

Demographic and clinical patterns of severe asthma in the Middle East

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Abstract:

BACKGROUND: Severe asthma is a major burden on health-economic resources; hence, knowing the epidemiology of these patients is important in planning and provision of asthma care. In addition, identifying and managing the comorbidities helps improve symptoms and reduce associated morbidity and mortality.

OBJECTIVES: Epidemiology of difficult asthma has not been well studied in the Middle East, so in this study, we present the demographic and clinical characteristics of severe asthma in the United Arab Emirates (UAE).

METHODS: We retrospectively reviewed the notes of severe asthma patients attending three tertiary care hospitals between May 2015 and December 2019. Data on baseline demographics, asthma characteristics, treatment, and comorbidities were collected.

RESULTS: We reviewed the notes of 458 patients (271 females and 187 males) that fulfilled the 2019 Global Initiative for Asthma guidelines for the diagnosis of severe asthma. The mean age was 47.7 (standard deviation 17.2) years. Males had significantly higher asthma control test scores (17.9 vs. 16, $P = 0.01$) and mean blood eosinophils (0.401 vs. 0.294, $P < 0.01$) than females. The most common comorbidity observed was allergic rhinitis (52.2%) followed by gastroesophageal reflux disease (27.1%). In total, 109 (23.8%) patients were on biological therapies with most patients being on omalizumab and dupilumab (29 and 18 patients, respectively). Most patients were nonsmokers (97.2%), and majority were of TH2-high phenotype (75.7%).

CONCLUSIONS: In this first report of severe asthma characteristics in the UAE, we found a pattern of female preponderance and most patients having a Th2-high phenotype. The findings are likely to help optimize asthma care in the region in the era of biologic therapies.

Keywords:

Airflow obstruction, allergic asthma, asthma, asthma epidemiology, severe asthma epidemiology, Th1/Th2

Asthma is a chronic lung disease characterized by airway inflammation and hyper-responsiveness affecting almost 300 million people worldwide.^[1] Asthma can be classified as mild, moderate, or severe, based on the intensity of treatment required to achieve asthma control.^[2] Severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS)

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to maintain good control or as asthma that is poorly controlled despite the use of maximal optimized therapy and treatment of contributory factors.^[3] Severe asthma is reported to affect about 5%–10% of asthmatics.^[2] It is important to differentiate severe asthma from difficult-to-treat asthma, which is defined as asthma that is poorly controlled due to correctable factors such as environmental allergens, comorbidities, poor medication compliance, and incorrect inhaler technique.^[3] While severe asthma is

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less prevalent than milder asthma severities, it remains a major cause of morbidity^[4] and mortality^[5,6] worldwide. In addition, it is associated with a major socioeconomic,^[7] psychological,^[8] and treatment^[9] burden.

The clinical characteristics and phenotypes of severe asthma patients have been previously reported from various parts of the world,^[10-12] and this knowledge has been particularly important for the development and application of novel biological therapies. In addition, severe asthma registries can be used for genetic profiling to help identify individuals who are genetically predisposed to severe asthma. Difficult asthma phenotypes, including patients with severe asthma, have not been well studied in the Middle Eastern populations. The United Arab Emirates (UAE) has no official severe asthma registry and as yet no published data describing the characteristics of these patients. Undoubtedly, it is necessary to understand local epidemiology and clinical characteristics of severe asthma to make better-informed local guidelines and treatment decisions. Therefore, we took the initiative to examine the demographic and clinical variables of severe asthma in a local population attending three tertiary care hospitals in the UAE between May 2015 and December 2019.

Methods

Subjects

We performed a retrospective chart review of all patients diagnosed with severe asthma according to the 2019 Global Initiative for Asthma (GINA) guidelines^[3] attending Cleveland Clinic Abu Dhabi (Abu Dhabi), Rashid Hospital (Dubai), and Zayed Military Hospital (Abu Dhabi), between May 2015 and December 2019. Patients were included if they had at least three visits to the asthma clinic, with the visits being at least 1 month apart, were on high-dose ICS with optimal inhaler technique, showed good compliance with medication, and had good control of the contributing/exacerbating factors. Patients with asthma-chronic obstructive pulmonary disease overlap syndrome and deceased patients were excluded. We identified a total of 604 patients that met the inclusion/exclusion criteria, of whom 458 were Emirati citizens and were used to form the cohort for the current analysis.

Study variables

The medical records of all participants were reviewed by a study team comprised of one or two researchers at each study site. Apart from basic demographic information, the Asthma Control Test (ACT) scores, fractional exhaled nitric oxide (FeNO) levels, eosinophil counts, and total immunoglobulin E (IgE) levels were also recorded. Comorbidities including body mass index, cigarette smoking, allergic rhinitis, hypertension,

gastroesophageal reflux disease (GERD), hyperlipidemia, diabetes, obesity, obstructive sleep apnea (OSA), nasal polyps, thyroid disease, bronchiectasis, depression, anxiety, osteoporosis, food allergy, eczema, and malignancies were documented.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cohort. Comparisons of categorical baseline characteristics in the cohort were performed using Pearson's Chi-squared test. Comparisons of continuous baseline characteristics were performed using Welch's two-sample *t*-test. We considered a *p*-value less than 0.05 to be statistically significant in our study.

Results

Baseline characteristics

A total of 604 patients fulfilled the 2019 GINA guidelines for the diagnosis of severe asthma. Among these, 458 patients (75.8%) were Emirati citizens, whereas 146 patients (24.2%) were expatriates. Since our objective is to study the demographics of the local Arab population, the expatriates were excluded from the analysis. Among the 458 patients, there were 271 females (59.2%) and 187 males (41%) [Table 1]. The mean \pm standard deviation age for females was higher than that for males (50.2 ± 16.6 years vs. 44.2 ± 17.4 years, $P = 0.002$), with a range between 14 and 92 years.

Age of asthma onset was available for 241 patients, of these 111 patients (46.1%) reported having been diagnosed with asthma in childhood, whereas 130 patients (53.9%) were diagnosed as adults.

Information about asthma phenotype, i.e., allergic versus nonallergic was available for 242 patients. Out of those, 148 patients (61.2%) were labeled as having allergic asthma and 35 patients (14.5%) suffered from eosinophilic asthma. Together these two groups made up the Th2 high phenotype (75.7%). The rest of the patients in the cohort (24.3%) were nonallergic/Th2 low phenotype.

We carried out statistical comparisons of asthma characteristics between males and females and identified significant differences in ACT scores and mean blood eosinophil count [Table 2]. A significantly higher mean ACT score and eosinophil count was observed in males compared to females (17.9 vs. 16, $P = 0.01$) and (0.401 vs. 0.294, $P < 0.01$), respectively. The mean IgE and FeNO levels were not significantly different across genders.

Comorbidities and modifiable risk factors

The most frequent comorbidity observed was

Table 1: Comparison of severe asthma characteristics between different studies

	Current study	Wang et al. ^[13]	Kim et al. ^[10]	Novelli et al. ^[12]
Number of patients	458	4990	489	72
Age (years), mean±SD	47.7±17.2	55.0±15.9	62.3±14.0	59.1±11.1
Male/female	187/271	2029/2957 (4 not specified)	220/269	25/47
Percentage females	59.2	59.3	54.9	65.3
Percentage nonsmokers	97.2	94.1	87.7	94.5
Blood eosinophils (10 ⁹ /L), mean±SD	0.344±0.420 (n=293)		0.429±0.860 (n=433)	0.285 (median)
Blood IgE (IU/mL), mean±SD	627.7.1±2049.7 (n=255)		466.0±736.0	275.9 (median)
FeNO (ppb), mean±SD	36.8±35.6 (n=64)		41.1±26.4	22.4 (median)
ACT score, mean±SD	16.7±5.7 (n=230)		16.5±5.9 (n=463)	19 (median)

FeNO=Fractional exhaled nitric oxide, SD=Standard deviation, ACT=Asthma control test, IgE=Immunoglobulin E

Table 2: Comparison of asthma characteristics between males and females

	Males	Females	P
ACT score, mean±SD	17.9±5.1 (n=87)	16±6.0 (n=143)	0.01
Mean serum IgE (IU/mL), mean±SD	641.5±869 (n=118)	615.7±2682.7 (n=137)	0.9
Mean blood eosinophils (10 ⁹ /L), mean±SD	0.401±0.457 (n=132)	0.294±0.383 (n=161)	<0.01
FeNO (ppb), mean±SD	41.7±44.5 (n=23)	34±29.8 (n=41)	0.5

FeNO=Fractional exhaled nitric oxide, SD=Standard deviation, ACT=Asthma control test, IgE=Immunoglobulin E

allergic rhinitis (52.2%), followed by GERD (27.1%), hypertension (26.9%), hyperlipidemia (26.0%), diabetes (25.3%), obesity (20.3%), OSA (14.0%), nasal polyps (11.1%), thyroid disease (9.6%), bronchiectasis (5.5%), eczema (3.9%), food allergy (3.7%), depression (3.5%), anxiety (3.5%), and osteoporosis (3.1%). Sixty-two patients (13%) had a history of past/present smoking. We analyzed the difference between genders in terms of comorbidities and found that GERD and depression were significantly more common in females while nasal polyps and eczema were more prevalent among males [Table 3].

Biological therapy

A total of 109 (23.8%) patients were receiving biological therapy for the treatment of severe asthma. The breakdown of the data according to the biological agents showed 56 (51.4%) patients on omalizumab, 29 (26.6%) patients on dupilumab, 18 (16.5%) patients on benralizumab, and 6 (5.5%) patients on mepolizumab.

Malignancy

Thirteen patients (2.8%) had a history of malignancy; the most common malignancies were breast, lung, and thyroid cancer, each found in three patients. Colon cancer was found in two patients, and bladder cancer and prostate cancer were each found in one patient.

Discussion

The scarcity of data on severe asthma not only in the UAE, but also in the Middle East as a whole necessitated this retrospective review in which we evaluated the demographic and clinical characteristics of patients with severe asthma in the UAE's local Arab

Table 3: Comorbidities according to gender

Comorbidity	Total	Males (%)	Females (%)	P
Allergic rhinitis	239	38.5	61.5	0.287
GERD	124	31.5	68.5	0.013
Hypertension	123	36.6	63.4	0.265
Hyperlipidaemia	119	37	63	0.319
Diabetes	116	36.2	63.8	0.238
Obesity	93	36.6	63.4	0.345
OSA	64	35.9	64.1	0.395
Nasal polyps	51	56.9	43.1	0.013
Thyroid	44	25	75	0.024
Bronchiectasis	25	44	66	0.738
Eczema	18	61.1	38.9	0.070
Food allergy	17	52.9	47.1	0.291
Depression	16	12.5	87.5	0.020
Anxiety	16	31.3	68.7	0.437
Osteoporosis	14	21.4	78.6	0.136

OSA=Obstructive sleep apnoea, GERD=Gastroesophageal reflux disease

population and compared our data with previously published international cohorts. One of the earliest reports of asthma prevalence in the UAE stated that asthma affects about 13.6% of children in the UAE.^[14] However, there is a variation in the asthma prevalence rates recently reported in the UAE; one report suggested that asthma affects at least 9.8% of the total UAE population,^[15] another report estimated that it affects 13% of the population^[16] and a third report estimated that asthma affects 4.9% of the population.^[2] The variation in prevalence rates may be due to the different methodologies used in each of the studies, where asthma definitions have differed from one study to another. With this in mind, it is sensible for us to estimate the asthma prevalence in that the UAE is about 8%–9%, similar to that found in Kuwait (9.5%) and Saudi Arabia (8.3%).^[2] The economic burden of asthma care

in the emirate of Abu Dhabi was reported to be around 29 million USD in 2014;^[17] however, with increasing use of biologics in the severe asthma subgroup, this cost is likely to increase significantly.

The mean age of our severe asthma cohort was 47.7 ± 17.2 , which is lower than the three studies we used for comparison [Table 1]. However, data from the Severe Asthma Research Program (SARP) registry^[18] reported a mean age of 37 years which is considerably lower than our cohort. This heterogeneity in the age of difficult asthma is interesting, being as high as 62.3 in Korea as reported by Kim *et al.*^[10] and as low as 37 in SARP, and it highlights that the care needs for these patient populations may be significantly different in the different parts of the world.

In our study, almost 54% of the patients had adult onset asthma. It has been reported that age of onset affects the response of severe asthma patients to biological therapy. Patients with adult onset usually respond better to anti-interleukin 5 (IL-5) or anti IL-5 receptor therapy, whereas patients with childhood onset disease respond better to anti-IgE therapy.^[3,19] Our cohort was the youngest cohort compared to cohorts from other global studies, and therefore, this could explain why more than half (51.4%) of our patients receiving biological therapy for severe asthma were on anti-IgE therapy (Omalizumab).

We observed a female predominance of 59% in our patient cohort which was no different from the studies we used for comparison. Although our observation is for severe asthma, it is well-known that females dominate all asthma severity groups. It has been suggested that sex hormones in females contribute to worse asthma symptoms compared to males, and animal studies have shown that oestrogen increased Th2-mediated airway inflammation, while androgens reduced it.^[20,21] This is a significant finding as it not only provides an explanation for the difference in asthma prevalence, onset, and severity between males and females, but also offers opportunities for further studies to be carried out to assess the difference in inflammatory pathways between males and females and potentially consider hormonal therapy for asthma.

In this study, we found that males had significantly higher mean blood eosinophil count and ACT scores than females ($P < 0.01$ and $P = 0.01$, respectively); this is in concordance with the previously reported data.^[18,22] This is an interesting observation firstly as previous studies have reported no gender-based differences in asthma control,^[23] and secondly because females in our cohort were older and more obese, which are parameters associated with worse asthma control.^[24,25]

Allergic rhinitis was the most prevalent comorbidity in our cohort (52.2%) as observed in other severe asthma cohorts.^[10,13] Allergic rhinitis is well known to coexist with asthma and according to some authors more than 80% of asthmatics have a diagnosis of allergic rhinitis.^[26] In addition, the presence of allergic rhinitis is thought to be associated with increased asthma severity.^[27,28] This connection between allergic rhinitis and asthma is not surprising as the “united airway disease” theory suggests that the upper and the lower airway are functionally a singular unit and the inflammatory/allergic disorders in one are bound to have similar effects on the other.^[29,30] Hence, it is not surprising that treatment of allergic rhinitis with nasal corticosteroids and the leukotriene receptor antagonists also seems to reduce asthma exacerbations and asthma-related respiratory symptoms.^[31,32]

Similar to other cohorts,^[10,12] GERD was the second most common co-morbidity observed in our patients (27.1%), and it is known to be more prevalent among asthmatics compared to the general population.^[33] We also observed a statistically significant difference in the prevalence of GERD between females and males (68.5% vs. 31.5%, respectively, $P = 0.013$). This finding has been reported in two other studies previously^[34,35] and is possibly due to the effect of estrogen on the lower esophageal sphincter; however, the mechanism is not entirely clear.

Anxiety and depression were each present in 3.5% of the patients. Previously, Kim *et al.* had reported a somewhat similar prevalence of anxiety and depression in their study which was 1.7% and 3.7%, respectively.^[10] We also observed a significant difference in the prevalence of depression between males and females with a female preponderance (females 87.5%, males 12.5%, $P = 0.02$) which is in accordance with a higher prevalence of depression in women in the general population.^[36]

These findings are important as depression is reported to be a risk factor for developing asthma,^[37] and both anxiety and depression are associated with poor asthma control.^[38]

The prevalence of nasal polyposis in the Middle East including the UAE has not been previously reported. In our patient population, nasal polyposis was present in 11.1% of the total cohort while Wang *et al.* reported the prevalence of nasal polyposis to be 7.3%.^[13] Nasal polyposis has been reported to be associated with greater asthma severity;^[39] however, we did not observe a significant difference in ACT scores between asthma patients with and without nasal polyps ($P = 0.5$). Interestingly, we observed a significant difference in the prevalence of nasal polyposis between males and females ($P = 0.013$), where males had a higher

prevalence (56.9% vs. 43.1%, $P = 0.013$) which is in concordance with previously reported data.^[40]

The choice of biologics for the treatment of asthma is expanding and phenotyping difficult asthma is the necessary first step in deciding the need and the choice of biologic therapy. Omalizumab is an anti-IgE monoclonal antibody that is approved by the Food and Drug Agency (FDA) in the treatment of moderate-to-severe allergic asthma.^[41] Mepolizumab (anti-IL5), Benralizumab (anti-IL5R), and Dupilumab (anti-IL4) are FDA approved for the treatment of severe eosinophilic asthma.^[42,43] Allergic asthma is well known to be the most common asthma phenotype worldwide,^[42] and in our cohort as well, asthma was predominantly allergic (61.2%). Wang *et al.* suggested that early onset asthma combined with high IgE levels predisposes patients to develop allergic asthma later on.^[13] Our cohort had the higher mean blood IgE levels than the compared studies [Table 1], and almost 50% of the patients were diagnosed with asthma during childhood, therefore, our findings support this suggestion by Wang *et al.* On the other hand, nonallergic asthma is suggested to be defined by late disease onset combined with lower IgE levels, as seen in one study.^[43] The patients who were identified as having nonallergic asthma in our study were predominantly diagnosed in adulthood and had a lower mean blood IgE compared to patients with allergic asthma; however, the difference in mean blood IgE levels was not statistically significant.

Our study is focused on the Emirati population and completely excludes the expatriate population. The genetic makeup of Emiratis could be different to the expatriate population, which would reflect on the prevalence of the different severe asthma phenotypes. The UAE government provides its citizens with a good quality health-care system administered by its Federal Ministry of Health, and this may explain the low prevalence of severe asthma in the country. In addition, while our study measures the prevalence of severe asthma across three major health-care centers in the UAE, the figure we report is not conclusive, as there may be patients receiving asthma care elsewhere in the country. Moreover, data on the prevalence of comorbidities among UAE nationals is not available; therefore, we were not able to determine whether the comorbidities we identified were truly raised in the Emirati population with severe asthma.

Conclusion

In summary, our study is the first to report the demographics, clinical phenotypes and treatment variables in a large cohort of Emirati patients diagnosed with severe asthma. Our findings provide important

information regarding the understanding of the disease in the region and highlight the need for establishing a national registry to identify the true prevalence and help improve the management of severe asthma in the UAE.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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