Does decision tree analysis predict oral ulcer activity-related factors in patients with Behçet's syndrome?

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Abstract

Objective
The study aimed to identify the interactions among treatment protocols and oral ulcer activity related factors in patients with Behçet's syndrome (BS) using the Classification and Regression Tree (CART) algorithm.

Methods
In this cross-sectional study, 979 patients with BS were included from16 centres in Turkey, Jordan, Brazil and the United Kingdom. In the CART algorithm, activities of oral ulcer (active vs. inactive), genital ulcer (active vs. inactive), cutaneous involvement (active vs. inactive), musculoskeletal involvement (active vs. inactive), gender (male vs. female), disease severity (mucocutaneous and musculoskeletal involvement vs. major organ involvement), smoking habits (current smoker vs. non-smoker), tooth brushing habits (irregular vs. regular), were input variables. The treatment protocols regarding immunosuppressive (IS) or non-IS medications were the target variable used to split from parent nodes to purer child nodes in the study.

Results
In mucocutaneous and musculoskeletal involvement (n=538), the ratio of IS use was higher in patients with irregular toothbrushing (ITB) habits (27.1%) than in patients with regular toothbrushing (RTB) habits (14.2%) in oral ulcer activity. In major organ involvement (n=441), male patients with ITB habits were more likely treated with IS medications compared to those with RTB habits (91.6% vs. 77.6%, respectively).

Conclusion
Male BS patients on IS who have major organ involvement and oral ulcer activity with mucocutaneous and musculoskeletal involvement have irregular toothbrushing habits. Improved oral hygiene practices should be considered to be an integral part for implementing patient empowerment strategies for BS.

Key words
Behçet's syndrome, oral ulcer, decision tree analysis

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Introduction

Behçet's syndrome (BS) is a chronic and multi-systemic inflammatory disorder characterised by oral and genital ulcers, cutaneous and musculoskeletal involvement as well as major organ involvement such as ocular, vascular, central nervous system and gastrointestinal involvement. Although the genetic background (HLA-B51) plays a role in the pathogenesis of the disease, immune dysregulation, hormonal and microbial factors are also implicated (1-5). Oral ulcers are common clinical manifestations lead to poor oral functions and impaired daily life in patients with BS. Oral ulcer is the key manifestation of the disease activity and may also be an indicator for the development of major organ involvement in BS (4, 6-13).

The oral environment is a dynamic ecosystem that is an integral part of overall health. Dysbiosis of the oral microbiome (14-16), infections caused by *Streptococci* and saliva immunity (3, 4, 17-21) as well as poor oral health leading to infection foci (22, 23) are all implicated in multifactorial nature of the disease pathogenesis. Increases in colonisations of various *Streptococci* strains, changes in the oral microbiome, molecular mimicry between bacterial antigens and human peptides can trigger an inflammatory response in genetically susceptible patients with BS (24-26). The oral mucosa is exposed to antigenic stimulations of oral microorganisms that have a pivotal role in the activation of immune responses and clinical manifestations in patients with BS. When the oral mucosal integrity is broken down by the development of oral ulcers, oral microorganisms and inflammatory mediators enter the systemic circulation through this route (2, 21, 27, 28).

Oral ulcers are also considered one of the main factors impeding remission BS at follow-up periods of active disease. Therefore, low disease activity related to oral ulcer activity is crucial for any treat-to-target strategies in BS (8-11). Immunosuppressive/immunomodulating (IS) medications, Non-IS medications, new treatment modalities such as Apremilast, topical medications, specific mouthwashes and the elimination of infection foci by dental and periodontal treatments are important options to control oral ulcer activity in individual patients with BS (11, 25, 27, 29-33). Tobacco smoking may also have a direct effect on the enhanced epithelial proliferation and systemic anti-inflammatory effects of nicotine (1, 11). However, this should not be an option because of the carcinogenic and fibrotic effects on the epithelium.

In this complex milieu and structure, it is important to deliver the treatment needs for oral ulcer activity together with associated factors in the disease management. Decision tree analysis (DTA) could be a suitable option to disaggregate treatment needs and compounding factors. It composes nodes and branches regarding alternative outcomes to understand relationships for large amounts of data. It chooses the "best" characteristics to partition the data into specific classes (34, 35). This method has been used to predict disease activity (36) and treatment response in rheumatoid arthritis (RA)(37) as well as to identify a high risk group for dental caries in school children (38). The Classification and Regression Tree (CART) algorithm, a type of DTA, has been used to develop a diagnostic algorithm for BS uveitis (39) and to predict relapse in intestinal BS (40). Therefore, the aim of this study was to identify the interactions among treatment protocols together with oral ulcer activity-related factors in patients with BS through the CART analysis.

Materials and methods

In this cross-sectional study, 1040 patients diagnosed as BS using international study group criteria (6) were included. The patients were followed in 16 centres from Turkey, United Kingdom, Jordan and Brazil. Sixty-one patients who were not using any medication were excluded, leaving a final dataset of 979 patients with BS in the study (Table I). The inclusion criteria for the study were being over 18 years of age and under medical control for BS. The presence of other chronic conditions leading to mucocutaneous manifestations, ocular, vascular or rheumatologic manifestations were exclusion criteria. Data were collected by using a ques-

tionnaire that covered age, gender, disease duration (years), frequency of medical visits/year, treatment protocols, activities of organ involvement during the last month, smoking habits (current smoker *vs*. non-smoker), frequency of tooth brushing per day and duration since the last dental visit (months) in the group. The number, healing time and pain status of oral ulcers were also noted during the last month using a 100-mm visual analogue scale (0:no pain-100: severe pain). Patients were grouped according to tooth brushing frequency (n=964; 1.33±0.99) as >once a day (35%), once a day (37.9%) and <once a day (27.1%) (41). Then, two groups were defined by dentists (GM and UK) as regular tooth brushing group (≥1/day; n=703; 72.9%) or as irregular tooth brushing group (<1/day; n=261; 27.1%).

Disease severity score was calculated according to organ involvement (42) and patients were grouped as having mucocutaneous and musculoskeletal involvement (n=538) *vs*. major organ involvement (n=411). Treatment protocols were categorised as non-immunosuppressive/non-immunomodulators (Non-IS) and IS medications (azathioprine, corticosteroids, anti-TNF agents and interferons) in both groups (Table I). The multicentre study was performed in accordance with the principles of the Declaration of Helsinki and the Ethical Committee of Marmara University Medical School (July 14 2017; No: 09.2017.497). Informed consent was obtained from all patients.

Statistical analysis
Statistical analysis was performed using SPSS 28.0 statistic programme (SPSS Inc, Chicago, IL, USA). Categorical variables were analysed using the Chi-square test. The Mann-Whitney U-test and Spearman correlation test were used to analyse non-normally distributed data. A *p*-value of ≤0.05 was considered statistically significant in this study.

Decision Tree Analysis
The decision-tree model was created using the CART algorithm with SPSS 28.0 (IBM Corp, Armonk, NY). The CART algorithm, developed by Brei-

man *et al*. in 1984 (34), builds recursively binary trees in which each node is divided into two subgroups that are more homogeneous. This process continues until no significant pair is found, and some variables may be used multiple times in the algorithm (34, 35). Predictive variables including activities of oral ulcer (active *vs*. inactive), genital ulcer (active *vs*. inactive), cutaneous involvement (active *vs*. inactive), musculoskeletal involvement (active *vs*. inactive), smoking habits (current smoker *vs*. non-smoker), gender (male *vs*. female), tooth brushing habits (irregular *vs*. regular), and disease severity (mucocutaneous and musculoskeletal involvement *vs*. major organ involvement) were used as input variables in the analysis.
The treatment protocol (Non-IS *vs*. IS) was used as the target variable to split

from parent nodes to purer child nodes in the study (Fig. 1). The data was split into a training sample (80%) used to train the algorithm (Supplementary Table S1) and a test sample (20%) (Supplementary Table S2) used to evaluate its performance (34). To assess the model performance, k-fold cross-validation (34, 35) was also adopted to assess the performance of the CART in this study.

Results
This cross-sectional study included 979 patients with BS (F/M: 505/474; mean age: 38.84±10.8 years). The profile of the group was presented in Table I. In mucocutaneous and musculoskeletal involvement, the ratio of IS use (25.1% in males and 22.4% in females) was found to be similar in both genders in this spectrum (*p*=0.476) whereas it was

Table I. The profile of patients with BS.

	n	%
Gender		
Female	505	51.6
Male	474	48.4
Total	979	100
Organ involvement		
Oral ulcer/genital ulcer	979/792	100/80.9
Cutaneous involvement/musculoskeletal involvement	764/550	78.0/56.2
Ocular involvement/vascular involvement	315/143	32.2 /14.6
Neurological involvement/gastrointestinal involvement	72/26	7.4/2.3
Positive pathergy test	490	50.1
Mucocutaneous and musculoskeletal involvement	538	55
Non-IS	411	76.4
IS	127	23.6
Total	538	100
Major organ involvement	441	45
Non-IS	126	28.6
IS	315	71.4
Total	441	100
Smoking habits		
Current smoker	236	24.1
Non-smoker	717	73.2
No response	26	2.7
Total	979	100
Tooth brushing habits		
Irregular tooth brushing habits (<1/day)	261	26.7
Regular tooth brushing habits (≥1/day)	703	71.8
No response	15	1.5
Total	979	100

	Mean	SD
Age (year)/education level (year)	38.84/9.18	10.80/4.11
Disease duration (year)/ Disease Severity Score	9.38/5.02	7.57/2.10
Frequency of medical visit during the previous year	3.62	2.64
Frequency of tooth brushing	1.33	0.99
Regular tooth brushing group (≥1/day)	1.68	0.90
Irregular tooth brushing group (<1/day)	0.35	0.33
Duration from last dental visit (month)	18.08	29.58

Fig. 1. The CART algorithm for oral ulcer activity in patients with BS.

found as 82.4% in males and 58.4% in females in major organ involvement (*p*<0.001).

Tooth brushing and education level
Patients who brushed their teeth regularly had a shorter duration since their last dental visit (16.18±25.67 months) than those who brushed irregularly (23.26±38.02 months) in the group (*p*=0.05). In mucocutaneous and musculoskeletal involvement and major organ involvement, the proportion of the female patients who brushed their teeth regularly was higher than that of male patients (n=232 77.3% *vs.* n=158 68.7% and n=157; 80.5% *vs.* n=156, 65.3%, respectively) (*p*=0.029; *p*<0.001).

In female patients, oral ulcer related pain was higher and duration from

the last dental visit was longer in patients with irregular tooth brushing (69.9±9.23; 21.2±32.9 months) that those in regular tooth brushing (56.8±10.12; 14.79±24.19 months) group in mucocutaneous and musculoskeletal involvement (p=0.002, p=0.030, respectively). In major organ involvement, the group who brushed their teeth regularly had a longer education period than the other groups (9.44±3.96 years *vs*. 5.60±3.66 years) (p<0.001) (Fig. 2).

In male patients, education period was longer in patients with regular tooth brushing habits than those in the irregular tooth brushing habits in both disease course (10.81±3.85 years *vs*. 8.98±4.09 years in mucocutaneous and musculoskeletal involvement and 10.31±4.20 years *vs*. 9.06±3.58 years in major organ involvement) (p=0.002, p=0.028, respectively). In mucocutaneous involvement, male patients who brushed their teeth irregularly had a longer disease duration than those who brushed regularly (9.27±7.62 *vs*. 7.52±6.83 years) (p=0.044) (Fig. 2).

Oral ulcer activity and disease-related factors
Oral ulcer activity (n=632, 64.4%) was associated with female gender and non-IS treatment protocol as well as activities of genital ulcer, cutaneous involvement and musculoskeletal involvement (p<0.05). Among non-smokers, the ratio of oral ulcer activity was higher in patients treated with non-IS medications than those treated with IS (p<0.001) but this relation was not seen in current smokers (p=0.692) (Table II).

Oral ulcer activity, tooth brushing and treatment protocols
In major organ involvement, male patients with irregular tooth brushing habits showed an increase in IS use compared to those with regular tooth brushing habits (p=0.007) despite similar clinical profiles and disease severity scores (p>0.05). Female patients with major organ involvement showed a decrease in IS use when oral ulcer activity was present (p=0.013). Regarding oral ulcer activity, patients with irregu-
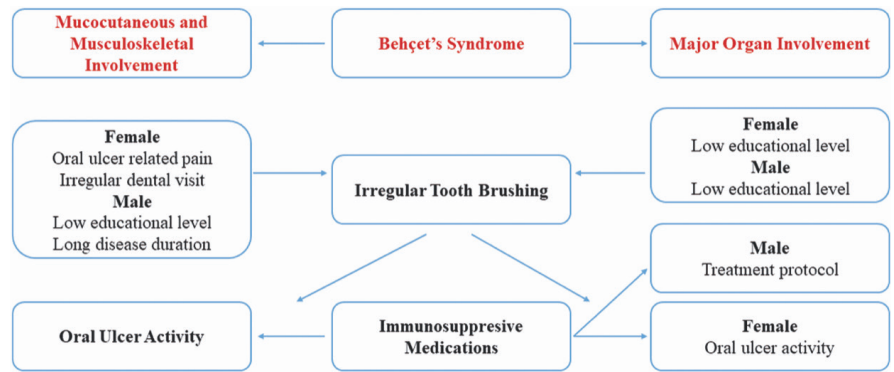

Fig. 2. Overview of relations among disease course, oral ulcer activity, tooth brushing and treatment protocols in BS.

Table II. Oral ulcer activity, related conditions and treatment protocols in BS.

	Oral ulcer inactive		Oral ulcer active		
	n	%	n	%	p
Gender					
Male	189	54.5	285	45.1	**0.006**
Female	158	45.5	347	54.9	
Total	347	100	632	100	
Genital ulcer activity					
Inactive	327	94.2	518	82	**<0.001**
Active	20	5.8	114	18	
Total	347	100	632	100	
Cutaneous activity					
Inactive	305	87.9	483	76.4	**<0.001**
Active	42	12.1	149	23.6	
Total	347	100	632	100	
Musculoskeletal activity					
Inactive	241	70.9	344	55.8	**<0.001**
Active	99	29.1	273	44.2	
Total	340	100	617	100	
Treatment protocols					
Non-IS	160	46.4	377	59.7	**<0.001**
IS	187	53.6	255	40.3	
Total	347	100	632	100	
Non-smoker					
Non-IS	110	45.8	299	62.7	**<0.001**
IS	130	54.2	178	37.3	
Total	240	100	477	100	
Current smoker					
Non-IS	48	49.5	73	52.5	0.692
IS	49	50.5	66	47.5	
Total	97	100	139	100	

lar tooth brushing habits were treated with IS medications in both disease courses (p=0.054 and p=0.006) (Table III, Fig. 1, 2).

Oral ulcer activity and decision tree model for treatment protocols
Since complex relations were observed in oral ulcer activity in preliminary analyses, the CART algorithm (n=979) created a prediction model with oral ulcer related factors with the treatment protocols that were the target variables (Fig. 1). The decision-tree model discriminated patients treated with IS from those treated with non-IS, with probabilities of IS use ranging from 14.2% (Node 15) to 91.6% (Node 10) in the final outcomes of the serial decision rules. The sensitivity, specificity, PPV, NPV, and accuracy of the model were 71.3%, 76.5%, 71.4%, 76.4%, and 74.2%, respectively. The overall risk of misclassification was found to

Table III. Associations among disease course, gender, treatment protocols and tooth brushing (TB) in BS.

		Mucocutaneous and musculoskeletal involvement					Major organ involvement				
		Irregular TB		Regular TB			Irregular TB		Regular TB		
		n	%	n	%	*p*	n	%	n	%	*p*
Female	Non-IS	50	73.5	182	78.4	0.412	11	28.9	73	46.5	0.067
	IS	18	26.5	50	21.6		27	71.7	84	53.5	
	Total	68	100	232	100		38	100	157	100	
Male	Non-IS	51	70.8	120	75.9	0.420	7	8.4	35	22.4	**0.007**
	IS	21	29.2	38	24.1		76	91.6	121	77.6	
	Total	72	100	158	100		83	100	156	100	
		Oral Ulcer (-)		Oral Ulcer (+)			Oral Ulcer (-)		Oral Ulcer (+)		
		n	%	n	%	*p*	n	%	n	%	*p*
Female	Non-IS	58	75.4	177	78.3	0.636	25	30.9	59	48.8	**0.013**
	IS	19	24.7	49	21.7		56	69.1	62	51.2	
	Total	77	100	226	100		81	100	121	100	
Male	Non-IS	63	75	113	74.8	1.0	14	13.3	28	20.9	0.170
	IS	21	25	38	25.2		91	86.7	106	79.1	
	Total	84	100	151	100		105	100	134	100	
		Non-IS		IS			Non-IS		IS		
		n	%	n	%	*p*	n	%	n	%	*p*
Oral Ulcer Active	Irregular	70	24.6	31	35.6	**0.054**	14	16.1	52	32.1	**0.006**
	Regular	214	75.4	56	64.4		73	83.9	110	67.9	
	Total	284	100	87	100		87	100	162	100	

be 25.8 % in the CART algorithm and 29.3% after performing 10-fold cross-validation in the group. Finally, results were found to show similar ratios for the correct classification of the model. According to the analysis, patients were divided in to 16 subgroups from the parent node to the leaf node. In mucocutaneous and musculoskeletal involvement branch, patients who didn't have active genital ulcers (node 3) and cutaneous involvement (node 7) were divided into two subgroups based upon presence or absence of an oral ulcer (node 14 and node 13). In patients with active oral ulcers, 14.2% of the patients who brushed their teeth regularly (≥1 per day) were treated with IS medications in this group (node 15). Besides, IS use was found to be 27.1% in active patients with irregular tooth brushing habits (node 16).

In the major organ involvement branch, the frequency of IS use was 77.6% in male patients with regular tooth brushing (node 9) whereas the frequency was 91.6% in male patients with irregular tooth brushing habits (node 10). In female patients, the frequencies of IS use were 51.2% in patients with active

oral ulcers (node 12) and 69.1% in patients without oral ulcers according to the CART algorithm (node 11). In addition, smoking and joint activity were not presented in the algorithm.

Discussion

The primary goals of treatment plans are to suppress inflammatory exacerbations, achieve remission and prevent tissue damage during the patient treatment priorities of heterogeneous clinical manifestations of BS patients (27, 30, 31, 43). To achieve these goals, this study aimed to identify the interactions among treatment protocols together with oral ulcer-related factors for optimal clinical practice in patients with BS through the CART algorithm.

The results of the study showed that oral ulcer activity was associated with genital ulcers, cutaneous manifestations and musculoskeletal activity as well as with female gender, receiving Non-IS treatment protocol and being non-smoker. These findings are consistent with previous studies that have shown co-occurrence of mucocutaneous symptoms and musculoskeletal manifestations in the heterogenous

spectrum of the disease (13, 44-46), especially in patients having oral ulcer activity related factors in BS (10, 11). In the study, the CART algorithm developed a decision tree model to predict treatment protocols for oral ulcer and associated factors from a pool of significant predictive factors including gender, disease severity, smoking, tooth brushing, active genital ulcer, cutaneous involvement and musculoskeletal involvement. The CART algorithm aims to define subgroups as homogenous as possible that share common characteristics until all terminal nodes are pure (34, 35). According to the algorithm, tooth brushing was found to be a terminal node shown at different levels of decision tree analysis. Patients with active oral ulcers who had irregular tooth brushing habits in mucocutaneous and musculoskeletal involvement showed an increase in IS use. Regular tooth brushing helps to improve oral hygiene by removing biofilm accumulation around teeth which causes dental and periodontal diseases. In other words, regular tooth brushing reduces the bacterial load in oral environment (22), and poor oral hygiene is

considered to be a risk factor for oral health, oral ulcer activity and disease severity in BS (22, 23, 33). Close associations are available between oral ulcers and oral microorganisms. Increased colonisations of salivary *S. mutans* (18), uncommon serotypes of oral *S.sanguis* (15, 17) and S. *salivarious* (15) are associated with oral ulcers in BS. *S. salivarius* is also more colonised at ulcer sites in BS compared to those in recurrent aphthous stomatitis (15). *Prevotella, Veillonella, Streptococcus* and *Haemophilius* are found to be abundant genera in the saliva of BS, whereas the proportion of *Akkermansia* is reduced (16). Increase in *Haemophilus parainfluenzae* and decrease in *Alloprevotella rava* and species in the genus *Leptotrichia* are also found in saliva of patients with BS (14). Following occurrence of dysbiosis in the oral environment, mucosal surfaces are exposed to these microbial factors, triggering inflammatory responses to develop oral ulcers by breaching mucosal barriers (2, 21, 27, 28).

Being among the key indicators of the disease activity, oral ulcers play a critical role in systemic activation. This is mainly due to disruption of oral mucosal barriers, which allows oral microorganisms and inflammatory mediators to reach the systemic circulation (1, 2, 11, 47). Eliminating infection foci with dental and periodontal treatment and with regular tooth brushing may also reduce the number of oral ulcers over a 6-month period without changing in systemic treatment protocols (33). Topical treatments regarding steroids, mouthwashes and mucosal protectants as well as improving oral health are first line treatments for the oral ulcer activity (33, 47). Moreover, systemic treatment protocols such as colchicine, antibiotics, steroids, IS and Apremilast are also used for treating oral ulcer activity (30, 48). Regular tooth brushing may help to decrease bacterial load in oral environment and to suppress inflammatory exacerbations of oral ulcers in BS patients. This approach is also in accordance with the EULAR guideline (30, 31).

Most of male patients with irregular tooth brushing were treated with IS

medications for major organ involvement according to the CART algorithm. Since male patients have generally a higher genetic risk and more severe disease manifestations compared to female patients in BS (5), IS medications are preferred to suppress inflammatory attacks leading to damage, mortality and morbidity as well as to provide remission (29, 30). When examining oral health in BS patients, elevated biofilm accumulation around teeth that occurs in patients without regular tooth brushing habits is found be a risk factor for severe disease course, particularly in male patients (22). Dental caries as well as need of tooth extraction due to uncured dental and/or periodontal infections are also observed as significant mediators for severe disease course, reflecting major organ involvement in male patients (2, 22, 23, 33).

Our previous results which demonstrated the importance of oral hygiene in male patients with major organ involvement were approved by this CART algorithm. With the understanding of these coexisting effects, clinicians can choose the best therapeutic approaches and provide recommendations on how to improve oral health tailored to specific needs of the patients. Finally, oral hygiene education, regular tooth brushing and dental visit should be recommended to improve oral health as patient empowerment strategies in BS (1, 2, 22, 33)

The CART algorithm showed that oral ulcer activity was the primary characteristic of terminal nodes in females with major organ involvement and a decrease in IS use was associated with the oral ulcer activity. In this spectrum, less severe disease course could be seen in female patients compared to males (29, 30). If female patients are older and in remission period for major organ involvement, their treatments could be continued by non-IS medications in the disease spectrum according to individual needs. Therefore, oral ulcer activity could be predicted in these patients (11, 29, 30).

Female patients regularly brushed their teeth compared to males in both disease courses. Those with regular tooth brushing more frequently visited

the dentist and felt less severe oral ulcer related pain in mucocutaneous and musculoskeletal involvement. This is likely due to being more knowledgeable about oral health, having better attitudes towards dental care and practicing better oral hygiene habits compared to males (49). Topical medications can reduce oral ulcer-related pain (47), thereby improving tooth brushing habits and helping to decrease IS use in patients with mucocutaneous and musculoskeletal involvement.

Long disease duration is a contributing factor to irregular tooth brushing habits in males with mucocutaneous and musculoskeletal involvement. Motivation of patients for oral hygiene may decrease due to oral ulcer activity in long disease duration. As it is known, irregular tooth brushing habit is linked to poor oral health (50). Since males are more likely to have poor oral hygiene habits and suffer from oral health problems (51, 52), elevated motivation for oral hygiene applications might have positive effects on the disease management in male patients.

Additionally, decrease in education year was also associated with irregular tooth brushing habits in both genders with major organ involvement. These results can be predicted as education, being the social determinant of health is defined among the non-medical factors that influence health outcomes (41). Education level is a strong predictor of a healthy life and awareness of health outcomes in the management of chronic disease (53, 54). It is also accepted as a predisposing factor that influences oral health behaviours and oral health status because it links to oral health literacy level, awareness of oral health outcomes and dentalcare use (55-58). Therefore, it is necessary to think the effects of education level in the disease management.

In this study, we aimed to identify oral ulcer-related factors with treatment protocols through the CART algorithm for the best clinical practice. This algorithm simplifies complex relationships by dividing them into significant subgroups. In clinical studies, decision tree analysis has been utilised for various purposes, including the prediction

of disease activity through the measurement of cytokines (36) and multirefractory and non-refractory patients by using simple measurements recorded in routine clinical practice for individual treatment protocols in an early stage of RA (37). Studies have shown that irregular dental attendance at a late stage of primary school and high levels of salivary *S.mutans* and male sex at an early stage of primary school are associated with a higher risk of dental caries (38). Similarly, the CART algorithm provides new insights for diagnosis and treatment protocols regarding ocular and gastrointestinal involvement in BS. Factors such as the presence of superficial retinal infiltration, occlusive retinal vasculitis and diffuse retinal capillary leakage, as well as absence of granulomatous anterior uveitis or choroiditis in individuals with vitritis were the factors that yielded the highest accuracy in CART analysis (39). Additionally, the new endoscopic scoring system developed by the CART algorithm may be able to predict clinical relapse in patients after performing surgical resection in intestinal BD (40).

The present study included a large number of patients from different countries and the results of the CART algorithm provided a model for characterising or individualising patients' treatment options in clinical practice. The study highlights the importance of patient empowerment strategies for performing tooth brushing, demanding dental care provision and being aware of oral health literacy. However, the main limitation was that intraoral examinations of patients were not performed to control the oral hygiene of patients at every centre in the study. Controlled clinical studies involving long-term follow-up data are necessary to design in different patient populations.

Consequently, male BS patients on IS who have major organ involvement and oral ulcer activity with mucocutaneous and musculoskeletal involvement have irregular tooth brushing habits. Improved oral hygiene practices should be considered to be an integral part for implementing patient empowerment strategies for BS.

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