

# Investigation of Relationship between Comorbid Factors and Excessive Dynamic Airway Collapse and Frequency of Hospitalization in Frequently Hospitalized COPD Patients

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## Abstract

**Objective:** “Frequent hospitalization” is defined as at least 2 hospitalizations per year in chronic obstructive pulmonary disease (COPD). However, we witness hospitalizations at 2–3-month intervals in some patients in our clinical practice. In our study, the factors considered to be associated with frequent hospitalizations were investigated in a selected patient group.

**Methods:** Thirty-four COPD patients being hospitalized at least twice per year were included in the study. The patients' demographic features, laboratory findings, physical activity scores, comorbidities, and respiratory functions were recorded. They underwent transthoracic echocardiography and fiberoptic bronchoscopy (FOB). The patients were categorized as Group 1 (patients hospitalized twice per year) and Group 2 (patients hospitalized more than twice per year). These groups were compared with regard to parameters considered to increase the frequency of hospitalization.

**Results:** Twenty-eight (82%) of the patients were male. The mean age was 65±8 (46-82) years, and the mean hospitalization number was 3.3±1.3 (2-6). There were 12 patients in Group 1 and 22 patients in Group 2. The rates of being in advanced age, showing lower physical activity, being in advanced stage, having disease for more than 10 years, and using a nebulizer and oxygen at home were found to be significantly higher in Group 2 than in Group 1. FEV<sub>1</sub> (expected %) level was 47.9% in Group 2, while it was 56% in Group 1 (p=0.003). The number of comorbidities was approximately 1.5 in Group 1 and 2.7 in Group 2 (p=0.014). Pulmonary hypertension (n=11) and heart failure (n=10) were identified only in Group 2 (p=0.003, p=0.006). Excessive dynamic airway collapse (EDAC) was detected in 17 (50%) patients through FOB, and 16 of them were in Group 2. Logistic regression analysis revealed the existence of EDAC and a low level of FEV<sub>1</sub> (expected %) as the independent factors that affected the number of hospitalizations.

**Conclusion:** It was suggested that the existence of EDAC and decreased FEV<sub>1</sub> can increase the frequency of hospitalization in COPD patients who are hospitalized frequently.

**Keywords:** Comorbidity, COPD, excessive dynamic airway collapse

## INTRODUCTION

The exacerbation is an important cause of morbidity and mortality in chronic obstructive pulmonary disease (COPD) and often leads to hospitalization. The frequency of exacerbations, reported to range from 0.5 to 3.5 per year, is related to the stage of the disease, and as the number increases, the progression of the disease is affected in a negative way (1, 2). In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, the exacerbations frequency of the disease was stated as 2.6 for stage 2 patients and 3.4 for stage 3 patients (3).

Our hospital is a branch hospital providing services for a great part of the Anatolian side of İstanbul. Most of the hospitalized patients have a diagnosis of COPD. It was observed that some patients were hospitalized more than twice in a year, and they had lengthy medical records. In fiberoptic bronchoscopy (FOB) examinations performed for various reasons, the frequent presence of excessive dynamic airway collapse (EDAC) in these patients caught our attention.

Excessive dynamic airway collapse is a central airway disorder that often accompanies COPD but is diagnosed rarely. It is characterized by a reduction of more than 50% in the cross-sectional area of the tracheal lumen during expiration due to flaccidity of the supporting tracheal cartilage (4). The bronchoscopic appearance of EDAC is accepted to be the “gold standard” for diagnosis. Excessive dynam-



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ic airway collapse is classified as tracheobronchomalacia (TBM) and tracheomalacia (TM) according to localization. Saber-sheath trachea is a form based on morphology. In this form, the coronal diameter of the trachea decreases, while the sagittal diameter increases, and the characteristic shape of the saber-sheath appears (4-8). The incidence of excessive dynamic airway collapse was reported to be 14% in patients who underwent FOB due to chronic cough, 5% in patients having any respiratory complaints, 13% in patients with a known pulmonary disease, and 44% in patients with chronic bronchitis (9-12). In the studies conducted, a rate of 57% was reported for the coexistence of COPD and EDAC (13). It is controversial whether EDAC that is seen in COPD is a complication of the disease or whether it is a comorbidity that accompanies COPD. However, it is believed that it plays an important role in the progression of COPD.

There are many studies suggesting that comorbid factors and factors, such as advanced age and low  $FEV_1$ , increase the frequency of hospitalization and mortality (14-16). On the other hand, we could not reach a study investigating the effect of EDAC on the frequency of hospitalization, which has a proven direct effect on the prognosis and morbidity of the disease and which has an important place in the management of COPD. Therefore, our study was conducted in order to investigate the presence of EDAC in addition to the comorbid factors considered to influence frequent hospitalization.

## METHODS

Thirty-four patients who were followed up in our inpatient clinic between January 2009 and January 2010, diagnosed with COPD in accordance with the GOLD guideline, and hospitalized twice or more within the last year were evaluated in this study. These 34 patients were in a stable condition. Their infection markers were negative [absence of purulent phlegm, fever, leukocytosis in the complete blood count, increased C-reactive protein (CRP), and infiltration in chest radiography], and they did not have respiratory acidosis in their arterial blood gas (ABG). Also, ethics committee approval was obtained for the study.

Detailed medical histories of the patients were taken. Their physical activity states and previous medical treatments [use of corticosteroid, long-term oxygen therapy at home (LTOT), use of nebulizer, bronchodilator therapies] were recorded. Peripheral blood examination, ABG analysis, and pulmonary imaging were performed, and pulmonary function test (PFT) was applied.

The values of the PFT carried out within the last year were taken as the basis in the study. For the patients who did not undergo PFTs in the last year, new PFTs were performed using a spirometry device (Spirolab S/N A 23, MIR Medical, Rome, Italy). The values were evaluated as absolute value and the percentage of the expected value for the patient's age and height. The stage of chronic obstructive pulmonary disease was determined according to PFT findings (3).

Body mass index (BMI) was calculated as the ratio of weight to the square of height ( $m^2$ ) and categorized into 4 groups in accordance with the recommendations of the World Health Organization (WHO) (17). Accordingly, patients having a BMI lower than 18.5 were accepted to be underweight (cachexia), patients with a BMI of 18.5 to 24.9 were accepted to be optimal weight, those with a BMI of 25 to 30 were accepted to be overweight, and those with a BMI above 30 were accepted as obese.

Right and left heart functions were evaluated through transthoracic echocardiography (TTE) (MyLab™40, Esaote, Genoa, Italy), performed by a cardiologist. The patients whose ejection fraction values were above 55% were considered to have normal left ventricular function, but the ones whose mean pulmonary artery pressure (PAP) was above 25 mm Hg were accepted to be pulmonary hypertension (PHT) patients (18, 19).

All patients who were included in the study underwent FOB (BF-1T60, Olympus, Fukushima, Japan) in the bronchoscopy laboratory of our service. They were administered sedation (midazolam 0.01-0.03 mg/kg, IV) before the process. During the process, oxygen was given through the nasal way, and vital findings were monitored. The existence of EDAC was evaluated by the physician who performed the procedure and was recorded, with its localization. Development of collapse that reduced the airway patency at a rate of more than 50% during expiration was defined as EDAC. Detection of EDAC only in the trachea was considered TM, and detection in one or two bronchus systems, in addition to the trachea, was evaluated to be TBM (5). Cases with a narrowed coronal diameter of the trachea but widened sagittal diameter were defined as "saber-sheath trachea" (6).

In order to determine the risk for anxiety and depression in the patients, the "Hospital Anxiety and Depression Scale" was employed (20, 21).

The presence of non-COPD diseases that were diagnosed through the examinations performed (physical examination, laboratory tests, imaging techniques), based on the patient's own statement, and diagnosed by another health center was considered to be comorbid conditions. The values of hemoglobin below 13 g/dL in males and below 12 g/dL in females were evaluated as anemia. Cardiovascular diseases were confirmed by a cardiologist. Systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg were accepted as arterial hypertension. Gastroesophageal reflux (GER), peptic ulcer, osteoporosis, diabetes mellitus (DM), hypertension (HT), coronary artery disease, obstructive sleep apnea syndrome (OSAS), and Parkinson's disease were recorded as comorbidities.

Physical activity measurement was performed using the International Physical Activity questionnaire developed by the International Group for Consensus of Physical Activity Measurements and standardized according to the definitions of physical activity in different countries with different sociocultural perspectives. In the short form of the questionnaire, the activities are divided into three groups-mild, moderate, and hard-and the frequency and duration of each activity are questioned. Each activity has a metabolic equivalent (MET) described in the literature. The questionnaire was given to all patients included in the study. Daily activities were summated in minutes, and weekly values were obtained. Mild activities were multiplied by 3.3, hard activities were multiplied by 4.0, and very hard activities were multiplied by 8.0. Total MET was calculated by adding up these three values. Patients with a MET value below 600 kcal/min were evaluated to be inactive, the ones with a MET value of 600 to 3000 kcal/min were considered to be moderately active, and the ones with a MET value above 3000 kcal/min were evaluated as over-active (22, 23).

The cases were put into two groups-patients hospitalized twice per year (Group 1) and patients hospitalized more than twice per year

(Group 2-and a comparative analysis was performed for evaluating the data obtained.

### Statistical Analysis

While evaluating the findings of the study, Statistical Package for Social Sciences (SPSS) software, version 16.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses. In addition to descriptive statistics (frequency, percentage, mean, standard deviation), Pearson chi-square test was used for comparing qualitative data. In comparison of quantitative data, Kruskal-Wallis test was employed for the parameters not displaying a normal distribution, and Mann-Whitney U-test was used for identification of the group causing a difference. The results were evaluated with 95% confidence intervals and at a significance level of  $p < 0.05$ . The factors affecting the frequency of hospitalization were investigated by logistic regression analysis using the "stepwise backward" method.

### RESULTS

Twenty-eight of 34 patients included in the study were male (82%), and the mean age was  $65 \pm 9$  (46-82) years. The mean cigarette use was found to be  $40 \pm 23$  packs-year. The number of hospitalizations in a year was 2-6, and the mean was  $3.3 \pm 1.3$ . The level of physical activity was low in 15 patients (44%). Six patients were cachectic, and 5 were obese, according to BMI. In the spirometric evaluation, the mean  $FEV_1$  was  $1.3 \pm 0.4$  L, and  $FEV_1$  (predicted %) was  $50.8 \pm 7.9$ . It was found that 22 patients had COPD for more than 10 years. In accordance with the GOLD guideline, 20 patients were stage 2, 10 patients were stage 3, and 4 patients were stage 4.

Of the patients, 88% ( $n=30$ ) had at least one comorbid disease diagnosed through the examinations and/or diagnosed by a physician, based on their own statement, and the most common comorbid diseases were systemic HT ( $n=16$ ), GER ( $n=14$ ), PHT ( $n=11$ ), and heart failure ( $n=10$ ), respectively. The "Hospital Anxiety Depression Scale" revealed anxiety in 5 patients and depression symptoms in 3 patients. When comorbid factors were classified according to GOLD staging, the incidence of heart failure and OSAS increased in parallel with increased stage. The comparison of comorbid factors in accordance with the stage of COPD is shown in Table 1.

The patients in our study were categorized into two groups: patients with 2 hospitalizations per year (Group 1) and patients with more than 2 hospitalizations (Group 2). The comparison of the groups according to the variables is summarized in Table 2. In Group 1, there were 12 patients, and there were no female patients. The mean age was 61 years. Group 2 included 22 patients (6 females, 16 males), and the mean age was 67.6 years, which was significantly higher than in Group 1 ( $p=0.031$ ). No significant relationship was found between gender and cigarette packs-year and the number of hospitalizations (respectively,  $p=0.055$ ,  $p=0.221$ ). The  $FEV_1$  and  $FEV_1\%$  values were 1.58 L and 56% in Group 1 and 1.21 L and 47.9% in Group 2. Accordingly, there was a negative relationship between the frequency of hospitalization and  $FEV_1$  ( $p=0.008$ ) and  $FEV_1\%$  ( $p=0.003$ ). Forty percent of the patients with GOLD stage 2 and all of the patients in stage 3 and 4 were included in Group 2 ( $p=0.001$ ). Of the patients having the disease for more than 10 years, 13.6% was in Group 1 and 86.4% was in Group 2 ( $p=0.001$ ). All of the patients with low physical activity level were involved in Group 2.

The mean comorbidity number was 1.5 in Group 1, while it was 2.7

**Table 1.** Comparison of comorbidities according to COPD stage

	Stage 2 (n=20)	Stage 3 (n=10)	Stage 4 (n=4)	p
Pulmonary hypertension	0	7	4	<0.001
Heart failure	1	5	4	<0.001
OSAS	0	5	0	0.001
Diabetes mellitus Type 2	4	1	2	0.246
Gastroesophageal reflux	6	6	2	0.269
Coronary artery disease	2	0	0	0.475
Hypertension	8	6	2	0.581
Depression	0	3	0	0.495

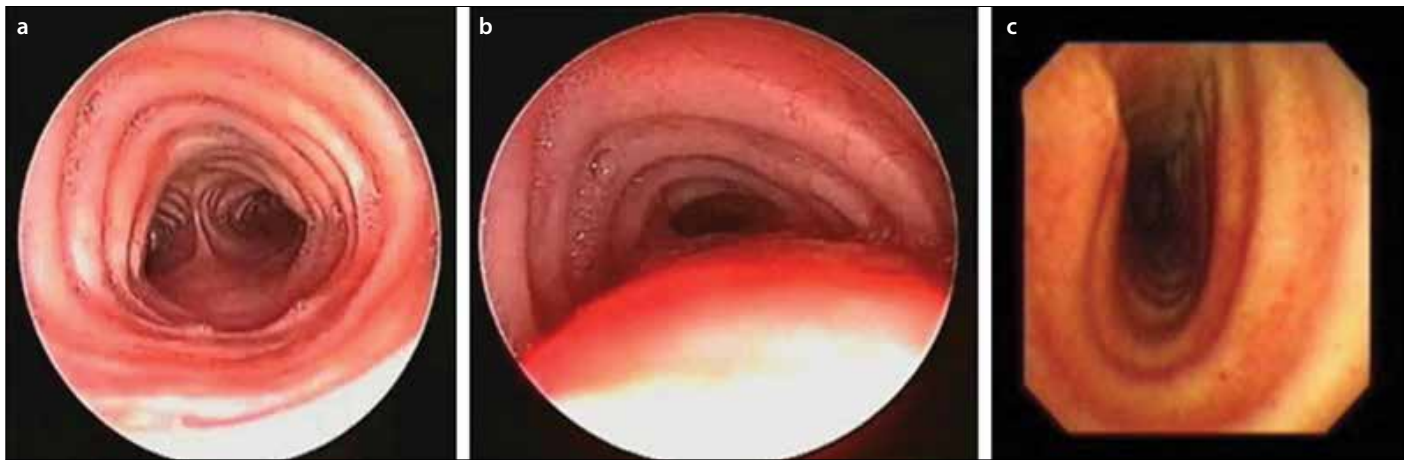
OSAS: Obstructive sleep apnea syndrome

**Table 2.** Comparison of variables according to frequency of hospitalizations per year

Characteristics	Group 1 (n=12)	Group 2 (n=22)	p
Gender (n): Female	0	6	0.055
Male	12	16	
Age (mean)	61.0	67.6	0.031
Smoking (packs-year) (mean)	33.4	43.6	0.221
Stage 2 COPD	12	8	0.001
Stage 3 and 4 COPD		14	
Duration of COPD: <10 years	9	3	0.001
Duration of COPD: >10 years	3	19	
$FEV_1$ mean (L)	1.58	1.21	0.008
$FEV_1$ predicted %	56.0	47.9	0.003
<b>Physical activity</b>			
Low	0	15	<0.000
Moderate and high	12	7	
Comorbidity (mean)	1.5	2.7	0.014
Pulmonary hypertension	0	11	0.003
Heart failure	0	10	0.006
Use of nebulizer	1	20	<0.000
Use of LTOT	1	12	0.009
Use of ICS	11	19	0.556
Presence of EDAC	1	16	<0.000

EDAC: Excessive dynamic airway collapse; ICS: inhaler corticosteroid; LTOT: long-term oxygen therapy

in Group 2. A change was detected in the order of frequently seen comorbidities between the two groups. Pulmonary hypertension and heart failure were not observed in Group 1 but were seen in 11 ( $p < 0.001$ ) and 10 ( $p < 0.001$ ) patients, respectively, in Group 2. In the patients using long-term oxygen therapy and nebulizer, the frequency of hospitalization was higher than in those not using them ( $p < 0.01$ ,  $p < 0.000$ , respectively). The rates of administration of bron-



**Figure 1. a-c.** Normal endobronchial system and sample images of EDAC patients: normal endobronchial system (a), tracheomalacia (b), and saber-sheath trachea (c)

**Table 3.** Bronchoscopy results according to group

	Group 1 (n)	Group 2 (n)	p
Tracheomalacia	0	2	
Tracheobronchomalacia	1	8	
Saber-sheath trachea	0	6	
Hypersecretion	3	4	0.67

chodilator therapy with a single drug or multiple drugs, use of long- or short-acting bronchodilator, and use of inhaler corticosteroid (ICS) were similar in both groups ( $p>0.05$ ).

The bronchoscopic evaluation carried out for the patients included in the study revealed EDAC in 17 patients (50%) (Figure 1). The presence of EDAC was observed in 11 male patients and in all female patients. Tracheobronchomalacia ( $n=9$ ) was the most common cause, with saber-sheath trachea ( $n=6$ ) and tracheomalacia ( $n=2$ ) observed less frequently. No major complication developed during and after bronchoscopy. The bronchoscopic findings are shown in Table 3. Excessive dynamic airway collapse was found in 16 of 22 patients included in Group 2 (72%), but it was seen in only 1 patient (8.3%) in Group 1.

For independent variables affecting the number of hospitalizations, regression analysis was performed with stepwise method. The model, generated using statistically significant parameters, was found to be strong for the analysis ( $F=20.823$ ;  $p<0.001$ ;  $R^2=0.598$ ). The presence of EDAC and a low level of  $FEV_1$  (predicted %) value were identified as independent factors that affected the frequency of hospitalization ( $p<0.05$ ,  $p<0.01$ , respectively). It was revealed that other variables ( $FEV_1$  mL, FVC,  $FEV_1/FVC$ , GOLD stage, MRCE) did not influence the frequency of hospitalization ( $p>0.05$ ).

## DISCUSSION

In our study, the factors significantly affecting the frequency of hospitalization were evaluated together in COPD cases, and the presence of EDAC and decreased  $FEV_1$  (predicted%) were found to be independent factors contributing to the frequency of hospitalization. It has been stated in many articles that  $FEV_1$  is significant in terms of both

prognosis and hospitalization frequency. However, the relationship between EDAC and hospitalization frequency was first suggested in this study. In our series, EDAC was detected in 72% of the patients in Group 2 but in only 1 patient (8.3%) in Group 1. In the presence of EDAC, adequate expectoration can not be reached due to complete or almost complete collapse during challenging expiration and coughing. Thus, in EDAC, secretions accumulating in the back can lead to exacerbation and increase the frequency of hospitalization.

In chronic obstructive pulmonary disease, with each exacerbation reported to be associated with a poor prognosis, the risk for longer hospitalization is higher than a previous hospitalization. Moreover, some studies revealed that hospitalization associated with exacerbation in COPD causes the disease to pass to the next advanced stage (24, 25). In the study of Garcia-Sanz et al. (26) that was conducted with 239 COPD patients, hospitalization was detected in 71% of patients in GOLD 3 and 4 stages. Özyılmaz et al. (27) identified a low level of  $FEV_1$  as an independent risk factor in frequent exacerbations requiring hospitalization. Cao et al. (28) found that hospitalization frequency was 2-fold higher in patients having COPD for more than 5 years, and a value of  $FEV_1$  below 50% was included among the causes of hospitalization. Similarly, in our study, low  $FEV_1$  (predicted%) value was detected as an independent risk factor, and it was observed that increased severity of the disease elevated the number of hospitalizations. Three or more hospitalizations per year were recorded for all of GOLD stage 3 and 4 patients.

In our series, the difference in gender did not vary for the patients with frequent hospitalization, but the mean age was found to be significantly higher in Group 2. There are some studies suggesting that these two parameters affect frequent hospitalization, as well as studies suggesting the opposite (29-31). Frequent hospitalization in advanced age can be related to decreased respiratory functions associated with age. There are some studies showing that low BMI increases frequent hospitalization and mortality (29, 31, 32). Although a direct relationship was not found between low BMI and the number of hospitalizations, all of the cachectic patients were situated in Group 2 in our study.

An interesting result of our study was the significant increase in the number of hospitalizations in patients using a nebulizer and LTOT at

home. Almagro et al. (15), in their study conducted with 606 patients, found the frequency of hospitalization to be higher in the patients (n=237) receiving LTOT, compared to other patients. These results, similar to ours, can be explained by ineffective oxygen therapy at home, the nebulizer device becoming an infection source after a while, and side effects resulting from frequent use of bronchodilator medications. On the other hand, the fact that patients using LTOT and nebulizer device had advanced-stage COPD and thus were situated in a group with a higher number of hospitalizations should be taken into consideration.

Some studies reported that there was an increase in frequent hospitalizations and mortality due to long-term oral corticosteroid use, and it was defended that this was resulted from side effects associated with steroid use (33, 34). Contrary to these studies, some results showing that the use of inhaler and systemic corticosteroid did not affect hospitalization were reported (35). In our study, there was no patient using long-term systemic corticosteroid, and the relationship between the use of inhaler steroid and frequent hospitalization was found to be insignificant. However, it is known that patients using a nebulizer often prefer the nebular form of corticosteroids. Therefore, it should be considered that frequent hospitalizations in patients using nebulizer can be associated with the side effects of corticosteroids.

One of the other important factors increasing the frequency of hospitalization is known to be comorbid diseases. The most common comorbid diseases in COPD are cardiovascular events, malnutrition, dysfunction and loss of skeletal muscles, cachexia, osteoporosis, anemia, lung cancer, GER, DM, metabolic syndrome, OSAS, depression, and anxiety (36, 37). Almagro et al. (15) found in their study, published in 2012, that 71% of patients requiring hospitalization at their emergency admission had a previous hospitalization, and they emphasized the importance of comorbid diseases. Taşçı et al. (38) evaluated 81 COPD patients who were hospitalized, and the presence of DM in 13 patients having 4 and 6 hospitalizations was thought to be remarkable. In our series, 88% of the patients had at least one comorbidity, and the most common comorbidities were HT, GER, PHT, heart failure, and type 2 DM, respectively. Pulmonary hypertension and heart failure were detected only in Group 2 patients.

The main limitation of our study is the low number of patients. Our hospital is a big branch hospital with a capacity of 605 beds. It is extremely busy, especially during winter, and the mean hospitalization due to a diagnosis of COPD is 340 in a month (39). Thereby, the cases with COPD occupy an important place in our clinical practice, and thus, we gain experience. However, the patients involved in our study were selected among patients only in our service (34 beds). Furthermore, applying of an invasive procedure affected the number of patients in a negative way. The second limitation is the insufficient number of female patients. The higher incidence of the disease in male patients might have resulted from the fact that the rate of smoking was higher in males than in females. Moreover, to say that EDAC was more frequently seen in females can be misleading because of the low number of patients. The third limitation can be that no stage 1 patient was involved in the study. Moreover, the insufficient number of stage 4 patients might have affected the results. However, our study was conducted with a selected patient group, including only the ones with a higher frequency of hospitalization, and they were generally COPD patients in the moderate and severe stages.

## CONCLUSION

In this study, it is remarkable that patients with frequent hospitalizations have different characteristics among them. The findings obtained made us to think that the concept of frequent hospitalizations could be used for more than 2 hospitalizations per year, instead of 2 and over per year, or that the concepts of “frequent hospitalizations” and “very frequent hospitalizations” could be emphasized.

In frequently hospitalized COPD patients, detection of comorbid diseases and application of appropriate treatments for these diseases will facilitate the management of COPD. Furthermore, it is important for clinicians to know that the presence of EDAC is a factor increasing the frequency of hospitalization in COPD patients, and awareness on this issue should be raised. Thus, more detailed examinations will be carried out for the diagnosis, and different treatment options will appear for the disease.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the local ethics committee.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept – T.Y., R.B., G.A.; Design – T.Y., G.A., R.B.; Supervision – T.Y., M.A., R.B.; Resource – M.A., G.A., F.T.; Materials – G.A., T.Y., R.B., G.G.; Data Collection and/or Processing – G.A., T.Y., R.B.; Analysis and/or Interpretation – T.Y., M.A., G.A.; Literature Review – M.A., G.A., F.T., T.Y.; Writing – T.Y., M.A., G.A.; Critical Review – F.T., G.A., G.G.

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