Journal of
Pulmonology and
Intensive Care

Original Article

DOI: 10.51271/JOPIC-0061

The effect of medication adherence on symptom control, airway inflammation and exacerbations in asthmatics*

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Cite this article: Akkale T, Badoğlu M, Mammadova S, Oğuzülgen İK, Türktaş H. The effect of medication adherence on symptom control, airway inflammation and exacerbations in asthmatics. *J Pulmonol Intens Care.* 2025;3(3):64-69.

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Received: 14/07/2025 ◆ **Accepted**: 12/08/2025 ◆ **Published**: 20/08/2025

ABSTRACT

Aims: In asthma patients with good compliance to treatment, symptoms, functional and inflammatory parameters are expected to be at normal levels. In our study, the effect of treatment compliance on asthma symptom control, airway inflammation, and attacks within 6 months in asthmatic patients was investigated.

Methods: 113 patients who have been diagnosed with asthma for at least 6 months and were under inhaler treatment were included in the study. Respiratory function tests, asthma control test (ACT) and Morisky 8 items medication adherence scale (MMAS-8) were performed and exhaled nitric oxide (FENO) levels were measured. After 6 months, patients were questioned about any asthma exacerbations in this 6 months period.

Results: According to ACT, 57.5% of patients were not under control. 49.6% of patients had poor medication adherence according to MMAS-8. 24.1% of patients had high FENO levels. There was no association between MMAS-8 scores and FENO levels (p=0.34 r=-0.091). There was positive correlation between ACT and MMAS-8 scores (r=0.371 p=0.001). ACT scores were higher in patients with low FENO levels (p=0.01). 11 asthmatics experienced asthma exacerbation during 6 months follow-up period. Medication adherence was not found to be a significant factor for exacerbations, however baseline ACT scores and FEV1 values were lower in patients who experienced asthma attacks (r=-0.107, p=0.002).

Conclusion: As a result, our study demonstrated that medication adherence determined by MMAS-8 is an important factor of asthma symptom control.

Keywords: Asthma control, adherence, airway inflammation, exacerbations

*This study was presented as a summary presentation at the 13th World Asthma Congress (Madrid, Spain, 12–15 March, 2016), as a poster at the Turkish Thoracic Society 18th Annual Congress (Antalya, 01–05 April, 2015), and received a poster presentation award in the field of asthma and allergy.

INTRODUCTION

Asthma is a chronic respiratory disease characterized by airway inflammation and bronchoconstriction. Achieving optimal asthma control is vital in reducing symptoms, preventing exacerbations, and improving the quality of life of patients.

The primary goal of current asthma treatment is to achieve disease control. Asthma control includes patient symptom control and assessment of future risks.[1,2] Achieving and maintaining optimal asthma control requires a combination of pharmacologic therapy and patient compliance with prescribed medications.[3,4] Noncompliance with medications negatively impacts the course of the disease in asthmatic patients and leads to increased airway inflammation, functional limitations, healthcare costs, decreased quality of life, emergency hospitalizations, and even increased mortality.[1,5]

In recent years, researchers have investigated the role of exhaled nitric oxide (FeNO) as a biomarker for asthma control and its potential association with patient adherence to treatment.[6] This study aimed to determine the effect of treatment adherence on asthma control and airway inflammation in patients with asthma, and to investigate the role of FeNO and treatment adherence in predicting future risk of asthma within the following 6 months. FeNO reflects

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eosinophilic airway inflammation through the measurement of nitric oxide produced by airway epithelial cells. Its levels are influenced by various factors such as smoking status, presence of respiratory infections, and asthma phenotype (e.g., eosinophilic vs. non-eosinophilic). According to GINA guidelines, FeNO measurement can support the diagnosis and monitoring of asthma in specific patient subgroups, particularly those with suspected type 2 inflammation or uncertain response to inhaled corticosteroids. Previous studies have also explored the relationship between medication adherence and FeNO, suggesting potential but inconsistent associations.

METHODS

Ethics

The protocol has been approved by the Gazi University Clinical Researches Ethics Committee (Date: 06.01.2014, Decision No: 09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

Data was collected from patients who consulted the chest diseases outpatient clinic and were diagnosed with asthma and used inhaler treatment. These cases were followed up prospectively for 6 months. Written informed consent was obtained from all patients who participated in the study.

The patient's age, gender, smoking history, educational status, employment status, length of time diagnosed with asthma, skin-prick test, asthma medications, comorbidities, non-asthma drugs used for comorbidity, and pulmonary function tests at admission were recorded. At the beginning of our study, FeNO measurement was performed for all patients with asthma who applied to our outpatient clinic. Patients were asked to complete the asthma control test (ACT) and the 8-item Morisky medication adherence scale (MMAS-8). 6 months after their admission, all patients were contacted by telephone or by scanning their file information, and they were questioned if they had an asthma attack that required systemic steroid use for at least 3 days within these 6 months. Smoking status was included as a covariate in statistical analysis to account for its known impact on FeNO levels.

Method of Data Collection

Cases: Patients who applied to the pulmonology outpatient clinic of our hospital for control purposes between 01/01/2014 and 01/07/2014 who were diagnosed with asthma at least 6 months before according to the guidelines of GINA (Global Initiative for Asthma) and the Turkish Thoracic Society and were treated with inhalers for at least 6 months were included. Patients who had an attack the previous month or had an acute lower respiratory tract infection were not included in the study because it would affect the FeNO value. Patients with asthma who had agreed to give informed written consent and who were able to read and fill out written questionnaires were prospectively included in the study.

Examined Parameters

Pulmonary function test (PFT): PFT measurement was performed using a Vmax 20 (Sensor Medics/VIASYS, Conshohocken, Pennsylvania, USA) device. The measurement was taken at least three times while the patients were at rest and the best result was included in the evaluation. Values were expressed as a percentage considering the absolute value and expected value.

Asthma control test (ACT): A printed ACT was given to the patients who were asked to read and fill in for themselves. The answers to the five questions were scored separately, and the patient's total score was determined. According to the total score, the cases were categorized into two groups: controlled (ACT>19) and uncontrolled (ACT≤19).[2,7,8]

Fractionated expiratory air nitric oxide measurement (FeNO): FeNO measurement was performed with a portable nitric oxide analyzer (NIOX MINO; Aerocrine, Solna, Sweden) that uses an electrochemical method in accordance with the ATS/ERS recommendations as previously described.[6,9,10] The FeNO measurement was taken before PFT in the patients. The unit of measurement was expressed as particles per billion (ppb) at an exhalation flow rate of 0.05 L/s during a single exhalation. The patients were asked to exhale in a comfortable sitting position, against the pressure of 5 cm H_2O created by the mouth particle with a flow rate of 0.05 L/sec, from the mouthpiece for 2–3 seconds until total lung capacity after inhalation through the mouthpiece that purifies the nitric oxide in the inspiratory air, without holding their breath. The duration of exhalation was kept above 6 seconds to reach the plateau concentration. The measured FeNO value was classified as: low=<5 ppb, normal=5–25 ppb, moderate=25–50 ppb, and high=>50 ppb.[9,10] In this study, a FENO value of >25 ppb was taken as the threshold value.

8-item Morisky medication adherence scale (MMAS-8): The validated Turkish translation of the MMAS-8 questionnaire was given to the patients to assess treatment compliance where 8 points was high, 6–7 points was moderate, and <6 points was low adherence.[11,12] Copyright owner (Morisky Medication Adherence Research, LLC) provided written permission to use the MMAS-8 questionnaire in this research.

Statistical Analysis

The research data were uploaded and evaluated using the SPSS 15.0 software. Descriptive statistics were presented as mean±standard deviation (mean±SD), median (minimum and maximum), frequency distribution, and percentage. In addition to descriptive statistics, Chi-square, Yates corrected Chi-square, and Fisher's exact tests were used. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk tests). When the variables were found not to fit a normal distribution, the Mann–Whitney U test, Kruskal–Wallis test, and Spearman's test were used for statistical significance and relationships. A binary logistic regression test also evaluated the relationship between drug adherence and asthma control. The statistical significance level was accepted as $p<0.05$. Additionally, a post-hoc power analysis for the primary outcome (association between MMAS-8 and ACT) indicated a statistical power greater than 80%, supporting adequacy of the sample size for this analysis.

RESULTS

The study included 113 patients diagnosed with asthma and who met the inclusion criteria. The demographic data of the patients are presented in **Table 1**. The asthma-related characteristics of the patients are presented in **Table 2**. Most patients (65.5%) had forced expiratory volume (FEV1)≥80%. 63 (55.8%) of patients were using a combination therapy that included inhaled corticosteroids, and most (77%) were non-atopic. Notably, only 8% of patients had severe asthma, which we acknowledge may limit the robustness of analyses related to exacerbations.

Table 1. Demographic characteristics of the patients

	n=113
Gender; n (%)	
Female	80 (70.8)
Male	33 (29.2)
Age, years, (mean±SD)	51.39±13.01
Smoking habit, n (%)	
Smokers	24 (21.2)
Non-smokers	70(61.9)
Ex-smokers	19 (16.8)
Asthma duration, yrs, (mean±SD)	7.87±8.09
Educational level, n (%)	
Primary school	46 (40.7)
High school	33 (29.2)
University	34 (30.1)
Presence of comorbidities* n (%)	
No	40 (35.4)
Yes	73 (64.6)
Number of comorbidities (mean±SD)	1.24±1.2

SD: Standard deviation, *Osteoporosis, heart failure, arrhythmia, diabetes mellitus, chronic liver disease, gastro esophageal reflux, sinusitis, rhinitis, malignancy

Regarding asthma symptom control, 57.5% (n=65) of patients had asthma that was under control (ACT≥20), while 42.5% (n=48) were not under control (ACT<20). Only 15 (13.3%) patients had high, and 42 (37.2%) had moderate adherence to asthma medications measured by the MMAS-8 questionnaire (**Table 2**).

FeNO measurement could not be performed in five of 113 patients as they could not perform the measurement maneuver. The mean FENO level of 108 patients was 19.9±15.37 ppb. Eighty-two patients (75.9%) had low, and 26 (24.1%) patients had high FENO levels (low: ≤25 ppb and high: >25 ppb) (**Table 2**).

The effect of medication adherence on asthma control was evaluated by comparing MMAS-8 with ACT. The mean ACT was significantly lower in the low adherent group (ACT was 19.5±3.45 for low, 21.7±3.8 for moderate, and 22.8±2.6 for high adherent groups, p=0.02). 41.1% (n=23) of the patients in the group with low medication adherence had well-controlled asthma with a ratio of 71.4% (n=30) in the group with moderate adherence and 80.0% (n=12) in the group with high adherence (p=0.02). It was shown that asthma symptom control improved as adherence rates increased (**Figure 1**). The odds of uncontrolled asthma were 5.74 (95% CI 1.45–22.6, p=0.013) in patients with low medication adherence compared with the high adherent group. A moderate positive correlation was observed between ACT and MMAS-8 values (r=0.371, p=0.001).

Table 2. Asthma-related characteristics of the patients

	n=113
FEV1; % predicted (mean±SD)	86.9±19.52
Cases according to FEV1 %, n (%)	
FEV1≥80%	74 (65.5)
FEV1 79-60%	30 (26.5)
FEV1<60%	9 (8)
Asthma treatment used; n (%)	
ICS*	50 (44.2)
Combination (include ICS) **	63 (55.8)
Asthma control status based on ACT	
Controlled	65 (57.5)
Uncontrolled	48 (42.5)
Level of medication adherence (MMAS-8 score); n (%)	
Low (MMAS-8<6 point)	56 (49.6)
Medium (MMAS-8=6-7 point)	42 (37.2)
High (MMAS-8 =8 point)	15 (13.2)
FENO levels (ppb); n: 108 (%)	
Low (FENO<25 ppb)	82 (75.9)
High (FENO≥25 ppb)	26 (24.1)
Asthma severity n (%)	
Intermittent	74 (65.4)
Mild	30 (26.5)
Severe	9 (7.9)
Use of drugs for comorbidity; n (%)	
Yes	60 (53.1)
No	53 (46.9)
Number of drugs used for comorbidity (mean±SD)	1.17±1.47

FEV1: Forced expiratory volume, SD: Standard deviation, ICS: Inhaled corticosteroids, ACT: Asthma control test, MMAS-8: 8-item Morisky medication adherence scale, FENO: Fractionated expiratory air nitric oxide measurement, * Low dose ICS, ** Low dose ICS-LABA, medium dose ICS-LABA, medium/high dose ICS and LTRA/LAMA

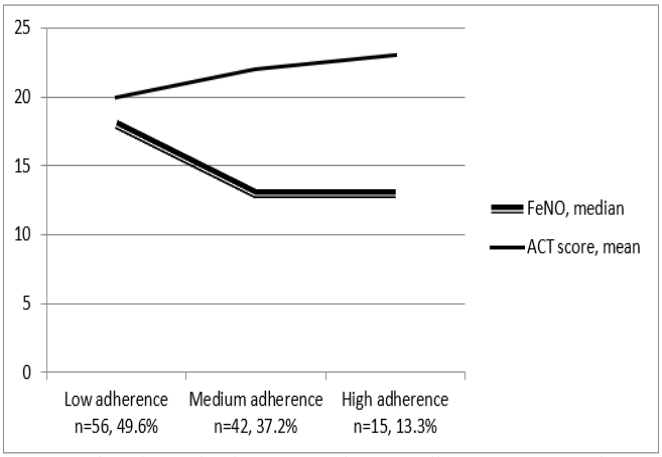

Figure 1. The relationship between medication adherence, FeNO and ACT
FENO: Fractionated expiratory air nitric oxide measurement, ACT: Asthma control test

The effect of medication adherence on airway inflammation was evaluated by comparing MMAS-8 with FeNO. The ratio of patients with asthma having high FeNO levels was non-significantly high in the low adherent group (FeNO levels >25 was measured in 33.3% for low, 15% for medium, and 14%

for high adherent groups, p=0.07). Median FeNO levels in different adherence groups are shown in **Figure 1**.

There was no statistically significant difference in adherence and asthma symptom control between the groups of different education levels (p=0.32). Furthermore, the asthma symptom control status (p=0.31), medication adherence (p=0.98), and FeNO levels (p=0.21) were not different between smokers and non-smokers. The median FeNO level of smokers (10.5 ppb) was significantly lower than non-smokers (15 ppb) and ex-smokers (19 ppb) as expected (p=0.002). There was no significant difference in medication adherence and gender (p=0.052). The relationship between the type of asthma medication used and ACT level, medication adherence, and FeNO levels could not be identified.

Asthma symptom control was worse in patients with high airway inflammation. The mean ACT of the patients in the low FeNO group (≤25 ppb) was 21±3.6 and 18.8±3.5 in the high (>25 ppb) FeNO group (p=0.01).

The presence of comorbidities was not different between adherent and non-adherent patient groups. Medication adherence was low in almost half of both groups with and without comorbidity. Asthma symptom control was not significantly different between patients with and without comorbidity. A poor but significant negative correlation was found between the number of existing comorbidities and FEV1 (r=–0.107, p=0.002). We recognize that adherence was assessed solely via the MMAS-8 questionnaire, without objective measures such as dose counters or pharmacy refill records. This is acknowledged as a limitation in the discussion.

Follow-up Evaluations After 6 Months

Four patients could not be contacted after 6 months, and follow-up data could not be obtained. Among the 109 patients who could be reached, 11 (10.1%) had at least one asthma exacerbation. One (0.9%) patient had three, and ten (9.2%) patients had one asthma exacerbation. At the 6-month follow-up, 72.7% of patients with an asthma exacerbation had uncontrolled asthma at initial evaluation. In comparison, the rate was 39.8% patients who did not have an asthma exacerbation—the initial mean ACT in patients who had an exacerbation was 17.5±3.7 and 20.8±3.5 for patients who did not (p=0.02). When comparing asthma medication use with exacerbation rates over a 6-month period, it was observed that 2.1% of patients using only inhaled corticosteroids (ICS) experienced exacerbations, whereas 16.4% of patients on combination therapy including ICS experienced exacerbations (p=0.03). The initial median FeNO levels of patients who had an exacerbation was 19±2.6 ppb and for those who did not was 15±1.3 (p=0.23; **Figure 2**).

The probability of having an exacerbation within 6 months was not associated with medication adherence, the presence of comorbidities, educational level, or the use of non-asthma drugs. However, the ratio of patients experiencing an exacerbation within 6 months was higher in the group using a combination therapy that included inhaled corticosteroids than the group using only inhaled corticosteroids medication (16.4% vs 2.1%, p=0.02). Patients who had an exacerbation had lower initial FEV1 than those who did not (65% vs 89.5%, p=0.007).

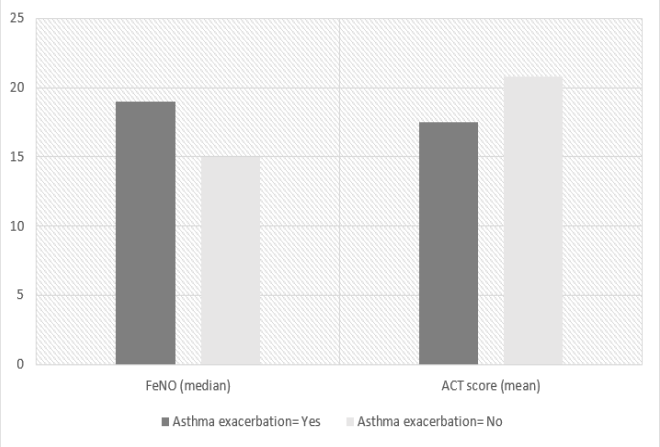

Figure 2. Comparison of the initial FeNO levels and initial ACT in patients who experienced or not an exacerbation during the 6 months period
FENO: Fractionated expiratory air nitric oxide measurement, ACT: Asthma control test

DISCUSSION

This study shows that asthma symptom control was worse in patients with asthma who are medication non-adherent and that FeNO values were higher in patients with uncontrolled asthma. In this patient group, ACT score and low FEV1 value are significant parameters in predicting asthma attacks at 6-month follow-up.

Adherence to treatment is crucial for achieving asthma control and managing inflammation effectively. In determining adherence, methods such as checking the last prescription date, identifying the number of medications obtained from reimbursement systems, use of dose counters, electronic inhaler monitors, and using specifically developed questionnaires can be beneficial.[13-15] Bårnes and Ulrik[16] investigated adherence levels to inhaler therapy among patients with asthma. From their extensive literature review, they identified an average adherence rate ranging from 22% to 63%. In this study, adherence was calculated as the total number of days of supplied medicine divided by the number of days of observation by linking the electronic prescriptions with the prescription fill information. Factors such as young age, being African American, having a low level of education, and having mild asthma were found to be associated with low adherence levels. Oguzülgen et al.[11] evaluated the criterion validity of the MMAS-8 adherence scale among patients with asthma in Turkiye. The findings revealed that 34.8% of patients exhibited high adherence to medication. In our study, the low and moderate treatment adherence rate was 86.8% and that factors such as education level, gender, medication used in asthma maintenance therapy, and the presence of additional comorbidities did not affect medication adherence.

Asthma control is expected to improve as medication adherence increases. In our study, as medication adherence assessed with MMAS-8 increased, the rate of asthma under control as measured by ACT increased. Woehrle et al.[17] investigated the relationship between medication adherence and symptom control in adults with asthma over a 90-day period using digital companion paired inhaler devices. At

baseline, 33% of patients had well-controlled asthma, which increased to 53.6% at the second ACT. It was concluded that improvement in medication adherence led to better asthma control, which corroborates our findings.

FeNO, a marker of eosinophilic airway inflammation, decreases with inhaler steroid treatment in patients with asthma and increases during an asthma attack.[18,19] In addition to asthma, FeNO can also increase because of eosinophilic bronchitis, bronchiectasis, and lower respiratory tract infections, but is low for smokers and those using steroid inhalers.[6] McNichol et al.[20] showed a greater reduction in FeNO in patients with poor treatment adherence in patients receiving directly observed inhaled corticosteroid therapy. In another study of 250 cases, low FeNO level in patients using inhaled corticosteroids correlated to high medication adherence.[21] In our study, although all patients were receiving inhaler corticosteroid treatment, FeNO was high in 24.1% of the cases and there was no association between MMAS-8 scores and FeNO levels (p=0.34 r=−0.091). This result can be explained by the fact that some of our patients were smokers or use inhaled corticosteroids. The lack of a statistically significant association between adherence and FeNO may relate to heterogeneous FeNO distribution, smoking habits, variations in inhaler technique, and treatment intensity differences.

Inflammation monitoring is also helpful in evaluating asthma control.[1,22] In the study by Gemicioğlu et al.[23] in which the FeNO level was investigated in different types of asthma, a negative correlation was found between the ACT score and FeNO (p<0.002, r=−0.31). Studies have reported no correlation between FeNO levels and FEV1 percentage, but there was a positive correlation between ACT score and basal FEV1 percentage (p=0.001, r=0.22).[24] As shown in other studies, it was emphasized that it would be more accurate to evaluate ACT together with respiratory function tests and FeNO measurements.[25] In our study, the mean ACT score in the group with high (>25 ppb) FeNO level was 18.8±3.5 and in the low (≤25 ppb) group 21±3.6 (p=0.01), and in 34% of patients with uncontrolled asthma, FeNO was above 25 ppb. Additionally, when patients with asthma were grouped as under control (ACT≥20) and uncontrolled (ACT<20), the median level of FeNO was same for both groups, which was considered to be related to the heterogeneous distribution of FeNO (minimum–maximum 5–90 ppb) and individual patient factors. However, it was thought that since all patients were receiving inhaled corticosteroids and other asthma maintenance treatments, some of them being active smokers and some having smoked in the past might be a factor.

In this study investigating the effect of patients' medication adherence on future risks and attacks, the attack rate of 113 patients during the 6-month follow-up was 10%. Contrary to what was expected, there was no statistically significant relationship between medication adherence and attack status, possibly because only 8% of the participants had severe asthma or 58% had their asthma symptoms under control. However, the number of patients with attacks in all three groups (low, medium, and high adherence) was low, which made it difficult to interpret the statistical results.

In a cohort study investigating factors that could predict an asthma attack, 43 of 154 asthma patients with a baseline FEV1 value of 72.62±17.96% had an attack within 4 months. In this study, the median FEV1 in those who had an asthma attack was 68% (55–79%), the median ACT score was 12 (10–16), and these rates were lower than in patients who did not have an asthma attack (p=0.013, p=0.003). However, the FeNO level of patients who had attacks was lower than those who did not have attacks (p=0.7).[26] In our study, the median FeNO level in patients who experienced attacks was 19±2.6 ppb (p=0.23), with a mean FEV1 of 65% (p=0.007), and a mean ACT score of 17.5±3.7 (p=0.02). However, FeNO levels were not different in patients who had or did not have an attack in this study. In patients using combination therapy that includes inhaled corticosteroids (ICS), a higher incidence of exacerbations was observed compared to those using only ICS. This finding could be attributed to the fact that these patients may have more severe asthma, with disease severity being a known risk factor for exacerbations.[27] Baseline ACT scores, FEV1 values, and comorbidity prevalence were compared between patients on combination therapy and those on ICS monotherapy, to better contextualize the higher exacerbation rate.

Limitations

A limitation of this study could be that the smoking status was not included among the patient selection criteria. Also, the very small number of patients who had an asthma attack might have played a role in some of the expected parameters not being statistically significant. If the number of patients were larger, the number of patients experiencing attacks might have increased further. Furthermore, the small number of exacerbation events reduced statistical power to detect associations with FeNO, adherence, and exacerbation risk, limiting generalizability.

CONCLUSION

This study showed that asthma symptom control was worse in patients with asthma who were medication non-adherent and FeNO values were higher in patients whose asthma was not under control. It was concluded that medication adherence, which can be easily evaluated with the MMAS-8 questionnaire, could contribute to the improvement of asthma control at patient follow-up. Our data also demonstrate the value of interpreting ACT, FEV1, and FeNO together when assessing asthma control in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The protocol has been approved by the Gazi University Clinical Researches Ethics Committee (Date: 06.01.2014, Decision No: 09).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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