ORIGINAL ARTICLE

Evaluation of Nicotine Addiction in Adolescents Ergenlerde Nikotin Bağımlılığının Değerlendirilmesi

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Abstract

Introduction: Those who start smoking during adolescence have a higher risk of developing an addiction. This study aimed to evaluate cigarette addiction in the adolescents who smoke.

Materials and Methods: Cross-sectional, observational, single center study. Two hundred sixty middle and late-aged adolescents 14 years and over who presented to the adolescent and pediatric polyclinic and declared that they were smokers were included in the study.

Results: In our study, 81 (31.2%) were female and 179 (68.8%) were male. The mean age of the 260 adolescents was 17.0 ± 1.5 years. The mean age at the first attempt was 13.9 ± 2.3 years, and the mean age of starting regular smoking was 14.2 ± 2.1 years. The age range at which the adolescents started smoking the most was 14-17 years (73%). According to the mFTQ test, approximately 70% of the adolescents and 90% according to the HONC test were nicotine dependent. Addiction scores of late-age adolescence were higher. We found that although males smoked more by percentage, sex was not associated with addiction. According to both tests related to addiction used in our study, as the number of cigarettes increases (mFTQ test: p<0.0001; HONC test: p<0.001) addiction also increases.

Conclusion: It was observed that there was a high rate of addiction among smokers. In addition, it was found that the age of starting smoking is low in our studyand the addiction increases as the age of starting smoking decreases.

Öz

Giriş: Ergenlik döneminde sigaraya başlayanların bağımlılık geliştirme riski daha yüksektir. Bu çalışma sigara içen adölesanlarda sigara bağımlılığını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Kesitsel, gözlemsel, tek merkezli çalışma. Adölesan ve pediatri polikliniğine başvuran ve sigara içtiğini beyan eden 14 yaş ve üzeri, iki yüz altmış orta ve geç dönem adölesan çalışmaya dahil edildi.

Bulgular: Çalışmamızda 81 (%31,2) kişi kız, 179 (%68,8) kişi erkekti. 260 adölesanın yaş ortalaması 17,0 \pm 1,5 yıldı. İlk denemedeki yaş ortalaması 13,9 \pm 2,3 yıl, düzenli sigaraya başlama yaş ortalaması ise 14,2 \pm 2,1 yıldı. Ergenlerin en çok sigaraya başladığı yaş aralığı 14-17 yaş aralığıydı (%73). mFTQ testine göre adölesanların yaklaşık %70'i, HONC testine göre ise %90'ı nikotine bağımlıydı. Geç ergenlik döneminde bağımlılık puanları daha yüksekti. Erkeklerin yüzde olarak daha fazla sigara içtiğini ancak cinsiyetin bağımlılıkla ilişkili olmadığını bulduk. Çalışmamızda bağımlılıkla ilgili kullanılan her iki teste göre; sigara içilen kişi sayısı arttıkça (mFTQ testi: p<0,0001; HONC testi: p<0,001) bağımlılık artmaktadır.



Sonuç: Sigara içenler arasında bağımlılık oranının yüksek olduğu gözlemlenmiştir. Ayrıca çalışmamızda sigaraya başlama yaşının düşük olduğu ve sigaraya başlama yaşı düştükçe bağımlılığın arttığı bulunmuştur.

Introduction

It is known that initiation and addiction to smoking often occur before the age of 20 years. Adolescence, which is considered the transition period from childhood to adulthood, is a period of rapid growth and development in which physical, psychological, social, and cognitive changes are experienced. During this period, adolescents see themselves as very strong physically and think that they will not be harmed, which leads them to engage in risky behaviors. It has been observed that cigarette addiction also begins in adolescence and continues in adulthood (1). In adolescents, the first dose of nicotine may leave a permanent mark on the brain and cause disruptions in the reward system in the brain. Nicotine withdrawal symptoms in adolescents can occur even with low cigarette consumption (2). This situation also paves the way for adolescents to become addicted more quickly. As noted in A Report of Surgeon General 2014, if people do not start smoking by the age of 26 years, they usually do not start thereafter (3).

Starting to smoke is the process in which psychodynamic factors are effective along with environmental and social conditions on the genetic background. The impact on the environment and society is undeniable. Individuals trying to find a place in society try to imitate role models. Considering the social learning theory, adolescents are affected by adults in two ways. The first is imitation. The second is to internalize the behavior of others. Reasons such as deterioration of balance in the family, substance addiction among parents, and neglect by the family lead individuals to substance addiction (4,5). In addition, peer and social influence and peer habits in adolescence are effective in starting and quitting smoking.

According to the World Health Organization, nicotine addiction is defined as follows: substance abuse, continuing to use the substance despite adverse effects, and the emergence of withdrawal symptoms in the person when trying to quit. According to the WHO, tobacco addiction is included in the international disease classification with F17 (6). According to DSM 5, nicotine addiction must have occurred in the last 12 months, and in order for addiction and withdrawal to be

defined, the smoker must meet at least 2 of the 11 current addiction criteria (7). The World Health Organization reports that the main element in substance addiction is the individual's lack of control over the substance. DSM defines it as the loss of control over the amount and duration of substance use. The Hooked on Nicotine Test is another test that measures nicotine addiction. According to the HONC Test, the onset of addiction can be defined as the moment when the individual loses full autonomy over tobacco use. Autonomy theory does not assume that all symptoms of addiction are a result of the pharmacological effects of nicotine. Autonomy theory assumes that what appears to be a single clinical syndrome actually represents a mixture resulting from multiple independent mechanisms. Therefore, no single mechanistic theory can explain all the features of the clinical syndromes of addiction. The autonomy model allows the reconciliation of competing addiction theories into a single model (8,9). In our study, we planned to see the results of these two tests on addiction in our study group and to obtain better results by using both tests together.

Although there are studies on the frequency of smoking, there is no study investigating nicotine addiction and withdrawal symptoms in adolescents in our country. The present study aimed to evaluate the addiction status of adolescents who smoke.

Materials and Methods

Study Design

The study was conducted at adolescent polyclinic, and general pediatrics polyclinic. Approval was obtained from the Education Planning Board for the study to be conducted in the adolescent outpatient clinic and general pediatric polyclinic of our hospital. This was a single-center, cross-sectional study conducted between January 2018 and January 2019. This cross-sectional study was approved by the local Ethics Committee of Keçiören Training and Research Hospital (date: 13.12.2017, approval number:1561). Our study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. Two hundred sixty adolescents aged 14 years and over, middle and late-age adolescents who smoked and presented to the outpatient clinic were included. Adolescents were classified as middle-age (age 14-17 years) and late-age (17-21 years) (10). Smoker patients with chronic diseases were not included in the study. A questionnaire developed by the researchers was administered to all adolescents face-to-face to those who agreed to participate in the study.

In the first part of the survey, the adolescent's age, sex, education level, education and occupation of the parents, with whom they lived, the number of siblings, the number of people living at home, the monthly income level of the family, the amount of pocket money received from the family, the age at which they first tried smoking, their family awareness of smoking, smoking at home, and sports habits. In the second part of the questionnaire, they were asked about their school status (private, state, vocational school), whether their friends at school smoked, their smoking in and around school, and whether or not smoking bans could be applied in their school or institution. After they were allowed to answer the questionnaire questions, the Modified Fagerström Test for Nicotine Dependence (mFTQ) and Hooked on Nicotine Checklist (HONC) were administered (11-13). The HONC Test is scored from 0 to 10.0 is considered no loss of autonomy, 10 is considered complete loss of autonomy. Up to 7 points in the HONC Test were considered dependent, 8 points and above were considered highly dependent. In the evaluation of the mFTQ Test, 0-2 points were defined as no dependency, 3-5 points as dependency, and 6 and above as highly dependent. Both test contents were given in Supplemental Files.

Statistical Analysis

The Statistical Package for the Social Sciences version 25.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics are given as numbers and percentages for qualitative variables, and as mean, median (25-75 percentile), standard deviation, minimum and maximum for quantitative variables. As univariate analyses, Student's t-test and one-way analysis of variance (one-way ANOVA) tests were used to compare group means. In cases of violation of the homogeneity assumption, Welch t and Welch ANOVA tests were used. The relationship between numerical

variables was examined using Pearson's correlation test. Backward multiple regression analysis was used in multivariate analyses. The analysis of the data was evaluated to the level of significance of p<0.05 at 95% confidence intervals.

Results

The mean age of the 260 adolescents included in the study was 17.0±1.5 years, with 177 (68.1%) middleage adolescents and 83 (31.9%) late-age adolescence. Two hundred (76.9%) of the adolescents lived with their parents, and 30 (11.5%) stated that they lived only with their mother or father due to the divorce of their parents. When the parental education levels of the adolescents were evaluated, it was determined that 89 (34.2%) of their mothers were high school graduates, 24 (9.2%) were university graduates, 114 (43.8%) of their fathers were high school graduates, and 39 (15%) were university graduates. The families of 164 (63.1%) adolescents knew that they smoked; the families of 96 (36.9%) adolescents were not aware of their smoking. One hundred twenty-two of the adolescents (46.9%) could smoke at home, and 138 (53.1%) stated that they did not smoke at home.

Two hundred thirty-eight (91.5%) adolescents stated that they had no health problems, and 22 (8.5%) said they did not have a chronic disease, but they were frequently sick (such as frequent upper respiratory tract infections, and allergies). One hundred thirty-one (50.4%) adolescents stated that they did sports, and 129 (49.6%) stated that they did not do any sports.

The mean age of regular smoking in adolescents was 14.2 (range, 6-20) years, and the mean age of first smoking was 14 (range, 5-20) years. The median number of cigarettes smoked per day was 10 (range, 5-20), and the median number of cigarettes smoked per week was 60 (range, 21-105). Among the adolescents in our study, the earliest age of starting smoking was 5 years, and the latest age was 18 years. The highest ratio to start smoking was between the ages of 14-17, and 73% of adolescents started smoking at an early age. Another remarkable finding was that 5.4% started smoking under the age of 10 years. Approximately 20% of adolescents started smoking between the ages of 10-13 years and only 2% started smoking after the age of 18 years.

There was no relationship between female and male gender with addiction according to the mFTQ

and HONC test (p=0.9559 for mFTQ and p=0.663 for HONC test). Addiction scores were found to be similar in both genders.

In our study, the number of cigarettes smoked by the subjects per day was found to be related to addiction in both tests. Addiction increased as the number of cigarettes smoked per day increased (p<0.001). Number of cigarettes used, and dependency relationship of both tests are shown in Table 1 and Table 2 separately.

When the factors that most affect smoking addiction in adolescents were examined, according to the mFTQ test, it was observed that the level of addiction increased with higher income levels of the family (p<0.001), high pocket money received from the family (p=0.001), the number of cigarettes smoked per day (p<0.001), and as the age of the adolescent increased (p<0.001). According to the mFTQ test scores, it was seen that the most effective factor in the addiction of adolescents was the number of cigarettes

smoked per day. As the number of cigarettes smoked per day increased, addiction increased (rs=0.687, p<0.001). According to the HONC test, age, the total income of the family, pocket money received from the family, and the number of cigarettes smoked per day were statistically significant (p<0.001, p=0.018, p=0.001, and p<0.001). The relationship between the demographic data of the adolescents and addiction is given in Table 3.

After univariate analyses, backward stepwise regression analysis was performed with the variables found to be significant in terms of mFTQ scores (dependent variable). In this method, all variables are included in the model, then the variable with the lowest contribution to the model is removed and the model is rebuilt, this process continues until a meaningful model is obtained. The overall model was found to be significant (F=46.319, p<0.001). The model explains approximately 56% of the variance in the mFTQ score (dependent variable). If the statistics

Demographic characteristics		Number of patients	Percentage (%)	
Conduc	Female	81	31.2	
Gender	Male	179	68.8	
	Middle adolescence (14-17)	177	68.1	
Age (years)	Late adolescence (18-21)	83	31.9	
	No	72	27.7	
Someone in the family who smokes	Middle adolescence (14-17) Late adolescence (18-21) No Yes Yes No Under 10 years old 10-13 years old 14-17 years old 18 years old and above 5 and below 6-10	188	72.3	
	Yes	202	77.7	
Buy a pack of cigarettes	No	58	22.3	
	Under 10 years old	14	5.4	
Age of starting smoking	10-13 years old	51	19.6	
	14-17 years old	190	73.1	
	18 years old and above	5	1.9	
	5 and below	90	34.6	
Number of signature modes down down	6-10	71	27.3	
Number of cigarettes smoked per day	11-15	29	11.2	
	16 and above	70	26.9	
	Not dependent	82	31.6	
Addiction according to mFTQ test	Dependent	101	38.8	
	Highly dependent	77	29.6	
	Not dependent	29	11	
Addiction according to HONC test	Dependent	138	53	
	Highly dependent	93	36	

HONC test scores and mFTC	Q test scores	arettes used with addicti	on according to	
Parameters	Number of patients	HONC test scores		
The relationship between the nu	imber of cigarettes and addiction			
6 or fewer cigarettes	90	2.6±2.4		
6-10 cigarettes	71	6.0±3.1	0 001*	
11-15 cigarettes	29	6.2±3.5	p<0.001*	
16 or more cigarettes	70	7.7±2.6		
Parameters	Number of patients	mFTQ test sco	res	
The relationship between the nu	umber of cigarettes and addiction			
6 or fewer cigarettes	90	1.9±1.6	0 001**	
6-10 cigarettes	71	3.9±1.7	p<0.001**	

Table 2. Examination of the relationship between the number of cigarettes used with addiction according to

Table 3. The relationship between the demographic data and addiction

	mFTQ test	score	HONC test score			
	Pearson r	p-value	Pearson r	p-value		
mFTQ score	1.000	-	0.720	<0.001*		
HONC score	0.720	< 0.001*	1.000	-		
Age	0.283	< 0.001*	0.267	<0.001*		
Family income	0.208	< 0.001*	0.146	0.018*		
Pocket money	0.247	0.001*	0.197	0.001*		
Age at first smoking	-0.190	0.002*	-0.112	0.041*		
Dependency duration (from the first cigarette)	0.133	0.031*	0.056	0.368*		
Cigarettes smoked per day	0.687	< 0.001*	0.543	<0.001*		
Modified fagerström test for nicotine dependence, HONC: Hooked on nicotine checklist, 'Pearson's rank correlation coefficient						

obtained are interpreted, a one-unit increase in the age variable causes a 0.17-unit increase in the mFTQ score, and if there is a smoker in the family, a 0.42-unit increase in the mFTQ score. If the family knows that the adolescent smokes, there is a 0.93 unit increase in the mFTO score, and each increase in the number of cigarettes smoked per day causes a 0.16 unit increase in the mFTO score. In addition, the mFTO score of those whose fathers have a high school education is 0.56 units higher than the score of those whose fathers are primary school graduates. The MFTO scores of those whose fathers are university graduates are 0.66 units higher than the scores of those whose fathers are primary school graduates. The three most

important variables that have the most significant impact on the mFTQ score are; Number of cigarettes smoked per day (Beta=0.52), knowing that the family smokes (Beta=0.19) and being able to smoke at home (Beta=0.13), respectively. The effects of demographic data on addiction according to the mFTQ test are shown in Table 4.

After univariate analyses, backward stepwise regression analysis was performed with the variables found to be significant in terms of mFTQ scores (dependent variable). In this method, all variables are included in the model, then the variable with the lowest contribution to the model is removed and the model is rebuilt, this process continues until a meaningful model is obtained. The overall model was found to be significant (F=33.368, p<0.001). The model explains approximately 44% of the variance in the HONC score (dependent variable). If the statistics obtained are interpreted, a one-unit increase in the age variable will result in a 0.268-unit increase in the HONC score, if there is a smoker in the family, a 1.023-unit increase in the HONC score, if the adolescent can afford to buy cigarettes, a -1.34-unit increase in the HONC score, and if the family knows that he smokes, a 1.54-unit increase in the HONC score. Each increase in the number of cigarettes smoked per day causes an increase of 0.159 units in the HONC score. The three most important variables that have the most significant impact on the HONC score are; Number of cigarettes smoked per day (Beta=0.34), knowing that the family smokes (Beta=0.21) and being able to buy cigarettes (Beta=0.16), respectively. The effects of demographic data on addiction according to the HONC test are shown in Table 5.

In our study, a strong correlation between the two tests was found at 0.720 in demonstrating cigarette addiction in adolescents.

Discussion

In this study, it was found that cigarette addiction in middle and late-age adolescents was 70% according to the mFTQ test and 90% according to the HONC test. According to both tests, it was determined that the most important factors affecting addiction were the number of cigarettes smoked per day, the amount of pocket money received from the family, and the high income of the family. It was determined that addiction increased when the family was aware of the smoking status and if the adolescent could smoke at home. In our study, it was observed that late-age adolescents were more dependent than middle-age adolescents. Addiction increased as the age of onset of smoking decreased. The mean age of regular smoking among the adolescents was 14.2±2.1 years, and the mean age of first smoking was 13.9±2.3 years. Surprisingly, the earliest age to start smoking was 5 years; 14 (5.4%)

adolescents started smoking under the age of 10 years. The highest ratio to start smoking was between the ages of 14-17, and 73% of adolescents started smoking at such an early age.

Early experience with smoking addiction and sexspecific risks have been the focus of some research. It has been shown that smoking affects the reward pathway more in men than in women and that the sex factor is the main driver of the relationship between cigarette craving and early relapse (14). Pogun et al. (15) showed that adolescents were more sensitive to nicotine exposure and that sex was one of the foundations of addiction development. In the study of Sylvestere et al. (16) on 240 girls and 184 boys that investigated nicotine addiction between the sexes, adolescent girls tended to be regular smokers and nicotine addicts due to their biologic and sex-specific social characteristics, but the only thing that did not differ between the sexes was the age of the first cigarette. In our study, we found that sex did not play an important role in addiction.

Table 4. Effects of demographic data on addiction according to mFTQ test						
	В	SH	Beta	Т	p-value	
Constant	-2.13	1.18		-1.80	0.072	
Age	0.17	0.07	0.11	2.41	0.016	
Family members are smokers, yes	0.42	0.23	0.08	1.809	0.072	
If the adolescent's family knows about their smoking, yes	0.93	0.25	0.19	3.72	<0.001	
Being able to smoke in the house, yes	0.60	0.26	0.13	2.32	0.021	
Cigarettes smoked per day	0.16	0.01	0.52	10.9	<0.001	
Father's education level high school, yes	0.56	0.22	0.12	2.53	0.012	
Father's education level university, yes	0.66	0.3	0.10	2.203	0.029	

Table 5. Effects of demographic data on addiction according to the HONC test					
	В	SH	Beta	t	p-value
Constant	-1.97	2.201		-0.895	0.372
Age	0.268	0.113	0.119	2.38	0.018
Family members are smokers, yes	1.023	0.384	0.131	2.66	0.008
Buys a pack of cigarettes	-1.34	0.49	0.16	-2.74	0.007
If the adolescent's family knows that smokes, yes	1.54	0.39	0.21	3.96	<0.001
Went to the public school, yes	1.06	0.38	0.13	2.8	0.005
Cigarettes smoked per day	0.159	0.02	0.34	6.1	<0.001
Smoking ban at school	-0.988	0.34	-0.13	-2.9	0.004

Brain development continues throughout adolescence. The binding of nicotine to nicotinic acetylcholine receptors in the midbrain is more severe in adolescence. For this reason, adolescents are more vulnerable to nicotine addiction (1). Starting to smoke at an early age and experiencing the first nicotine exposure at an early age cause adolescents to become more addicted in their future lives. Studies in experimental animals have shown that as a result of nicotine exposure during adolescence, many genes affecting neuroplasticity in the brain are affected and cause permanent changes in nicotine-related brain regions (17,18). In the study of Kendler et al. (19) of 175 male-male and 69 female-female monozygotic twins, one twin started smoking 2 years earlier than the other and genetic and environmental factors were tried to be stabilized. It was shown that the earlier the twins started smoking, the higher their dependency in their later life than their twins who started smoking late. Lamin et al. (20) found that the age at the first cigarette attempt was 7-12 years (19.3%), 13-17 years old (63.2%), and 18-22 years (17.5%). When we separated the adolescents according to the smoking age range, 14 (5.4%) started smoking at the age of 10 years or younger, 51 (19.6%) started smoking between the ages of 11-13 years, 190 (73.1%) started aged 14-17 years, and five (1.9%) started aged 18 years and over. Similar to both studies, trying smoking and starting to use cigarettes regularly coincided with the middle adolescence period. In terms of public policy, we think that making access to cigarettes difficult for this age group, reducing the initiation of smoking, and delaying the age of starting smoking will reduce both the development of addiction and smoking-related morbidity and mortality.

In adolescents, the time between trying the first cigarette and starting regular cigarette smoking can be very short, and nicotine addiction can develop within weeks. Adolescents' nicotine addiction levels should be determined and timely intervention should be made. Different addiction scales are used to determine addiction levels in young people. In this regard, it is very important to better understand the relationship between nicotine addiction scales, understand the developmental stages of symptoms, and which symptoms are more associated with addiction. In our study, without defining the relationship between the internal dynamics of the HONC test and the mFTQ

test with addiction, we analyzed the parameters that we investigated with the HONC test and the mFTQ test, both within themselves and between each other, and showed the relationship between both tests regarding addiction. There are few studies in the published literature examining the relationship between the HONC test and the mFTQ. In the study of Wellman et al. (21) with 1130 adult smokers, the correlation between the HONC test and the mFTO was shown as 0.83. We think that the fact that the 6-item Fagerström adult test was used in the study of Wellman et al. (21) is the main source of the difference in compatibility between the two tests. The HONC test is more sensitive in detecting the onset of nicotine dependence, with 50% of occasional smokers and 100% of current smokers ticking at least one HONC test item in a youth study (22). Focusing on the mFTQ, a more sensitive and valid test can be defined by complementing the HONC test, which is more sensitive in catching young people with low nicotine addiction who are exposed to very low levels of tobacco use. In the study conducted by McPearson et al. (23) with 109 adolescent smokers aged 14-18 years (58% of whom were girls, and the mean age was 16.8 ± 1.1 years), the condition of smoking at least 1 cigarette in the last 1 month was sought. It was determined that 95.5% of the participants said yes to at least one HONC test question. In our study, 88.8% of the participants answered yes to at least one of the HONC questions.

Another nicotine addiction that is not seen in our study population but is becoming more widespread in our country and the world is e-cigarette use. In the United States, adolescents use e-cigarettes and similar products more than other tobacco products (24). The availability of flavored products, social influences, and the effects of nicotine may affect adolescents' initiation and continuation of these products (25,26). In a study conducted by Audrain-McGovern et al. (27) in the state of Philadelphia with 1808 adolescents, internal and external factors that led to an increase in the number of days of e-cigarette use in 30 days and in the number of days of use in 30 months were investigated, and depression was determined to be the factor that caused the most increase in e-cigarette use. It was emphasized that two different adolescent groups should be focused on in the fight against e-cigarettes. A high-risk group that started using e-cigarettes early and another group with a low-risk profile that started

using e-cigarettes late. The timing and content of prevention studies should be different for each group.

Study Limitations

The most important limitation of the study was the detection of adolescents who smoked. We think most of the adolescent families weren't aware of their child's smoking. Since the patients came to the hospital with their families, we think that we were able to detect a small portion of the adolescents who smoked.

Conclusion

In conclusion, we showed in this study that most of the adolescents who smoked were at the addiction level and that the age of onset of smoking coincided with the middle adolescence period. We found that the factor most associated with addiction among smoking adolescents was the number of cigarettes smoked. We showed that mFTQ and HONC tests had a strong and significant relationship with smoking addiction among adolescents in our country. In both tests, we found that the number of cigarettes smoked and the family's awareness of their child's smoking was highly associated with addiction. This is the first study conducted in our country to measure addiction levels in adolescents using the mFTO and HONC tests. In our study on addiction, we tried to minimize errors by using two different scales given the knowledge that each scale has its strengths and weaknesses in determining addiction, and we showed that these two scales gave consistent results in adolescents in our country. To reduce adolescents' access to cigarettes, the right steps should be taken to implement a ban on sales to those aged under 18 years and practices should be reconsidered to reduce their access to cigarettes. We think that peer education models should be widespread in schools to prevent adolescents from starting smoking and to reduce the frequency of smoking. Considering that trying to smoke in adolescence carries a greater risk of addiction, it would be useful to take precautions specific to this age period.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the local Ethics Committee of Keçiören Training and Research Hospital (date: 13.12.2017, approval number:1561). Our study was conducted in accordance with the ethical principles

of the World Medical Association Declaration of Helsinki.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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