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Evaluating the FEV_1/FVC ratio in the lower range of normality as a marker of worse clinical outcomes in asthmatic subjects without airway obstruction

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ABSTRACT

Background: We should continually improve tools for evaluating asthma. The aim of this study was to evaluate whether the FEV_1/FVC ratio in the lower range of normality is associated with worse outcomes in asthmatics without airway obstruction.

Methods: We screened asthmatics at eight clinics. Subjects answered the Asthma Control Questionnaire and underwent spirometry. We assigned individuals without airway obstruction in three groups according to the post bronchodilator FEV_1/FVC ratio: lower range of normality, intermediary range of normality and upper range of normality. Asthma outcomes were hospital admission due to asthma during the preceding year, non-controlled asthma symptoms and moderate-high inhaled maintenance therapy need.

Results: In subjects from six to 18 years old, the rate of hospital admission was higher in the group with FEV_1/FVC ratio in the lower range of normality as compared with the other two groups but the frequency of non-controlled symptoms of asthma and moderate-high dose of inhaled maintenance therapy need was similar. From 19 to 59 years old, the rate of moderate-high inhaled maintenance therapy need was higher in the group with FEV_1/FVC ratio in the lower range of normality as compared with the other two groups, but the frequency of hospital admissions and non-controlled symptoms of asthma was similar. Above 59 years old, there was no difference in clinical asthma outcomes between lung function groups.

Conclusions: FEV_1/FVC ratio in the lower range of normality is a marker of worse clinical outcomes in asthmatics without airway obstruction.

1. Introduction

Asthma is a chronic disease, usually characterized by labile respiratory symptoms, bronchial hyperresponsiveness and chronic inflammation of the airways [1]. Some asthmatic subjects develop non-inflammatory airway abnormalities, named bronchial remodeling. Epithelial detachment, basement membrane thickening, smooth muscle hypertrophy and new vessel formation characterize bronchial remodeling [2]. Airway inflammation or airway contraction without concomitant inflammation may lead to bronchial remodeling in subjects with asthma [2,3].

Subjects with bronchial remodeling may lose lung function and, eventually, develop airway obstruction [4,5]. Loss of lung function and airway obstruction due to asthma have been a matter of extensive investigation. Preventing these conditions is important because airway obstruction is associated with more asthma symptoms and medication requirement [6]. Inhaled corticosteroids (ICS) maintenance therapy may minimize loss of lung function and airway obstruction in asthmatic subjects [7], but may jeopardize growth rate in children and predispose to osteoporosis in adults [8]. Thus, it is meaningful that we continually improve the tools that guide titrating asthma maintenance therapy as to provide the best possible medication benefits while minimizing adverse events.

Airway obstruction is one among others criteria that points toward the need of up-titrating asthma maintenance therapy, but it would be helpful identifying an earlier lung function marker for better management of asthma. Such hypothetical lung function marker might contribute for preventing worse clinical outcomes and airway obstruction. Currently, the main criterion for airway obstruction is the FEV_1/FVC ratio below the lower limit of normality (LLN) [9]. The value of a

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Table 1
Clinical characteristics of children and adolescents (6–18 years old) without post-bronchodilator airway obstruction, grouped according to the post bronchodilator FEV_1/FVC ratio.

	FEV_1/FVC in the lower range of normality (n = 78)	FEV_1/FVC in the intermediate range of normality (n = 153)	FEV_1/FVC in the upper range of normality (n = 77)	P
Age in years - median (IQ)	12 (10–15)	12 (10–15)	14 (12–16)	<0.01
Female gender - n (%)	38 (49)	75 (49)	28 (36)	0.16
Body mass index - median (IQ)	20 (18–24)	20 (18–24)	20 (17–21)	0.10
Smoking mother - n (%)	14 (18)	9 (6)	0 (0)	<0.01
Chronic rhinitis - n (%)	75 (96)	144 (94)	73 (95)	0.80
First asthma symptom before 12 years old - n (%)	76 (97)	148 (97)	73 (95)	0.65
Duration of asthma, in years - median (IQ)	9 (6–13)	10 (7–12)	12 (8–15)	0.08
Duration of asthma without treatment, in years - median (IQ)	6 (2–10)	5 (2–10)	8 (3–12)	0.03
Moderate-high dose of inhaled medications for asthma - n (%)	8 (10)	14 (9)	4 (5)	0.48
Low adhesion to maintenance therapy, Morisky score > 1 - n (%)	13 (30)	21 (24)	11 (28)	0.74
Subjects that reported HA visits for asthma during last year - n (%)[a]	11 (14)	10 (7)	2 (3)	0.02
Non-controlled asthma symptoms according to the ACQ_6 - n (%)	22 (28)	35 (23)	10 (13)	0.06
Peripheral blood eosinophil count - median (IQ)	350 (280–632)	420 (256–638)	370 (180–787)	0.94
Total IgE - median (IQ)	501 (255–1113)	468 (267–1246)	537 (143–1084)	0.77
Peripheral blood eosinophil count > 400 cells per mm^3 - n (%)	36 (46)	81 (53)	36 (47)	0.63
Total IgE > 160 UI/dl - n (%)	67 (87)	133 (87)	54 (71)	0.06
FVC % of predict, pre bronchodilator - median (IQ)	114 (101–121)	115 (105–127)	109 (99–118)	0.01
FEV_1% of predict, pre bronchodilator - median (IQ)	89 (81–99)	104 (94–117)	105 (96–118)	<0.01
FVC % of predict, post bronchodilator - median (IQ)	117 (108–130)	118 (109–129)	111 (102–126)	<0.01
FEV_1% of predict, post bronchodilator - median (IQ)	98 (89–108)	112 (103–121)	113 (102–125)	<0.01

HA - Hospital admission.
Comparisons between three groups: Chi-Square test for categorical variables and Kruskal-Wallis test for ordinal and continuous variables.
We applied a post hoc test to identify the difference between two groups.
[a] FEV_1/FVC in the lower range of normality was different from the two other groups in the post hoc test.

FEV_1/FVC ratio in the lower range of normality as a marker of clinical outcomes in asthmatic subjects without airway obstruction is unknown. We hypothesize that this is an early lung function marker of worse asthma outcomes. The primary aim of this study was to evaluate whether the FEV_1/FVC ratio in the lower range of normality is associated with worse clinical outcomes in asthmatic subjects without airway obstruction. The secondary aim was to evaluate whether this lung function parameter is associated with systemic biomarkers of atopic and eosinophilic asthma.

2. Material and methods

2.1. Study population

We conducted this study in Jundiaí, a 400,000-inhabitant median-high income industrial city in Brazil. We screened consecutive subjects that attended an appointment at eight public and private outpatient clinics, from August 2017 to July 2019. The Institutional Review Board of the Jundiaí School of Medicine approved the study (approval number 2.198.023). All subjects signed informed consent.

2.2. Inclusion and exclusion criteria

The physicians in charge at the outpatient clinics referred to the research team all consecutive asthmatic subjects who showed up for an appointment. The research team screened the subjects according to the inclusion/exclusion criteria. The inclusion criteria were asthma diagnosis, age above six years and have been following-up with a physician during the preceding six months. Exclusion criteria were previous smoking history above nine pack years, current smoking, pregnancy or any concomitant illness that might compromise the assessment of asthma control.

The research team validated the diagnosis of asthma at the study visit. The tools for asthma diagnosis were clinical examination, spirometry and chest radiography, the latter for exclusion of alternative diagnoses. Two chest physicians experienced in caring for asthma subjects validated the asthma diagnosis independently. In case of disagreement between these physicians, we did not enroll the subject in the study. The physicians interviewed and examined the volunteers, reviewed medical records and lung function tests. Clinical evidences of asthma were recurrent wheezing, cough or dyspnea lasting more than one year, symptoms improvement after inhaled corticosteroids and relieved by bronchodilator. Lung function should show more than 12% variation of the Forced Expiratory Volume in the first second (FEV_1) within a lung function test or between two lung function tests performed during the preceding 12 months. The attending physician requested a computerized tomography of the chest for all subjects with severe asthma. We excluded subjects with relevant radiological abnormalities.

2.3. Study design

This is a cross-sectional study. The volunteers answered a standard questionnaire for collection of clinical information and the Asthma Control Questionnaire (ACQ_6) to assess the severity of asthma symptoms

Table 2
Clinical characteristics of young adults (19–39 years old) without post-bronchodilator airway obstruction, grouped according to the post bronchodilator FEV_1/FVC ratio.

	FEV_1/FVC in the lower range of normality (n = 47)	FEV_1/FVC in the intermediate range of normality (n = 95)	FEV_1/FVC in the upper range of normality (n = 48)	P
Age in years - median (IQ)	33 (25–37)	32 (27–37)	34 (27–36)	0.94
Female gender - n (%)	32 (68)	70 (74)	32 (67)	0.63
Body mass index - median (IQ)	28 (24–32)	28 (24–31)	25 (23–29)	0.14
Smoking mother - n (%)	16 (34)	18 (19)	13 (27)	0.13
Chronic rhinitis - n (%)	37 (79)	84 (88)	42 (88)	0.28
First asthma symptom before 12 years old - n (%)	37 (79)	64 (67)	30 (63)	0.21
Duration of asthma, in years - median (IQ)	24 (16–33)	22 (13–29)	21 (10–31)	0.40
Duration of asthma without treatment, in years - median (IQ)	18 (8–25)	17 (6–26)	13 (3–23)	0.18
Moderate-high dose of inhaled medications for asthma - n (%)[a]	19 (40)	22 (23)	6 (12)	<0.01
Low adhesion to maintenance therapy, Morisky score > 1 - n (%)	4 (10)	15 (18)	9 (21)	0.31
Subjects that reported HA visits for asthma during last year - n (%)	2 (4)	3 (3)	2 (4)	0.93
Non-controlled asthma symptoms according to the ACQ_6 - n (%)	15 (32)	33 (35)	15 (31)	0.90
Peripheral blood eosinophil count - median (IQ)	288 (134–474)	273 (158–463)	211 (123–437)	0.43
Total IgE - median (IQ)	321 (117–726)	241 (74–614)	145 (42–332)	0.07
Peripheral blood eosinophil count > 400 cells per mm^3 - n (%)	16 (36)	30 (32)	14 (30)	0.85
Total IgE > 160 UI/dl - n (%)	30 (64)	57 (60)	21 (44)	0.07
FVC % of predict, pre bronchodilator - median (IQ)	99 (89–105)	97 (88–102)	91 (81–103)	0.11
FEV_1% of predict, pre bronchodilator - median (IQ)	83 (71–91)	89 (83–100)	96 (82–107)	<0.01
FVC % of predict, post bronchodilator - median (IQ)	104 (92–111)	98 (91–105)	91 (84–105)	0.01
FEV_1% of predict, post bronchodilator - median (IQ)	90 (79–98)	97 (89–107)	99 (89–110)	<0.01

HA - Hospital admission.
Comparisons between three groups: Chi-Square test for categorical variables and Kruskal-Wallis test for ordinal and continuous variables.
We applied a post hoc test to identify the difference between two groups.
[a] FEV_1/FVC in the lower range of normality was different from the two other groups in the post hoc test.

[10]. We obtained a peripheral blood sample for analyzes. Subjects underwent a spirometry according to the ATS protocol with a Koko® device updated with the Brazilian values of normality.

2.4. Definition of airway obstruction and FEV_1/FVC ratio in the lower range of normality

Criteria of airway obstruction were post bronchodilator FEV_1/FVC ratio below the LLN and FEV_1 below 80% of predicted. We calculated the LLN of each individual according to the equation obtained from Cerveri et al. [9]. We decided not using the fixed FEV_1/FVC ratio at 0.7 because this criterion may overestimate or underestimate airway obstruction depending on the age range [9]. For each individual without airway obstruction, we calculated how much the post bronchodilator FEV_1/FVC ratio obtained from the lung function test was above the LLN. For this purpose, we used the following equation: [(FEV_1/FVC - LLN) x 100]/LLN. We used this index to categorize three groups of non-obstructed asthmatics: FEV_1/FVC ratio in the lower range of normality were individuals below the 25th percentile, FEV_1/FVC ratio in the intermediary range of normality were individuals between the 25-75th percentiles and FEV_1/FVC ratio in the upper range of normality were individuals above the 75th percentile.

2.5. Definition of asthma outcomes

Asthma outcomes were any hospital admission due to asthma that have occurred during the preceding year, non-controlled symptoms of asthma and the necessity of moderate-high dose of inhaled maintenance therapy. We validated the patient-reported hospital admission by means of reviewing the printed report emitted by the hospital. In Brazil, provide patients with a printed report describing the hospital admission is a regular practice at discharge. All subjects that reported a hospital admission provided a printed hospital report. All reports confirmed that the subjects stayed more than 24-h in a hospital ward due to asthma exacerbation. The criterion of non-controlled symptoms of asthma was the ACQ_6 score above 1.5. The ACQ questionnaire measures the severity of asthma symptoms during the last seven days. Leite et al. validated the questionnaire for the Portuguese language of Brazil [10]. The criteria of moderate-high dose of inhaled maintenance therapy need was the self-report of using ≥800 mcg of inhaled budesonide or equivalent associated with a long acting $beta_2$ agonist (LABA) during the last three months and failure in down-titrating the medicine. We validated maintenance therapy self-reports against outpatient medical records. We also evaluated adherence to maintenance therapy by applying the Morisky questionnaire. The Morisky questionnaire score varies from zero to four. Score above one indicates low adherence to treatment [11].

2.6. Systemic biomarkers of atopic and eosinophilic asthma

Subjects provided a peripheral blood sample for total IgE test (Automated chemoluminescence assay) and eosinophil count (Automated hematology analyzer). We defined as atopic asthmatics the individuals with total IgE above 160 UI/dl, because this is the lower limit of normality by the automated chemoluminescence assay, and as

Table 3
Clinical characteristics of old adults (40–59 years old) without post-bronchodilator airway obstruction, grouped according to the post bronchodilator FEV_1/FVC ratio.

	FEV_1/FVC in the lower range of normality (n = 62)	FEV_1/FVC in the intermediate range of normality (n = 124)	FEV_1/FVC in the upper range of normality (n = 63)	P
Age in years - median (IQ)	48 (44–56)	50 (44–55)	52 (47–56)	0.16
Female gender - n (%)	43 (69)	94 (76)	50 (79)	0.42
Body mass index - median (IQ)	28 (26–32)	29 (27–34)	30 (27–35)	0.09
Smoking mother - n (%)	17 (27)	30 (24)	13 (21)	0.67
Chronic rhinitis - n (%)	48 (77)	101 (82)	49 (79)	0.75
First asthma symptom before 12 years old - n (%)	32 (52)	49 (40)	12 (19)	<0.01
Duration of asthma, in years - median (IQ)	28 (11–39)	26 (7–41)	15 (4–31)	0.02
Duration of asthma without treatment, in years - median (IQ)	21 (6–36)	22 (4–38)	5 (1–27)	0.01
Moderate-high dose of inhaled medications for asthma - n (%)[a]	38 (61)	51 (41)	27 (42)	0.03
Low adhesion to maintenance therapy, Morisky score > 1 - n (%)	6 (11)	22 (20)	11 (20)	0.38
Subjects that reported HA visits for asthma during last year - n (%)	2 (3)	5 (4)	1 (2)	0.67
Non-controlled asthma symptoms according to the ACQ_6 - n (%)	24 (39)	47 (38)	48 (24)	0.11
Peripheral blood eosinophil count - median (IQ)	210 (138–355)	230 (160–326)	162 (103–271)	<0.01
Total IgE - median (IQ)	192 (93–559)	122 (34–311)	54 (25–207)	<0.01
Peripheral blood eosinophil count > 400 cells per mm^3 - n (%)[b]	11 (19)	23 (19)	3 (6)	0.04
Total IgE > 160 UI/dl - n (%)[a]	37 (59)	52 (42)	17 (27)	<0.01
FVC % of predict, pre bronchodilator - median (IQ)	96 (84–104)	90 (81–100)	95 (81–102)	0.07
FEV_1% of predict, pre bronchodilator - median (IQ)	78 (70–86)	84 (76–92)	93 (81–105)	<0.01
FVC % of predict, post bronchodilator - median (IQ)	102 (93–109)	93 (85–104)	95 (82–104)	<0.01
FEV_1% of predict, post bronchodilator - median (IQ)	82 (77–92)	88 (83–97)	98 (84–110)	<0.01

HA - Hospital admission.
Comparisons between three groups: Chi-Square test for categorical variables and Kruskal-Wallis test for ordinal and continuous variables.
We applied a post hoc test to identify the difference between two groups.
[a] FEV_1/FVC in the lower range of normality was different from the two other groups in the post hoc test.
[b] FEV_1/FVC in the lower range of normality was different only from the FEV_1/FVC in the upper range of normality in the post hoc test.

eosinophilic asthmatics the individuals with peripheral blood eosinophil count above 400 cells per mm^3, because eosinophil count above this cutoff have been associated with worse asthma outcomes [12].

2.7. Statistical analyses

We compared asthma outcomes between three lung function categories of subjects without airway obstruction: FEV_1/FVC ratio in the lower range of normality, FEV_1/FVC ratio in the intermediary range of normality and FEV_1/FVC ratio in the upper range of normality. Analyses were stratified per age range because age has a major effect on asthma phenotypes and severity [13]. Four age ranges were set: six to 18 years old, 19–39 years old, 40–59 years old and above 59 years old. Chi-Square test was used for comparing categorical variables while the Kruskal-Wallis test compared ordinal variables. We also used the Kruskal-Wallis test for comparing continuous variables because the distribution was not normal. A *post hoc* test was applied for identifying the difference between two groups. The statistical package was SPSS 22.0.

We also compared some asthma severity outcomes between subjects with FEV_1/FVC ratio in the lower range of normality and subjects with airway obstruction. These analyses were performed for testing whether the concepts of FEV_1/FVC ratio in the lower range of normality and airway obstruction can differentiate two distinct populations or if they are only overlapping concepts. We used the Mann-Whitney test for comparing continuous variables because the distribution was not normal. The statistical package was SPSS 22.0.

3. Results

The physicians in charge at the outpatient clinics referred 1,326 asthmatic subjects for being evaluated for the inclusion/exclusion criteria by the research team, but 272 subjects decided not to participate and 38 were not enrolled as they did not meet the inclusion/exclusion criteria. Therefore, we enrolled 1,016 subjects. The number of subjects without airway obstruction was 912: 308 subjects from 6 to 18 years old, 190 subjects from 19 to 39 years old, 249 subjects from 40 to 59 years old, 165 subjects above 59 years old. Asthmatic subjects with airway obstruction comprised 104 individuals: five subjects from 6 to 18 years old, 20 subjects from 19 to 39 years old, 34 subjects from 40 to 59 years old, 45 subjects above 59 years old.

Among subjects from six to 18 years old without airway obstruction, the proportion of subjects with hospital admission was higher in the group with FEV_1/FVC ratio in the lower range of normality as compared with the other two lung-function groups. We also demonstrated a trend towards association between lung function and non-controlled symptoms of asthma and total IgE above 160 UI/dl. However, no association was observed between lung function and the proportion of subjects using moderate-high dose of inhaled maintenance therapy or peripheral blood eosinophil count above 400 cells per mm^3 (Table 1).

In the sample of subjects from 19 to 39 years old without airway obstruction, the proportion of subjects using moderate-high dose of

Table 4
Clinical characteristics of elderly (above 59 years old) without post-bronchodilator airway obstruction, grouped according to the post bronchodilator FEV_1/FVC ratio.

	FEV_1/FVC in the lower range of normality (n = 41)	FEV_1/FVC in the intermediate range of normality (n = 82)	FEV_1/FVC in the upper range of normality (n = 42)	P
Age in years - median (IQ)	67 (63–71)	67 (63–72)	69 (64–72)	0.74
Female gender - n (%)	27 (66)	58 (71)	33 (79)	0.42
Body mass index - median (IQ)	27 (24–31)	29 (26–34)	32 (29–34)	<0.01
Smoking mother - n (%)	8 (20)	14 (17)	12 (28)	0.32
Chronic rhinitis - n (%)	25 (61)	48 (59)	29 (69)	0.52
First asthma symptom before 12 years old - n (%)	15 (37)	21 (26)	5 (12)	0.04
Duration of asthma, in years - median (IQ)	24 (10–50)	15 (5–46)	7 (3–21)	<0.01
Duration of asthma without treatment, in years - median (IQ)	23 (7–49)	11 (1–43)	4 (1–20)	0.02
Moderate-high dose of inhaled medications for asthma - n (%)	27 (66)	44 (54)	20 (48)	0.23
Low adhesion to maintenance therapy, Morisky score > 1 - n (%)	3 (8)	7 (9)	3 (8)	0.94
Subjects that reported HA visits for asthma during last year - n (%)	1 (2)	1 (1)	0 (0)	0.60
Non-controlled asthma symptoms according to the ACQ_6 - n (%)	10 (24)	19 (23)	14 (33)	0.46
Peripheral blood eosinophil count - median (IQ)	235 (115–349)	223 (120–390)	192 (113–278)	0.31
Total IgE - median (IQ)	183 (25–520)	61 (14–194)	31 (6–142)	0.03
Peripheral blood eosinophil count > 400 cells per mm^3 - n (%)	8 (20)	21 (26)	4 (10)	0.06
Total IgE > 160 UI/dl - n (%)[a]	21 (53)	24 (31)	9 (22)	0.01
FVC % of predict, pre bronchodilator - median (IQ)	92 (83–104)	86 (78–100)	86 (75–103)	0.46
FEV_1% of predict, pre bronchodilator - median (IQ)	76 (69–83)	80 (71–94)	87 (79–104)	<0.01
FVC % of predict, post bronchodilator - median (IQ)	98 (87–106)	92 (81–103)	87 (77–102)	0.07
FEV_1% of predict, post bronchodilator - median (IQ)	79 (75–88)	86 (74–101)	93 (81–108)	<0.01

HA - Hospital admission.
Comparisons between three groups: Chi-Square test for categorical variables and Kruskal-Wallis test for ordinal and continuous variables.
We applied a post hoc test to identify the difference between two groups.
[a] FEV_1/FVC in the lower range of normality was different from the two other groups in the post hoc test.

inhaled maintenance therapy was higher in the group with FEV_1/FVC ratio in the lower range of normality as compared with the other two lung-function groups. We did not observe association between lung function and the proportion of subjects with hospital admission or non-controlled symptoms of asthma. It was observed a trend towards association between lung function and total IgE above 160 UI/dl, but peripheral blood eosinophil count was not associated with lung function (Table 2).

Among subjects from 40 to 59 years old without airway obstruction, the proportion of subjects using moderate-high dose of inhaled maintenance therapy was higher in the group with FEV_1/FVC ratio in the lower range of normality, but there was only a trend towards association between lung function and non-controlled symptoms of asthma. There was no association between lung function and hospital admission. FEV_1/FVC ratio in the lower range of normality was associated with total IgE above 160 UI/dl and peripheral blood eosinophil count above 400 cells per mm^3 (Table 3).

We did not observe association between lung function and asthma severity outcomes among subjects above 59 years old without airway obstruction. In this age range, FEV_1/FVC ratio in the lower range of normality was associated with total IgE above 160 UI/dl, but the association was only borderline for the peripheral blood eosinophil count above 400 cells per mm^3 (Table 4).

As compared with FEV_1/FVC ratio in the lower range of normality, airway obstruction was associated with higher symptoms score in subjects below 39 years old (Fig. 1) and with greater ICS maintenance therapy need in adults and elderly (Fig. 2).

4. Discussion

Our study demonstrates that, in asthmatic children and adolescents without airway obstruction, the FEV_1/FVC ratio in the lower range of normality is associated with higher hospital admission rate as compared with other two groups of lung function. Identifying markers of severe exacerbation in children and adolescents with asthma is essential because young asthmatics are more susceptible to near fatal and fatal attacks as compared with adults with asthma [14]. We also observed that, in adults, the FEV_1/FVC ratio in the lower range of normality was associated with more inhaled maintenance therapy need as compared with other two groups of lung function, which might explain the non-difference in hospital admission rate and symptoms severity between lung-function groups. Hospital admissions and more inhaled maintenance therapy need are markers of asthma severity, thus, we have shown association between FEV_1/FVC ratio in the lower range of normality and worse asthma outcomes across almost all age ranges, except elderly. This study provides useful information to clinical practice, as it is the first evidence to our knowledge indicating that the best possible FEV_1/FVC ratio might be a better target than accepting any normal lung function. However, longitudinal studies are still recommended for investigating whether the FEV_1/FVC ratio in the lower range of normality should unleash up-titrating asthma maintenance therapy. We acknowledge this is not the first attempt for identifying a novel lung-function marker of asthma outcomes. Boutin et al. investigated the Forced Expiratory Flow in small lung volumes (FEF 25–75), but it proved of limited utility to clinical practice [15]. Among current and former smokers, low FVC values without airway obstruction (Prism) was

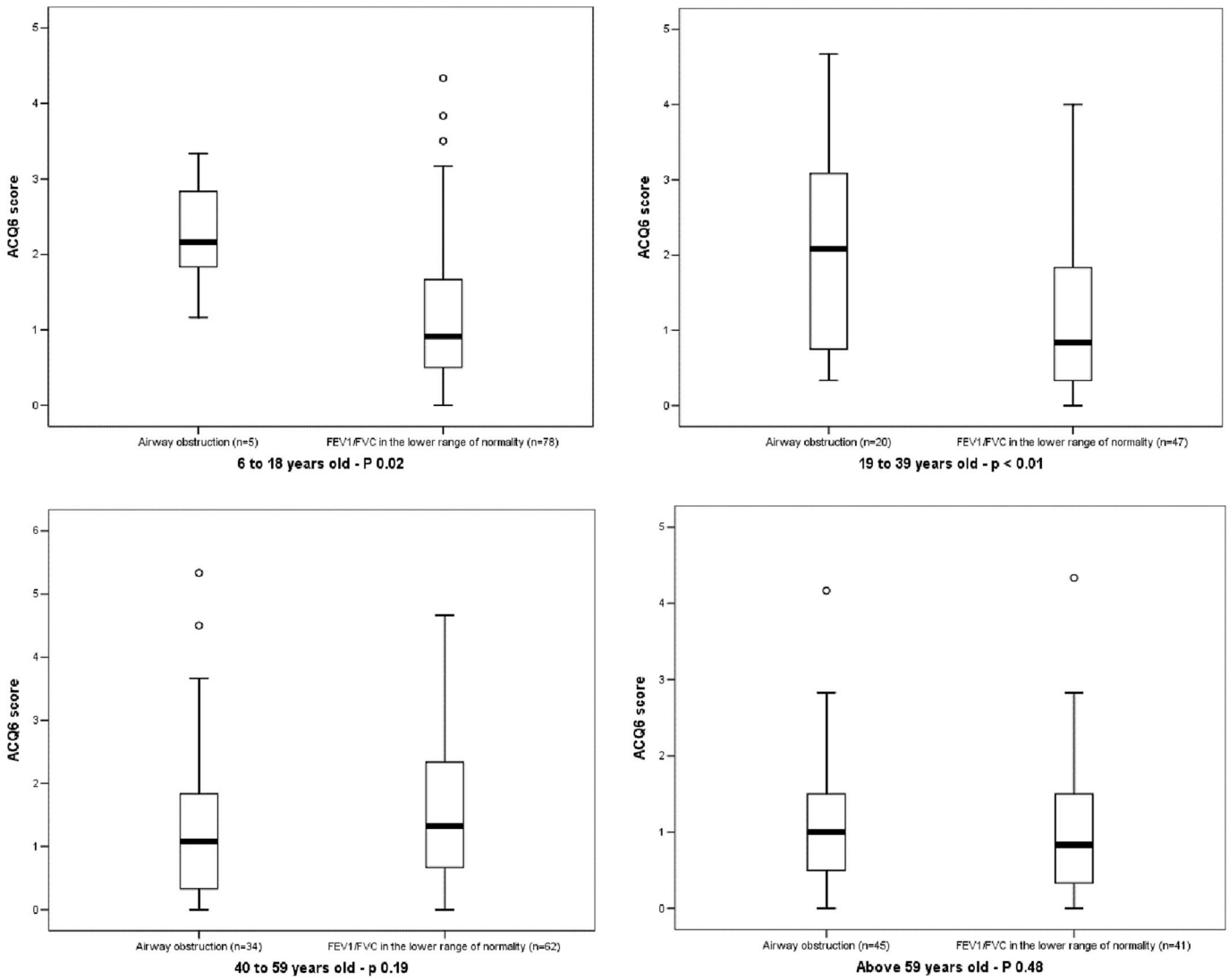

Fig. 1. Comparison of symptoms score between subjects with airway obstruction and subjects with FEV1/FVC in the lower range of normality, according to age range.

associated with worse clinical outcomes, but the meaning of the Prism lung function pattern for asthmatic subjects is unknown [16].

There are evidences showing small airway obstruction [17] and remodeling [18] in some asthmatic subjects with spirometry within the normal range. Ideally, physicians should detect these subjects early and manage therapy for reversing the small airway impairment. However, accessing small airways is challenging as oscillometry and plethysmography, though accurate and sensible tools for evaluating small airways [19], are not available in most settings. Our results support future studies for investigating the FEV_1/FVC ratio in the lower range of normality as a marker of small airway impairment.

Elder subjects with asthma have lower total IgE values and less atopy as compared with young asthmatics [13], but we cannot infer, based on these evidences, about the non-involvement of IgE in the immunopathology of asthma in elderly. Our study showed association between high total IgE values and FEV_1/FVC ratio in the lower range of normality in elderly. Total IgE might participate in the immunopathology of asthma in this age range, in spite of the low values in serum, which would explain the effectiveness of anti-IgE antibody therapy in subjects above 60 years old [20].

Eosinophilic asthma is associated with exacerbations and non-controlled symptoms [12,21], but the relationship between this asthma phenotype and lung function is poorly understood. There is no convincing evidence that eosinophil targeted therapy improves lung function in subjects with asthma [22], as only recently this topic have been a matter of investigation. Our study demonstrated some association between eosinophilic asthma and FEV_1/FVC ratio in the lower range of normality, somewhat encouraging new studies on this issue.

One endpoint of this study was hospital admission due to asthma. We validated the patient-reported hospital admission by means of reviewing the printed report emitted by the hospital at discharge. All subjects who reported a hospital admission provided a printed hospital report. All reports were valid as they described more than 24-h stay in a hospital ward due to asthma exacerbation. Thus, the criterion for capturing hospital admissions was effective. One limitation of our study were the non-large sample size, but we could identify some interesting differences between groups. We did not measure specific IgE to identify atopic asthma and we did not obtain induced sputum to count eosinophils, but total IgE and peripheral blood eosinophil came out useful biomarkers. It is meaningful emphasizing that we adopted the FEV_1/FVC ratio below the lower limit of normality for defining airway obstruction because the fixed FEV_1/FVC ratio at 0.7 may underestimate or overestimate airway obstruction depending on the age range [9]. We believe our results can be generalized as we evaluated consecutive asthmatic subjects from all severities and socioeconomic strata, attended at eight outpatient clinics across the city. Finally, comparisons between subjects with FEV_1/FVC

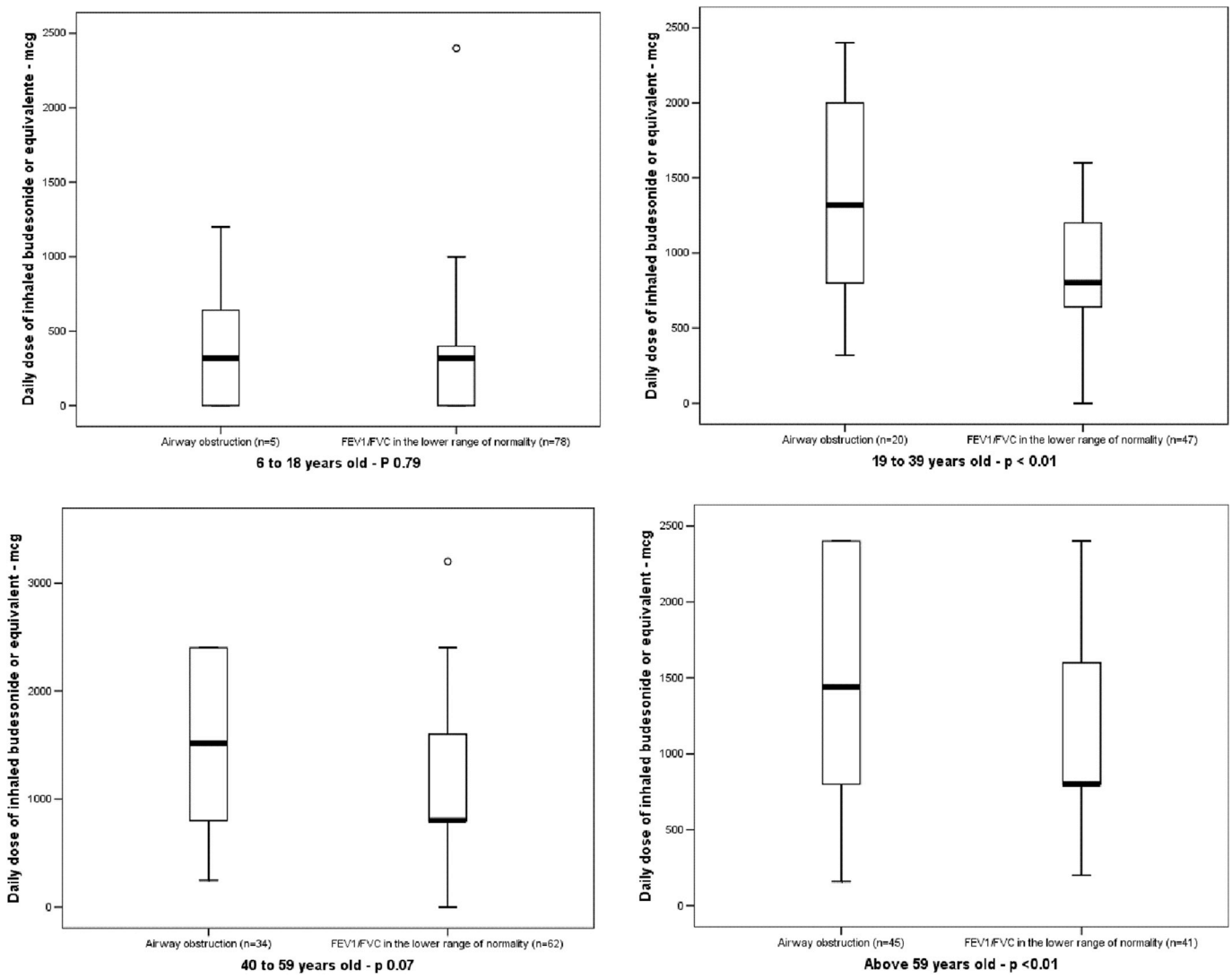

Fig. 2. Comparison of inhaled corticosteroid need between subjects with airway obstruction and subjects with FEV_1/FVC in the lower range of normality, according to age range.

ratio in the lower range of normality and subjects with airway obstruction have shown statistically significant differences in asthma outcomes, indicating that these two lung-function groups are not overlapping concepts, but represent different populations.

5. Conclusion

We conclude that the FEV_1/FVC ratio in the lower range of normality is a marker of worse clinical outcomes in asthmatic subjects without airway obstruction and it is associated with systemic biomarkers of atopic and eosinophilic asthma. We believe future longitudinal studies should investigate whether striving for the best possible FEV_1/FVC ratio by increasing inhaled maintenance therapy would be more appropriate than accepting any normal lung function test in subjects with asthma. We also believe future studies should evaluate whether the FEV_1/FVC ratio in the lower range of normality is a marked of small airway impairment.

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Declaration of competing interest

Cintia Mingotti, Jose Sarinho, Katia Stanigher, Juçara Silva, Eduardo Roquette, Evaldo Marchi and Eduardo Vieira Ponte declare no conflict of interest.

CRediT authorship contribution statement

Cintia Mingotti: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft. **Jose Sarinho:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft. **Katia Stanigher:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft. **Juçara Silva:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft. **Eduardo Roquette:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft. **Evaldo Marchi:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Writing - original draft. **Eduardo Vieira Ponte:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision,

Validation, Writing - original draft.

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