

Epidemiology

Sore throat in primary care project: a clinical score to diagnose viral sore throat

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Abstract

Objective. Viral agents cause the majority of sore throats. However, there is not currently a score to diagnose viral sore throat. The aims of this study were (i) to find the rate of bacterial and viral causes, (ii) to show the seasonal variations and (iii) to form a new scoring system to diagnose viral sore throat.

Methods. A throat culture for group A beta haemolytic streptococci (GABHS) and a nasopharyngeal swab to detect 16 respiratory viruses were obtained from each patient. Over a period of 52 weeks, a total of 624 throat cultures and polymerase chain reaction analyses were performed. Logistic regression analysis was performed to find the clinical score.

Results. Viral infection was found in 277 patients (44.3%), and GABHS infection was found in 116 patients (18.5%). An infectious cause was found in 356 patients (57.1%). Rhinovirus was the most commonly detected infectious agent overall (highest in November, 34.5%), and the highest GABHS rate was in November (32.7%). Analysis of data provided a scoring system, called the Mistik Score, to diagnose viral sore throat. The predictive model for positive viral analysis included the following variables: absence of headache, stuffy nose, sneezing, temperature of $\geq 37.5^{\circ}\text{C}$ on physical examination, and the absence of tonsillar exudate and/or swelling. The probability of a positive viral analysis for a score of 5 was 82.1%.

Conclusion. The Mistik Score may be useful to diagnose viral sore throat. We suggest its use either alone or in combination with the Modified Centor Score.

Key words: Diagnose, sore throat, primary care, viral, score.

Introduction

Sore throat is a very common problem seen in general practice. Documented group A beta haemolytic streptococci (GABHS) is found in 15%–30% of children and in 10% of adults (1). Viral agents cause the majority of sore throats (2). Many scores have focused on the diagnosis of GABHS in patients with a sore throat; this is important because GABHS requires treatment with antibiotics. However, at present there is not a score to directly diagnose viral sore throat for a physician who suspects that the aetiology is viral.

The aim of treatment for a sore throat is to prevent complications, such as acute rheumatic fever (3). However, this has resulted

in an antibiotic prescription rate that is much higher than the actual GABHS infection rate. In a survey of antibiotic prescribing in UK general practice, half of all patients presenting with coughs, colds and viral sore throats were prescribed an antibiotic (4). Shallcross and Davies (5) reported that innovative ways must be found to reduce the level of antimicrobial prescribing in primary care. The problem in using antibiotics for a sore throat which is presumed to be viral is the emergence of bacteria which are resistant to antibiotics.

There are 4 derived and 12 validated clinical decision rules to diagnose streptococcal pharyngitis in children (6). The problem in using these decision rules is their low positive predictive values, which makes them less used in clinical practice. Throat culture is still

used as a gold standard laboratory test. New generation rapid antigen tests are better. However, they cannot be used alone or instead of throat culture (7). The clinical manifestations of GABHS and nonstreptococcal pharyngitis overlap broadly (8). The Centor Score is used for the diagnosis of GABHS sore throat (9). The Modified Centor Score, which includes the evaluation of the age of patients with a sore throat, was described by McIsaac *et al.* (2). Although these two scores and many others are used for the diagnosis of GABHS sore throat, there is need to improve the criteria, in order to prevent the unnecessary use of antibiotics throughout the world.

The aims of this study were (i) to find the rate of bacterial and viral causes of sore throats, (ii) to show the seasonal variations and (iii) to form a new scoring system to diagnose viral sore throat which may reduce overuse of antibiotics.

Methods

Study population

Patients with a sore throat, who had applied to Bunyamin Somyurek Family Medicine Centre which is located in the centre of Kayseri province, were included in the study. Patients of any age or gender may apply to their family physicians for any medical problems. A family physician examines approximately 600 sore throat patients in a year. The family physicians were asked to include one sore throat patient for every week in the study. Sore throat patients with a history suggesting infectious causes who were between the ages of 3 and over and agreed to participate in the study were included. The patients with non-infectious causes such as postnasal drip, low humidity in the environment, irritant exposure to cigarettes or smog and malignant disease were not included in the study. Informed consents were obtained from adults and the parents of the children.

Questionnaire

The patients' histories and clinical findings were recorded in detail. A questionnaire consisting of demographic data questions and complaints was given to the patients and the physical examination findings were also recorded. In order to minimise observer variations or discrepancies, training was given to the family physicians by an ear, nose and throat specialist.

Setting and procedure

The study was conducted in a Family Medicine Centre, in which 12 family physicians work. A throat culture for GABHS and a nasopharyngeal swab to detect 16 respiratory viruses were obtained from each patient. The study was started in the first week of June 2013 and samples were taken for 52 weeks. Throat swab cultures were collected from the patients and swab specimens were inoculated to 5% sheep blood agar. After overnight incubation of the plates at 37°C, the plates were evaluated for the presence of GABHS. Nasopharyngeal swab specimens were collected from the patients and placed in viral transport media (Copan, Italy). The specimens were sent to the virology laboratory for respiratory virus testing.

A total of 624 throat cultures and polymerase chain reaction (PCR) analyses were performed. An Anyplex II RV16 Detection kit (Seegene, Korea) was used to detect 14 RNA viruses and two DNA viruses including human adenovirus (ADV), influenza A and B viruses (FluA, FluB), human parainfluenza viruses 1/2/3/4 (PIV1/2/3/4), human rhinovirus A/B/C (HRV A/B/C), human respiratory syncytial viruses A and B (RSV-A, RSV-B), human bocaviruses 1/2/3/4 (BoV1/2/3/4), human coronaviruses 229E, NL63 and OC43 (CoV-229E, CoV-NL63, CoV-OC43), human metapneumovirus (MPV) and human enterovirus (EV) (coxsackievirus).

Statistical analysis

Univariate and multivariate binary logistic regression analyses were performed to find the factors predicting viral infection. Every factor in the history of the patient and physical examination was evaluated one by one. The statistically significant factors in univariate binary logistic regression analysis were included in the model by using multivariate binary logistic regression with the backward Wald method. In the logistic regression analysis, there was a statistically significant difference only in the analysis of viruses compared with bacteria, bacteria plus virus and no microbiological cause. There was no statistically significant difference when the no microbiological cause group was added to the virus group as presumed viral infection. The model was formed according to the equation below (9).

$$P = \frac{e^{\beta_0 + \beta_1 X_1 + \dots + \beta_k X_k}}{1 + e^{\beta_0 + \beta_1 X_1 + \dots + \beta_k X_k}},$$

where 'P' stands for probability. One point was given for the presence of each variable in the model (9). The probability of the presence of viral infection was calculated for each score. If the score is 0, 1 or 2 there is no virus, and if it is 4 or 5 a virus is present. When the score is 3, a decision is made by putting the score in the logistic regression model. When the coefficients are placed, $P < 0.5$ means there is no virus and $P \geq 0.5$ means a virus is present. The probability changes depending on the presence of different types of variable combinations.

Receiver operating characteristic (ROC) curve analysis was performed between the scores and the PCR analysis results. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood and negative likelihood ratio were calculated for the scores and the signs and symptoms, which were statistically significant. Throat culture and PCR analysis were used as reference standards for the Modified Centor Score and the score to diagnose viral sore throat, respectively. The level of significance was considered at 5%.

Results

Patients' characteristics

Over a period of 52 weeks, 624 patients were included in the study. The mean age of the patients was 25.50 ± 17.71 (range 3–85, median 21). Of the patients, 42.0% were male, and 58.0% were female. Sixty-four patients (10.3%) were preschool children, 268 (42.9%) were students, 152 (24.4%) were housewives, 32 (5.1%) were retired and the remaining 108 (17.3%) were government employees and those working in the private sector. In our study, age was not statistically significant in the logistic regression analysis for the Modified Centor Score and the Mistik Score. The distribution of viral infection versus GABHS according to age group is given in [Supplementary Figure s1](#).

Viral analysis and throat culture

Of the 624 sore throat patients included in the study in the period June 2013–June 2014, viral infection was found in 277 patients (44.3%), and GABHS infection was found in 116 patients (18.5%). An infectious cause was found in 356 patients (57.1%), whereas no infectious cause was found in 268 patients (42.9%). Thirty-seven patients (5.9%) had both GABHS and viral infections. Viral infection only was found in 240 (38.4%) of the patients, and GABHS infection only was found in 79 patients (12.6%) ([Table 1](#)).

Detected viruses

The detected viruses are shown in Table 2. The coronavirus types were: OC43 (21), NL63 (8) and 229E (10). The parainfluenza types were: PIV1 (15), PIV 2 (1), PIV3 (11) and PIV4 (5). Four viruses were detected in one patient (rhinovirus, parainfluenza 4, bocavirus and enterovirus). In another patient, three viruses were detected (rhinovirus, coronavirus OC43 and coronavirus 229E). Sixteen patients had two virus infections including rhinovirus [six with enterovirus, three with parainfluenza (two PIV1, one PIV3), three with influenza A, two with coronavirus (OC43 and NL63), one with ADV, and one with RSV A]. There were two virus combinations of influenza A (three with influenza B, two with coronavirus 229E). Two other two-virus combinations (PIV1 plus PIV3, and coronavirus 229E plus RSV B) were also found.

Twenty-three patients had rhinovirus with GABHS. Five patients had influenza A and GABHS. Three patients had parainfluenza (PIV1) and GABHS. Two patients had RSV and GABHS (one RSV A and one RSV B). Three other patients had coronavirus (OC43), ADV, and metapneumovirus in combination with GABHS infection. One patient had rhinovirus plus enterovirus plus GABHS.

Rhinovirus was the most commonly detected infectious agent overall (highest in November at 34.5%, lowest in March at 16.6%) (Supplementary Figure s2). The highest GABHS rate was in November (32.7%) and the lowest in June (6.5%).

Evaluation with the Modified Centor Score

Of the patients, 170 (27.2%) had Modified Centor Scores of zero or less, 359 (57.5%) had scores between 1 and 3, and 95 (15.2%) had scores of 4 or more. It has been stated that empiric antibiotic treatment may be considered in patients with a score of 4 or more (10). There were 35 (5.6%) patients with a Centor Score of 4 and 95 (15.2%) patients with a Modified Centor Score of 4 or more in our study. The throat culture results were sent to the general practitioners by e-mail in approximately 48 hours. However, the design of this study did not include an intervention to reduce the antibiotic prescription rates. In general, the patients were treated based on

Table 1. Distribution of viral and GABHS infections

Infection	Frequency	Percent
Virus	240	38.4
GABHS ^a	79	12.6
GABHS and virus	37	5.9
None	268	42.9
Total	624	100.0

^aGroup a beta haemolytic streptococci.

Table 3. Infection type and Modified Centor Scores

Infection	Modified Centor Score							Total
	-1	0	1	2	3	4	5	
Virus	19	60	62	47	21	24	7	240
GABHS ^a	2	4	7	13	24	18	11	79
GABHS and virus	0	4	8	5	8	10	2	37
None	27	54	76	54	34	15	8	268
Total	48	122	153	119	87	67	28	624

^aGroup a beta haemolytic streptococci.

their symptoms and the physical examination findings. In case of a GABHS positive throat culture result, the prescription of the patient was rapidly evaluated for the presence of an antibiotic. In this study, 489 (78.4%) patients were prescribed an antibiotic by their general practitioners.

Infection type and the Modified Centor Scores are given in Table 3. Viruses caused a Modified Centor Score of 4 or 5 on many occasions (HRV 23, PIV 3, coronavirus 3, FLUB 2, HEV 2, MPV 2, RSV 1, ADV 1, and two virus infections seven times).

Score to diagnose viral sore throat

The predictive model for positive viral analysis included the following variables: absence of headache, stuffy nose, sneezing, temperature of $\geq 37.5^\circ\text{C}$ on physical examination and the absence of tonsillar exudate and/or swelling (Table 4). The logistic regression model is given in Supplementary Figure s3.

The probability of a positive viral analysis for scores of 0 to 5 was 8.3%, 14.7%–20.4%, 25.2%–36.3%, 42.2%–55.3%, 61.9%–70.7% and 82.1%, respectively. No GABHS was present in patients with a score of 5.

In order to generalise the results, we randomly split our data as 70% (training data) for ROC model building and 30% (validation data) for validation. We defined cut-off values for each variable in the training data and assessed the performances in the validation data. The performance results of each factor are given in Table 5. The sensitivity of this score, called the 'Mistik Score', was 60.2% and the specificity was 72.5%. The positive predictive value was 62.5% and the negative predictive value was 70.5%. The positive likelihood ratio was 2.19 and the negative likelihood ratio was 0.55. The Mistik Score was compared with the Modified Centor Score as a clinical decision rule, which is used for the diagnosis of GABHS,

Table 2. Results of viral analysis

Virus	Frequency	Percent
Rhinovirus	153	24.5
Coronavirus	39	6.2
Parainfluenza	32	5.1
Influenza A	29	4.6
Enterovirus	15	2.4
RSV ^a	14	2.2
Influenza B	10	1.6
Adenovirus	6	0.9
MPV ^b	6	0.9
Bocavirus	2	0.3
None	347	55.6

^aRespiratory syncytial virus.

^bMetapneumovirus.

Table 4. Score to diagnose viral sore throat

Variables	Points	OR ^a	95% CI ^b	
			Lower	Upper
Absence of headache	1	1.975	1.285	3.035
Stuffy nose	1	2.081	1.330	3.257
Sneezing	1	2.811	1.799	4.393
Temperature ($\geq 37.5^{\circ}\text{C}$)	1	1.765	1.094	2.845
Absence of tonsillar exudate and/or swelling	1	1.823	1.181	2.815
Total score	5	–	–	–

^aOR = odds ratio.

^bCI = confidence interval.

Table 5. Comparison of 'Mistik Score' and Modified Centor Score

	Sensitivity (%)	Specificity (%)	PPV ^a (%)	NPV ^b (%)	LR+ ^c	LR–
Mistik Score variables						
Absence of headache	45.8	62.4	48.1	60.2	1.22	0.87
Stuffy nose	71.1	56.0	55.1	71.8	1.61	0.52
Sneezing	55.4	74.3	62.2	68.6	2.16	0.60
Temperature ($\geq 37.5^{\circ}\text{C}$)	30.1	68.5	35.1	63.4	0.95	1.02
Absence of tonsillar exudate and/or swelling	63.9	51.4	50.0	65.1	1.31	0.70
Mistik Score	60.2	72.5	62.5	70.5	2.19	0.55
Modified Centor Score variables						
Absence of cough	77.5	56.4	20.7	94.5	1.77	0.39
Tonsillar exudate and/or swelling	82.5	57.2	22.1	95.7	1.92	0.30
Fever ($>38.0^{\circ}\text{C}$)	16.3	92.3	23.6	88.2	2.11	0.90
Anterior cervical lymphadenopathy	66.3	69.5	24.2	93.3	2.17	0.48
Ages 3–14	46.4	69.0	47.0	68.5	1.50	0.78
Modified Centor Score	62.9	78.5	40.1	90.3	2.93	0.47

^aPPV = positive predictive value.

^bNPV = negative predictive value.

^cLR = likelihood ratio.

as there is no other score at present for the diagnosis of viral sore throat.

In our study, the sensitivity of the Modified Centor Score was 62.9%, the specificity was 78.5%, the positive predictive value was 40.1%, and the negative predictive value was 90.3%. The positive likelihood ratio was 2.93 and the negative likelihood ratio was 0.47. The positive predictive values of the Mistik Score and the Modified Centor Score were found for each month, and varied between 47.8%–65.2% and 31.0%–62.5%, respectively. The diagnostic accuracy of the Mistik Score was 68%, and that of the Modified Centor Score was 75%. There was a negative correlation between the Modified Centor Score and the Mistik Score ($r = -0.357$, $P < 0.001$).

Discussion

Statement of principal findings

This study demonstrated to us, by means of laboratory findings, that viral infection was found in 44.3% of the patients and GABHS infection was found in 18.5%. An infectious cause was found in 57.1% of the patients, whereas no infectious cause was found in 42.9%. Thirty-seven (5.9%) patients had both GABHS and viral infections. Viral infection only was found in 240 (38.4%) of the patients and GABHS infection only was found in 79 patients (12.6%). Rhinovirus was the most commonly detected infectious agent overall (highest in November, 34.5%), and the highest GABHS rate was in November (32.7%). Viral sore throat can have a Modified Centor Score of 4 or

5. We have described herein a score to diagnose viral sore throat with the following variables: absence of headache, stuffy nose, sneezing, temperature of $\geq 37.5^{\circ}\text{C}$ on physical examination and the absence of tonsillar exudates and/or swelling.

Strengths and limitations

The strength of our study was that we worked on laboratory proven viral infections, instead of presumed viral infections, and showed the clinical association of signs and symptoms with a score which could make a major difference in the clinical approach of many family physicians and other doctors. The first variable of the score is absence of headache. It has been reported that although headache is not one of the Centor criteria, it is a commonly looked for symptom of strep throat and is associated with GABHS infection in both children and adults (11). Stuffy nose and sneezing are the most common symptoms caused by respiratory viruses. Although rhinovirus, the most common virus, is not thought to cause fever, Bellei *et al.* (12) reported a 50.5% incidence of fever in rhinovirus related cases in their study. This is in agreement with the Mistik Score's fever criterion. The presence of the fever variable in both bacterial and viral scores is possible because fever is observed in both kinds of infections. Also, the difference in the temperature levels may explain how fever may be present in both scores. Exudative tonsillitis is commonly associated with ADV, EBV, and GABHS infection, although influenza virus, parainfluenza virus or enteroviruses have been reported (13–15). We had few cases of ADV and enterovirus infections or

influenza and parainfluenza infections in our study. However, the absence of tonsillar exudates is a criterion of the Mistik Score.

The limitation of this study was that we did not ask the doctors in the study to change their routine practice and only prescribe antibiotics according to culture results. This resulted in a high antibiotic prescription rate of 74.8% in the presence of an 18.5% GABHS infection rate. Another limitation of this study was that it was designed to identify only GABHS and 16 respiratory viruses. Certain bacteria that are sometimes found in sore throat, such as group B, C and G streptococci (*Streptococcus dysgalactiae* spp. *equisimilis*, *Streptococcus anginosus* group), fusobacterium (*F. necrophorum*) and also some other viral causes like herpes simplex virus, Epstein-Barr virus and cytomegalovirus were not identified in our study (16). These might have been the cause of sore throat in cases in which no germs were identified. However, it has been stated that in 20% to 65% (average 30%) of patients with pharyngitis, no infectious pathogen can be found (16). This suggests to us that examining these microorganisms may only provide an increase of approximately 10%, or no increase in the identification rate in clinical practice. Therefore, identification of these aetiological agents will probably not change the variables of the Mistik Score.

Comparison with existing literature

The aetiology of sore throat has been described in many textbooks and studies. Primary bacterial pathogens were stated as 30% in children aged 5- to 11-years old, 15% in adolescents and 5% in adults with pharyngitis. Viruses were identified in 15%–40% of children and in 30%–80% of adults. Rhinovirus has been stated as the most common viral agent (16). The overall GABHS rate of 18.5% and virus rate of 44.3% are in agreement with these findings. In addition, rhinovirus was the most common aetiological agent in our study.

The spectrum of respiratory viruses stated as the causative agent in sore throat, and the rate of GABHS differ from study to study. Chi *et al.* reported a virus rate of 29.6% and a GABHS rate of 1.7%. Viruses mixed with bacteria were found in 11.1% of cases. They suggested that routine throat cultures and antibiotics are not indicated in children with acute pharyngitis (15). In our study, the bacterial and viral rates are higher, and mixed infection is lower. We cannot suggest not using antibiotics considering the high rates of GABHS in our study. Hashigucci and Matsunobu reported a 10.7% GABHS rate, a 33.9% rate for viruses, and no etiological pathogens in 28.6% of cases. ADV was the most common virus (19.6%). The rate of 42.9% for no aetiological agent in our study is higher when compared with their study, but in agreement with other results (6,17). Laguna-Torres *et al.* (18) reported that the influenza A was the most common virus in influenza-like illness patients (25.1%). Our study shows that the rhinovirus was the most common virus, and this seems to be more reasonable when the ailment is a sore throat.

Many studies have been conducted in an attempt to find a score to diagnose bacterial sore throat, so that the unnecessary use of antibiotics can be prevented. In the first study by Centor *et al.* it was reported that knowing that a patient has a 56% chance of having GABHS on culture may be very helpful in decision making (9). In our study, we found that the chance of having a viral sore throat on PCR analysis was 82.1% by using the Mistik Score. The variables of absence of headache, stuffy nose, sneezing, temperature of $\geq 37.5^{\circ}\text{C}$ on physical examination, and the absence of tonsillar exudates and/or swelling were already symptoms and signs known to be indicators of viral infection.

The increase in the diagnostic test accuracy of a score may enable its use by a large number of physicians. The Centor Score's

sensitivity was reported as 49%, and the specificity as 82% (19). In our study we used the Modified Centor Score because of the presence of children. The Modified Centor Score had a sensitivity of 62.9% and a specificity of 78.5% in our study. The Mistik Score's sensitivity was higher than that of the Centor Score and similar to that of the Modified Centor Score. The specificity of the Centor Score was higher than those of the Modified Centor Score and the Mistik Score. Smeesters *et al.* suggested a new clinical score with a sensitivity of 41%, a specificity of 84% and a positive likelihood ratio of 2.6 for low-resource settings. They used a cut-off value and stated that the use of this score would prevent 41%–55% of unnecessary antibiotic use (20). The same calculation was performed for patients with a Mistik Score of 3–5. According to this calculation, the use of the Mistik Score could have prevented 30.7% of unnecessary antibiotic use.

The positive predictive value when using a Modified Centor Score of 4 was reported as 48% by Mazur *et al.* (21). In our study, a Modified Centor Score of 4 had a positive predictive value of 46.4%. However, the best cut-off point was with a score of 3, which had a positive predictive value of 40.1%. Our score had a positive predictive value of 62.5%, which seems to be better than that of the Modified Centor Score. The importance of a negative likelihood ratio has been stated as an important factor for use as a clinical criterion (6,21). A negative likelihood ratio of under 0.2 is considered useful. In our study, the negative likelihood ratios of the Modified Centor Score and the Mistik Score were 0.47 and 0.55, which were both higher than the desired level. The diagnostic accuracy of the Modified Centor Score (75%) in our study was a little higher than that of the Mistik Score (68%). This suggests to us that the Mistik Score may be used as well as the Modified Centor Score.

Implications

The use of the Mistik Score may be analysed with an example. A 5-year-old child may present to his/her general practitioner with the complaints of sore throat, runny nose and cough. The history and physical examination of the patient reveal absence of headache, stuffy nose, sneezing, cough and the absence of tonsillar exudates and/or swelling. This patient has a Centor Score of zero, and a Modified Centor Score of one. A Modified Centor Score of one indicates a 5%–10% risk of GABHS infection, and no further testing or antibiotics are suggested for this patient (7,22). In this patient, the Modified Centor Score may only suggest presumed viral infection. However, the Mistik Score has proven viral infection with PCR analysis results (61.9%–70.7%, with a score of four). If this patient had a fever of $>38.0^{\circ}\text{C}$, this would make the Modified Centor Score two, and the Mistik Score would be five. It is possible to determine that the infection is 82.1% viral by using the Mistik Score. The use of the Modified Centor Score alone with a score of two will make further testing necessary in the case of a viral (rhinovirus) infection (7).

The presence of a low Modified Centor Score may suggest probable viral sore throat, but this score is not valid for showing viral infection. In addition, a low Mistik Score is not valid for showing bacterial infection. A physician may choose to use one of these scores to decide on the aetiology of sore throat. However, knowing the probabilities of both bacterial and viral sore throats may result in a better evaluation.

Conclusions

The analysis of our data allowed us to produce a scoring system to diagnose viral sore throat. Our score for diagnosing viral sore throat has slightly lower sensitivity and specificity, a higher positive predictive

value and a lower negative predictive value when compared with the Modified Centor Score. The 'Mistik Score' may be useful to diagnose viral sore throat either alone or in combination with the Modified Centor Score, which is used for the diagnosis of GABHS in sore throats.

Funding: this study was funded by the Scientific Research Council of Erciyes University (ERUBAP, Project No. TOA-2012-4148).

Ethical approval: Erciyes University Ethics Committee approved this study (Date: 07.08.2012, No. 2012/464).

Conflict of interest: the authors have no financial or proprietary interest in any of the instruments or products used in this study.

Supplementary material

Supplementary material is available at *Family Practice* online.

Acknowledgements

We presented this study as a poster at the Royal College of General Practitioners, Annual Primary Care Conference 2013, 3–5 October 2013, Harrogate, UK. The authors would like to thank Assistant Professor Ferhan Elmali for his assistance in statistical analysis, and Isabel Steel for her comments and Erciyes University Editing Office for help in editing.

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