Asthma in the Real-World: The Relevance of Gender

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Keywords

Asthma · Gender · Severity · Control · Lung function · Type 2 inflammation · Real-world setting

Abstract

Background: The possible gender impact on asthma arouses current and outstanding interest, but few studies addressed this issue in the real-world setting. **Objective:** This cross-sectional study tested the hypothesis of a potential difference between asthmatic males and females in a real-life setting, such as a third-level asthma clinic. **Methods:** A total of 499 asthmatic outpatients (301 females and 198 males, mean age 58.25 years) were consecutively visited. The visit included history, asthma control, and severity grade, physical examination, lung function, fractional exhaled nitric oxide assessment, and blood sample for biomarkers. **Results:** There were more females than males (about 3 of 5). Asthmatic females smoked less ($p < 0.0001$) than males and had higher FEV₁ ($p = 0.0022$) and FVC ($p = 0.0004$) values than asthmatic males. **Conclusions:** Gender difference was associated with smoking and lung function impairment; thus, this issue should be carefully considered in asthmatic patients in daily clinical practice.

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Introduction

Asthma is a common disease characterized by typical symptoms, reversible bronchial obstruction, bronchial hyperresponsiveness, and airway inflammation. The control of asthma is the cornerstone strategy in the management of patients with asthma as stated by the Global Initiative for Asthma (GINA) document [1]. The asthma control evaluation should be based on a global assessment of respiratory symptoms, lung function, bronchial inflammation, existing comorbidity, risk factors, and compliance and adherence to treatments. The perception of asthma control may be assessed in a standardized way by the Asthma Control Test (ACT) questionnaire. Asthma is also characterized by bronchial inflammation, there are different inflammatory patterns, including type 2 inflammation that may be defined by blood eosinophils, serum IgE, fractional exhaled nitric oxide (FeNO), and allergy documentation [2].

The evaluation of the gender impact on asthma arouses current and outstanding interest and is an interesting research field as recently pointed out [3]. Asthmatic adult

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Table 1. Demographic and clinical characteristics of the study participants ($n = 505$)

Characteristics	Overall
Gender, n (%)	
Males	198 (39.68)
Females	301 (60.32)
Mean age $\pm$ SD	58.25 $\pm$ 15.07
Mean BMI $\pm$ SD	26.84 $\pm$ 5.48
Mean age at onset $\pm$ SD	37.03 $\pm$ 18.96
Smoking, n (%)	
Never smoker	274 (54.91)
Past smoker	175 (35.07)
Current smoker	50 (10.02)
Chronic rhinosinusitis	179 (35.45)
FVC (% of pred.)	100.11 $\pm$ 18.08
FEV ₁ (% of pred.)	83.94 $\pm$ 21.2
FEV ₁ /FVC	81.78 $\pm$ 13.5
RV pathologic ($\geq$ 120%)	215 (52.18%)
Mean ACT $\pm$ SD	20.66 $\pm$ 3.66
Mean FeNO $\pm$ SD	38.63 $\pm$ 31.25
Asthma severity grade	
1	63 (12.63%)
2	47 (9.42%)
3	162 (32.46%)
4	115 (23.05%)
5	112 (22.44%)
Blood eosinophils >300/mL	169 (39.67%)
Total IgE (>100 IU)	151 (51.54%)
Type 2 inflammation	395 (81.44%)
Exacerbations/year	
$\leq$ 1	362 (79.04%)
2	42 (9.17%)
>2	54 (11.79%)
OSAS	26 (5.15%)
Arterial hypertension	159 (31.49%)
Bronchiectasis	36 (7.13%)
Allergy	268 (53.07%)
Diabetes mellitus	33 (6.53%)
Osteoporosis	39 (7.72%)
Beclio HFA dosage (μ g/day)	300.8 $\pm$ 219.25
LABA	388 (77.76%)
Oral corticosteroids	18 (3.61%)
Biologics	53 (10.62%)

females have a predominant prevalence: 9.7 versus 5.7% in males [4] and a predominance of nonallergic asthma [5]. Also, asthmatic females have more severe morbidity than males, such as more visits, hospitalizations, and death rates [6]. Sex hormones may substantially contribute to this gender difference [7, 8].

On the other hand, most studies derived from big trials or international surveys that are usually conducted on very selected or multi-ethnic asthmatic populations [9].

Therefore, the present cross-sectional study tested the hypothesis of the potential difference between asthmatic males and females in a real-world setting. The aim was to evaluate the possible association between gender and some demographical, clinical, and functional parameters in a group of asthmatic outpatients visited at a third-level asthma clinic.

Material and Methods

Patients

This observational cross-sectional study included 499 asthmatic outpatients. They were referred to an asthma clinic for a specialist visit and were sequentially recruited. Clinical data and patient history were obtained at recruitment. The visit included detailed history, clinical examination, body mass index (BMI) measurement, spirometry, FeNO measurement, skin prick test, blood sampling for eosinophils and total IgE, ACT questionnaire and treatment step level, from step 1 (short-term/periodic use of low dose ICS) to step 5 (at least long-term use of high dose ICS: fluticasone propionate >500 μ g plus LABA), according to the GINA document [1].

The diagnosis of asthma was performed considering the history of typical symptoms and the documented demonstration of reversible bronchial obstruction, after bronchodilation testing and/or methacholine challenge.

Continuous variables were given as means and standard deviations (SD), whereas categorical variables as number and/or percentage of subjects. The gender effect on the demographical and clinical characteristics was screened using logistic or multinomial regression for categorical outcomes and linear regression analysis for continuous outcomes. The likelihood ratio (LR) test was used as a test of statistical significance, and the estimated p values were adjusted for multiple comparisons by the Bonferroni correction method. Those models with a gender-associated p value <0.05 were then selected for the multivariate analysis, where the gender effect was corrected for age and BMI. Differences with a p value < 0.05 were selected as significant. Data were acquired and analyzed in R 3.6.2 software environment [10].

Results

A total of 499 (301 females, 60.32%) asthmatic outpatients were enrolled in the study. As regards the demographic and clinical characteristics in the whole sample, the mean age was 58.25 (SD = 15.07) years, BMI 26.84 (SD = 5.48), the age at asthma onset 37.03 (SD = 18.96) years, 274 (54.91%) were never smokers, 175 (35.07%) past smokers, and 50 (10.02%) current smokers, 179 (35.45%) had chronic rhinosinusitis, 26 (5.15%) OSAS, 159 (31.49%) arterial hypertension, 36 (7.13%) bronchiectasis, 33 (6.53%) type II diabetes mellitus, and 39 (7.72%) osteoporosis (Table 1). As regards lung function,

Table 2. Descriptive statistics and univariate analysis (*n* = 499)

Characteristics	Descriptive statistics		Regression analysis	
	Gender		estimated OR (95% CI)	<i>p</i> value
	male	female		
Smoking*				<0.0001
Never smokers	78 (39.39%)	196 (65.12%)	1	
Past smokers	95 (47.98%)	80 (26.58%)	0.34 (0.23 to 0.5) [§]	
Current smokers	25 (12.63%)	25 (8.31%)	0.4 (0.22 to 0.73) [§]	
Asthma severity grade				0.9999
1	24 (12.12%)	39 (12.96%)	1	
2	24 (12.12%)	23 (7.64%)	0.59 (0.27 to 1.27) [§]	
3	67 (33.84%)	95 (31.56%)	0.87 (0.48 to 1.59) [§]	
4	43 (21.72%)	72 (23.92%)	1.03 (0.55 to 1.94) [§]	
5	40 (20.2%)	72 (23.92%)	1.11 (0.58 to 2.1) [§]	
Oral corticosteroids	10 (5.05%)	8 (2.66%)	0.51 (0.19 to 1.32) [◇]	0.9999
Becllo HFA dosage	296.97 (217.49)	303.32 (220.73)	6.35 (−33.1 to 45.81) [#]	0.9999
Biologics	18 (9.09%)	35 (11.63%)	1.32 (0.73 to 2.44) [◇]	0.9999
LABA	149 (75.25%)	239 (79.4%)	1.27 (0.83 to 1.94) [◇]	
Exacerbations/year				0.3893
≤1	147 (84.97%)	215 (75.44%)	1 [§]	
2	8 (4.62%)	34 (11.93%)	2.91 (1.31 to 6.46) [§]	
>2	18 (10.4%)	36 (12.63%)	1.37 (0.75 to 2.5) [§]	
Chronic rhinosinusitis	73 (36.87%)	106 (35.22%)	0.93 (0.64 to 1.35) [◇]	0.9999
Blood eosinophils >300	80 (48.48%)	89 (34.1%)	0.55 (0.37 to 0.82) [◇]	0.0923
Total IgE >100 IU	65 (59.09%)	86 (46.99%)	0.61 (0.38 to 0.99) [◇]	0.9999
Type 2 inflammation	164 (84.97%)	231 (79.11%)	0.67 (0.41 to 1.08) [◇]	0.9999
OSAS	9 (4.55%)	17 (5.65%)	1.26 (0.56 to 3.01) [◇]	0.9999
Arterial hypertension	58 (29.29%)	101 (33.55%)	1.22 (0.83 to 1.8) [◇]	0.9999
Bronchiectasis	14 (7.07%)	22 (7.31%)	1.04 (0.52 to 2.12) [◇]	0.9999
Allergy	107 (54.04%)	158 (52.49%)	0.94 (0.66 to 1.35) [◇]	0.9999
Diabetes mellitus	11 (5.56%)	22 (7.31%)	1.34 (0.65 to 2.93) [◇]	0.9999
Osteoporosis	16 (8.08%)	22 (7.31%)	0.9 (0.46 to 1.78) [◇]	0.9999
Age	58.41 (15.02)	58.15 (15.13)	−0.26 (−2.97 to 2.46) [#]	0.9999
BMI	26.81 (4.53)	26.86 (6.05)	0.05 (−1 to 1.1) [#]	0.9999
Age at onset	36 (17.93)	37.68 (19.59)	1.68 (−1.82 to 5.18) [#]	0.9999
FVC %pred.*	95.82 (16.58)	103 (18.5)	7.18 (3.96 to 10.4) [#]	0.0004
FEV ₁ %pred.*	79.32 (20.24)	86.98 (21.31)	7.66 (3.89 to 11.43) [#]	0.0022
FEV ₁ /FVC	82 (14.21)	81.64 (13.05)	−0.36 (−2.99 to 2.28) [#]	0.9999
RV >120% pred.	96 (55.81%)	119 (49.58%)	0.78 (0.52 to 1.15) [◇]	0.9999
ACT	21.19 (3.53)	20.33 (3.7)	−0.86 (−1.54 to 0.19) [#]	0.3437
FeNO	39.17 (28.17)	38.27 (33.16)	−0.9 (−7.17 to 5.37) [#]	1.0000

Characteristics: the outcome was taken into account. Descriptive statistics: outcome of descriptive statistics, % and mean with standard deviation were reported for categorical and continuous outcome, respectively. Estimate (95% CI): linear regression coefficient with 95% CI (marked with #), and odds ratios, estimated using logistic (marked with [◇]) or multinomial (marked with [§]) regression, were reported. *p* value: the likelihood ratio *p* value adjusted for multiple comparisons by the Bonferroni correction method. * Outcomes entered in multivariate analysis (see Statistical Methods for more details). *p* values <0.05 were reported in bold.

the mean percentages of predicted values were: FVC 100.11 (SD = 18.08), FEV₁ 83.94 (SD = 21.2), FEV₁/FVC 81.78 (SD = 13.5); mean FeNO was 38.63 (SD = 31.25). The mean ACT was 20.66 (SD = 3.66). As regards the

asthma severity grade, 63 outpatients (12.63%) had grade 1, 47 (9.42%) grade 2, 162 (32.46%) grade 3, 115 (23.05%) grade 4, and 112 (22.44%) grade 5; 362 (79.04%) had ≤1 exacerbation/year, 42 (9.17%) 2, and 54 (11.79%) >2. As

regards type 2 inflammation, 169 (39.67%) had >300 blood eosinophils, 151 (51.54%) total IgE >100, and 268 (53.07%) allergy, in particular, 226 (44.75%) were polyallergic and 193 (38.22%) were allergic to perennial allergens (house dust mites and pets). Two hundred and fifteen (52.18%) outpatients had abnormal RV. As regards current treatment, 388 (77.76%) used LABA, 18 (3.61%) oral corticosteroids, and 53 (10.62%) biologics (omalizumab or mepolizumab); the mean ICS beclomethasone-equivalent dosage was 300.8 (SD = 219.25) µg.

The univariate analysis showed significant gender difference concerning smoking status, FVC, and FEV₁, as analytically reported in Table 2 (*p* values: <0.0001, 0.0004, and 0.0022, respectively). The subsequent multivariate analysis confirmed significant gender association with smoking status, FVC, and FEV₁ corrected for age and BMI (LR *p* values <0.0001). In particular, past smoking was less likely in female outpatients than in males (OR with 95% CI = 0.33; 0.22: 0.51). Current smoking was less likely in female outpatients (OR with 95% CI = 0.42; 0.21: 0.83). Moreover, higher FVC was more likely in females than in male patients (OR with 95% CI = 8.07; 4.71: 11.42) as well as FEV₁ (OR with 95% CI = 8.05; 4.16: 11.94).

Discussion

The present real-world study demonstrated that there was a clear prevalence of asthmatic females and a significant association of gender with smoking and lung function. On the contrary, there was no significant difference concerning the other considered parameters. The current outcomes are consistent with a recent study conducted in patients with severe asthma and included in the German asthma net cohort [11]. Milger et al. [11] reported a significant difference between asthmatic males and females concerning lung function, namely females had higher values of FEV₁, FVC, MEF₂₅, and DLCO. Moreover, females had work limitations. Even though this study was restricted to severe asthma, the findings confirmed that asthmatic females were more numerous than males. This is a well-known finding, in fact asthma is usually more prevalent in asthmatic females than in males [4, 12]. However, this difference is likely dependent on the peculiar hormonal pattern, in fact, in prepubertal children, there is a prevalence of males, but there is no significant difference between genders concerning lung function and other clinical parameters [13, 14].

Moreover, females had a better lung function than asthmatic males. These authors hypothesized that a pos-

sible explanation of this outcome could depend on the higher percentage of patients with smoking history in male compared with female patients. Consistently, the current study confirmed that asthmatic females were more frequently never or past smokers than males. This finding may easily explain the better lung function that has been detected in females, and the negative impact of smoking on lung function is well-known [15].

However, the present real-world study had a main limitation because it was performed cross-sectionally, so further longitudinal studies should be performed to confirm these findings. On the other hand, the real-world setting allowed to represent the daily practice of a third-level asthma clinic, including a wide range of asthma severity.

In conclusion, females with asthma have less propensity to smoke and better lung function than males when evaluated in a real-life setting. On the other hand, there are no clinically relevant differences between genders about asthma control GINA grade as well as inflammatory parameters. Thus, about asthma management in daily clinical practice, it is important to pay attention to gender, mainly concerning the lung function assessment.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the local Ethics Committees of San Luigi Gonzaga University Hospital (Prot. No. 4478/2017). All adult participants provided written informed consent to participate in this study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.L.M.R. designed the study and revised the draft; S.L., F.B., and V.C. managed clinical data; A.E.S. and F.G. analyzed the data; G.C. wrote the paper.

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