

Dupilumab as a treatment for allergic fungal rhinosinusitis: a case series*

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Abstract

Background: Allergic Fungal Rhinosinusitis (AFRS) is a subtype of chronic rhinosinusitis; it is a hypersensitivity reaction against fungi, and patients often have asthma in addition to high serum IgE levels. Certain patients with AFRS have relapsing disease with variable severity despite maximal treatment. Herein, we report our multicenter case series study of dupilumab use in Saudi Arabia for treating patients with severe forms of recalcitrant AFRS.

Methods: This study is a case series from Saudi Arabia aiming to evaluate patients with difficult to treat AFRS before and after dupilumab therapy. Inclusion criteria included all patients above 16 years of age diagnosed with AFRS based on Bent and Kuhn Criteria and did not improve despite maximal medical and surgical therapy. Immunocompromised patients and those who did not receive dupilumab for at least three months were excluded. Patients' demographics, clinical, laboratory, and radiological data were analyzed, looking for pre- and post-dupilumab treatment response patterns in 7 different parameters. These parameters included the SNOT-22 questionnaire, serum IgE and eosinophils levels, Lund-Mackay (LMK) and Meltzer scores, subjective olfactory function, and lastly, number of surgeries.

Results: Nine patients met the inclusion criteria, of which three were females, and six were males. The age ranged from 16-60 with a mean of 34.1. SNOT-22 and olfaction scores averages improved markedly three months post-treatment. Nine patients had their IgE levels recorded before starting treatment and three months afterward. The pre-treatment IgE level range was 346-13,360 IU/mL with a mean of 3098.8 IU/mL, while the post-treatment range was 12- 700 IU/mL with a mean of 270.1IU/mL, showing a dramatic decrease of 91.28%. Eosinophils count recorded before treatment and three months after starting dupilumab showed a decrease of 57.5%. Records of Meltzer and Lund Mackay (LMK) scores revealed improvement in post-treatment scores.

Conclusion: Results revealed improvement three months post-dupilumab treatment in multiple parameters in patients with AFRS. These parameters reflect treatment outcomes in subjective, radiological, and laboratory aspects.

Introduction

Allergic Fungal Rhinosinusitis (AFRS) is a subtype of chronic rhinosinusitis characterized by non-invasive fungal hyphae and eosinophilic mucin within the sinuses. AFRS is a hypersensitivity reaction against the fungus in the paranasal sinus, and patients often have high serum IgE levels and asthma ^(1,2).

AFRS is more common in males and presents in the age range of 21 – 31 years old ⁽³⁾. In addition, it is mainly found in areas with high humidity and accounts for up to 32% of all chronic rhinosinusitis (CRS) cases undergoing Endoscopic Sinus Surgery (ESS) in these areas. It was also found in the same study from the United States of America (USA) that the age of presentation

ranged from 10-71 years with a mean of 28 years, and African Americans accounted for 61.1% of the AFRS subgroup, followed by Caucasians (38.9%) (4,5).

The framework of AFRS diagnosis relies mainly on Bent & Kuhn criteria, which include major criteria such as type 1 hypersensitivity, nasal polyposis, positive fungal stain, eosinophilic mucin without invasion, and characteristic CT findings. In addition, minor criteria have been suggested such as asthma, bone erosion, fungal culture, serum eosinophilia and Charcot-Leyden crystals, and unilateral predominance (6).

While the treatment approach for this subtype of chronic rhinosinusitis (CRS) is multimodal, the treatment remains surgical debridement followed by a course of topical or oral steroids to decrease the chance of recurrence postoperatively that has been reported in 50% of patients with type 2 disease (7,8).

Biologics, such as dupilumab, have been approved as a treatment option for conditions such as asthma, atopic dermatitis, and CRSwNP, which are mainly characterized by type 2 inflammation and clinical trials (NCT01920893, SINUS-24, and SINUS-52) studied the use of dupilumab in CRSwNP have shown improvement in symptoms after the medication (9,10). Based on these results, in 2019, the United States Food and Drug Administration (FDA) approved the use of dupilumab for CRSwNP (11). Indications for biological treatment in CRSwNP include the presence of bilateral nasal polyps, evidence of type 2 inflammation, the need for systemic steroids, poor quality of life, anosmia, and comorbid asthma. If a patient has a history of surgery, only three criteria are required, while at least four are needed if the patient has no history of surgery (7).

While medical or surgical treatments can control the symptoms of AFRS, certain patients continue to suffer from relapsed disease with variable severity despite maximal medical and surgical therapy.

Herein, we report our multicenter case series study of dupilumab use in treating patients with severe forms of AFRS after exhausting all medical and surgical treatment options that failed to control their symptoms and, more importantly, improve their quality of life.

Methodology

This multicenter case series study from Saudi Arabia aims to evaluate patients with difficult to treat AFRS before and after starting dupilumab. Inclusion criteria included: all patients above 16 years of age diagnosed with AFRS based on Bent and Kuhn Criteria (5), those who underwent extended functional endoscopic sinus surgery, and patients who did not improve despite maximal medical therapy, including the need for systematic corticosteroids during the past year. In contrast, immunocompromised patients and those who did not receive dupilumab for at least three months were excluded. All patients received dupilumab 600mg for the first dose, followed by 300mg every

Table 1. SNOT-22 and subjective olfaction pre-and post-dupilumab treatment.

Patient	Pre-Treatment (SNOT-22)	Post-Treatment (SNOT-22)	Pre-Treatment Olfaction (subjective)	Post-Treatment Olfaction (subjective)
Patient #1	Severe	Mild	Normosmia	Normosmia
Patient #2	Severe	Mild	Anosmia	Normosmia
Patient #3	Severe	Moderate	Anosmia	Hyposmia
Patient #4	Moderate	Mild	Anosmia	Normosmia
Patient #5	Moderate	Mild	Anosmia	Normosmia
Patient #6	Severe	Moderate	Hyposmia	Normosmia
Patient #7	Mild	Mild	Normosmia	Normosmia
Patient #8	Severe	Not Available	Hyposmia	Not Available
Patient #9	Moderate	Not Available	Anosmia	Not Available

two weeks for a total duration of 3 months.

Patients' demographics, clinical, laboratory, and radiological data were analyzed, looking for pre- and post-dupilumab treatment patterns in 7 different parameters. These parameters included Sinonasal Outcomes Test -22 (SNOT-22) questionnaire (12), serum IgE and eosinophils levels, Lund Mackay (LMK) scores (13), Meltzer scores (14), subjective olfactory function, and number of surgeries.

This study was approved by the institutional review boards (IRBs) from all the following participating hospitals, King Faisal Specialist Hospital & Research Centre, King Saud University Medical City in the capital Riyadh (central region), Johns Hopkins Aramco Healthcare (JHAH) in Daharan city (eastern region), and lastly Aseer Central Hospital in Asser city (southern region).

Results

Our study included nine patients who met the inclusion criteria, of which 33.3% were females (n=3) and 66.6% were males (n=6). The age ranged from 16-60 with a mean of 34.1.

Sinonasal Outcomes Test -22 (SNOT-22) questionnaire

SNOT-22 scores were obtained before starting the therapy, and three months afterward, we used Shamim Toma et al. score stratification system into mild (score of 8-20), moderate (score of 21-50), and severe (score more than 50), and these stages were used to evaluate response to treatment (15). Pre-treatment, 5 patients (55.5%) reported having severe symptoms while mild and moderate were reported by 1 (11.1%) and 3 (33.3%) patients, respectively, with a total of nine patients. Seven patients answered the questionnaire for the post-treatment SNOT-22 scores, while the remaining two patients' responses were not recorded (Table 1). The results showed that two patients (22.2%) reported impro-

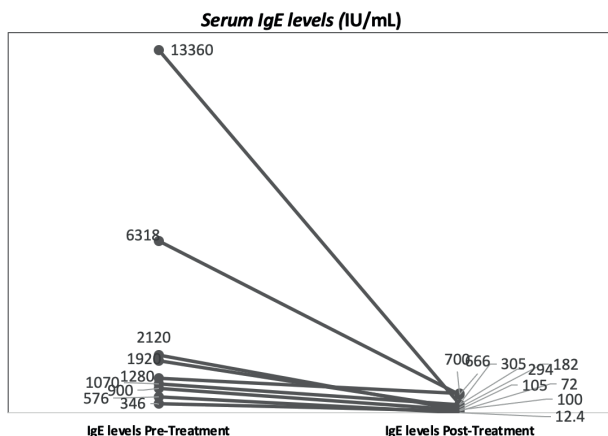


Figure 1. Serum IgE Levels pre-and post-dupilumab treatment.

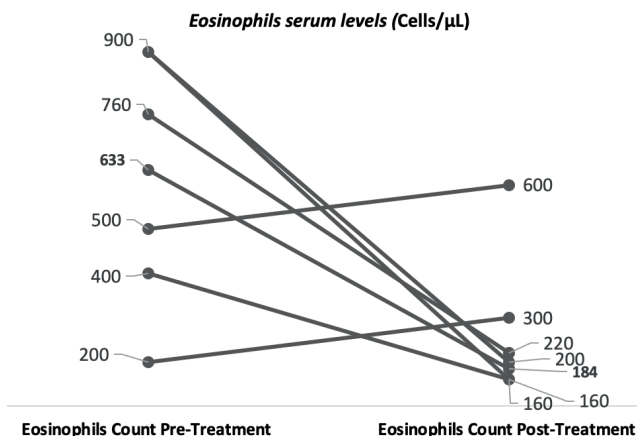


Figure 2. Serum eosinophils count pre-and post-dupilumab treatment.

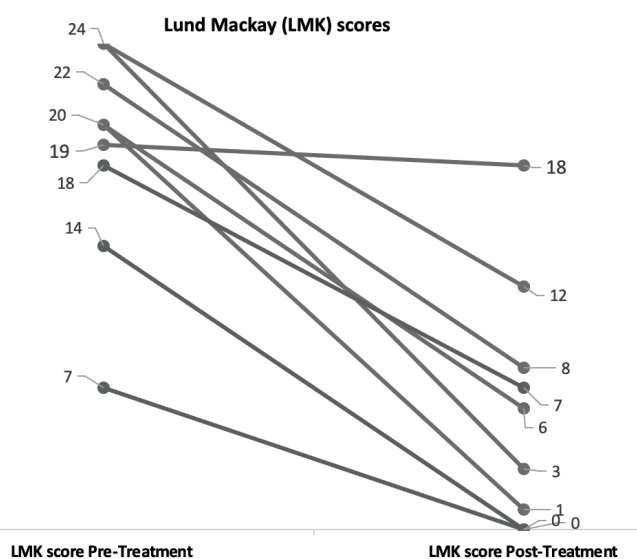


Figure 3. LMK scores pre-and post-dupilumab treatment.

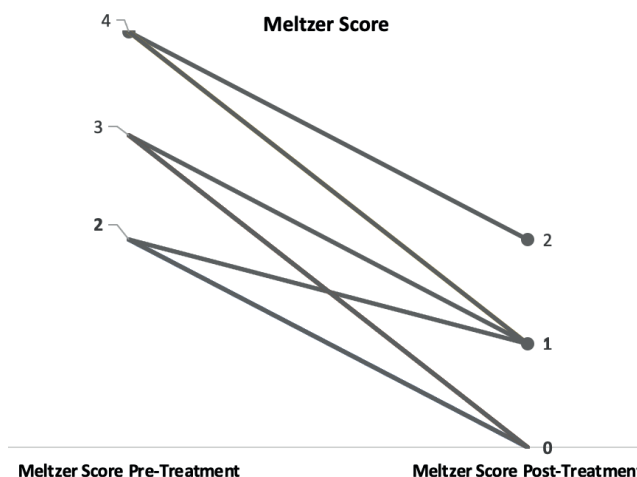


Figure 4. Melzer scores pre-and post-dupilumab treatment.

vement by two stages (from severe to mild), and four patients (44.4%) reported improvement by 1 stage (from severe to moderate or moderate to mild). Lastly, only one patient (11.1%) reported no change in their mild pre-treatment score. The remaining two patients' pre-treatment scores were severe and moderate, with no post-treatment score as they had not repeated the questionnaire.

In addition to the overall score, SNOT-22 was used to assess patients' subjective olfactory function (Table 1) and categorize them into normosmia, hyposmia, or anosmia. Pre-treatment five patients (55.5%) reported being anosmic, while hyposmia was reported in two (22.2%) and normosmia in the remaining two (22.2%) patients. Post-treatment subjective olfactory function was reported in seven patients, as two did not undertake the SNOT-22 post-treatment as mentioned above. As a result, three (33.3%) patients reported improvement from anosmia to normosmia while one (11.1%) patient reported improving from

anosmia to hyposmia, one (11.1%) patient from hyposmia to normosmia and the remaining two (22.2%) patients reported no change from their baseline normosmia status. The last two patients had reported hyposmia and anosmia with no post-treatment status.

Serum IgE levels

All nine patients had their IgE levels recorded before starting treatment and three months afterward. The pre-treatment IgE level range was 346-13,360 IU/mL with a mean of 3098.8, while the post-treatment level range was 12- 700 IU/mL with a mean of 270.1, showing a dramatic decrease in the mean levels by 91.3% after initiating treatment as shown in (Figure 1).

Eosinophils serum levels

Seven out of the nine patients had their eosinophils count recorded before starting the treatment and three months after treatment. The pre-treatment level range was 200-900 cells/µL

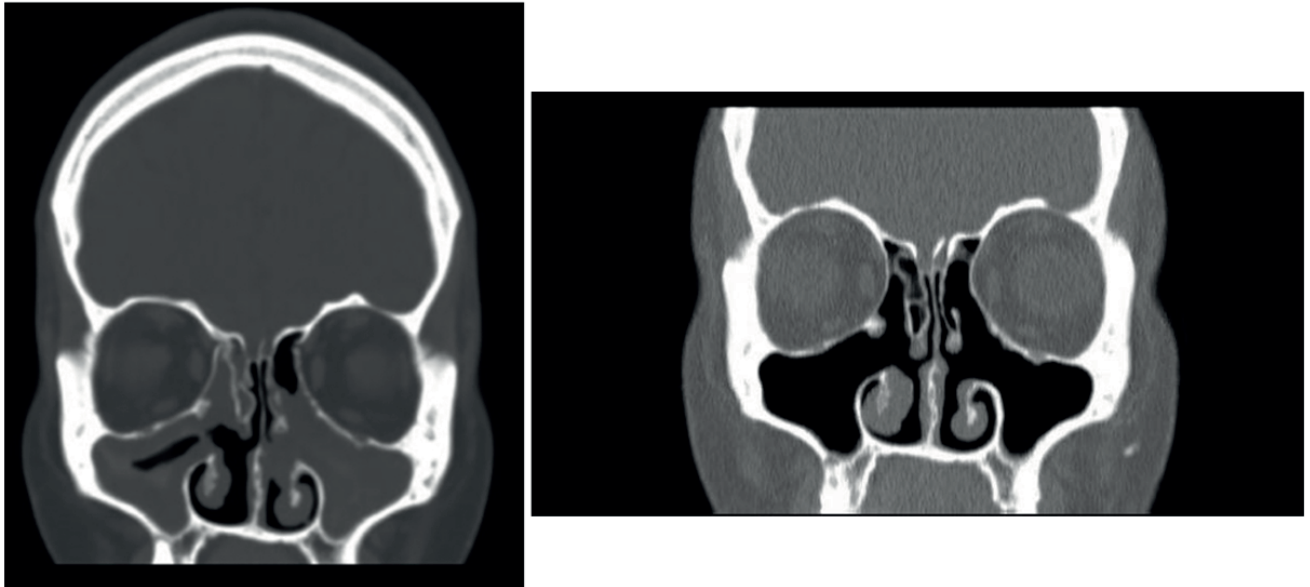


Figure 5. CT scan for one of the patients in our study. Left: Pre-treatment CT scan of the paranasal sinus showing opacified paranasal sinus. Right: Post-treatment CT scan showing clear paranasal sinus after 3 months of dupilumab.

with a mean of 613.3, while the post-treatment range was 160-600 Cells/ μ L with a mean of 260.6, showing a decrease in the mean levels by 57.5%. Two out of the seven patients had a mild increase in their serum eosinophils count (Figure 2).

Lund Mackay (LMK) and Meltzer scores

Lund Mackay (LMK) scores were reported in all nine patients with a post-treatment decrease from 16.8 to 6.1. Meltzer score averaged 0.6 after three months of dupilumab compared to a score of 3.0 before initiating treatment (Figures 3 and 4).

Number of surgeries

One final parameter we used to assess the disease course after dupilumab was the need for surgery after treatment. Before dupilumab, the average number of surgeries for all nine patients was 3.1, ranging from 1-7. However, post-treatment, none of the patients required surgery or steroids at the 3-month follow-up.

Discussion

AFRS is considered a type 2 inflammatory response and type 1 hypersensitivity reaction characterized by eosinophilic (allergic) inflammation^(1,2). Pant and Macardle have shown that patients with AFRS exhibit defective CD-8 T-cell response to fungi, suggesting that this alteration may permit local fungal accumulation in these patients, and fungal/allergic hypersensitivity can exacerbate the resultant inflammatory response⁽¹⁶⁾.

The role of fungus in the immunopathogenesis of AFRS lies mainly in how the fungal elements promote the innate immune cells to secrete cytokines such as IL-4, IL-5, and IL-13 that induce type 2 immune response in addition to the activation of the

adaptive immune system, which leads to high levels of IgE as seen in type 1 hypersensitivity reactions^(17,18).

In certain regions such as India, North Africa, and the Middle East, AFRS is believed to be more prevalent⁽¹⁹⁾, and multiple reports illustrated advanced and more complex presentations⁽²⁰⁻²⁴⁾. Certain patients still suffer from relapsed symptoms of AFRS, impacting their quality of life despite proper multiple sinus surgeries and maximal medical therapy.

In our region, AFRS has been reported in 11.8% of patients in a study that included 390 patients with chronic rhinosinusitis from multiple regions in Saudi Arabia⁽²⁵⁾. Another study with 406 patients with CRS reported that AFRS accounted for 14.5% of patients⁽²⁶⁾; in addition, AFRS with nasal polyps has been reported to be 12.1% in a study that included 91 patients admitted for Functional Endoscopic Sinus Surgery (FESS)⁽²⁷⁾.

Although all included patients in our multicenter study underwent the recommended treatment plans, their conditions did not improve, therefore; via a multidisciplinary team approach including Rhinologists, Immunologists, and pulmonologists, a more holistic method of approaching the disease was utilized to maximize benefit and help patients who suffer from a relapsing disease⁽²⁸⁾.

The core of the multimodal approach to treat AFRS remains to be functional endoscopic sinus surgery; thus, complete evacuation of the paranasal sinuses from the fungi and eosinophilic mucin is of utmost importance to decrease the chances of recurrence. However, a pre-operative CT scan is essential to verify the disease's presence and extent^(1,2).

The use of oral corticosteroids post-operatively with or without

topical corticosteroids has demonstrated short- and long-term benefits regarding recurrence and symptom improvement. However, antifungals have limited data for use in AFRS patients⁽¹⁰⁾. Biologics, such as dupilumab, have been approved for diseases such as asthma, atopic dermatitis, and chronic eosinophilic rhinosinusitis in which all their underlying pathophysiologies are type 2 inflammation, which further supports the use of dupilumab in AFRS⁽¹⁾.

Dupilumab is a monoclonal antibody against IL-4 and alpha chain which is also present in IL-13, and by blocking IL-4 and the shared chain, it subsequently blocks signaling for both cytokines, thus inhibiting type 2 inflammation⁽²⁸⁾. Dupilumab has been approved as a treatment option for conditions such as asthma, atopic dermatitis, and CRSwNP, which are mainly characterized by type 2 inflammation⁽⁹⁻¹¹⁾.

Clinical trials (NCT01920893, SINUS-24, and SINUS-52) that studied the use of dupilumab in CRSwNP have shown improvement in symptoms after the medication^(9,10). Based on these results, in 2019, the United States Food and Drug Administration (FDA) approved the use of dupilumab for CRSwNP⁽¹¹⁾.

In this study, the authors followed the treatment plan based on European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS), including initiating treatment and assessing responsiveness to biologics in recalcitrant patients with evidence of type 2 inflammation⁽¹⁰⁾.

This work provides a higher level of evidence than previously reported regarding the use of dupilumab in AFRS. To the best of our knowledge, the use of dupilumab in AFRS was reported by Lo et al.⁽²⁹⁾, Alotaibi et al.⁽³⁰⁾, and Bulkhi et al.⁽³¹⁾ in which all patients had improvement in their recalcitrant AFRS after failing multimodal therapy to control their symptoms.

In a case series from Saudi Arabia, four patients diagnosed with AFRS received dupilumab 300mg biweekly for five months. All patients reported a significant improvement in their symptoms in addition to improvement in other parameters such as SNOT-22, Asthma Control Test (ACT), and in 2 patients, a reduction in serum eosinophils count⁽³¹⁾.

These findings are consistent with our findings in this case series which provide initial evidence for using dupilumab in AFRS.

We aimed to assess the response to dupilumab in multiple domains, evident by factoring subjective and objective methods to bring forward the best possible standardization and subsequent results.

Regarding IgE levels, a drop of 91.28% and a decrease in Eosinophils count by 57.3% reflects how the drug affects patients' serology of interest. In addition, LMK and Meltzer scores dropped from 3 to 0.6 and 16.8 to 6.1, respectively, which projects improvement in both radiological (Figure 5) and endoscopic assessments.

One final yet, important domain was subjective improvement reported by patients. SNOT-22 score dropped to mild in all

patients except for two patients reporting having moderate symptoms (were severe pre-treatment). These results were coupled by the fact that all patients reported being normosmic except for one reporting hyposmia (was anosmic pre-treatment) reflects a significant improvement in quality of life and patient satisfaction, making our research, to the best of our knowledge, one of the first to provide a higher level of evidence for the use of dupilumab in AFRS treatment.

The authors provided the best possible data standardization to study the efficacy and outcomes of dupilumab use in recalcitrant AFRS. However, given that dupilumab was approved to be used in 2019 for CRSwNP by the FDA, the needed results from randomized control trials might require a longer time to be available to the scientific community⁽³²⁾.

Limitations of this study are the small sample size and the use of subjective olfactory testing; however, case series such as our paper are essential in establishing an early evidence base for new treatments or technologies⁽³³⁾.

Conclusions

The analyzed data of the included patients revealed improvement after a minimum of 3 months of dupilumab treatment in multiple parameters. These parameters aim to reflect treatment outcomes on multiple subjective, laboratory, and radiological aspects. The defined measuring parameters were SNOT-22, IgE levels, eosinophils' count, LMK score, Meltzer score, and the number of surgeries.

List of abbreviations

AFRS: Allergic Fungal Rhinosinusitis; ACT: Asthma Control Test; CRS: Chronic rhinosinusitis (CRS); CRSwNP: Chronic rhinosinusitis with nasal polyps; CT: Computed tomography; ESS: Endoscopic Sinus Surgery; EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps 2020; FDA: Food and Drug Administration; FESS: Functional Endoscopic Sinus Surgery; IL: Interleukin; KF&RC: King Faisal Specialist Hospital and Research Center; LMK: Lund Mackay; SNOT-22: Sinonasal Outcomes Test -22.

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Authorship contribution

NHA: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration; AMZ: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision,

Project administration; SA: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; AHA: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; RKA: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; RK: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; MZ: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; SS: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; KA: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; LA: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration; MYA: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; HAA: Methodology, Validation, Formal analysis,

Investigation, Resources, Data Curation, Visualization, Supervision, Project administration; SA: Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Visualization, Supervision, Project administration.

Ethics approval and consent to participate

This study was approved by the institutional review boards (IRBs) from all the following participating hospitals, King Faisal Specialist Hospital & Research Centre, King Saud University Medical City in the capital Riyadh (central region), Johns Hopkins Aramco Healthcare (JHAH), in Dahran city (eastern region), and lastly Aseer Central Hospital in Asser city (southern region). Informed consents were collected from all participants, and all test details were explained to participants before they consented to join the study. All participants were informed of their rights.

Availability of data and materials

On request, all data and study protocol can be made available.

Conflict of interest

None declared.

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