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Assessment of the role of fractional exhaled nitric oxide as a predictor of airway eosinophilia and corticosteroid responsiveness in patients with chronic cough

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) can be used as a rapid indicator of eosinophilic airway inflammation and steroid responsiveness in patients with bronchial asthma, but this role in chronic cough is still questionable. So, this study was carried out to assess the role FeNO as a predictor of airway eosinophilia and inhaled steroids responsiveness in patients with chronic cough. This prospective study included 70 patients with undiagnosed chronic cough and 20 healthy non-smoker control group. Sputum eosinophils % and FeNO were measured before and after a 4-week treatment trial with high dose inhaled corticosteroids. The optimal cut-off value of FeNO to predict sputum eosinophilia and the responsiveness of cough for corticosteroids were determined.

Results: Forty-five patients (64.3%) of the studied 70 patients with chronic cough responded to the 4-week trial of inhaled steroids. In the steroid responder group, FeNO and sputum eosinophils % were significantly higher than in the non-responder group. There was a significant positive correlation between FeNO and sputum eosinophils %. The optimal cut-off value of FeNO to detect airway eosinophilia was 33 ppb (with 65% sensitivity and 80% specificity) The ROC AUC was 0.757 and the optimal cut-off value of FeNO to predict corticosteroids responsiveness was 34.5 ppb (with 85% sensitivity and 90% specificity). The ROC AUC was 0.835.

Conclusion: FeNO can be used as a rapid and non-invasive diagnostic tool of airway eosinophilic inflammation and as a predictor for steroid responsiveness in patients with chronic cough.

Keywords: Chronic cough, Eosinophil, Fractional exhaled nitric oxide

Background

Cough is a protective reflex that helps in aspiration prevention and airway clearance. However, pathologically excessive cough is a frequent disabling complaint [1, 2]. Chronic cough is common with a prevalence of 5–10% and can be so severe to the degree that affects the quality of life, with complications such as urine incontinence and cough syncope [2–4].

Proper diagnosis of chronic cough is often difficult. Eosinophilic airway inflammation is a common cause of chronic cough. Patients with chronic cough may be evaluated for airway eosinophilic inflammation. Objective tests, like induced sputum analysis for diagnosing airway eosinophilia, may be the most accurate indicator of eosinophilic airway inflammation, but it is time-consuming and needs expert interpretation [5].

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Exhaled nitric oxide can be used as a rapid, simple, and non-invasive alternative indicator of eosinophilic airway inflammation and steroid responsiveness in patients with bronchial asthma, but this role in chronic cough is still questionable [6].

Objectives

To assess the role FeNO as a predictor of airway eosinophilia and inhaled steroids responsiveness in patients with chronic cough

Methods

This prospective study included 70 patients with chronic cough (29 males and 41 females with mean age of 46.75 ± 10.89) and 20 healthy control group (9 males and 11 females with mean age of 43.68 ± 12.89), and the included patients were recruited from the outpatient pulmonary clinics at Najd Hospitals (Saudi Arabia) from the period of March 2015 to January 2017. Written consents were received from the patients and the ethical committee approved the study.

Inclusion criteria

Adult patients (≥ 18 years old) with undiagnosed chronic cough (for ≥ 8 weeks) with normal chest X-ray and normal spirometry.

Exclusion criteria

- Patients with history or physical examination suggested specific causes of cough
- Patients with detected pulmonary abnormalities by chest X-ray
- Patients with abnormal spirometry
- Patients with a smoking history
- Patients who received corticosteroids in the preceding 4 weeks
- Patients with chronic cough were subjected to the following:
- Complete medical history
- General and local chest examination
- Chest radiological investigations
- Spirometry was done according to ATS guidelines. Airway reversibility test was considered positive when there was an improvement in FEV1 of 12% and > 200 mL from baseline after 20 min of inhalation of a short-acting B2 agonist [7].
- Sputum eosinophils count: induced sputum was done by the inhalation of 4.5% hypertonic saline. Sputum samples were differentiated from saliva if alveolar macrophages were present, and the percentage of squamous cells was less than 10%. Cytospins were stained by using May-Grunwald Geimsa. On every slide, 400 cells non-squamous cells were counted, and a total leukocytes and differential cell count was done [8].

FeNO measurement was done according to ATS/ERS recommendations using NIOX MINO, Aerocrine, AB, Solna, Sweden, and was recorded as parts per billion. Measurement was done while the patients were in a sitting position. Patients were asked for full inhalation, and without holding the breath, the patient was asked to expire at a flow of 50 mL/s until a plateau was maintained for ≥ 2 s. The mean value of three FeNO measurements was recorded. FeNO measurement was done before spirometry [9].

Assessment of cough severity was done by using cough symptom score (CSS) which consists of two subjective questions about cough frequency in the day and at night. CSS score ranges from 0 (no cough at all) to 10 (most severe cough) [10].

Management protocol for chronic cough was followed according to the guidelines [11]. Sputum eosinophilia was defined as induced sputum eosinophils % ≥ 3% [11, 12]. The studied patients received a trial of 4 weeks of high dose inhaled steroids, and patients were assessed for response to inhaled steroids (non-responders, partial responders, and complete responders) blinded to the FeNO results. Spirometry and FeNO tests were repeated after the treatment trial.

Complete responders were considered when cough disappeared completely, partial responders when the CSS decreased by one or more, and non-responders when the cough worsened or was not improved by a marked degree [13].

Study design

Prospective observational study.

Statistical methods

SPSS 19 (IBM Corporation, Armonk, NY, USA) was used for data analysis. Continuous variables are presented as mean ±SD. Categorical variables were presented as frequencies and percentages. Student's t test was used for analyzing quantitative variables, and the chi-square test was used for categorical data. Receiver operating characteristic curve was used to determine the optimal cut-off value of FeNO (ppb) to predict airway eosinophilia and corticosteroids responsiveness. The optimal cut-off value was determined from the best sum of sensitivity and specificity. Statistical significance was present when $p < 0.05$.

Results

This study included 70 patients with chronic cough (29 males and 41 females with mean age of 46.75 ± 10.89) and 20 healthy control group (9 males and 11 females with mean age of 43.68 ± 12.89. Table 1 shows that

Table 1 Baseline characteristics of the studied patients with chronic cough and the healthy control group

Parameter	The studied patients with chronic cough (n = 70)	The healthy control group N = (20)	p
Age (years) (means ± SD)	46.75 ± 10.89	43.68 ± 12.89	0.132
Male gender n (%)	29 (41.4%)	9 (36%)	0.4
BMI(kg/m^2) (means ± SD)	30.15 ± 3.11	31.236 ± 5.17	0.137
FVC % pred. (means ± SD)	95.75 ± 2.62	95.98 ± 2.84	0.371
FEV1, % pred. (means ± SD)	86.2 ± 4.74	86.67 ± 3.89	0.523
FEV1/FVC (means ± SD)	88.92 ± 5.001	86.67 ± 3.89	0.22
FeNO (ppb) (means ± SD)	38.27 ± 18.01	18.37 ± 5.82	< 0.001
Sputum eosinophils %	6.46 ± 4.07	1.20 ± 0.34	< 0.001

BMI body mass index, *FeNO* fractional exhaled nitric oxide, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s

there is statistically non-significant differences between the studied patients with chronic cough and the healthy control group as regards to age, gender, body mass index, FEV1% pred., FVC% pred., or FEV1/FVC, while FeNO (ppb) and the sputum eosinophils % were significantly higher in the studied patients with chronic cough.

In this study, complications of cough were present in 46(66%) patients of the studied 70 patients with chronic cough: 37 patients had urine-incontinence, 4 patients had urine-incontinence and cough syncope, and 5 patients had conjunctival hemorrhage.

Table 2 shows that there is statistically non-significant relation between steroid response and either age, gender, body mass index, CSS, or FVC% pred. of the studied patients, while there is statistically significant relation between steroid response and all of FEV1% pred., FEV1/FVC, FeNO (ppb), and sputum eosinophil% .

Table 2 Baseline characteristics of the studied patients according to steroid therapy responsiveness

Parameter	Steroid responders	Steroid non-responders	p
	N = 45(64.3%)	N = 25(35.7%)	
Age(years) (means ± SD)	47.711 ± 11.885	45.04 ± 9.104	0.333
Male gender n (%)	20 (44.4%)	9 (36%)	0.492
BMI(kg/m^2) (means ± SD)	30.044 ± 3.275	30.36 ± 2.856	0.688
CSS	8.3 ± 1.4	7.9 ± 1.6	0.394
FVC % pred. (means ± SD)	96.295 ± 2.12	94.80 ± 3.149	0.06
FEV1, % pred. (means ± SD)	83.533 ± 2.801	91.00 ± 3.606	< 0.001
FEV1/FVC (means ± SD)	85.556 ± 2.312	95.00 ± 1.607	< 0.001
FeNO (ppb) (means ± SD)	48.333 ± 11.576	20.16 ± 8.452	< 0.001
Sputum eosinophils % (means ± SD)	9.062 ± 4.496	1.780 ± 0.847	< 0.001

BMI body mass index, *FeNO* fractional exhaled nitric oxide, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, *CSS* cough symptom score

In this study, there was significant decrease of FeNO after treatment in the steroid responsive patients with chronic cough while the change of FeNO was non-significant in the non-responsive group as shown in Table 3.

This study showed that there is statistically significant positive correlation between FeNO (ppb) and sputum eosinophils % among the studied patients with chronic cough (r 0.666 and $p < 0.001$) as shown in Fig. 1.

In the current study, there is statistically significant positive correlation between FeNO (ppb) and post-treatment reversibility of FEV1% among the studied patients with chronic cough (0.611 and $p < 0.001$) as shown in Fig. 2.

In the current study, the best cut-off value for FeNO level for predicting sputum eosinophilia was 33 ppb (with 65% sensitivity and 80% specificity) The ROC AUC was 0.757 as shown in Fig. 3.

In the current study, the best cut-off value for FeNO level for predicting steroid responsiveness was 34.5 ppb (with 85% sensitivity and 90%% specificity) The ROC AUC was 0.835 as shown in Fig. 4.

Discussion

In the current study, 45 patients (64.3%) of the included 70 patients with chronic cough responded to the 4 weeks trial of inhaled steroids. In the steroid responder group, FeNO and sputum eosinophils % were significantly higher than in the non-responder group. There was a significant positive correlation between FeNO and sputum eosinophils % and the reversibility of FEV1 after steroid treatment. The optimal cut-off value of FeNO to detect airway eosinophilia was 33 ppb (with 65% sensitivity and 80% specificity) The ROC AUC was 0.757 and the optimal cut-off value of FeNO to detect positive response to the steroid was 34.5 ppb (with 85% sensitivity and 90% specificity). The ROC AUC was 0.835.

Chronic cough is a frequent clinical problem that can badly affect the quality of life. Eosinophilic airway inflammation is a common cause of chronic cough. Objective tests like induced sputum analysis for diagnosing airway eosinophilia are preferred to empiric treatment with steroids in patients with chronic cough [4, 5]. However, this test is time-consuming and requires experienced personnel and so its use is usually limited to specialized centers [1, 5]. FeNO has been suggested as a simple, rapid, and non-invasive marker for eosinophilic airway inflammation [14]. So, the aim of this study was

Table 3 FeNO before and after treatment in the studied patients with steroid responsive and non-responsive cough

	FeNO level (ppb) before treatment	FeNO level (ppb) after treatment	p
Steroid responsive cough	48.33 ± 11.57	20.16 ± 12.45	0.018
Steroid non-responsive cough	20.16 ± 12.45	19.8 ± 12.36	0.13

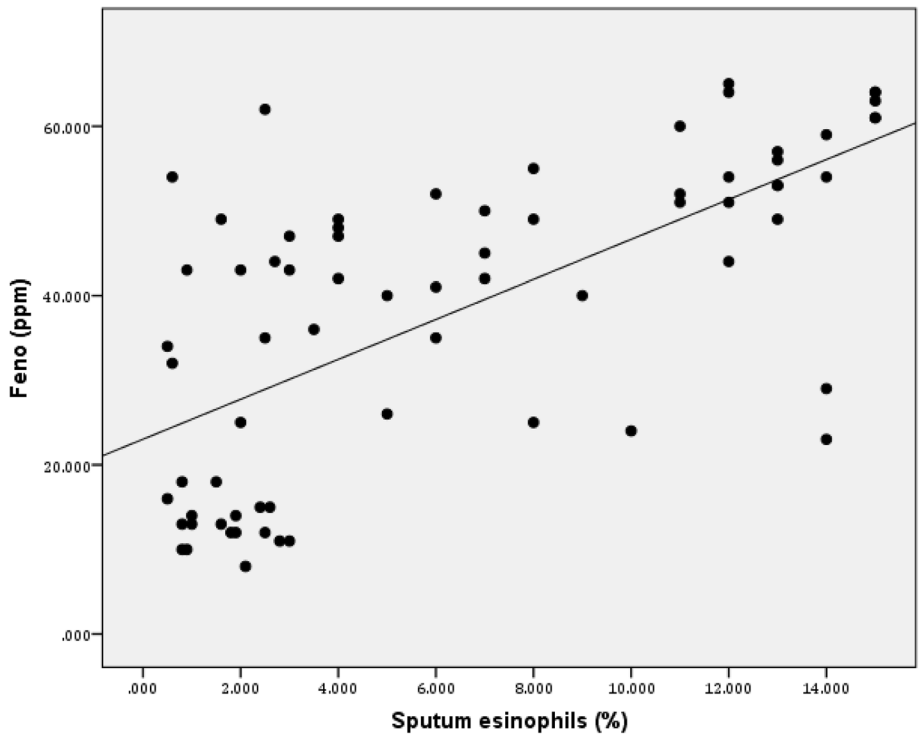

Fig. 1 Scatter dot graph showing significant positive correlation between Feno and sputum eosinophil

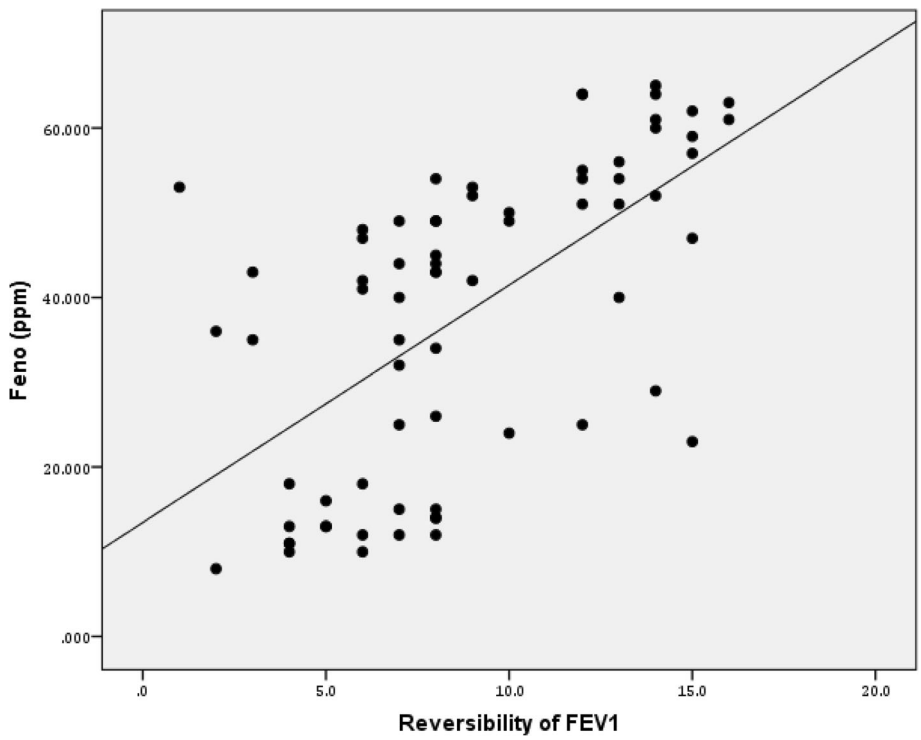

Fig. 2 Scatter dot graph showing significant positive correlation between Feno and post-treatment reversibility of FEV1

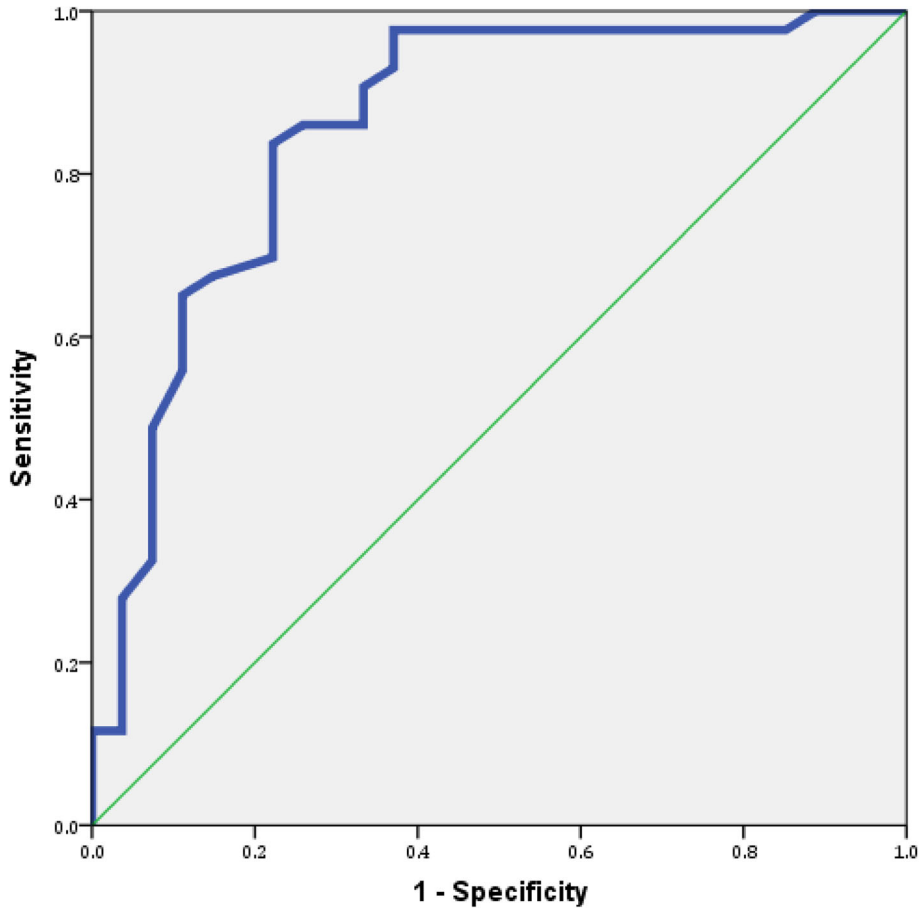

Fig. 3 ROC curve showing performance of FENO in diagnosis of eosinophilia among the studied patients

to assess the role of exhaled nitric oxide as a predictor of airway eosinophilia and inhaled steroids responsiveness in patients with chronic cough.

This study showed a significant positive correlation between FeNO and induced sputum eosinophils %. This result is similar with that reported in previous studies [14, 15] which have reported that FeNO significantly correlated with the sputum eosinophils count in the studied patients with chronic cough. Also in a previous study, FeNO levels were found to be sensitive and specific marker to differentiate eosinophilic from non-eosinophilic airway inflammation in patients with bronchial asthma [16].

In this study, the optimal cut-off value of FeNO to detect airway eosinophilia was 33 ppb (with 65% sensitivity and 80% specificity). The ROC AUC was 0.757.

In this study, there was significant decrease of FeNO after treatment in the steroid responsive patients with chronic cough while the change of FeNO was non-significant in the non-responsive group as shown in Table 3.

Corticosteroids are considered the main anti-inflammatory therapy in eosinophilic airway diseases. Inhaled corticosteroids are commonly used for chronic cough [11, 17, 18]. ICSs are effective for the treatment of eosinophilic bronchitis and for cough variant asthma, and high dose of inhaled corticosteroids may be more potent than a low to moderate doses [11].

In the current study, 45 patients (64.3) of the included 70 patients with chronic cough responded to the 4-week trial of high dose inhaled steroids. This finding is in agreement with a previous study which reported corticosteroids responsiveness in 57.0% of the studied patients with chronic cough [14]. Lack of response of cough to the treatment with inhaled steroids can be explained by the presence of causes other than airway eosinophilic inflammation and may be due to the need of more aggressive anti-inflammatory medications in patients with airway eosinophilic inflammation.

Our study showed that FeNO level was significantly higher in patients with chronic cough who responded to corticosteroid than the non-responder patients and that the optimal cut-off level of FeNO for distinguishing patients with chronic cough who responded to corticosteroids therapy from non-responders was 34.5 ppb (with

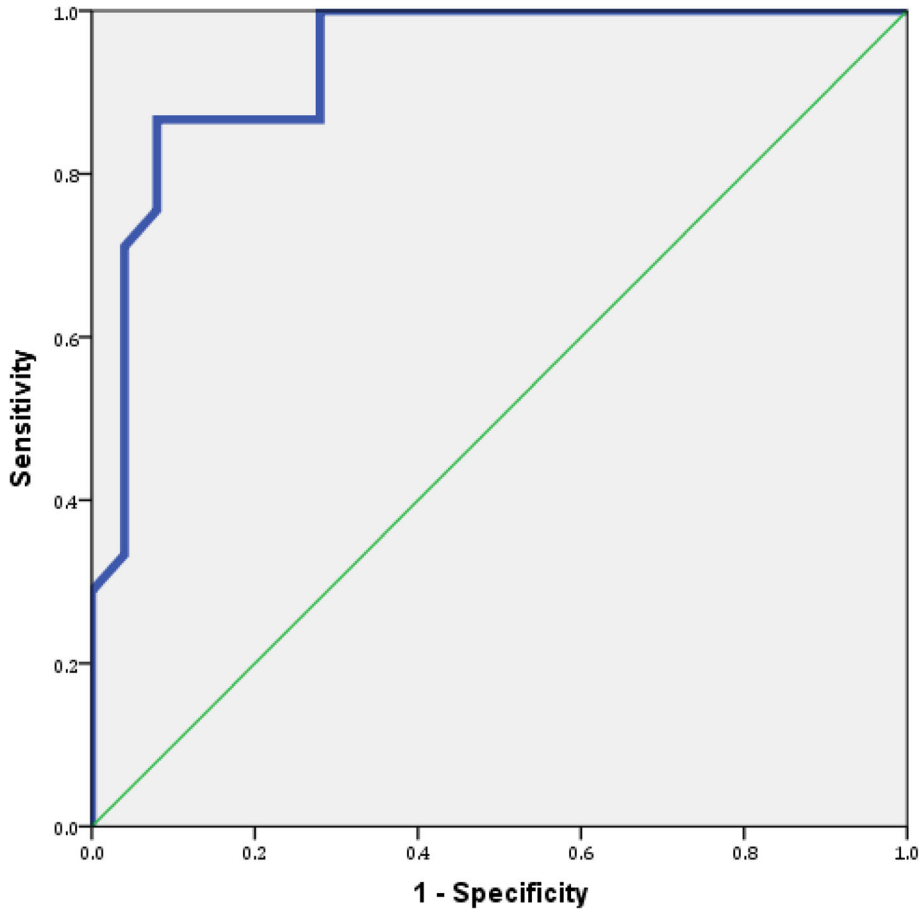

Fig. 4 ROC curve showing performance of FENO in diagnosis of steroid response among the studied patients

85% sensitivity and about 90% specificity). The ROC AUC was 0.835. Our result support published findings of previous studies which reported that the optimal cut-off levels of FeNO for diagnosing cough variant asthma or eosinophilic bronchitis in patients with chronic cough were between 30 and 40 ppb [14, 19].

Limitations of this study include the small sample size.

Conclusion

The findings of this study suggest that FeNO can be used as a rapid, easy predictor for airway eosinophilic inflammation and as a predictor for steroid responsiveness in patients with chronic cough.

Abbreviations

FeNO: Fractional exhaled nitric oxide; FVC: Forced vital capacity

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Authors' contributions

ES chose the title of this research and patient collection. ES and HA shared in methods and paper writing. All authors have read and approved the manuscript.

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Availability of data and materials

Not applicable

Ethics approval and consent to participate

Written consents were received from the patients, and the ethical committee of Nagd Hospitals (Saudi Arabia) approved this study. The committee reference number is not available.

Consent for publication

Not applicable

Competing interests

There are no conflicts of interest.

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