortopedi ve travmatoloji pratiğinde görülen her yaralanma enkaz altında kalındığında da gözlemlenebilir, bunlar basit kas ezilmesinden damar yaralanmalı pelvis kırığına kadar uzanan bir yelpazede olabilir. Ortopedistin temel işlevi, hızlı teşhis ve doğru tedaviyi yaparak hayatı ve uzuvları kurtarmaktır. Ekstremite ve aksiyal iskelet yaralanmalarının yönetiminde ilk adım yaralı bölgenin doğru şekilde immobilizasyonudur; servikal spinal segment için boyunluk gibi. Güvenli bir hava yolunun sürdürülmesi ve hemodinamik stabilizasyon için geniş çaplı intravenöz erişim de travma geçirmiş hastaların yönetiminin önceliğidir. Ortopedi ve travmatoloji ile ilgili olarak cerrahi işlemler şu şekilde sınıflandırılabilir; acil bakım, acil ameliyatlar, gecikmiş ameliyatlar ve planlı ameliyatlar. Tüm bu cerrahi işlemler yapılırken hastanın genel durumunun takibi ve tedavisi için multidisipliner bir yaklaşım uygulanmalıdır..

Anahtar Kelimeler: Afet, travma, ezilme yaralanması, amputasyon, ekstremite kurtarma

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INTRODUCTION

Earthquakes have caused major morbidity and mortality in earthquake-prone countries worldwide (1). When we investigated the past decade, we encountered a series of dire earthquakes in Turkiye [(Muradiye/Van (1976); Gölcük/Kocaeli (1999) and Pazarcık/Kahramanmaraş (2023)]. Numerous researchers have estimated that the next earthquake is likely to happen in Istanbul, Turkiye's most populous city (2). Turkiye has suffered a recent devastating earthquake, therefore revisiting the literature and reviewing the practical approach may be useful for clinicians. Because an earthquake is a natural disaster, it is impossible to predict and prevent it with current technology. Nonetheless, the harm of earthquakes can be decreased with operative catastrophe planning and successful emergency assistance (3, 4). It is a major challenge for medical systems, especially when destruction is massive in large-scale earthquakes. One of the ways to overcome this challenge is to examine the practices made at the time of previous disasters together with their missing and faulty aspects (5, 6). For this reason, comprehensive evaluations should be made about the causes, characteristics, and treatment of injuries after each earthquake disaster.

Triage of patients

First aid and triage organization are essential for the medical care of those trapped under the rubble after an earthquake. The first step after an earthquake is the rescue of those who are under the rubble. Rescued patients should be transported quickly to safe areas for further management. Kuwagata et al. reported an analysis of the Hanshin-Awaji earthquake, which included 2702 traumatized patients (7). In that population, one-third of the patients were treated in hospitals surrounding the area and had a mortality rate of 3%. The remaining patients were treated in the hospitals affected by the earthquake and faced a higher mortality rate of 8%. Patients should be evaluated by general surgeons, orthopedists, anesthesiologists, and internal medicine physicians as soon as they reach the health center. Orthopedic surgeons play a central role in the care provided to the patients trapped under the rubble because injuries in which patients have survived are mostly orthopedic. Kanchan et al. investigated an epidemiological outcome after the Nepal earthquake in 2015 (8). In that study, they reported on a series of 238 patients, the majority of which were related to orthopedic surgical procedures (77.7%).

Surgical procedures related to orthopedics and traumatology can be classified as follows; emergency care, emergency surgeries, delayed surgeries, and planned surgeries. This surgical treatment algorithm's success relies on the accuracy of indication, timing, and orderly practice. In the Pakistan earthquake in 2005, there were 40,000 traumatized patients, including 55% major injuries, 60% limb injuries, 20% cavity injuries, 2% spinal injuries, and 1% head injuries (9). Oda et al. reported 372 cases of crush syndrome, which can be partitioned into the lower extremities (74%), followed by the upper extremities (10%), and the trunk (9%) (10). Every injury seen in orthopedics and traumatology practice can be observed with being under the rubble; these can be in a spectrum ranging from simple muscle crush to pelvis fracture with vascular injury. The main function of the orthopedist is to perform a quick diagnosis and accurate treatment to save the life and extremities.

Management of orthopedic injury

Crush injuries, and bone and soft-tissue trauma are the most important injuries which can be seen after an earthquake. The first step in the management of limb and axial skeletal injuries is accurate immobilization of the injured region, such as a cervical collar for the cervical spinal segment. Maintaining a safe airway and large-bore intravenous access for hemodynamic stabilization are also priorities in traumatized patients.

1. Emergency care: The primary intervention is to control the bleeding caused by penetrating injuries and to provide hemodynamic stabilization. If there is minor bleeding, applying direct pressure on the wound by using clean gauze will be sufficient to control it. If there is major bleeding, the patient should be stabilized immediately with a multidisciplinary approach and vascular surgeons. Another emergency care resulting in trauma is an uncontrollable hemorrhagic pelvic fracture, a major cause of patient mortality (11). Managing this life-threatening situation is difficult and requires aggressive methods. Hemodynamic stabilization with blood transfusion and crystalloid solution via large-bore intravenous cannula is an effective protocol for improving hypovolemic shock. The use of other supportive care measures, such as external fixations, angiography and embolization, and pelvic packing to stop or reduce bleeding may also be effective (12, 13).

2. Emergency surgery: Fasciotomy is one of the most critical emergency surgeries due to crush injuries after an earthquake, followed by open fracture debridement, amputation, simple suturing, and external fixation (14). Crush injury of a limb typically comprises closed crushes suffered by victims due to prolonged immobilization under the rubble. In a patient with compartment syndrome after a crush injury, it should be considered that crush syndrome may develop which requires early diagnosis and a therapeutical approach. The decision for both medical and surgical treatment should be made quickly. Most patients who developed compartment syndrome have pain (especially by passive extension of the joint), loss of motor function, missing arterial pulse and capillary filling, pares-

thesia, and parlor. It should be remembered that compartment syndrome will not develop after every crush injury. It has been reported that 15% of patients with crush injuries develop compartment syndrome (15). However, fasciotomy following clinical suspicion gives us the best chance to optimally save the extremities and is a critical factor in managing crush syndrome (16). Fasciotomy provides the maintenance of circulation and prevents the necrosis of muscles. There is still controversy regarding the proper timing of fasciotomy to avoid irreversible ischemic changes. The ischemic necrosis of muscles can become permanent in 8 hours (16). However, this procedure holds the risk of fluid loss from the wound, and the risk of the infections (Figures 1, 2). In one study, Michaelson emphasized that the fasciotomy procedure should not be performed and conservative treatment should be chosen in patients with crush injuries (17). Another study suggested that patients suffering closed crush injuries that are treated with late fasciotomy (≥24 hours) faced worse outcomes than conservatively treated ones (18). Fasciotomy areas require frequent inspection to check for signs of vascular deterioration, inadequate fasciotomy, or emerging infection.

Figure 1: A 16-year-old boy who was trapped under the rubble in the Kahramanmaraş earthquake. Fasciotomy was performed on both cruris for the prevention of necrosis of muscles. The left distal crus developed necrosis and amputation was performed below the knee.

- Amputation: Acute renal failure and cardiac arrhythmias may develop due to myoglobinuria and hyperkalemia after necrosis of large muscle masses in crushed patients after an earthquake. In earthquake victims who develop these clinical conditions despite preventive treatments such as medical treatment and fasciotomy, limb amputation may be required (19). Amputation of a limb with or without circulation but with tissue continui-

Figure 2: A 15-year-old patient who was trapped under the rubble in the Kahramanmaraş earthquake developed necrosis and infection after fasciotomy.

Table 1: Mangled Extremity Severity Score.

	Points
Age, year	
>30	0
30 – 50	1
>50	2
Shock	
Systolic blood pressure >90mmHg	0
Transient hypotension	1
Persistent hypotension	2
Limb ischemia	
Pulse reduced or absent, perfusion normal	1*
Pulseless; diminished capillary refill, paresthesias	2*
Cool, paralyzed, numb, no sensation	3*
Tissue injury	
Low-energy (simple fracture, stab wounds)	1
Medium-energy (open or chain fractures, dislocation)	2
High-energy (crush injury)	3
Very high-energy (high contamination and extensive)	4

*double the score if ischemia duration >6 hours
A score of 6 or less is associated with 100% limb salvage rate.
A score of 7 or more is associated with 100% amputation rate.

Figure 3: A 17-year-old boy who was trapped under rubble in the Kahramanmaraş earthquake for a long time (more than 24 hours). Amputation above the knee was performed on this patient.

ty is a crucial decision for orthopedics and traumatology specialists, patients, and their relatives (20). It is helpful to use specific scoring systems, Mangled Extremity Severity Score (MESS) (Table-1) (21) and Injury Severity Score (ISS), when making the difficult decision to preserve with conservative treatments, fasciotomy, and debridement or amputation of the crushed limb. If the extremity circulation is insufficient and necrosis is increasing despite protective procedures such as fasciotomy, amputation should be performed without delay (Figure 3). In the Van earthquake, amputation was performed in one-third of the patients who underwent fasciotomy due to complications such as sepsis during the follow-up, and one-third died despite all efforts (22). Since the general condition of these patients can suddenly deteriorate, surgical procedures should be determined meticulously.

- Debridement: It is a priority to intervene in patients with soft tissue injuries, especially with open fractures. According to Kanchan et al., open reduction and internal fixation were the most routinely performed surgeries, followed by debridement in 238 cases (61.7% and 13.9%, respectively) (8).

3. Planned surgery: The above-mentioned surgical procedures can be performed under emergency conditions, perhaps in non-sterile environments. In patients with a crush injury with a bone fracture, a temporary external fixator can be applied to the injury condition (damage control orthopedics). Improving the physiological state is also an essential strategy of orthopedics damage control. Damage control orthopedics can delimitate the primary trauma, prevent further detriment and reduce morbidity and mortality (23). Patients with crush injuries and suitable soft tissue conditions can be included in planned surgeries and performed at the appropriate time. Finally, appropriate surgical management of spinal fractures and traumatic spinal cord injury, which carry high morbidity and mortality rates is also essential.

CONCLUSION

Although technology has advanced substantially, the essential skill of orthopedic surgeons in triaging many crushed patients to manage the available resources remains a critical issue. The most crucial intervention point is evaluating those people trapped under the rubble after an earthquake. Patients should be triaged according to the priority order from saving lives to simple debridement. While performing all these surgical procedures, a multidisciplinary approach should be applied to monitor and treat the patient's general condition.

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