



The Impact of COVID-19 on Cervical Cancer Screenings and Clinical Outcomes of Patients: A Single-Center Tertiary Healthcare Service Experience

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ABSTRACT

Objective: The COVID-19 pandemic has negatively affected cancer screening activities all over the World. The accumulating data suggest that delayed admissions to screening and clinical assessments are associated with increased morbidity and mortality in cancer. This study aimed to provide data on cervical cancer screenings and clinical outcomes comparatively before and during the pandemic.

Method: This study retrospectively compared the demographic and clinical characteristics, screening test results, and colposcopy assessments of women admitted to the Obstetrics and Gynecology Department of a tertiary-care university hospital before and after March 11, 2020, considered as the date of announcement of the COVID-19 pandemic.

Results: A total of 382 patients with a median age of 32 years were included (174 in pre-pandemic and 208 in pandemic periods). In HPV DNA analyses, serotypes reported as high-risk were significantly increased to 22.1%, while others had minor changes in the pandemic. In cytological studies, normal cytology results were significantly decreased to 32.8% from 45.9%, and the ASC-US diagnoses were significantly increased from 12.8% to 27.4%. In addition, the colposcopy examinations revealed that the cold knife cone was increased from zero to 15.3%, routine follow-up was decreased from 88.2% to 71.4%, normal pathologies were decreased from 40.4% to 30.1%, and CIN1 and CIN2 decreased, but CIN3 rose from 3.6% to 6.6%. The HPV DNA and colposcopy follow-up were significantly increased during the pandemic.

Conclusions: This study is the first report on the increased numbers of diagnoses of advanced lesions in cervical cancer screenings during the pandemic compared to the pre-pandemic admissions in Turkey. Our results imply the need for immediate actions to normalize cervical cancer screenings to avoid any further morbidity and mortality. High-risk HPV-DNA results in the Covid period were found to be higher than before the Covid period.

Keywords: Cervical cancer, screening, cervical smear, cytology, colposcopy, clinical outcomes, COVID-19, pandemic, Turkey

COVID-19'un Serviks Kanseri Taramaları ve Hastaların Klinik Sonuçları Üzerindeki Etkisi: Üçüncü Basamak Tek Merkezde Sonuçları

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Öz

Amaç: COVID-19 pandemisi kanser taramalarını tüm dünyada olumsuz etkilemiştir. Artan kanıtlar taramaların ve klinik değerlendirmelerin gecikmesinin kansere bağlı morbidite ve mortalite artışı ile ilişkili olduğunu göstermektedir. Bu çalışmanın amacı pandemi öncesindeki ve sürecindeki servikal kanser taramaları ve klinik sonuçlara ilişkin verilerin sunulmasıdır.

Yöntem: Bu çalışmada COVID-19 pandemisinin duyurulduğu 11 Mart 2020 tarihinden önceki ve sonraki dönemde üçüncü basamak bir üniversite hastanesinin Kadın Hastalıkları ve Doğum Bölümüne başvuran kadınlara ait demografik ve klinik özellikler, tarama testi sonuçları ve kolposkopi değerlendirmeleri retrospektif olarak karşılaştırılmıştır.

Bulgular: Çalışmada ortalama yaşı 32 olan toplam 382 hasta (174 pandemi öncesi, 208 pandemi sonrası dönem) yer almıştır. HPV DNA analizlerinde yüksek-riskli olarak tanımlanan serotiplerin oranları pandemi döneminde belirgin şekilde artarak %22.1'e ulaşmış, diğer serotiplerde ise minör değişimler meydana gelmiştir. Sitolojik değerlendirmelerde normal sitoloji sonuçlarının %45,9'dan %32,8'e düştüğü, ASC-US tanılarının %12,8'den %27,4'e arttığı görülmüştür. Ayrıca, kolposkopi değerlendirmelerinde konizasyon oranları 0'dan %15,3'e ulaşmış, rutin takip oranları %88,2'den %71,4'e düşmüş, normal patoloji oranları %40,4'ten %30,1'e gerilemiş, CIN1 ve CIN2 görülme oranı düşerken CIN3 oranları %3,6'dan %6,6'ya yükselmiştir. HPV DNA ve kolposkopi ile takip oranları da pandemi döneminde belirgin artış göstermiştir.

Sonuç: Bu çalışma, pandemi öncesi dönem ile karşılaştırıldığında, Türkiye'de servikal kanser taramalarında tanı konan ilerlemiş lezyon sayılarında pandemi dönemindeki artışı bildiren ilk çalışmadır. Bulgularımız morbidite ve mortalitede ortaya çıkabilecek artışların önlenmesi için servikal kanser taramalarının en hızlı şekilde normale dönmesi gerektiğinin önemini vurgulamaktadır.

Anahtar sözcükler: Servikal kanser, tarama, servikal smear, sitoloji, kolposkopi, klinik sonuçlar, COVID-19, pandemi, Türkiye

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Introduction

Undoubtedly, the COVID-19 pandemic is currently the unrivaled public health problem of our century. Since the World Health Organization declared the novel coronavirus disease spread from the Hubei city of the Wuhan state in China as a pandemic on March 11, 2020, approximately more than 260 million cases were diagnosed, and more than 5 million people lost lives globally due to this disease¹. The consequences of the pandemic affected all domains of daily life, including admission to health services as well. The routine or elective care was temporarily suspended due to the lockdowns, the avoidance of individuals and postponing any uncritical health problems, and the allocation of the available workforce to the COVID-19 cases in healthcare facilities^{2,3}.

Several previous studies reported decreased admissions for critical diseases like cancers, cardiac events, and cerebral infarcts, particularly during the first pandemic wave⁴⁻⁶. However, the consequences of delayed admission to regular healthcare have not been adequately evaluated. Notably, the temporal changes in the screening programs and regular admissions for planned follow-up visits for screenings during the pandemic are under-addressed, implied by the low number of studies on the topic. Nevertheless, several reports declared that all cancer screenings were decreased during the COVID-19 stay-at-home orders were effective, but this decrease continued after these orders were lifted. A study from the Centers for Disease Control and Prevention (CDC) reported a dramatic decline reaching roughly 80% in cervical cancer screenings⁷. Unfortunately, no statistical data on the temporal changes in screening rates was released by the regulatory authorities in Turkey. However, a survey conducted among 1520 family physicians working at primary healthcare in 75 provinces (out of 81) in Turkey in December 2020 suggested that screenings were decreased over 90% during the pandemic⁸. These estimated decreases in screenings and admissions to hospitals are theoretically expected to diagnose advanced diseases or lesions in the subsequent period.

Based on the limited availability of evidence on the changes in the pathological characteristics of cervical lesions detected in screenings, this study aimed to elucidate temporal changes in advanced-disease diagnoses by comparing pre-pandemic and pandemic periods for patients' general demographic and clinical characteristics.

Material and Methods

This study was conducted as a retrospective chart review on the demographic and clinical data of patients admitted for screening and clinical examination to the Obstetrics and Gynecology Department of the Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey. The admissions were grouped into pre-pandemic

and pandemic periods from January 15, 2018 to September 29, 2021, delimited on March 11, 2020.

The study's primary objective was to evaluate the temporal changes in the clinical severity of the cervical lesions determined by screenings, clinical examinations, colposcopy, and relevant pathological assessments. Secondary objectives were comparisons of demographic characteristics, HPV serotype distributions, and treatment and follow-up protocols between the study periods.

Following these objectives, the primary outcome was the final pathological assessments after colposcopy. The secondary outcome measures were basal demographic and clinical characteristics and anthropometric measurements, results of HPV characterization and cytological examinations from cervical samples, and distribution of final treatment and follow-up strategies after colposcopy assessments.

The study protocol was reviewed and approved by the local ethical committee of the Ondokuz Mayıs University Faculty of Medicine on 2021000620-1 and approval number of 2021/620.

Statistical Analyses

The descriptive statistics were presented using median and interquartile range (IQR – 25th-75th percentiles) for continuous data and frequency and percent for categorical variables. The two-time period-groups as pre-pandemic and pandemic were the independent groups of the study, and the continuous and categorical variables were compared between these independent groups using the Mann-Whitney U test and Chi-square test, respectively. A type-I error level of 5% was considered the threshold for the statistical significance ($p < 0.05$). All hypotheses were tested in a two-tailed design using the SPSS 25 software (IBM Inc., Armonk, NY, USA).

Results

Data of 382 patients with a median age of 32 years were included in the analyses. Basal demographic characteristics and medical and obstetric histories were presented in Table 1. About 40.6% of patients were smokers, and 22.7% had at least one comorbidity, most frequently thyroid diseases (9.2%), anemia (4.1%), and diabetes mellitus (2.4%). Obstetric histories revealed patients had a median gravida, para, and alive child number of 1. According to the admission date, 174 (45.5%) and 208 patients (54.5%) were admitted before and after the pandemic. Comparisons of basal demographic and clinical characteristics revealed that smoking rates (49.5% vs. 32.7%, $p = 0.001$) and gravida ($p = 0.047$) and para ($p = 0.022$) were higher among patients admitted in the pandemic.

The HPV characterization from the cervical samples showed that 53.4% of patients were HPV negative, and among the patients with a positive test result, the most frequent serotypes were reported to be high-risk

genotypes (12%), HPV16 (18.6%), and HPV18 (6.5%). Comparisons between pre-pandemic and pandemic periods revealed that the serotypes reported as high-risk were significantly increased to 22.1% (p<0.001), but no other significant differences regarding the distribution of serotypes (Table 2). Other high-risk HPV types than those mentioned in the table 2 are also categorized in this section.

Table 3 summarizes the cervical cytology assessments of patients. Accordingly, about 39.1% of patients had a

normal cytology assessment. The proportion of patients with normal cytology was 45.9% before the pandemic, significantly decreasing to 32.8% during the pandemic (p=0.010). Among the abnormal cytology assessments, the most frequent diagnosis was ASC-US (20.4%), followed by LGSIL (14.8%). The ASC-US diagnoses were significantly increased from 12.8% to 27.4% in the pandemic (p<0.001). Although not explicitly reported, the cytology results grouped as “other” were also increased from 1.2% to 9.1% during the pandemic (p<0.001).

Table 1. General patient characteristics

	Studyperiods			p
	Allpatients (n=382)	Pre-pandemic (n=174)	Pandemic (n=208)	
	Median [IQR] / n (%)	Median [IQR] / n (%)	Median [IQR] / n (%)	
Demographics				
Age (years)	32 [26-36]	32 [27-36]	31 [26-36]	0.38
Height (cm)	160 [157-165]	160 [158-165]	160 [156-164]	0.13
Weight (kg)	65 [56-75]	65 [56-75]	65 [55-75]	0.84
BMI (kg/m2)	24.9 [21.9-29.1]	24.7 [21.9-29.2]	25.1 [22.2-29]	0.46
Smoking	155 (40.6)	53 (32.7)	102 (49.5)	0.001
Medicalhistory				
Anycorbidity	84 (22.7)	39 (24.1)	45 (21.6)	0.58
Thyroiddiseases	34 (9.2)	14 (8.6)	20 (9.6)	0.75
Anemia	15 (4.1)	9 (5.6)	6 (2.9)	0.20
Diabetesmellitus	9 (2.4)	4 (2.5)	5 (2.4)	1.0
Hypertension	7 (1.9)	4 (2.5)	3 (1.4)	0.70
Asthma-Bronchitis	7 (1.9)	3 (1.9)	4 (1.9)	1.0
FamilialMediterranean Fever	4 (1.1)	1 (0.6)	3 (1.4)	0.64
Hepatitis-B	3 (0.8)	1 (0.6)	2 (1.0)	1.0
PolycysticOvary Syndrome	3 (0.8)	1 (0.6)	2 (1.0)	1.0
Other*	10 (2.7)	5 (3.1)	5 (2.4)	0.75
Obstetrichistory				
Gravida	1 [1-2]	1 [1-2]	1 [1-2]	0.047
Para	1 [1-1]	1 [1-2]	1 [1-1]	0.022
Alive	1 [1-1]	1 [1-1]	1 [1-1]	0.14

*: Vertigo, depression, hemorrhoid, cardiac

Table 2. HPV characterization from cervical samples

	Studyperiods			p
	Allpatients (n=382)	Pre-pandemic (n=174)	Pandemic (n=208)	
	n (%)	n (%)	n (%)	
HPV serotypes				
Negative	204 (53.4)	101 (58.0)	103 (49.5)	0.096
High-risk	46 (12.0)	-	46 (22.1)	<0.001
HPV16	71 (18.6)	35 (20.1)	36 (17.3)	0.48
HPV18	25 (6.5)	9 (5.2)	16 (7.7)	0.32
HPV39	14 (3.7)	7 (4.0)	7 (3.4)	0.73
HPV35	13 (3.4)	8 (4.6)	5 (2.4)	0.24
HPV56	11 (2.9)	5 (2.9)	6 (2.9)	1.0
HPV52	10 (2.6)	5 (2.9)	5 (2.4)	1.0
HPV59	10 (2.6)	5 (2.9)	5 (2.4)	1.0
HPV31	9 (2.4)	6 (3.4)	3 (1.4)	0.31
HPV58	9 (2.4)	5 (2.9)	4 (1.9)	0.74
HPV68	9 (2.4)	6 (3.4)	3 (1.4)	0.31
HPV51	8 (2.1)	5 (2.9)	3 (1.4)	0.48
HPV33	7 (1.8)	4 (2.3)	3 (1.4)	0.71
HPV66	6 (1.6)	5 (2.9)	1 (0.5)	0.097
HPV45	5 (1.3)	2 (1.1)	3 (1.4)	1.0
Other	4 (1.0)	-	4 (1.9)	0.13

Table 3. Cervical cytology assessments

	Studyperiods			p
	Allpatients (n=382)	Pre-pandemic (n=174)	Pandemic (n=208)	
	n (%)	n (%)	n (%)	
Cervicalcytology				
Normal	140 (39.1)	79 (45.9)	61 (32.8)	0.010
ASC-US	73 (20.4)	22 (12.8)	51 (27.4)	<0.001
LGSIL	53 (14.8)	25 (14.5)	28 (15.1)	0.89
HGSIL	25 (7.0)	12 (7.0)	13 (7.0)	1.0
Infection	25 (7.0)	16 (9.3)	9 (4.8)	0.098
ASC-H	7 (2.0)	4 (2.3)	3 (1.6)	0.72
AGC	6 (1.7)	2 (1.2)	4 (2.2)	0.69
AIS	1 (0.3)	1 (0.6)	-	0.48
Other	19 (5.3)	2 (1.2)	17 (9.1)	<0.001
Inadequatesample	9 (2.5)	9 (5.2)	-	0.001

ASC-US: Atypicalsquamouscells of undetermined significance; LGSIL: Lowgradesquamousintraepitheliallesion; HGSIL: High gradesquamousintraepitheliallesion; ASC-H: Atypicalsquamouscells, cannotexcludehigh-gradesquamousintraepitheliallesion; AGC: Atypicalglandularcells; AIS: Adenocarcinoma in situ

Table 4. Outcomes of colposcopy assessments

	Studyperiods			p
	Allpatients (n=382)	Pre-pandemic (n=174)	Pandemic (n=208)	
	n (%)	n (%)	n (%)	
Treatment				<0.001
Follow-up	289 (79.2)	149 (88.2)	140 (71.4)	
Coldknifecone	30 (8.2)	0 (0.0)	30 (15.3)	
LEEP afterpunchbiopsy	17 (4.7)	8 (4.7)	9 (4.6)	
Hysterectomy	14 (3.8)	7 (4.1)	7 (3.6)	
Other	15 (4.1)	5 (3.0)	10 (5.1)	
Time totreatment				0.39
Sameday	226 (83.4)	55 (78.6)	171 (85.1)	
1-7 days	21 (7.7)	6 (8.6)	15 (7.5)	
8-30 days	11 (4.1)	5 (7.1)	6 (3.0)	
>30 days	13 (4.8)	4 (5.7)	9 (4.5)	
Pathology				0.009
Normal	126 (34.8)	67 (40.4)	59 (30.1)	
Cervicitis	95 (26.2)	35 (21.1)	60 (30.6)	
CIN 1	43 (11.9)	24 (14.5)	19 (9.7)	
CIN 2	19 (5.2)	10 (6.0)	9 (4.6)	
CIN 3	19 (5.2)	6 (3.6)	13 (6.6)	
Squamouscarcinoma	12 (3.3)	8 (4.8)	4 (2.0)	
Endocervicalpolyp	11 (3.0)	2 (1.2)	9 (4.6)	
Cervicitis + other	5 (1.4)	-	5 (2.6)	
Cervicitis + endocervicalpolyp	3 (0.8)	-	3 (1.5)	
CIN 1 + cervicitis	1 (0.3)	-	1 (0.5)	
Adenocarcinoma	1 (0.3)	-	1 (0.5)	
Adenosquamouscarcinoma	1 (0.3)	1 (0.6)	-	
Other	26 (7.2)	13 (7.8)	13 (6.6)	
Follow-upby				<0.001
Smear	124 (34.1)	104 (62.7)	20 (10.1)	
Smear+HPV	106 (29.1)	32 (19.3)	74 (37.4)	
Smear+HPV+Colposcopy	91 (25.0)	12 (7.2)	79 (39.9)	
Colposcopy	43 (11.8)	18 (10.8)	25 (12.6)	

LEEP: Loopelectrosurgicalexcisionprocedure; CIN: Cervicalintraepithelialneoplasia

All patients have undergone an adequate colposcopy assessment with evident transformation zones observed. The treatments after colposcopy were follow-up in 79.2% of cases, followed by cold knife cone (8.2%), LEEP after punch biopsy (4.7%), and hysterectomy (3.8%). However, the distribution of treatments during the study periods was significantly different (p<0.001). The follow-up was

decreased from 88.2% to 71.4%, and the cold knife cone was increased from zero to 15.3%. The time to treatment was similar between patients admitted before and after the pandemic (p=0.39). However, final pathologies after colposcopy were significantly different (p=0.009), which showed that normal pathologies were decreased from 40.4% to 30.1%, cervicitis was increased from 21.1% to

30.6%, CIN1 and CIN2 decreased, but CIN3 rose from 3.6% to 6.6%. The follow-up strategies were also significantly different between study periods, in which the follow-up solely with cervical smear was decreased from 62.7% to 10.1%, but the utilization of HPV and colposcopy along with the smear was significantly increased ($p < 0.001$) (Table 4).

Discussion

The health domain of daily life in the World has been significantly affected during the COVID-19 pandemic in multiple aspects as physical and psychological well-being. The global actions to limit the spread of the disease were rapidly collapsed, and many countries responded to the announcement of the pandemic by stay-at-home orders, lockdowns, social prevention, or limitation recommendations or regulations. This situation resulted in postponed or delayed admissions to healthcare facilities for routine follow-ups and even symptomatic diseases. Although this immediately affected critical health conditions, delayed admissions for screenings or non-urgent complaints are hypothesized to diagnose advanced diseases than expected if individuals were admitted without delays. This study was based on this hypothesis and comparatively evaluated the characteristics and clinical outcomes of patients admitted for cervical cancer screening in a tertiary-care healthcare facility between the pre-pandemic and pandemic periods.

The primary outcome of this study was the increased proportion of advanced diseases in the final pathological assessments after colposcopy examinations, suggested by the decreased normal and early lesions in pathological assessments compared to raised advanced lesions as CIN3 in the pandemic period. There were minor changes in other lesions between study periods, but low numbers of cases prevented further conclusions. Besides diagnosing more advanced diseases in final pathological examinations, the treatments administered were also significantly different between periods, which showed decreased follow-up approach and increased cold knife conization. Moreover, the follow-up plans were also significantly different between periods as lessened follow-up by only smear assessment and increased follow-ups with additional procedures as HPV analyses and colposcopy examinations during the pandemic. Although these imbalances support the hypothesis of this study, the factors yielding these results might vary in a broader range than expected. Additional findings suggested that the smoking rates and median gravida and para of patients admitted during the pandemic were higher than the pre-pandemic. Although there is no national study on the changes in smoking prevalence in our country, previous studies reported that an increase in smoking might be observed during the pandemic due to the increased psychological distress factors⁹, which might be an explanation for the increased smoking rates among our patients during the pandemic. However, we concluded that the increased median gravida and para were temporal differences and might be associated with the

changes in admission patterns. The proportion of patients admitted during the pandemic was slightly higher and associated with the referral of patients to our center from other hospitals that decreased their capacity for routine healthcare services. This change in admission patterns might also cause different obstetric history characteristics between the two study periods.

The International Agency for Research on Cancer (IARC) has published a comprehensive cross-sectional survey evaluating the impact of the COVID-19 pandemic on cancer screening programs in selected low- and middle-income countries (LMICs) and reported that screening, diagnostic, and treatment services were decreased more than half of their capacities in the pre-pandemic period in 61.1%, 44.4%, and 22.2% of participant LMICs, respectively. These decreases were not only the concerns of the LMICs but also evident in other studies conducted in developed countries, such as the number of women screened for breast cancer in Australia was only 1000 in April 2020, which was expected to be 70,000; and participation to the cancer screening programs was decreased by 62% to 96% in the USA¹⁰. These decreases are directly related to the severe impact of the pandemic on daily life. Still, they might also be associated with secondary pathways such as the allocation of public resources to urgent care, decreased income during the pandemic, financial difficulties maintaining routine and non-urgent healthcare, shifts in health beliefs, and risk perception towards acute conditions from long-term health conditions, etc. The precipitating factors might vary between populations and based on individual factors, but the delays in screenings and early diagnoses are supposed to contribute to the increased sum of diagnosing advanced diseases and cancer deaths¹¹. Besides these negative impacts on the disease burden, the backlogs due to delayed screenings may also increase the workload on healthcare services as daily life returns to its default state.

As for all cancer screening activities, cervical cancer screenings were also affected negatively during the pandemic. Several professional societies such as the American College of Obstetricians and Gynecologists, the Italian Society for Colposcopy and Cervico-Vaginal Pathology, and the British Society for Colposcopy and Cervical Pathology announced recommendations regarding triage and safe postponing care. Based on this background, the European Federation for Colposcopy and the European Society of Gynecological Oncology also released their considerations for cervical cancer screening during the pandemic and covered the management of screening programs, screen-positive women, and preinvasive and invasive lesions of the lower genital tract¹². Accordingly, the high-risk groups and lesions were recommended to be evaluated without delay and in a four-week period, which may be elongated to 6 to 12 months in low or no risk groups. The results of our study did not include the analyses regarding the delayed duration of screening or management of patients per se but evaluated the changes in the distribution of

pathological patterns in the screenings and colposcopy assessments as surrogate markers. Besides the outcomes of colposcopy assessments mentioned above, the comparisons regarding cervical cytological examinations revealed important clues suggesting detecting advanced conditions resembled by less normal cytology and more ASC-US. Moreover, the HPV DNA characterizations also revealed increased serotypes classified as high risk during the pandemic. One might suggest that the changes in the cervical pathologies may be related to changes in patient characteristics, such as the admission of women who already have a high-risk background. Still, as far as we were able to analyze, the basal patient characteristics were similar between periods, shifting the interpretations towards delayed diagnosis in the pandemic.

In conclusion, the delays in cancer screenings are evident in the world, but the net outcomes of delayed admissions are still under investigation. To the best of our knowledge, no nationwide or large-scale studies evaluated or reported the changes in cervical cancer screenings and their outcomes. Therefore, this study is the first report on the increased numbers of diagnoses of advanced lesions in cervical cancer screenings during the pandemic compared to the pre-pandemic admissions. To summarize the findings, the cervical smear assessments, including HPV serotype distribution, cytological assessments, colposcopy examinations, and final pathological evaluations, all have clues suggesting the cervical pathologies are diagnosed in advanced stages, which can be related to delayed admission during the COVID-19 pandemic. Besides these strengths of this study, the retrospective nature of the design allowed it to analyze only the typical sociodemographic characteristics of patients recorded in clinical visits, which may be encountered as a limitation for unavailability of conducting analyses for potential confounders that should have biased the outcomes. Nevertheless, every bit of information is critical in these unprecedented times. Our results will inform future studies and policy-making efforts about the consequences of the delayed admissions and the immediate need to normalize the screening and management of women regarding cervical pathologies.

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