Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2022;47(4):1463-1470
DOI: 10.17826/cumj.1139145

ARAŞTIRMA / RESEARCH

Comparison of psychotropic drug preferences and side effects in old and young patients with schizophrenia and schizoaffective disorder

Şizofreni ve şizoafektif bozukluğu olan yaşlı ve genç hastalarda psikotrop ilaç tercihleri ve yan etkilerinin karşılaştırılması

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Cukurova Medical Journal 2022;47(4):1463-1470

Abstract

Purpose: The current study investigates the preferred psychotropic drug treatments and their tolerability in elderly patients (EP) with a diagnosis of schizophrenia or schizoaffective disorder compared to younger patients (YP).

Materials and Methods: The study included 154 EP and 195 YP with schizophrenia/schizoaffective disorder admitted to the outpatient unit at a university hospital in the last decade. The medical records of the patients were reviewed. The types and doses of antipsychotic drugs used by each patient, use of other psychotropic drugs, ongoing complaints, drug-related side effects and compliance with treatment were also examined.

Results: Second generation antipsychotic use was higher in YP (88% in YP, 80% in EP). Antipsychotic equivalent doses were found 266.63 mg in EP, 522.21 mg in YP, that also higher in the YP group. The use of clozapine (7% in EP, 37% in YP) and mood stabilizers (4.5% in EP, 18% in YP) were higher in YP. There was a higher rate of dose reduction of antipsychotic drugs in EP (21.5% in YP, 52% in EP). When the groups were compared in terms of the reasons of antipsychotic dose reduction, it was more frequent in EP due to side effects (21.4% in YP, 40% in EP), while the dose reduction due to remission was more common in YP (78.6% in YP, 60% in EP) .

Conclusion: Lower doses of antipsychotics in EP suggests milder symptoms or lower tolerability. The higher clozapine and mood stabilizer use in YP can be explained by avoiding side effects like extrapyramidal, cardiovascular and metabolic side effects that are more frequent in EP.

Keywords: Elderly, schizophrenia, schizoaffective disorder, antipsychotics, mood stabilizers

Öz

Amaç: Bu çalışma, şizofreni veya şizoaffektif bozukluk tanılı yaşlı hastalarda (YH) genç hastalara (GH) kıyasla tercih edilen psikotrop ilaç tedavilerini ve bunların tolere edilebilirliğini araştırmaktadır.

Gereç ve Yöntem: Çalışmaya son on yılda bir üniversite hastanesine başvuran şizofreni/şizoaffektif bozukluğu olan 154 YH ve 195 GH dahil edildi. Hastaların tıbbi kayıtları incelendi. Ayrıca her hastanın kullandığı antipsikotik ilaç türleri ve dozları, diğer psikotrop ilaçları kullanımı, şikayetlerinin devam etmesi, ilaç yan etkileri ve tedaviye uyumu incelendi.

Bulgular: İkinci kuşak antipsikotik kullanımı GH'de daha yüksekti (GH'de %88, YH'de %80). Antipsikotik eşdeğer dozları YH'de 266.63 mg, GH'de 522.21 mg olup, GH'da daha yüksek bulunmuştur. Klozapin (YH'de %7, GH'de %37) ve duygudurum düzenleyici (YH'de %4.5, GH'de %18) kullanımı GH'de daha yüksekti. YH'de antipsikotik ilaçların doz azaltım oranı daha yüksekti (YH'de %52, GH'de %21.5). Gruplar antipsikotik doz azaltımı nedenleri açısından karşılaştırıldığında yan etkiler nedeniyle YH'de daha sık (GH'de %21.4, YH'de %40), GH'de remisyona bağlı doz azaltımı daha sıktı (GH'de %78.6, YH'de %60).

Sonuç: YH'de daha düşük antipsikotik dozları, daha hafif semptomlar veya daha düşük tolere edilebilirlik olduğunu düşündürür. GH'de klozapin ve duygudurum düzenleyici kullanımının yüksek olması, YH'de daha sık görülen ekstrapiramidal, kardiyovasküler ve metabolik yan etkiler gibi yan etkilerden kaçınılması ile açıklanabilir.

Anahtar kelimeler: Yaşlı, Şizofreni, Şizoafektif Bozukluk, Antipsikotikler, Duygudurum Düzenleyiciler

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Geliş tarihi/Received: 01.07.2022 Kabul tarihi/Accepted: 05.08.2022

INTRODUCTION

Schizophrenia and schizoaffective disorder are one of the psychiatric disorders in which psychosis is the determinant and these are chronic disorders characterized by disruptions of perception, thought and behavior as well as a widespread effect on personal, social and occupational functioning[1]. In the clinical manifestation of schizophrenia, positive symptoms such as delusions, hallucinations, disorganized speech and behavior; negative symptoms such as impoverishment in thought content, social withdrawal, affective blunting; cognitive symptoms such as deficits in attention, memory and executive functions exist. Additionally, in order for a patient with these symptoms to be diagnosed with schizophrenia, the current symptoms must last for at least 6 months and the symptoms must not be better explained by another disorder. Schizoaffective disorder, on the other hand, is defined as a psychotic disorder in which a major mood disorder accompanies remission and relapses in addition to the basic symptoms of schizophrenia during the illness according to the 5th version of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5)[2]. Two disorders can not be mutually differentiated from each other since many patients may exhibit both clinical manifestations during their lives[3].

Individuals with a diagnosis of schizophrenia have a shorter life expectancy than the general population due to antipsychotic side effects, cardiovascular and metabolic comorbidities, smoking and alcohol use, malnutrition, inactivity, decreased health-seeking behavior, and a higher risk of suicide[4]. Besides increase in the number of elderly population may also give rise to increase number of elderly individuals with schizophrenia[5]. It is estimated that by 2050, more than 400 million adults worldwide will be aged 65 and over (26.3% of the total population)[6], while 10 million people with schizophrenia will be over the age of 60[7]. In many developed countries, people aged 55 and over account for one quarter or more of schizophrenia patients[7]. Older patients with schizophrenia is also of great importance for Turkey, where the lifetime prevalence is estimated to be 8.9 per 1000 people[8].

Antipsychotic drugs are the first choice for the treatment of schizophrenia spectrum disorders. These drugs are especially effective for positive symptoms, however they are not sufficent enough for treating negative symptoms of schizophrenia. Antipsychotics are generally divided into two classes as the first generation (FGA) and the second generation (SGA). SGAs generally have less neurological/extrapyramidal side effects such as rigidity, akathisia, tardive dyskinesia, dystonia, parkinsonism, and anticholinergic side effects compared to FGAs. SGAs are suggested to worsen negative or cognitive symptoms less[9]. Although SGAs are preferred over FGAs in terms of some side effects; extrapyramidal side effects, hyperprolactinemia, neutropenia, agranulocytosis, weight gain, increased insulin resistance, increase in serum lipids, prolongation of QTc, cardiovascular side effects are also associated with the use of SGAs. Despite the above-mentioned side effects, antipsychotics, which are of great benefit for treating schizophrenia, play a fundamental role in the treatment regardless of the age of the patient. Mood stabilizers such as lithium, and some antiepileptic drugs, anxiolytics, and antidepressants can also be used as adjunctive treatments[9].

Schizophrenia is a chronic disease, therefore patients often require lifelong antipsychotic therapy[10]. The treatment of schizophrenia in elderly patients (EP) differs in many ways from the treatment of younger patients (YP). One of the most important reason for this is that the pharmacokinetics and pharmacodynamics of most drugs in the elderly are different from those in young people. Additionally, comorbidities are more common in elderly individuals and, as a result, multiple drug use requires consideration of drug-drug interactions. Regulation of blood pressure and body temperature also decrease with aging and the receptors become more sensitive. As a result the side effects are more common and severe in the elderly[11]. Despite such important issues, EP with a diagnosis of schizophrenia were often overlooked in studies. The antipsychotic doses are not usually adjusted according to age during the course of the disorder. Although studies suggest lower doses of antipsychotics in EP, these recommendations are not always followed in clinical practice[10]. Therefore, the present study aims to evaluate the preferences of psychotropic drug regimens and their tolerability in EP diagnosed with schizophrenia and schizoaffective disorder at a university clinic and to compare them with YP. Thus, for the follow-up of elderly patients with schizophrenia, attention will be drawn to the effects and side effects of antipsychotic drugs that may differ from younger patients. It is thought that

this study will highlight important issues about geriatric psychiatric literature as well as clinical practice.

In this study, there are hypotheses that lower equivalent antipsychotic doses are used in EP, that the use of long-acting antipsychotics is rare in EP, and that side effects are more common in the elderly.

MATERIALS AND METHODS

Sample

All patients over the age of 65 (n=154) who were admitted to the Geriatric Psychiatry outpatient clinic of Ankara University Faculty of Medicine, Department of Psychiatry between January 2010 and January 2020 and were diagnosed with Schizophrenia and Schizoaffective Disorder according to the 10th version of the International Classification of Diseases[12] (ICD-10 diagnostic codes F20&F25) were included.

The YP group (n=195) consisted of patients aged between 20-50 years, with a diagnosis of F20&F25. Since the number of YP who were admitted during this period was higher, YP sample of the study was randomly selected. To ensure randomization, YP who were admitted in the first three rows every month for a decade were included in the study. Medical records of a total of 349 patients were reviewed with the approval of the university hospital administration and Ankara University Faculty of Medicine Ethics Committee (approval no: I7-461-20).

Procedure

In this clinic, each patient examination is systematically written into the patients' files by the examining physician. The reliability of the file information is high. The psychotropic drugs used by each patient at the last control were taken into account. The types and doses of the drugs they used were recorded, and the equivalent doses of the antipsychotic drugs in terms of chlorpromazine were calculated. In addition to the antipsychotic drugs used by the patients, the use of other psychotropic drugs, ongoing complaints, drug-related side effects and compliance with treatment were also examined. The psychiatric and other medical comorbidities of the patients were also recorded.

Statistical analysis

Independent sample t-test or Mann-Whitney U test (antipsychotic equivalent doses) was used to compare the groups in terms of continuous variables. Examination of the differences between the categorical parameters (diagnosis, gender, rates of drug use, side effects, remission, dose reduction and adherence to treatment) was carried out by the $\chi 2$ test and corrected by the Fisher's exact test. All tests applied were two-tailed, and a p value of 0.05 or less was considered statistically significant. Data were analyzed by using SPSS version 23.

RESULTS

Of the EP included in the study, 86% (n=132) had schizophrenia, 14% (n=22) had schizoaffective disorder; 81% (n=158) of YP were diagnosed with schizophrenia and 19% (n=37) with schizoaffective disorder. 48% of EP and 45% of YP were women. There was no difference between the two patient groups in terms of diagnosis and gender. The sociodemographic data of the patients are presented in Table 1, in detail.

Approximately 9% (n=14) of EP were using FGAs p.o, 80% (n=123) were using SGAs p.o. 7% (n=13) of YP were using FGA p.o., 88% (n=171) were using SGA p.o. While there was no significant difference between the two groups in terms of FGA p.o. use (X^2= 0.7, p=0.40), p.o SGA use was found to be higher in younger patients (X^2= 3.97, p=0.046). However the statistical difference was small. There was no significant difference between the two groups in terms of long-acting FGAs (X^2= 0.006, p=0.940) and SGAs (X^2= 0.85, p=0.36). The use of more than one antipsychotic was found to be higher in YP (X^2=6.11, p=0.01). Antipsychotic equivalent dose was calculated as M=266.63 mg in EP and M=522.21 mg in YP. When antipsychotic equivalent doses were compared, it was found to be higher in the YP group (Z=-7.24, p<0.001). The use of clozapine was also higher in YP (X^2=42.1, p<0.001). The drug use in the patient groups is summarized in Table-2.

Psychotropic drugs apart from antipsychotics were also examined. There was no significant difference between the use of antidepressant drugs (X^2=0.22, p=0.640) and benzodiazepines (X^2=2.84, p=0.09) in EP or YP. The use of mood stabilizers was higher in the YP group (X^2=14.6, p<0.001).

Table 1. Sociodemographic characteristics of the patients

		Elderly patients (n: 154)	Young patients (n: 195)	p
Diagnosis, n (%)	F20-SCH F25-SAD	132 (86%) 22 (14%)	158 (81%) 37 (19%)	1.350
Gender, n (%)	Females Males	74 (48%) 80 (52%)	88 (45%) 107 (55%)	0.300
Mean Age, (min-max)		71 (65-92)	34 (20-50)	
Education, n (%)	Not defined Uneducated Literate Primary school Secondary school High school University	43 (28%) 11 (7%) 6 (4%) 39 (25%) 7 (5%) 15 (10%) 33 (21%)	44 (23%) 2 (1%) 0 (0%) 20 (10%) 29 (15%) 75 (38%) 25 (13%)	
Marital status, n (%)	Not defined Single Married Widow Divorced	27 (17.5%) 20 (13%) 79 (51.3%) 16 (10.4%) 12 (7.7%)	40 (20.5%) 121 (62.1%) 25 (12.8%) 0 (0%) 9 (4.6%)	

min, minimum; max, maximum; p<0.05; statistically significant; n,noun

Table 2. Use of psychotropic drugs

Drugs		Elderly patients (n=154)	Young patients (n=195)	p
FGA	Total, n (%) Haloperidol Chlorpromazine Trifluoperazine Zuclopenthixol Pimozide Flupenthixol	14 (9%) 5 5 0 1 7 0	13 (7%) 4 4 1 0 3 1	0.400
SGA	Total, n (%) Olanzapine Quetiapine Risperidone Aripiprazol Amisulpride Ziprasidone Paliperidone Sulpride Clozapine	123 (80%) 31 44 30 9 6 0 11 1 11	171 (88%) 32 21 29 20 12 1 14 6 72	0.046*
Long-acting FGA		17 (11%)	21 (11%)	0.936
Long-acting SGA		30 (20%)	46 (24%)	0.356
Multiple antipsychotic use		45 (29%)	82 (42%)	0.013*
Clozapine		11 (7%)	72 (37%)	<0.001*
Antipsychotic equivalent doses, mg (median)		266.63	522.21	<0.001*
Other psychotropic drugs	Antidepressants Mood stabilizers Benzodiazepines Anticholinergic drugs	59 (38%) 7 (4.5%) 7 (4.5%) 36 (25%)	70 (36%) 35 (18%) 18 (9%) 32 (16%)	0.640 <0.001* 0.090 0.055

FGA; first generation antipsychotics, SGA; second generation antipsychotics; *,p<0.05;statistically significant, mg, miligram; n,noun

There was no significant difference between the groups in terms of the use of anticholinergic drugs (X^2=3.68, p=0.055). There was no difference between the groups in terms of reporting general side effects (X^2=0.76, p=0.700). When side effects were classified and compared between groups, no significant difference was found between the two groups, except for tardive dyskinesia, gastrointestinal side effects, and hyperprolactinemia-related side effects. Adverse effects related to tardive dyskinesia were found to be higher in the elderly (X^2= 7.5, p=0.006), gastrointestinal (X^2=8, p=0.004) and hyperprolactinemia- related side effects (X^2:18.5, p<0.001) were higher in the YP group. Table 3 presents the detailed data on the side effects. There was no significant difference between the patient groups in terms of remission rates (X^2=0.08, p=0.784) and adherence to treatment (X^2=0.59, p=0.442). In the follow-up of EP, attempts to reduce the dose of antipsychotics were more common (X^2=35, p<0.001). While antipsychotic dose reduction was higher in the EG due to side effects, dose reduction was more common in the YP group due to achievement of remission with a lower dose (X^2=4.26, p=0.039).

Table 3. Side effects of antipsychotic drugs

	Elderly patients (n=154)	Young patients (n=195)	p
Total side effects	81 (53%)	107 (55%)	0.7
Parkinsonism	60 (39%)	62 (32%)	0.16
Hyperprolactinemia	0 (0%)	22 (11%)	<0.001*
Sedation	9 (6%)	12 (6%)	0.9
Neutropenia (for Clozapine)	1 (0.5%)	3 (2%)	0.2
Gastrointestinal side effects	1 (1%)	13 (7%)	0.004*
Weight gain	10 (6.5%)	17 (9%)	0.44
Tardive Dyskinesia	8 (5%)	1 (0.5%)	0.006*

*, p<0.05: statisticall significant; n,noun

DISCUSSION

The present study evaluates and compares psychotropic drug preferences in elderly and young patients with schizophrenia/schizoaffective disorder. The results of the study supported that there was no difference between the young and old patient groups in terms of FGA use, while the use of SGAs was found to be just a bit higher in YP. This difference may be due to the initiation of treatment with SGA more frequently in YP. With the discovery of chlorpromazine and subsequently other FGAs in the 1950s, schizophrenia patients began to be treated on a drug-based basis. After the demonstration of the effectiveness of clozapine in the late 1980s, other SGAs were discovered and SGAs with significantly less extrapyramidal side effects began to be preferred[9]. Today, SGAs, which are known to have metabolic and cardiovascular side effects, are still often the first choice for the treatment of psychosis[13]. This may be the reason of higher SGA use in YP. Both the equivalent doses of antipsychotics and the simultaneous use of more than one antipsychotic were found to be higher in YP compared to the elderly. This indicates worse clinical symptoms in YP. Although the use of combined antipsychotics is not recommended in the treatment guidelines[9], a higher frequency of combined antipsychotic use was observed in YP. However, in a study conducted in 6 countries in 2004 in which high-dose antipsychotic use was evaluated in 2399 patients with schizophrenia, it was observed that high-dose antipsychotic use was more common in the elderly[14]. It was stated that this was not the case for Japan, one of the countries included in this study, and high-dose antipsychotic use was more common at young ages in Japan[14]. Despite this result, it was found that the dose of antipsychotic used in more than one study was inversely proportional to age. In the study by Leslie et al., it was observed that elderly schizophrenic patients used antipsychotics below the dose recommended more often than others, and combined antipsychotic use was less than YP[15]. In 2 studies involving schizophrenic patients aged 45 years and older, it was found that antipsychotic doses decreased as age increased[16,17]. In the study of Uchida et al. in 2008, it was found that the relationship between age and the prescribed antipsychotic dose was an inverted U-shaped curve in both inpatients

and outpatients. That is, the prescribed dose of antipsychotics increased with age during the third decade, then remained stable and decreased after the fifth decade[18]. The relationship between age and antipsychotic dose, described as an inverted U, was also replicated in a recent study[19]. Therefore, the lower equivalent antipsychotic dose in EP in our study is in parallel with previous literature. Additionally, in the follow-up of elderly schizophrenia patients, attempts to reduce the dose of antipsychotics were found to be higher than younger ones.

In our study, it was found that the use of clozapine was higher in young people. This result can be explained by avoiding the side effects of clozapine such as agranulocytosis, gastric hypomotility, decreased seizure threshold and cardiovascular side effects in the elderly. In this sense, one of the most important side effects of clozapine is agranulocytosis or neutropenia. Previous studies showed increased risk of neutropenia in old age, but the risk of agranulocytosis seemed to be similar[20]. The risk of seizures, that is also another important side effect of clozapine, does not seem to increase with age[20]. Metabolic changes due to clozapine are one of the long-term side effects. Although the results for the elderly are scarce, studies showed that weight gain and metabolic syndrome associated with antipsychotics were lower in the elderly than in younger individuals[21]. Although there is no consistent scientific evidence that clozapine has more side effects or causes death with advancing age[22], the high prevalence of comorbidities in the elderly and the increased risk of drug interactions, falls, and constipation limit its use[20].

The use of mood stabilizer (MS) drugs was more frequent in YP. One of the reasons for this is the limited use of MS drugs in EP due to hyponatremia, extrapyramidal and cardiovascular side effects. One of the most commonly used MS is lithium. Lithium can be used in EP, especially in bipolar disorder, schizoaffective disorder and depression. Although the efficacy of lithium is high in the EP group[23], changes such as decresed renal functions and body water increase side effects and toxicity of lithium[24]. A few of the other MS known to be used in the elderly are valproate, carbamazepine/oxcarbazepine, and lamotrigine. These drugs, which are also anticonvulsants, can cause many side effects, especially in EP. Valproate clearance is decreased and there is an increase in neurological side effects and other side effects such as thrombocytopenia in the elderly[25]. Carbazepine/Oxcarbazepine may also cause hyponatremia, neurological side effects, and blood dyscrasias in the elderly[25]. Because of the risk of allergic reactions, care should be taken when using lamotrigine in the elderly, as in all age groups. Such risks of side effects may cause physicians to hesitate when prescribing MS to the elderly.

There was no difference between the reporting of side effects and the use of antiparkinsonian drugs in both groups. The result that the side effects in general, which we expected to be more common in elderly patients, were equal in both groups can be explained by using lower doses of antipsychotics in EP. When the side effects were examined separately, it was found that tardive dyskinesia was more common in elderly schizophrenic patients. As it is well-known, the frequency and severity of tardive dyskinesia increase with age[26]. Although this situation was thought to be related to the duration of antipsychotic exposure in the past, we now know that it cannot only be explained by this. In addition to exposure, the aging brain's sensitivity to antipsychotics also has a major impact on the development of tardive dyskinesia[26].

Another result of our study was that hyperprolactinemia and associated side effects were found to be more common in YP. A recent review also noted that many of the known side effects of high prolactin levels decreased with age[27]. However, hyperprolactinemia is very importantfor the aging patient, especially because of the risk of osteoporosis and fracture, and should be followed closely. Gastrointestinal side effects such as constipation, diarrhea, nausea and vomiting were also reported with a higher frequency in the YP group. This finding contradicts the previous studies reporting that gastrointestinal side effects, especially constipation, increased with age[28]. The reasons for this may be that lower doses of antipsychotics in EP or that such side effects are relatively less frequently associated with the drug and reported to the doctor in the elderly. Our study reveals the differences in the treatment of schizophrenia patients in the growing geriatric population from the younger group. It sheds light on the treatment in this patient group, which we will encounter more frequently in the future, and contributes to the literature on the subject. However, our study also includes several limitations. First of all, current study is a retrospective one, therefore the medical records may not reflect all data of the

patients. It should also be kept in mind that the sample was selected from a single center-a university hospital, consisted of patients who were treatment-resistant, and therefore did not reflect all patients with schizophrenia/schizoaffective disorder. Also a priori power analysis was not performed. Moreover, the use of more than one psychoactive drugs is frequent in this sample of patients, therefore there may be a bias in terms of the side effects of antipsychotic drugs. Future studies with prospective designs may eliminate these limitations.

In this study, psychotropic drug preferences and side effects in EP with schizophrenia/schizoaffective disorder were compared with those of YP. The findings support that lower doses of antipsychotic drugs are used and dose reduction is more preferred due to the high risk of side effects in EP. Despite the use of lower doses of antipsychotic drugs in EP, the remission rates were similar in both groups, suggesting that psychotic symptoms ease with age. However, these results cannot reveal a definite causality and should be repeated as they were obtained from a single center. However, in the light of the data obtained from this study, it is clear that psychotropic drug therapy in EP with schizophrenia differs from that in YP in many ways, and more research is needed in this population.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ZUH, BY, ZT, ETÖK; Veri toplama: ZUH, BY, ZT, ETÖK; Veri analizi ve yorumlama: ZUH, BY, ZT, ETÖK; Yazı taslağı: ZUH, BY, ZT, ETÖK; İçeriğin eleştirel incelenmesi: ZUH, BY, ZT, ETÖK; Son onay ve sorumluluk: ZUH, BY, ZT, ETÖK; Teknik ve malzeme desteği: ZUH, BY, ZT, ETÖK; Süpervizyon: ZUH, BY, ZT, ETÖK; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Ankara Üniversitesi İnsan Araştırmaları Etik Kurulundan 01.09.2020 tarih ve İ7-461-20 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design: ZUH, BY, ZT, ETÖK; Data acquisition: ZUH, BY, ZT, ETÖK; Data analysis and interpretation: ZUH, BY, ZT, ETÖK; Drafting manuscript: ZUH, BY, ZT, ETÖK; Critical revision of manuscript: ZUH, BY, ZT, ETÖK; Final approval and accountability: ZUH, BY, ZT, ETÖK; Technical or material support: ZUH, BY, ZT, ETÖK; Supervision: ZUH, BY, ZT, ETÖK; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from the Human Research Ethics Committee of Ankara University with the decision dated 01.09.2020 and numbered I7-461-20.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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