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Severe asthma treatment patterns: A multicenter observational study in the Gulf region

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ABSTRACT

Background: While crucial to the assessment and improvement of asthma control, insights on treatment practices in patients with severe diseases across Gulf nations are lacking. This observational study describes the treatment patterns of adolescents and adults with severe asthma across four countries of the Gulf region and evaluates current levels of asthma control; quality of life (QoL); exacerbation frequency; and the application of cellular, protein, and respiratory biomarkers in assessing asthma severity and inflammation.

Methods: Patients (aged >12 years, body weight ≥40 kg) with clinician-diagnosed, severe asthma (guided by the 2018 Global Initiative for Asthma definition) were included in this cross-sectional, multicenter, observational study conducted in the four Gulf countries of Kuwait, Oman, Qatar, and the United Arab Emirates. Data on demographics, treatment patterns, and laboratory parameters (blood eosinophil count [BEC], levels of serum immunoglobulin E [IgE], and fractional exhaled nitric oxide [FeNO]) were extracted from the medical records of patients during a 12-month retrospective period and transcribed onto case report forms. At the Enrollment visit, patients assessed their asthma control and QoL with the self-administered Asthma Control Questionnaire (ACQ) and a standardized version of the Asthma Quality of Life Questionnaire (AQLQ(S)), respectively.

Results: Among the 243 patients analyzed, (mean [standard deviation (SD)] age, 48.4 [13.9] years; female, 67.5%), the inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) combination was the most prescribed asthma medication (n = 240; 98.8%). Most patients were classified as "uncontrolled," (n = 173; 71.2%) and the majority (n = 206; 84.8%) experienced ≥1 exacerbation(s) in the preceding 12 months. The mean (SD) ACQ score was 2.1 (1.2), which indicated uncontrolled asthma, and the mean (SD) total AQLQ(S) score was 4.7 (1.4), suggesting "some limitation" in overall QoL. BECs during the 12-month period were elevated in most patients (>300 cells/μL [n = 183; 41.7%], 150–300 cells/μL [n = 138; 31.4%], <150 cells/μL [n = 118; 26.9%]), suggesting an eosinophilic asthma phenotype, although no standardized threshold by

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which to define eosinophilia has yet been confirmed. This study revealed that the biomarkers BEC, serum IgE, and FeNO concentrations were obtained inconsistently by the participating centers.

Conclusions: Despite recommended ICS/LABA therapy being prescribed to most patients for their severe disease, the majority experienced uncontrolled asthma and exhibited elevated BECs. These findings indicate the need for enhanced treatment strategies to improve and sustain asthma control in the Gulf region.

Keywords: Asthma control, Biomarkers, Gulf, Quality of life, Severe asthma

INTRODUCTION

Asthma, a chronic, heterogeneous, respiratory disease characterized by multiple symptoms, including wheezing, dyspnea, chest tightness, cough,[1] and reversible airflow limitation,[2,3] is associated with high rates of morbidity and mortality.[4] Globally, the prevalence of asthma is estimated to vary between 1.0% and 18.0%,[3] and in 2015, it affected approximately 358 million patients,[5] placing a substantial burden on healthcare systems worldwide. Despite the magnitude of the disease, information on the epidemiology and disease burden of asthma in the Gulf region remains scarce and the small sample sizes of available data limit generalizability to wider, global populations.[4,6] Asthma prevalence in the Middle East ranges from 4.4% to 7.6%.[4] According to the 2009 Asthma Insights and Reality in the Gulf and the Near East (AIRGNE) survey, the degree of asthma control in the Gulf does not align with the goals specified in more recent asthma management guidelines.[7]

Currently available anti-inflammatory and bronchodilator drugs have proven effective in achieving satisfactory asthma control in most patients.[8] Inhaled corticosteroids (ICS) are considered the mainstay of asthma management[9] and are the recommended first-line therapy in adults and children with moderate-to-severe disease.[10,11] Combination therapy with an ICS and long-acting β_2 agonist (LABA) is the preferred treatment option for uncontrolled asthma.[9] Alternatively, add-on therapy with a leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), monoclonal antibody–based biologic, or low-dose oral corticosteroid (OCS) is recommended.[10,12] Severe disease is reported in approximately 3.0%–10.0% of patients with asthma.[13] While most can be controlled with currently available monotherapies or combined agents, some patients experience severe, symptomatic episodes despite treatment with recommended therapies.[14–16]

A population-based study that accessed large-scale, prescribing databases suggested that 3.6% of patients with persistent asthma experience severe, uncontrolled disease,[15] often refractory to standard treatment and associated with a diminished quality of life (QoL), suboptimal asthma control, and increased risk of death.[13]

Severe eosinophilic asthma (SEA) is characterized by eosinophilic inflammation, increased asthma exacerbation rates, diminished lung function, insufficient symptom control, and lower QoL compared with non-eosinophilic asthma.[17] Blood eosinophil counts (BECs) $\geq$400 cells/μL have demonstrated an association with increased frequency and severity of clinical asthma exacerbations and poor disease control.[18] Recent evidence suggests that BECs may serve as a practical biomarker for SEA given their reliability in diagnosis, rapid accessibility, and cost-effectiveness as well as their predictive value for a positive therapeutic response.[19] Additionally, use of fractional exhaled nitric oxide (FeNO) as a predictor of subsequent loss of asthma control and lung function has been reported.[20,21] Other possible biomarkers for severe asthma include serum immunoglobulin E (IgE)[22] and serum periostin, as heightened concentrations of these parameters have been shown to suggest the presence of severe type 2/eosinophilic airway inflammation.[23]

With respect to novel biologics, it has been reported that monoclonal antibodies such as

mepolizumab and reslizumab, which target interleukin-5 (IL-5), offer effective treatment options for patients with severe, uncontrolled eosinophilic asthma.[17,24,25] These agents abate asthma exacerbation rates and mitigate symptoms by reducing BECs. The use of biologics may curtail patient exposure to high doses of OCS, thereby curbing the risk of glucocorticoid-related adverse effects.[24,26]

Limited observational data have been published on the clinical approaches to managing severe asthma in the Gulf region, and further insights on treatment strategies may improve disease control in that area. Herein, we report the real-world treatment patterns among patients with severe asthma in the Gulf region across a 12-month retrospective evaluation.

METHODS

Study design

This was a cross-sectional, multicenter, observational study of patients with severe asthma, conducted across the four Gulf countries of Kuwait, Oman, Qatar, and the United Arab Emirates (UAE). Patients were enrolled from 10 sites during the 12-month period of December 31, 2017, to January 3, 2019. Retrospective data on patient characteristics were extracted from their medical records and transcribed onto case report forms (CRF) or prospectively collected from patients at the time of their study visit. Information on case management was extracted from medical records, while data on asthma control and QoL were obtained from patient questionnaires administered at a single enrollment visit to the respective study site.

The centers were selected to ensure a representative, geographic sample of patients with severe asthma and were indicative of clinical management practices in the Gulf region. Eligible patients were enrolled at presentation for a routine clinic visit. To minimize selection bias, the investigators consecutively invited every eligible patient to participate in the study until they achieved their target cohort.

Objectives

The primary objective of the study was to describe treatment patterns in patients with severe asthma across the four Gulf countries during the 12 months prior to the site visit. Secondary objectives were to assess a) the degree of asthma control at enrollment, b) exacerbation frequency during the preceding 12 months, c) current QoL status, d) BEC(s) during the previous months, and e) concentrations of serum IgE in the 12 month pre-enrollment period. An exploratory objective was established to secure 12-month, retrospective evidence of the presence and levels of FeNO.

Study population

Patients aged >12 years, with a body weight of ≥40 kg, and diagnosed with severe asthma (Step 4/5 per 2018 Global Initiative for Asthma [GINA] recommendations)[3] who required regular treatment with medium- or high-dose ICS (patients aged 12–17 years) or high-dose ICS plus LABA for at least 12 months in advance of enrollment met the inclusion criteria to participate in this study. Patients who refused to provide informed consent or had a recorded, primary diagnosis of a clinically important pulmonary disease other than severe asthma, i.e., chronic obstructive pulmonary disease, bronchiectasis, active tuberculosis, that in the opinion of the investigator, would limit the ability of the patient to participate in the study were excluded. Additionally, patients with an intellectual disability or those unable to read or write were excluded.

Data source and variables

All data were collected and entered directly into the electronic data capture (EDC) system. Study sites assumed the responsibility for entering extracted patient data into a secure, internet-based, EDC study database through an electronic case report form (eCRF). Prospective screening, enrollment, and data collection were conducted during a one-day study visit, and no follow-up visits were required.

The following variables were abstracted over the 12-month retrospective period from medical records: demographics and lifestyle variables (age, height, weight, sex, and smoking status); treatment received during the prior 12 months: short-acting muscarinic antagonist [SAMA], long-acting muscarinic antagonist [LAMA], LABA, LTRA, ICS monotherapy, OCS, parenteral corticosteroids,

theophylline, biologics, and non-asthma medications; exacerbations; and biomarkers (BEC, serum IgE, and FeNO).

An exacerbation was defined as any of the following events: asthma-related hospital attendance or admission, emergency room (ER) visit, or administration of an OCS burst or a single dose of parenteral (intramuscular or intravenous) corticosteroids.

At the study visit, asthma control was assessed with the Asthma Control Questionnaire (ACQ), which contains seven questions related to the five, top scoring symptoms; spirometry for percent predicted forced expiratory volume in 1 s (FEV1); and frequency of daily rescue bronchodilator use.

The ACQ exhibits strong measurement properties and is fully validated for use in both clinical practice and clinical trials.[27] An ACQ score of $\leq$0.75 reflects controlled asthma; between $>$0.75 and $\leq$1.25 reflects borderline uncontrolled asthma; and $>$1.25 reflects uncontrolled asthma. Also, at the time of the study visit, patients completed the standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]). The questionnaire consists of 20 items and has been fully validated with strong measurement properties.[28] Each item on the questionnaire is scored from 1 to 7, with a score of 1 indicating "totally limited" and a score of 7 indicating "not at all limited."

Statistical analysis

All analyses were descriptive and performed using Statistical Analysis Software (SAS), version 9.4. Data were presented as overall (aggregate data across all countries) and by individual, participating country. All data were analyzed as they were recorded on the eCRFs. The proportion of missing data was reported for each variable.

Primary objective analysis

The number and percentage of patients using each type of asthma medication during a sequential, retrospective 12-month period were described.

Secondary/exploratory objectives analysis

The number and percentage of patients with asthma exacerbations during the 12-month, pre-enrollment interval were described. Additionally, exacerbations that precipitated ER visits, hospitalizations, and acute therapy with an oral or parenteral corticosteroid were described.

The current level of asthma control was assessed at the study visit based on the ACQ summary score (sum of all ACQ items), described as mean (standard deviation [SD]) and the number and percentage of patients with "controlled" vs "uncontrolled" disease was computed.

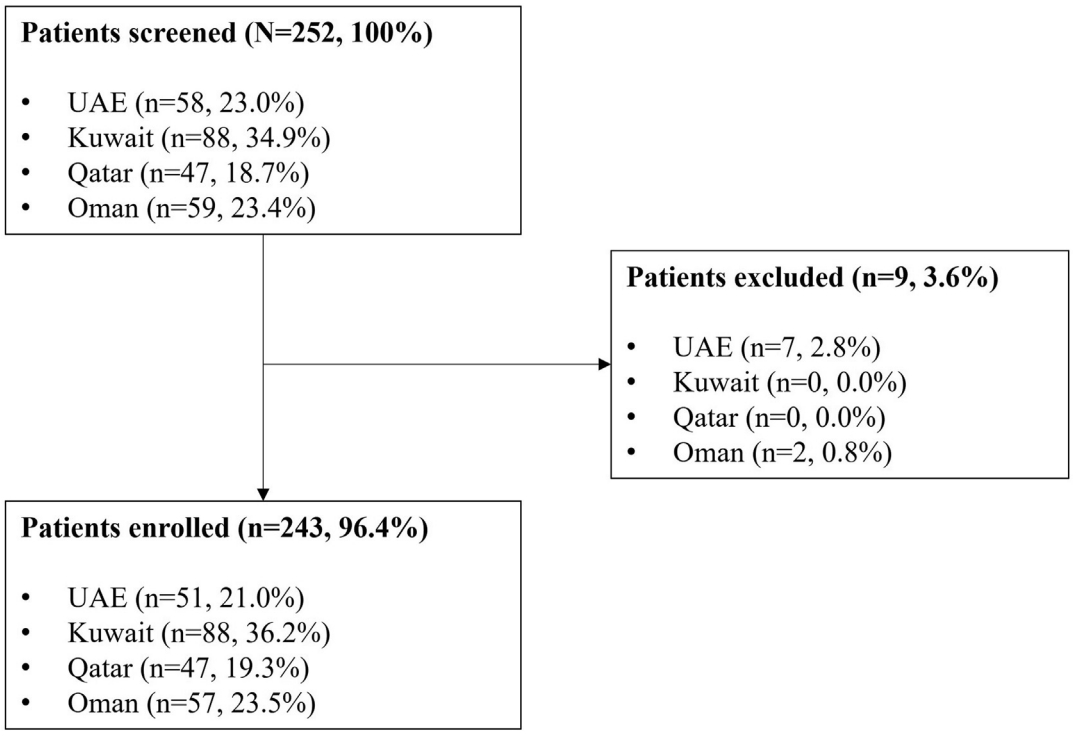
Also, at this single, enrollment visit, QoL was rated with the AQLQ(S) summary score (sum of all items on the AQLQ[S]), described as mean (SD).

BECs were described as mean (SD) and n (%) at the study visit and across the preceding 12-month period to assess repeated measurements, i.e., first measurement, second measurement, etc. Of the total number of BECs obtained throughout the 12-month period, the number and percentage of measurements were categorized as $<$150 cells/μL, 150–300 cells/μL, and $>$300 cells/μL.

Other biomarker (IgE and FeNO) concentrations were calculated as the mean (SD) for the preceding 12 months to assess repeated measurements, the number and frequency of IgE levels separated by thresholds of $<$30 IU/mL and $\geq$30 IU/mL and for FeNO by cut points of $<$25 ppb; 25–50 ppb; and $>$50 ppb (an indicator of eosinophilic inflammation).

Sample size

This was an observational study without a testable, pre-defined hypothesis. Rather, it aimed to address descriptive objectives. Considering an alpha error of 5% and a statistical power of 80% to identify significant differences within a sample of $\geq$10.0% in the mutually exclusive asthma treatment patterns of the study population, a recruitment target of approximately 250 patients with severe asthma was considered sufficient to address the study objectives.



Lack of fulfillment of inclusion criteria, n (%)	UAE (n=51)	Kuwait (n=88)	Qatar (n=47)	Oman (n=57)	Overall (N=243)
Age above 12 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body weight of ≥40 kg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diagnosed by a physician with severe asthma, who requires regular treatment with medium- or high-dosage ICS (patients aged 12-17 years) OR high-dosage ICS plus LABA for at least 1 year before enrollment	7 (12.1)	0 (0.0)	0 (0.0)	2 (3.4)	9 (3.6)
Fulfilment of exclusion criteria, n (%)					
Patient refuses to consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Another clinically important pulmonary disease is considered to be the primary diagnosis, other than severe asthma (i.e., COPD, major bronchiectasis, active tuberculosis, and other conditions considered by the principal investigator)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mentally disabled patient or inability to understand the study questions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unable to read/write	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Fig. 1 Disposition of patients with severe asthma. ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; COPD, chronic obstructive pulmonary disease; UAE, United Arab Emirates

	UAE (n = 51)	Kuwait (n = 88)	Qatar (n = 47)	Oman (n = 57)	Overall (N = 243)
Sex					
Total	51 (100.0)	88 (100.0)	47 (100.0)	57 (100.0)	243 (100.0)
Male	20 (39.2)	27 (30.7)	20 (42.6)	12 (21.1)	79 (32.5)
Female	31 (60.8)	61 (69.3)	27 (57.4)	45 (78.9)	164 (67.5)
Age (years)					
Total	51 (100.0)	88 (100.0)	47 (100.0)	57 (100.0)	243 (100.0)
Mean (SD)	49.2 (15.8)	48.9 (14.8)	52.8 (10.8)	43.3 (11.5)	48.4 (13.9)
Age groups (years)					
Total	47 (92.2)	81 (92.0)	44 (93.6)	51 (89.5)	223 (91.8)
12–18	1 (2.1)	1 (1.2)	(0.0)	(0.0)	2 (0.9)
19–30	4 (8.5)	6 (7.4)	(0.0)	5 (9.8)	15 (6.7)
31–40	12 (25.5)	11 (13.6)	6 (13.6)	16 (31.4)	45 (20.2)
41–50	8 (17.0)	17 (21.0)	7 (15.9)	16 (31.4)	48 (21.5)
>51	22 (46.8)	46 (56.8)	31 (70.5)	14 (27.5)	113 (50.7)
Missing values	4 (7.8)	7 (8.0)	3 (6.4)	6 (10.5)	20 (8.2)
Age at diagnosis (years)					
Total	47 (92.2)	88 (100.0)	47 (100.0)	56 (98.2)	238 (97.9)
Mean (SD)	32.9 (18.6)	30.9 (17.2)	30.7 (13.0)	28.3 (11.3)	30.6 (15.5)
Missing values	4 (7.8)	0 (0.0)	0 (0.0)	1 (1.8)	5 (2.1)
BMI (kg/m^2)					
Total	51 (100.0)	88 (100.0)	47 (100.0)	57 (100.0)	243 (100.0)
Mean (SD)	30.3 (6.0)	31.7 (7.7)	30.8 (5.5)	31.1 (7.3)	31.1 (6.9)
BMI class (kg/m^2)					
Total	51 (100.0)	88 (100.0)	47 (100.0)	57 (100.0)	243 (100.0)
Underweight: <18.5	0 (0.0)	1 (1.1)	0 (0.0)	2 (3.5)	3 (1.2)
Normal range: 18.5–24.9	12 (23.5)	16 (18.2)	7 (14.9)	8 (14.0)	43 (17.7)
Pre-obesity: 25.0–29.9	9 (17.6)	23 (26.1)	17 (36.2)	19 (33.3)	68 (28.0)
Obesity class I: 30.0–34.9	20 (39.2)	21 (23.9)	8 (17.0)	12 (21.1)	61 (25.1)
Obesity class II: 35.0–39.9	6 (11.8)	15 (17.0)	13 (27.7)	9 (15.8)	43 (17.7)

(continued)

	UAE (n = 51)	Kuwait (n = 88)	Qatar (n = 47)	Oman (n = 57)	Overall (N = 243)
Obesity class III: ≥40	4 (7.8)	12 (13.6)	2 (4.3)	7 (12.3)	25 (10.3)
Smoking status					
Total	51 (100.0)	88 (100.0)	47 (100.0)	57 (100.0)	243 (100.0)
Cigarette smoker	4 (7.8)	4 (4.5)	2 (4.3)	0 (0.0)	10 (4.1)
Waterpipe smoker	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)	2 (0.8)
Ex-smoker	6 (11.8)	4 (4.5)	2 (4.3)	1 (1.8)	13 (5.3)
Nonsmoker	41 (80.4)	78 (88.6)	43 (91.5)	56 (98.2)	218 (89.7)

Table 1. (Continued) Sociodemographic and lifestyle characteristics at the study visit. *All values are presented as n (%), unless otherwise specified. BMI, body mass index; SD, standard deviation; UAE, United Arab Emirates*

RESULTS

Patient disposition

Overall, 252 patients (Kuwait [n = 88; 34.9%], Oman [n = 59; 23.4%], UAE [n = 58; 23.0%], and Qatar [n = 47; 18.7%]) were screened for enrollment, of whom 243 (96.4%) entered the study. Nine[9] patients did not meet the inclusion criteria and were excluded. Most study participants were enrolled from Kuwait (n = 88; 36.2%), followed by Oman (n = 57; 23.5%), UAE (n = 51; 21.0%), and Qatar (n = 47; 19.3%) (Fig. 1).

Baseline demographic, lifestyle, and clinical characteristics

The mean patient (SD) age was 48.4 (13.9) years, with the majority (n = 161; 72.2%) aged 41 years or older (Table 1). Most patients were female (n = 164; 67.5%) and had never smoked (n = 218; 89.7%). The mean (SD) age at asthma diagnosis was 30.6 (15.5) years, and the mean (SD) body mass index (BMI) for the overall population was 31.1 (6.9) kg/m^2. More than half of the patients were obese with a BMI of ≥30.0 kg/m^2 (n = 129; 53.1%). No notable differences were observed in sex, age, BMI, or smoking status by country. The majority of the study participants had at least one comorbidity (n = 205; 84.4%), with the proportion ranging from 66.7% in Oman to 100.0% in Qatar (Table 2).

The most frequently reported comorbidities were rhinitis (n = 137; 27.3%), chronic metabolic conditions (n = 81; 16.2%), gastroesophageal reflux disease (GERD) (n = 63; 12.6%), and cardiovascular conditions (n = 50; 10.0%). A baseline spirometry was conducted in most patients (Table S1).

Treatment patterns during the 12-month period

Overall, an ICS/LABA combination was the most prescribed asthma medication (n = 240; 98.8%), followed by LTRA (n = 190; 78.2%), biologics (n = 120; 49.4%), and LAMA (n = 118; 48.6%) during the 12 months preceding study entry (Table 3). Less commonly used treatments included SAMA (n = 41; 16.9%), OCS (n = 30; 12.3%), theophylline (n = 28; 11.5%), and ICS monotherapy (n = 6; 2.5%). The use of ICS/LABA combinations was comparable across countries (96.6% in Kuwait to 100.0% in the UAE, Qatar, and Oman). Similarly, the use of ICS monotherapy was comparable across countries, ranging from 0.0% in Qatar to 3.9% in the UAE. The use of LTRA, biologics, LAMA, SAMA, OCS, and theophylline varied across countries. Omalizumab was the most prescribed biologic, followed by mepolizumab, and the proportion of patients prescribed biologics varied from 29.8% in Qatar to 78.4% in the UAE. A summary of the patients prescribed therapies adjunctive to ICS/LABA during the 12-month retrospective period is provided in Table S2.

Frequency of exacerbations during the 12-month period

Overall, most patients (n = 206; 84.8%) experienced at least one exacerbation during the 12-

	UAE (n = 51)	Kuwait (n = 88)	Qatar (n = 47)	Oman (n = 57)	Overall (N = 243)
Number of patients with at least one comorbidity	38 (74.5)	82 (93.2)	47 (100.0)	38 (66.7)	205 (84.4)
No comorbidities	13 (25.5)	6 (6.8)	0 (0.0)	19 (33.3)	38 (15.6)
Total number of comorbidity occurrences[a]	85 (100.0)	162 (100.0)	178 (100.0)	76 (100.0)	501 (100.0)
Rhinitis	17 (20.0)	51 (31.5)	45 (25.3)	24 (31.6)	137 (27.3)
Chronic metabolic conditions[b]	16 (18.8)	25 (15.4)	27 (15.2)	13 (17.1)	81 (16.2)
GERD	7 (8.2)	23 (14.2)	26 (14.6)	7 (9.2)	63 (12.6)
Nasal polyps	4 (4.7)	13 (8.0)	4 (2.2)	4 (5.3)	25 (5.0)
Cardiovascular	8 (9.4)	12 (7.4)	21 (11.8)	9 (11.8)	50 (10.0)
Urticaria[c]	2 (2.4)	7 (4.3)	4 (2.2)	1 (1.3)	14 (2.8)
Depression	3 (3.5)	1 (0.6)	0 (0.0)	0 (0.0)	4 (0.8)
Vit D deficiency	3 (3.5)	0 (0.0)	28 (15.7)	3 (3.9)	34 (6.8)
Others	25 (29.4)	30 (18.5)	23 (12.9)	15 (19.7)	93 (18.6)

Table 2. Types of comorbidities at the study visit. *All values are presented as n (%), unless otherwise specified. GERD, gastroesophageal reflux disease; UAE, United Arab Emirates; Vit D, vitamin D [a]Patients could have more than one comorbidity [b]Chronic metabolic conditions include diabetes mellitus and hypertension [c]Urticaria conditions include chronic idiopathic urticaria, chronic spontaneous urticaria, chronic spontaneous urticaria and angioedema, chronic urticaria, and urticaria*

	UAE (n = 51)	Kuwait (n = 88)	Qatar (n = 47)	Oman (n = 57)	Overall (N = 243)
ICS	2 (3.9)	3 (3.4)	0 (0.0)	1 (1.8)	6 (2.5)
ICS/LABA	51 (100.0)	85 (96.6)	47 (100.0)	57 (100.0)	240 (98.8)
LAMA	22 (43.1)	45 (51.1)	25 (53.2)	26 (45.6)	118 (48.6)
OCS	19 (37.3)	5 (5.7)	5 (10.6)	1 (1.8)	30 (12.3)
LTRA	48 (94.1)	48 (54.5)	44 (93.6)	50 (87.7)	190 (78.2)
Theophylline	6 (11.8)	6 (6.8)	1 (2.1)	15 (26.3)	28 (11.5)
SAMA	13 (25.5)	10 (11.4)	2 (4.3)	16 (28.1)	41 (16.9)
Biologics	40 (78.4)	43 (48.9)	14 (29.8)	23 (40.4)	120 (49.4)
Mepolizumab	3 (7)	0 (0)	7 (47)	3 (13)	13 (11)
Omalizumab	38 (93)	43 (100)	8 (53)	21 (88)	110 (89)
Other asthma medications	36 (70.6)	1 (1.1)	1 (2.1)	0 (0.0)	38 (15.6)

Table 3. Use of asthma medications during the 12-month retrospective period. *All values are presented as n (%), unless otherwise specified. Mepolizumab and omalizumab prescription counts are not mutually exclusive, because a patient could have more than one biologic agent prescribed to him or her. ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SAMA, short-acting muscarinic antagonist; UAE, United Arab Emirates*

	UAE (n = 51)	Kuwait (n = 88)	Qatar (n = 47)	Oman (n = 57)	Overall (N = 243)
Frequency of asthma exacerbations					
0 exacerbation	13 (25.5)	3 (3.4)	13 (27.7)	8 (14.0)	37 (15.2)
≥1 exacerbation	38 (74.5)	85 (96.6)	34 (72.3)	49 (86.0)	206 (84.8)
1	18 (35.3)	30 (34.1)	14 (29.8)	15 (26.3)	77 (31.7)
2	8 (15.7)	18 (20.5)	7 (14.9)	5 (8.8)	38 (15.6)
≥3	12 (23.5)	37 (42.0)	13 (27.7)	29 (50.9)	91 (37.4)
Exacerbations leading to ER visits					
0 ER visit	11 (28.9)	30 (35.3)	3 (8.8)	9 (18.4)	53 (25.7)
≥1 ER visit	27 (71.1)	55 (64.7)	31 (91.2)	40 (81.6)	153 (74.3)
1	13 (34.2)	28 (32.9)	13 (38.2)	10 (20.4)	64 (31.1)
2	7 (18.4)	10 (11.8)	11 (32.4)	3 (6.1)	31 (15.0)
≥3	7 (18.4)	17 (20.0)	7 (20.6)	27 (55.1)	58 (28.2)
Exacerbations leading to hospitalizations					
0 hospitalization	26 (68.4)	72 (84.7)	26 (76.5)	47 (95.9)	171 (83.0)
≥1 hospitalization	12 (31.6)	13 (15.3)	8 (23.5)	2 (4.1)	35 (17.0)
1	9 (23.7)	7 (8.2)	5 (14.7)	2 (4.1)	23 (11.2)
2	2 (5.3)	3 (3.5)	2 (5.9)	0 (0.0)	7 (3.4)
≥3	1 (2.6)	3 (3.5)	1 (2.9)	0 (0.0)	5 (2.4)
Exacerbations leading to acute oral or parenteral corticosteroid administration					
0 administration	16 (42.1)	32 (37.6)	2 (5.9)	29 (59.2)	79 (38.3)
≥1 administration	22 (57.9)	53 (62.4)	32 (94.1)	20 (40.8)	127 (61.7)
1	15 (39.5)	16 (18.8)	14 (41.2)	11 (22.4)	56 (27.2)
2	2 (5.3)	10 (11.8)	6 (17.6)	2 (4.1)	20 (9.7)
≥3	5 (13.2)	27 (31.8)	12 (35.3)	7 (14.3)	51 (24.8)

Table 4. Asthma exacerbations during the 12-month retrospective period. *All values are presented as n (%), unless otherwise specified. ER, emergency room; UAE, United Arab Emirates*

	UAE (n = 51)	Kuwait (n = 88)	Qatar (n = 47)	Oman (n = 57)	Overall (N = 243)
ACQ score					
Total	47 (92.2)	88 (100.0)	47 (100.0)	57 (100.0)	239 (98.4)
Mean (SD)	2.1 (1.3)	2.1 (1.2)	2.0 (1.1)	2.2 (1.3)	2.1 (1.2)
Missing values	4 (7.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.6)
Asthma control					
Patients with controlled asthma score ≤0.75	7 (13.7)	9 (10.2)	7 (14.9)	12 (21.1)	35 (14.4)
Patients with borderline uncontrolled asthma score >0.75 to ≤1.25	7 (13.7)	13 (14.8)	8 (17.0)	3 (5.3)	31 (12.8)
Patients with uncontrolled asthma score >1.25	33 (64.7)	66 (75.0)	32 (68.1)	42 (73.7)	173 (71.2)
Missing values	4 (7.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.6)
AQLQ(S) score					
Total	51 (100.0)	88 (100.0)	47 (100.0)	57 (100.0)	243 (100.0)
Mean (SD)	4.2 (1.5)	5 (1.2)	4.7 (1.3)	4.6 (1.4)	4.7 (1.4)

Table 5. ACQ summary score and Asthma Questionnaire (AQLQ(S)) total score at the study visit. *All values are presented as n (%), unless otherwise specified. ACQ, asthma control questionnaire; AQLQ(S), Asthma Quality of Life Questionnaire; SD, standard deviation; UAE, United Arab Emirates*

month look-back period, ranging from 72.3% in Qatar to 96.6% in Kuwait (Table 4). Moreover, 153 (74.3%) patients experienced exacerbations that prompted at least one ER visit, with the proportion ranging from 64.7% in Kuwait to 91.2% in Qatar. Thirty-five[35] (17.0%) asthma exacerbations necessitated at least one hospitalization, with proportions varying from 4.1% in Oman to 31.6% in the UAE and 127 (61.7%) exacerbations required at least one acute oral or parenteral corticosteroid administration, with proportions ranging from 40.8% in Oman to 94.1% in Qatar. While 65.5% of enrolled patients were prescribed biologics in addition to ICS/LABA, a higher proportion of patients prescribed biologics as an add-on experienced one exacerbation (32.5%) compared to those who did not receive a prescription for an add-on biologic (19.0%). All Kuwaiti patients [n = 20 (60.6%)] prescribed a biologic experienced one or more exacerbations, with the majority experiencing a single event (Table S3).

Level of asthma control among severe asthma patients at the study visit

Almost all patients completed the ACQ (n = 239; 98.4%) at their respective study visit (Table 5). The mean (SD) score for the overall patient population was 2.1 (1.2). No notable between-country differences were observed in the mean ACQ score. For most patients, asthma was categorized as "uncontrolled" (n = 173; 71.2%), ranging from 64.7% in the UAE to 75.0% in Kuwait. Based on ACQ scores, 31 (12.8%) patients were classified with "borderline uncontrolled" asthma, with a frequency of 5.3% in Oman and 17.0% in Qatar, In only 35 (14.4%) patients was asthma considered "controlled," and their proportions ranged from 10.2% in Kuwait to 21.1% in Oman.

QoL of severe asthma patients at the study visit

All patients completed the AQLQ(S) (n = 243; 100.0%) at their enrollment visit (Table 5). The

	UAE (n = 51)	Kuwait (n = 88)	Qatar (n = 47)	Oman (n = 57)	Overall (N = 243)
Blood eosinophil counts (cells/μL)					
Number of patients with at least one eosinophil measurement	45 (88.2)	72 (81.8)	45 (95.7)	50 (87.7)	212 (87.2)
Missing values	6 (11.8)	16 (18.2)	2 (4.3)	7 (12.3)	31 (12.8)
Total number of eosinophil measurements[a]	137 (100)	126 (100)	102 (100)	74 (100)	439 (100)
EOS <150 cells/μL	35 (25.5)	25 (19.8)	38 (37.3)	20 (27.0)	118 (26.9)
EOS 150–300 cells/μL	46 (33.6)	36 (28.6)	34 (33.3)	22 (29.7)	138 (31.4)
EOS >300 cells/μL	56 (40.9)	65 (51.6)	30 (29.4)	32 (43.2)	183 (41.7)
Serum IgE concentration (IU/mL)					
Number of patients with at least one IgE measurement	36 (70.6)	33 (37.5)	37 (78.7)	42 (73.7)	148 (60.9)
Missing values	15 (29.4)	55 (62.5)	10 (21.3)	15 (26.3)	95 (39.1)
Total number of IgE measurements[a]	45 (100)	39 (100)	39 (100)	44 (100)	167 (100)
IgE levels <30 IU/mL	3 (6.7)	1 (2.6)	1 (2.6)	5 (11.4)	10 (6.0)
IgE levels ≥30 IU/mL	42 (93.3)	38 (97.4)	38 (97.4)	39 (88.6)	157 (94.0)
FeNO breath test					
FeNO, first measurement (ppb)					
Total	3 (5.9)	0 (0.0)	35 (74.5)	0 (0.0)	38 (15.6)
Mean (SD)	114 (38.7)	0 (0.0)	39.9 (42.0)	0 (0.0)	45.7 (46.0)
FeNO, second measurement (ppb)					
Total	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Mean (SD)	116 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0)	116.0 (0.0)

Table 6. Distribution of biomarkers: blood eosinophil, serum IgE, and serum FeNO levels during the 12-month retrospective period. *All values are presented as n (%), unless otherwise specified. EOS, eosinophil; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IU/mL, international units per milliliter; μL, microliter; ppb, parts per billion; SD, standard deviation; UAE, United Arab Emirates [a]Patients could have more than one measurement*

mean (SD) total AQLQ(S) score was 4.7 (1.4), indicating "some limitation" in QoL, and no notable, between-country difference in this score was detected. In response to the question "overall, among all the activities that you have done during the last 2 weeks, how limited have you been by your asthma?," 56 (23.0%) patients responded that they were at least "moderately limited;" 7 (2.9%) patients were "severely limited;" 25 (10.3%) patients were "very limited;" and 24 (9.9%) patients were "moderately limited" (Table S4).

Distribution of blood eosinophil levels during the 12-month period

In most patients, at least one BEC was obtained (n = 212; 87.2%), their proportion ranging from 81.8% in Kuwait to 95.7% in Qatar (Table 6). Of the 439 BEC assays performed throughout the 12-month retrospective period, 183 (41.7%) contained >300 cells/μL; 138 (31.4%) contained 150–300 cells/μL; and 118 (26.9%) contained <150 cells/μL by volume. For 151 (62.1%) patients,

BECs were recorded at their single study visit with a mean (SD) count of 394.8 (555.3) cells/μL (Table S5). BECs were quantified a maximum of 10 times throughout the 12-month look-back period (Table S6). One hundred twelve (46.1%) and 53 (21.8%) study participants provided two and three samples, respectively for BECs, while less than 10% of patients underwent more frequent assessments.[4–10]

Distribution of serum IgE concentrations during the 12-month period

On at least one occasion, serum IgE concentrations were determined for more than 60% of patients in all four participating countries, with the exception of two Kuwaiti centers, which recorded relevant data for only 37.5% of their patients with severe asthma (Table 6). Of the total 167 serum IgE measurements obtained across the 12 preceding months, the majority of recorded levels were ≥30 IU/mL (n = 157; 94.0%), with only 10 (6.0%) <30 IU/mL.

Serum IgE concentrations were tested a maximum of three times in the 12 months prior to the study visit. For the initial assessment (n = 148; 60.9%), the mean (SD) IgE level was 736.0 (966.1) IU/mL; for the second (n = 17; 7.0%) and third measurements (n = 2; 0.8%), the mean (SD) IgE levels were 1665.9 (2247.4) IU/mL and 1313.0 (1581.1) IU/mL, respectively, which were considerably elevated above the ≥30 IU/mL threshold for adult patients with severe disease (Table S7).

Distribution of FeNO levels during the 12-month period

Overall, 38 (15.6%) patients provided an initial FeNO value and only one (0.4%) patient participated in a second FeNO breath test (Table 6). Almost all measurements of the FeNO biomarker were performed in Qatar residents with asthma (n = 35; 74.5% for the initial diagnostic test), followed by the UAE (n = 3, 5.9% for the first measurement; n = 1, 2.0% for the second measurement). The mean (SD) values for the first and second FeNO breath tests were 45.7 (46.0) and 116.0 (0.0) ppb, respectively, based on a threshold of 25–50 ppb in adults. FeNO was neither assessed in Kuwait nor in Oman.

DISCUSSION

Results from this cross-sectional, observational study of treatment patterns for severe asthma in the Gulf region provide valuable, real-world evidence on asthma management practices in patients with severe disease (GINA Step 4/5), current data on which are scarce. In this study, ICS/LABA combinations were the most prescribed asthma medication (98.8%), followed by LTRA (78.2%), biologics (49.4%), and LAMA (48.6%). Asthma treatment patterns were found to align with the GINA guidelines for management of asthma,[29] which recommend ICS/LABA and add-on therapies such as LTRA, LAMA (tiotropium bromide), biologics (e.g., anti-IgE, anti-IL-5/5R, anti-IL-4R), and OCS for treatment of severe disease (Step 5).

Despite these recommendations, most patients (71.2%) fulfilled the criteria for uncontrolled asthma per the ACQ, with a mean (SD) score of 2.1 (1.2). Suboptimal asthma control was also reflected by the high proportion of exacerbations, impaired QoL, elevated BEC, and high OCS usage. Our findings align with those of the 2009 Asthma Insights and Reality in the Gulf and Near East (AIRGNE) survey, which reported inadequate disease control in Gulf regions, likely due to multifactorial contributions of deficient patient education, infrequent lung function monitoring, and regional influences such as high rates of smoking and the paucity of primary care networks within Gulf nations.[7] While the overall use of ICS/LABA combinations and ICS monotherapy was comparable across countries, variations were observed in the selection of other asthma medications. This might be attributed to differences in practice habits, medication availability, and healthcare reimbursement or cost-of-drug. According to the 2018 GINA recommendations for difficult-to-treat asthma,[30] in patients prescribed high-dose ICS/LABA who fulfill the criteria for residual type 2 airway inflammation with allergic or eosinophilic biomarkers, targeted biologics are recommended *only* if they are available or affordable, as observed in the UAE, one of the wealthiest participating countries in this study, which reported the highest percentage of prescription biologics (78.4%). In other cases, non-biologic, add-on therapy with a LABA, LAMA, LTRA, and/or

macrolide, if clinically warranted, may be considered.[30]

In 41.7% of enrolled patients, the BECs recorded in the 12 months prior to the study visit exceeded 300 cells/μL. At baseline, the mean (SD) BEC was 394.8 (555.3) cells/μL, suggestive of severe eosinophilic asthma (SEA), which is characterized by an eosinophilic-induced, immune modulatory response of uncontrolled airway inflammation, which increases the risk of asthma exacerbations.[31] Furthermore, patients in whom eosinophilic airway inflammation persists despite high-dose ICS treatment are typically considered to have severe asthma, marked by poor symptom control, frequent exacerbations, fixed airflow limitation, and OCS dependency.[31]

Indeed, in addition to elevated BECs, most patients with asthma in our study were categorized by the ACQ as "uncontrolled" and experienced more than one exacerbation. The mean (SD) total AQLQ(S) score was 4.7 (1.4), which suggested "some limitation" in overall QoL, and more than one-fifth of patients ascribed at least moderate limitation in their activities to asthma. These findings substantiate those of previous research, which demonstrated that severe asthma is significantly associated with diminished QoL as well as substantial loss of productivity and functional impairment.[32,33] Most of the patients (84.8%) enrolled in this study experienced at least one exacerbation during the 12-month pre-enrollment period. While this is a cause for concern, the large number of exacerbations recorded in this study could likely be attributed to disease severity, considering the enrollment of patients at GINA Step 4/5. Indeed, a previous large database study of patients with asthma in the US and UK (n = 222,817 and n = 211,807, respectively) reported that an increase in exacerbation frequency correlated with greater severity of disease.[34] Of the total serum IgE concentrations obtained throughout the 12-month data collection interval, the vast majority were ≥30 IU/mL (94.0%), suggesting more severe disease as elevated IgE is associated with atopy, airway hyperresponsiveness, bronchial wall thickening, and severe asthma.[35] Similarly, the high levels of FeNO reported in this study also indicate severe disease since elevated concentrations have been associated with the atopic phenotype among asthmatics.[36] Alternatively, given that the mean (SD) BMI of patients enrolled in this study was 31.1 (6.9) kg/m^2, obesity-related factors such as poor treatment response[37] may account, to some degree, for the high number of recorded exacerbations events. This observation further underscores the need for clinician-guided dietary and lifestyle modification in overweight or obese patients with asthma.[38]

Several biomarkers such as BEC and serum IgE, FeNO, and periostin levels have been recommended as diagnostic components in confirming the presence of severe asthma with the goals of devising an optimal therapeutic regimen, monitoring medication adherence, and assessing therapeutic response.[39,40] However, underutilization of asthma biomarkers was noted in this study. In the 12-month retrospective period, most patients (87.2%) provided a single sample for BEC, while 46.1% and 21.8% demonstrated evidence of blood eosinophilia in two (mean: 541.3 cells/μL) and three (mean: 415.5 cells/μL) assays, respectively. More frequent measurements[4–10] were performed in <10.0% of patients. These findings indicate that BEC is not conducted routinely in clinical practice, which is worrisome as extensive research has shown the utility of BECs in predicting response to asthma medications, including corticosteroids and biologics.[35,41] Further, since corticosteroid therapy is associated with a reduction in BEC,[42,43] its use as a biomarker could provide practical guidance to clinicians on treatment-related decisions.[43] Several international guidelines[3,44] suggest BEC evaluation to inform management algorithms in patients with SEA. Results from clinical trials have supported the efficacy of new biologics that inhibit eosinophil-specific ILs, including the anti-IL-5 and anti-IL-5Rα monoclonal antibodies (mepolizumab and benralizumab, respectively), in markedly reducing asthma exacerbations and significantly improving patient QoL.[24–26] These targeted monoclonal antibodies decrease circulating eosinophils and improve asthma control in patients with SEA, in particular those with elevated baseline BECs.[45] To capitalize on these newly available anti-asthmatic agents, it becomes imperative to diagnose eosinophilic asthma at an early stage through the acquisition and assay of routine BECs. In this context, patient- and physician-centered

education and awareness programs focused on the use of biomarker-guided diagnosis and evaluation may facilitate their wider adoption by community healthcare providers with the principal objective of improving clinical outcomes in patients with SEA.

In a similar manner, serum IgE concentrations were not assayed regularly across the nine study sites. In most patients (60.9%), a single serum IgE profile was obtained at baseline, while a low proportion of patients provided specimens for two or three measurements (7.0% and 0.8%, respectively). Exhaled FeNO concentrations were calculated a maximum of two times during the 12-month look-back period. Thirty-eight (15.6%) patients participated in at least one FeNO breath test, while only 0.4% provided two FeNO samples for analysis. This indicates minimum-to-no use of FeNO as a biomarker in routine clinical practice. These results are perhaps unsurprising considering the lack of well-established guidelines for healthcare providers with respect to the appropriate application and interpretation of FeNO in a clinical setting.[46] Nevertheless, the utility of FeNO as a surrogate marker of ICS response to guide treatment-related decisions has been demonstrated in several studies.[47,48] The omission of biomarker references in clinical practice compounds the high incidence of poor disease control despite the prescription of preferred treatment options for GINA Step 4/5 asthma, stressing the unmet medical need in patients with SEA for alternative, affordable, and available therapies that facilitate an individualized approach to case management.

It is also important to consider the limitations of this study. First, selection bias is possible, given the cross-sectional, observational design of this study. As participation in the study was voluntary and based on sequential invitation of eligible candidates by the site investigators, participating patients may have differed from non-participating patients in terms of certain factors such as demographics, clinical characteristics, including the presence or absence of comorbidities, and disease severity. Thus, targeted enrollment sampling in this study may not represent the general population of patients with severe asthma residing in the Gulf region. Second, missing data are a limitation arising from the extraction of patient information recorded in medical charts during routine office or clinic visits, whereby some entries may be more comprehensive and readily available than others. In that regard, patient data may have been captured non-systematically in a narrative or note format. Third, prescription data were extracted from individual medical records and pharmacy records do not reflect actual asthma medication usage; information on adherence was not captured in this study. Fourth, asthma control and QoL were assessed by means of self-reported questionnaires, which risk recall bias in that patients were asked to recollect symptoms, activities, emotional function, medication usage, and environmental exposures that had occurred from 1 to 2 weeks before completing the questionnaires. Fifth, due to the utilization of physician-diagnosed asthma as an inclusion criterion in this study, it is possible that asthma was inaccurately diagnosed in some patients as has been reported previously.[49] Finally, owing to the low number of patients recruited from centers in each of the four countries, it was not possible to test for statistically significant between-country differences in treatment patterns, asthma control, QoL, and BECs, among others.

CONCLUSION

Although most patients (98.8%) were prescribed ICS/LABA, the preferred controller/reliever option across GINA treatment steps, the majority experienced uncontrolled asthma and eosinophilia (BEC >300 cells/μL). Additionally, the majority of patients reported one or more exacerbations in the 12 months prior to their single study visit, and more than one-fifth of patients reported at least moderate asthma-induced activity limitations. The use of various asthma biomarkers differed across Gulf countries, marked by inconsistent testing of BECs, serum IgE, and FeNO. These findings suggest the value of enhanced disease management strategies to improve asthma control and alleviate the personal toll and socioeconomic burden associated with severe disease. In the era of personalized medicine, a "one size fits all approach" can be argued as outdated, if not inappropriate in most cases, and further research should be undertaken to elucidate the different phenotypes of asthma and their potential correlation with biomarkers of disease severity, type 2 airway inflammation, and therapeutic response.

Importantly, improved clinician and patient awareness of the utility of biomarkers and their respective predictive abilities is necessary to facilitate their broader adoption in routine practice.

Abbreviations

ACQ, Asthma Control Questionnaire; AQLQ(S), standardized version of the Asthma Quality of Life Questionnaire; BEC, blood eosinophil count; BMI, body mass index; CRF, case report form; EDC, electronic data capture; ER, emergency room; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL-5, interleukin-5; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; ppb, parts per billion; QoL, quality of life; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SEA, severe eosinophilic asthma; UAE, United Arab Emirates

Author Contributions

All authors contributed to the conceptualization, data curation, formal analysis, investigation, methodology, resources, validation, visualization, original draft preparation, and review and editing. HF was responsible for funding acquisition. MAA and HF were responsible for project administration and supervision.

Financial Disclosure Statement

Funding support for the study was provided by AstraZeneca. Representatives of the sponsor were involved in study design; data collection, analysis, and interpretation; and revision of the manuscript.

Ethical considerations

Ethical approval for the study was obtained from the Ministry of Health, Standing Committee for Coordination of Health and Medical Research (695/2017) in Kuwait; Ministry of Health and Prevention (MoHAP) Research and Ethics Committee (41-2018-MOH-DR), Zayed Military Hospital Ethics Committee (2017.12), Cleveland Clinic Abu Dhabi Research Ethics Committee (A-2018-018), and Dubai Scientific Research Ethics Committee (DSREC), Dubai Health Authority (DSREC-01/2018_08) in UAE; Scientific Research Committee of Royal Hospital (SRC#107/2017), and Medical Research Ethics Committee, College of Medicine and Health Sciences, Sultan Qaboos University in Oman; and Hamad Medical Corporation Institutional Review Board (MRC-02-18-055) in Qatar. The study was performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, Good Pharmacoepidemiology Practice, and the applicable legislation on observational studies. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting. Written informed consent was obtained from all study participants.

Agreement to publish the work and editorial policy confirmation and agreement

All authors agree to publish this work. All authors confirm and agree to the editorial policy. Authors confirm that their manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

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Data availability statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Registration ClinicalTrials.gov Identifier: NCT03387722

Declaration of competing interests

Saif Al Mubaihsi received a grant from AstraZeneca. Hisham Farouk is an employee of AstraZeneca. All other authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100647.

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