

An example of a comprehensive approach to increase the access to evidence-based tobacco cessation support for smokers with rheumatic diseases

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ABSTRACT

INTRODUCTION For a comprehensive approach to adult smoking cessation, contributions by all physicians are more relevant than individual efforts. This study is an example of a collaboration that aims to increase access to smoking cessation assistance for smokers with rheumatic diseases.

METHODS For this prospective cohort study, data were collected from adult current smokers diagnosed with inflammatory rheumatic disease. Brief cessation interventions were implemented by their primary rheumatology physician and they were informed about the smoking cessation service of the hospital. Upon their acceptance, their appointment to SCC was immediately arranged within the schedule of the clinic. After the intervention, their quit status was evaluated and confirmed by exhaled air carbon monoxide measurement at third month. Multivariate logistic regression models were used to evaluate the associated factors with successful quit status. **RESULTS** The mean age of the total 184 patients was 45.5

(SD=12.4) years, and 43.4% were female. The majority consisted of patients with rheumatoid arthritis (46.1%) and ankylosing spondylitis (38.0%). Of the patients, 117 (63.5%) were willing to quit. At third month, quit rate of the total group was 13.5%; 21.3% of the willing group, and 0% among the non-willing group. Among the willing group, 39% of those admitted to the cessation clinic and 14% of the non-admitters had successfully quit smoking (p<0.05). Application to the smoking cessation clinic had the highest association with successful quit attempts (OR=8.126; 95% CI: 2.488-26.536). The Fagerström test score (OR=0.672; 95%) CI: 0.506–0.892) and the income level (OR=0.269; 95% CI: 0.089-0.810) were negatively associated determinants. **CONCLUSIONS** The highest cessation success was achieved in patients who applied to the smoking cessation outpatient clinic. Rheumatologists should build an effective bridge with smoking cessation centers for their smoker patients.

INTRODUCTION

The harmful effects of tobacco exposure have been proven to be directly related to the etiopathogenesis, clinical course, and response to treatment of inflammatory rheumatic diseases such as rheumatoid arthritis (RA)^{1,2}. In most rheumatic diseases, smoking is associated with increased risk of cardiovascular disease, as well as greater disease severity, higher incidence of disease, and decreased treatment response³⁻⁷. Prevention of tobacco smoke exposure and smoking cessation assistance are of vital importance in this group of patients. However, studies have shown that this link is not sufficiently recognized by individuals with rheumatic diseases⁸. In a qualitative study, 19 adult patients (12 with RA and 7 with systemic lupus erythematosus, SLE) were included to deeply evaluate the common barriers to and facilitators of smoking cessation. Commonly discussed barriers were determined to be: viewing smoking as a 'crutch' in the midst of rheumatic diseases, rarely receiving



cessation counseling in rheumatology, and very limited awareness that smoking may worsen rheumatic diseases or reduce the effectiveness of some rheumatological medications. In the same study, it was reported that most patients were unaware of the increased health risk of smoking. Few were aware of the physiological effects of smoking on rheumatic diseases, and none had heard that smoking may reduce the effectiveness of rheumatic disease medications8. In another international study, a survey was sent to the rheumatologists participating in the multinational Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) group. Rheumatologists from 44 departments in 25 countries (16 European) completed the survey. The survey involved 395 rheumatologists, of whom 25 (6.3%) were smokers, and 199 nurses for patient education, of whom 44 (22.1%) were smokers⁹. The reported findings were that primary rheumatology physicians and allied health professionals such as nurses who carry out the diagnosis, the follow-up and treatment this group of patients, stated that they could not support their patients sufficiently in smoking cessation⁹. Although it is a risk factor that adversely affects the severity of rheumatic diseases, and despite the recommendations of smoking cessation guidelines, it has been reported that smoking cessation counselling was provided in 10% of rheumatology applications¹⁰, and it has been reported that requests to the smoking quitline increased 26 times after the implementation of a smoking cessation assistance protocol specific to the rheumatology clinic¹¹.

There are more than 300 smoking cessation outpatient clinics (SCCs) in Turkey. Smoking cessation counselling services and access to free pharmacological smoking cessation treatments are provided through SCCs. Applications can be made by appointment or as an outpatient, through the Central Physician Appointment System (MHRS)¹². However, it has been reported in a recent study that smokers are not sufficiently aware of the existence of these outpatient clinics or what kind of services they provide¹³. It is known that all healthcare providers should have basic knowledge and equipment to help their patients who smoke to quit smoking and should apply this brief cessation interventions (5As/5Rs) at every opportunity¹⁴. From the same perspective, rheumatology physicians have an effective role in smoking cessation assistance.

Therefore, this study is an example of a collaboration that aims to increase access to smoking cessation assistance for smokers with rheumatic diseases.

METHODS

Sample and setting

Patients who applied to the tertiary care public healthcare unit, at the Recep Tayyip Erdoğan University Education and Research Hospital's Rheumatology outpatient clinic, between 1 March and 31 October 2022, were included in this prospective cohort study.

Inclusion criteria

Among the patients aged ≥ 18 years who presented to the rheumatology outpatient clinic, current smokers with at least one of the rheumatic disease diagnoses were included in the study.

Exclusion criteria

Those with a diagnosis of active mental disorder and those who refused to participate in the study were excluded.

Rheumatological disease diagnoses

Rheumatological disease diagnoses were confirmed according to rheumatology guidelines American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 RA classification criteria¹⁵, Assessment of SpondyloArthritis International Society (ASAS) classification criteria for both axial and peripheral ankylosing spondylitis^{16,17}, 2006 Classification of Psoriatic Arthritis (CASPAR) for psoriatic arthritis¹⁸, 2012 Systemic Lupus International Collaborating Clinics (SLICC) for SLE¹⁹, Tel Hashomer diagnostic criteria for familial Mediterranean fever²⁰, 2014 International Criteria for Behcet's Disease (ICBD) and ACR/EULAR 2015 GOUT classification criteria^{21,22}.

Study protocol

In this prospective cohort study, after obtaining written informed consent from the patients who were eligible for participation in this study, a visual brochure that shows the link between arthritis and the tobacco exposure, and how the quitting smoking will affect their disease course, and decrease the need of medications such as corticosteroid, were given to the patients to read. Afterwards, a data collection form was filled in (Supplementary file). The data collection form consisted of 4 parts: 1) demographic characteristics and past medical history; 2) questions regarding smoking behavior and knowledge about the link between tobacco exposure and rheumatologic diseases; 3) FTND questionnaire; and 4) past quit attempts and readiness of quit evaluation (5As/5Rs), and the follow-up quit status at 3rd month. For patients who were willing to quit smoking, the primary rheumatology physician communicated directly with the pulmonologist, who was also the investigator of this study in the same hospital, and appointments for the pulmonology smoking cessation outpatient clinic were arranged immediately for the closest counselling date, which is usually within the following one month (1 week to 4 weeks). Those who were not willing to quit smoking were informed that they could make an appointment through national quitlines.

Smoking cessation clinic's implementation

Patients' participation in the smoking cessation clinic program clinic was evaluated with pulmonary function tests and chest radiographs, and the presence of comorbidities,



cardiac or psychiatric diseases were asked. Available patients were registered in the tobacco dependence treatment monitoring system, and nicotine replacement therapy in the form of nicotine patches (25 mg transdermal nicotine) was initiated free of charge. The details of the counselling were described previously^{23,24}. Each patient received enough nicotine patches for 2–3 weeks by hand and instructed to initiate the use of the patches in their target quit date and not to smoke after initiation of NRT. Their control smoking cessation appointments were arranged according to the patient's target quit date plan. At control visits, after use of initial nicotine patches for 3 weeks, the dosage of nicotine patches was decreased to 15 mg for 3 weeks and their third appointments were scheduled.

Follow-up, and CO measurement

Patients were telephoned by the rheumatology physician after 3 months. Their quit status, attendance to smoking cessation outpatient clinic appointments, initiated smoking cessation treatments, and duration of treatment, were asked. Those who stopped smoking from the target quit date were defined as a 'quitter'. Those who continued to smoke after the target quit date were defined as a 'non-quitter'. Those who declared that they quit smoking after their target quit date, were invited to the smoking cessation outpatient clinic for expired air carbon monoxide (CO) concentration measurement performed by the pulmonologist (DK). For CO measurement the Smokerlyzer 0086 Bedfont est.1976 was used, and levels <0.7 ppm were accepted for a quitter. Anyone 'lost to follow-up' was regarded as a non-quitter.

Statistical analysis

The minimum sample size required for the study was calculated as 145 individuals with 95% power and 30% effect size at α =0.05 level using G-Power 3.1.9.7 software. Both the independent variable (readiness to quit) and the independent variable (quit status at 3rd month) were dichotomous. Data were analyzed using IBM SPSS Statistics for Windows. Armonk, NY, USA, IBM Corp. software was used to analyze the data. The numerical data obtained in the study are presented as mean and standard deviation if they show a normal distribution, and with median and interquartile range if they do not show a normal distribution. Categorical data are presented as frequencies and percentages. Relationships between categorical data were evaluated by chi-square test. The distribution characteristics of continuous data were determined by Kolmogorov Smirnov test, the differences between the groups of variables showing normal distribution were evaluated by t-test, and the differences of variables not showing normal distribution were evaluated by Mann Whitney U test. The significance level was set at p<0.05 in all statistical analyses. Factors affecting quit success such as age, gender, income level, body mass index (BMI), rheumatological treatment duration, Fagerström test for nicotine dependence (FTND) score, and access to evidencebased smoking cessation treatments, were determined by multivariate logistic regression.

RESULTS

Among a total of 1040 patients aged \geq 18 years who applied to the rheumatology outpatient clinic between 1 March and 31 October 2022, 184 (17.6%) were current smokers. According to the brief smoking cessation interventions applied to 184 current smokers, 117 (63.5%) were found to be willing to quit smoking and 67 (36.4%) were found not to be willing.

Table 1 compares various characteristics of patients willing and unwilling to quit smoking. Among the 184 patients, the mean age was 45.5 years (SD=12.4), 43.4% were female, 38% were employed, 50% had an education level of high school or above, 82% were married, and 47.8% had an income of minimum wage or below. In terms of rheumatic diseases, 46.1% had rheumatoid arthritis (RA), 38% had ankylosing spondylitis (AS), and 15.7% had other rheumatic diseases (psoriatic arthritis, systemic lupus erythematosus, gout, familial Mediterranean fever, Behcet's disease). The mean age at diagnosis was 39.5 years (SD=12.6), median duration of diagnosis was 36 (IQR: 7) months, and median duration of treatment was 36 (IQR: 72) months.

The median age at initiation of smoking was 19.50 (IOR: 7.00), and the median FTND score was 4.00 (IQR: 4.00). Spouses/partners of 27.1% of the patients were current smokers, and 50% of the patients answered 'no idea' when asked whether there was a relationship between smoking and rheumatic diseases. The proportion of patients who had at least two previous quit attempts was 51%. Among all patients, 90.7% had never received smoking cessation assistance, and 10.3% had applied to smoking cessation outpatient clinics in their previous attempts. In this study, 37 patients (20.1%) had applied to a smoking cessation outpatient clinic after 5As/5Rs interventions. Among the patients, 117 (63.5%) were willing to quit smoking and 67 (36.4%) were not willing. In the willing group, the mean FTND scores were lower and the proportion of patients who had previously tried to quit smoking at least 2 times was higher (Table 1). In the third month, the rate of smoking cessation in the willing group was 21.3%, while the rate of smoking cessation in the non-willing group was 0 (p<0.05). Among those who were willing, 36 (30.7%) attended the smoking cessation outpatient clinic appointment, nicotine patches were initiated in all of those who applied to the smoking cessation outpatient clinic, and the rate of smoking cessation in the third month was higher among those who applied than those who did not apply (39% vs 13.6%) (Table 2). Those who did not apply for smoking cessation outpatient clinic appointments stated during telephone calls that they could not apply for their appointments due to special reasons (such as agricultural time, travelling, etc.).

The 5As intervention was applied to the willing patients and 5Rs was applied to the non-willing patients. Those who

Table 1. Characteristics of patients according to their desire to quit smoking within the Recep Tayyip Erdoğan University Education and Research Hospital's Rheumatology outpatient clinic, Turkey 2022 (N=184)

Characteristics	Total (N=184) n (%)	Willing to quit (5As) (N=117) n (%)	Not-willing to quit (5Rs) (N=67) n (%)	р
Age (years), mean (SD) (range:19-81)	45.5 (12.4)	45.7 (12.9)	45.9 (11.7)	0.710
Gender				0.375
Female	80 (43.4)	48 (60)	32 (40)	
Male	104 (56.5)	69 (66.3)	35 (33.7)	
BMI (kg/m ²), median (IQR)	26.89 (5.42)	26.78 (5.36)	27.11 (5.92)	0.725
Employment status				0.687
Actively employed	70 (38.0)	47 (40.1)	23 (34.3)	
Unemployed	86 (46.7)	52 (44.4)	34 (50.7)	
Retired	28 (15.2)	18 (15.3)	10 (14.9)	
Education level				0.878
Primary school and lower	92 (50)	59 (50.4)	33 (49.2)	
High school and higher	92 (50)	58 (49.5)	34 (50.7)	
Marital status				0.428
Married	151 (82)	19 (16.2)	14 (20.8)	
Single	33 (17.9)	98 (83.7)	53 (79.1)	
Income level				0.068
Minimum wage and lower	88 (47.8)	50 (42.7)	38 (56.7)	
Higher than minimum wage	96 (52.1)	67 (57.2)	29 (43.2)	
Rheumatologic diagnoses				0.978
Rheumatoid arthritis	85 (46.1)	54 (46.1)	31 (46.2)	
Ankylosing spondylitis	70 (38.0)	45 (38.4)	25 (37.3)	
Other rheumatologic diseases	29 (15.7)	18 (15.3)	11 (16.4)	
Diagnosis age (years), mean (SD)	39.5 (12.6)	39.2 (13.2)	40.0 (11.3)	0.670
Diagnosis duration, median (IQR)	3.00 (7.00)	4.00 (8.00)	3.00 (7.00)	0.517
Treatment duration, median (IQR)	36.00 (72.00)	36.00 (84.00)	24.00 (60.00)	0.243
Smoking initiation age (years), median (IQR)	19.50 (7.00)	19.00 (8.00)	20.00 (6.00)	0.814
Smoking packs/year, median (IQR)	17.50 (21.50)	18.00 (23.50)	16.00 (18.00)	0.821
FTND score, median (IQR)	4.00 (4.00)	3.00 (3.00)	4.00 (5.00)	0.034
Smoker couple/partner presence				0.046
Present	50 (27.1)	26 (22.2)	24 (35.8)	
Absent	134 (72.8)	91 (77.7)	43 (64.1)	
Household smokers, median (IQR)	1.00 (2.00)	1.00 (2.00)	1.00 (2.00)	0.321
Does tobacco cause rheumatologic diseases?				0.645
Yes	57 (30.9)	39 (33.3)	18 (26.8)	
No	35 (19.0)	22 (18.0)	13 (19.4)	
No idea	92 (50)	56 (47.8)	36 (53.7)	
Previous quit attempts				0.012
At least once	90 (48.9)	49 (41.8)	41 (61.1)	

Continued

Table 1. Continued

Characteristics	Total (N=184) n (%)	Willing to quit (5As) (N=117) n (%)	Not-willing to quit (5Rs) (N=67) n (%)	р
More than once	94 (51.0)	68 (58.1)	26 (38.8)	
Cessation methods in previous quit attempts				0.142
NRT or varenicline	17 (9.2)	10 (8.5)	7 (10.4)	
No support	167 (90.7)	107 (91.4)	60 (89.5)	
Previous admissions to smoking cessation clinics				0.967
Never	165 (89.6)	105 (89.7)	60 (89.5)	
At least once	19 (10.3)	12 (10.2	7 (10.4)	
Admission to smoking cessation clinics during study period				<0.001
Applied	37 (20.1)	36 (30.7)	1 (1.4)	
Did not apply	147 (79.8)	81 (69.2)	66 (98.5)	
Quit status at 3 months				< 0.001
Quitters	25 (13.5)	25 (21.3)	0	
Non-quitters	159 (86.4)	92 (78.6)	67 (100)	

FTND: Fagerström test for nicotine dependence.

Table 2. Cessation status of those who underwent 5As according to their applications to smoking cessation outpatient clinics (N=117)

	Total (N=117) n	Quitters (N=35) n (%)	Non-quitters (N=92) n (%)	р
Applied to smoking cessation clinic	36	14 (38.9)	22 (61.1)	0.02
Did not apply to smoking cessation clinic	81	11 (13.6)	70 (86.4)	

Table 3. Factors associated with quit success of patients willing to quit among patients within the Recep Tayyip Erdoğan University Education and Research Hospital's Rheumatology outpatient clinic, Turkey 2022 (N=117)

	OR	95% CI	р
Age (per 1 age increment)	0.99	0.94-1.03	0.746
At least high school graduate (Ref: primary school and lower)	1.13	0.34-3.75	0.834
Body mass index (per 1 unit increment)	1.12	0.98-1.28	0.088
Treatment duration (per 1 year increment)	1.00	0.99-1.00	0.929
Male (Ref: Female)	2.69	0.82-8.80	0.100
Household smokers	1.39	0.80-2.41	0.231
Admitted to SCC (Ref: not admitted)	8.12	2.48-26.53	0.001
FTND score (per 1 score increase)	0.67	0.50-0.89	0.006
Higher income level than minimum wage (Ref: equal and less than minimum wage)	0.26	0.08-0.81	0.020

Factors affecting quit success were determined by multivariate logistic regression, the model was not adjusted for any variable. FTND: Fagerström test for nicotine dependence.

Figure 1. Among the total sample of 184 patients, 117 were willing to quit and 67 were not-willing. Quit rate at third month was highest among those admitted to the smoking cessation rheumatology outpatient clinic, Recep Tayyip Erdoğan University Education and Research Hospital, 1 March – 31 October 2022



Figure 2. Among those admitted to the smoking cessation rheumatology outpatient clinic (36), the majority did not follow control visit appointments, Recep Tayyip Erdoğan University Education and Research Hospital, 1 March – 31 October 2022



received 5As intervention were immediately scheduled for smoking cessation appointments at the same hospital. Those who underwent 5Rs and were not willing to quit smoking at that moment, were informed about access to smoking cessation outpatient clinics. All 117 patients who were willing to quit smoking and who were administered the 5As, were given an appointment date and time at the smoking cessation outpatient clinic; 36 (30.7%) of them applied, while 81 (69.2%) did not apply for various reasons. In the third month, all 184 patients were contacted by telephone, and it was found that the smoking cessation rate of the total sample was 13.5%, the willing group was 21.3%, those who attended the smoking cessation outpatient clinic appointments were 39%, and those who did not attend the



Figure 3. Among the nicotine replacement treatment-initiated group (36), only 3 followed the recommended treatment duration and the proportion of quitters was highest among them, Recep Tayyip Erdoğan University Education and Research Hospital, 1 March – 31 October 2022



smoking cessation outpatient clinic appointments were 14% (Figure 1). Those who stated that they had quit smoking were invited for CO measurements and all of them had exhaled CO levels between 0 and 3 ppm. Among those who were not willing to quit smoking, only 1 person had applied to the smoking cessation outpatient clinic and none of them had quit smoking when their smoking cessation status was investigated (Figure 1).

According to the number of control visits of the patients who applied to the smoking cessation outpatient clinic, 55.5% of the patients did not come to the control after the first application and the cessation rate of this group was 25%, while the remaining patients applied at least once and their cessation rates were higher (Figure 2). Figure 3 shows the quitters' numbers according to nicotine replacement therapy use durations.

Table 3 shows the multivariate logistic regression model of patients who were willing to quit. There was a positive association between the smoking cessation success among those who applied to the smoking cessation outpatient clinic compared to those who did not (OR=8.12; 95% CI: 2.48–26.53) and there was a negative association with the FTND score (OR=0.67; 95% CI: 0.50–0.89), and those whose income was above the minimum wage were less successful in quitting than those with an income below the minimum wage (OR=0.26; 95% CI: 0.08–0.81).

DISCUSSION

This study is a prospective cohort study conducted on smokers with rheumatoid arthritis and has shown that the factor that increases smoking cessation rates is access to evidence-based smoking cessation support. It has also shown that rheumatologists, who are primary physicians, have the potential to form an effective bridge with smoking cessation centers in order to increase this access. It is an example of the all-out struggle of all healthcare professionals with a new approach to quitting tobacco. To enhance this approach, physicians should receive competent, comprehensive training on tobacco cessation assistance in the medical education curriculum. In our new study, in which we tested a pilot application of this, it was determined that physician candidates did not consider themselves sufficient and competent in this regard²⁵. A number of barriers to accessing smoking cessation assistance have been reported. These vary widely, originating from patients as well as physicians and/ or healthcare systems. Barriers for physicians include not feeling competent in providing cessation assistance. If it is healthcare related, the reasons include not being able to find an appointment or smoking cessation treatments not being reimbursed. If it is patient-related, as in our findings, factors such as high FTND addiction levels, socioeconomic disadvantaged groups, etc. are negatively associated barriers to smoking cessation^{24,26}.

With the effective implementation of brief quit interventions, quit rates can increase up to 10%, and in our study, this rate was 14%. In other words, those who were given only suggestions and did not receive any help to quit smoking also quit. Here, the importance of clearly explaining the connection between tobacco exposure and disease to the patient by the physician is known²⁵. In this

study, we explained with visual demonstrations that RA and joint damage, pain, the need for CS use, and the increase in inflammation are triggered by tobacco exposure. In our study, half of the patients answered 'No idea' to the question: 'Do you think smoking causes rheumatic diseases?', and 19% answered 'No'. In studies conducted on individuals with rheumatic diseases, the lack of knowledge status of patients on this subject has been determined, therefore it was observed that the participants wanted more information about the relationship between RA and smoking from the rheumatologist and nurse²⁷. In another study, information about the effects of smoking on RA and anti-rheumatic medications played an important role in facilitating smoking cessation²⁸. In a study conducted on rheumatology patients, oral and written information emphasizing the benefits of smoking cessation was given by rheumatologists at the beginning. A questionnaire covering the patients' addiction status and previous quit attempts was completed. In the third month, a follow-up visit was made by the nurse to determine the patients' smoking cessation status (reduction, quitting, etc.), the need for pharmacological treatment and for verbal support. In addition, telephone interviews were made with the patients at 3, 6 and 12 months. The smoking cessation rates of the 152 patients who participated in the study were 11.8% in the 3rd month, 14.4% in the 6th month, and 15.7% in the 12th month. Among the patients, 19% had reduced smoking by more than 50% in 12 months²⁹. In our study, among a total of 184 patients who were current smokers, 13.5% quit smoking in the third month. This constituted 21.3% of the willing group. None of the nonwilling group had quit smoking. Smoking cessation rates were similar to those found in the literature. In addition, in our study, the measurement of CO in exhaled air in smokers who quit smoking was advantageous in the clinical evaluation of nicotine dependence and had a positive effect on patients.

According to the 2008 smoking cessation guidelines, it was recommended that brief smoking cessation interventions should be applied to every patient and smoking cessation assistance should be provided only to those who are willing to quit smoking³⁰. However, according to new approaches, it is recommended to start smoking cessation treatments even for individuals who are not ready to quit smoking³¹. In our study, the unwilling individuals were only told that they could apply to the smoking cessation outpatient clinic by making an appointment and it was learnt that only 1 of them applied. How our results would be if all patients were directly assisted to quit smoking regardless of their readiness to quit smoking is an issue that needs to be investigated and real-life application studies are needed in this regard.

Another important finding in this study was that 81 of the 117 patients who were willing to quit smoking did not apply, although an appointment was immediately arranged for all 117 patients at the smoking cessation outpatient clinic of the same hospital. They stated during telephone calls that they could not apply for their appointments due to special reasons (such as agricultural time, travelling, etc.). In the new smoking cessation guidelines, it is stated that immediate initiation of treatment increases the success of smoking cessation, therefore, it is more effective to start the treatment of patients who want to quit smoking immediately³¹.

Strength and the limitations

Our study addresses an important issue of integrating smoking cessation interventions across health disciplines and collaboration between services. Also, evaluation of quit status by validation of exhaled breath CO measurement is another strength. However, due to the study design, its limitations are response bias, recall bias, and the potential lack of generalizability to other settings.

CONCLUSIONS

Our findings show that the smoking cessation rates of current smokers with inflammatory rheumatic diseases will increase with the effective implementation of brief cessation interventions by primary physicians and that this practice is an effective method. This practice is an example and guidance for all branches, especially rheumatology physicians, and should be disseminated by all disciplines.

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The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

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