Increased adiposity-to-muscle ratio and severity of sinusitis affect quality of life in asthma: Computed tomographic analysis

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Background: Deteriorated sinusitis and increased adiposity relative to muscle mass may affect quality of life in patients with asthma. However, whether these effects are observed regardless of intrapulmonary pathology is unknown.

Objectives: We evaluated the correlation of the cross-sectional ratio of abdominal visceral fat (VF) to erector spinae muscle (ESM) and sinus findings based on Lund-Mackey scoring system (LMS) on computed tomography (CT) with the impaired score of the Asthma Quality of Life Questionnaire (AQLQ), regardless of airway and parenchymal disease, in patients with asthma.

Methods: We recruited participants from the Hokkaido-based severe asthma cohort who had completed AQLQ and CT examination at the entry. The participants were divided into high (highest) and low (other quartiles) groups on the bases of the extrapulmonary indices. Multivariate analysis examined the association of VF/ESM for the adiposity-to-muscle ratio and LMS with AQLQ after adjusting for the airway fractal dimension for airway index and percentage of low attenuation volume to lung volume for parenchymal index.

Results: No significant differences were observed in VF/ESM and LMS in terms of sex. The AQLQ score in the high VF/ESM group and high LMS group was lower than those in low VF/ESM group and low LMS group (63 male and 100 female subjects). High VF/ESM (estimate [95% confidence interval] (−0.43 [−0.61, −0.25]) and high LMS scores (−0.22 [−0.41, −0.03]) were associated with low AQLQ scores when adjusted for age, body mass index, smoking status, blood eosinophil count, and intrapulmonary CT indices.

Conclusions: Increased VF relative to ESM mass and high LMS may deteriorate asthma-related quality of life, regardless of presence of intrapulmonary disease. (J Allergy Clin Immunol Global 2024;3:100277.)

Key words: *Abdominal visceral fat, adiposity, asthma, computed tomography, erector spinae muscle, Lund-Mackey Score, sinusitis*

Asthma, a lifelong disease, can develop at any age. Asthma accumulates a heavy socioeconomic burden worldwide because of its high prevalence during childhood and adulthood.[1] Progress in therapeutic agents, particularly inhaled corticosteroids (ICS), has significantly decreased asthma-related mortality. Discovery of new biologic therapies has significantly affected the management of severe asthma. However, total control remains to be achieved.[2] The treatable-trait approach has enabled the individual assessment of specific treatable symptoms, facilitating the implementation of personalized medicine.[3] Treatable comorbidities, such as obesity and rhinosinusitis, are common pathologies that affect the quality of life (QoL) of patients with asthma.[4]

Airflow obstruction and airway alteration on computed tomography (CT) have been associated with adiposity and sinusitis.[5,6] Thus, differentiating the effect of extrapulmonary lesions from intrapulmonary lesions on clinical outcomes may facilitate personalized medicine. CT has been used to simultaneously assess specific intra- and extrapulmonary regions in clinical practice. On the basis of this advantage of CT, the relationships of CT-based intra- and extrapulmonary indices with symptoms, QoL, exacerbations, and mortality have been explored in patients with chronic obstructive pulmonary disease (COPD), which is well known to be a systemic inflammatory disease. Vascularity,[7,8] left ventricle size,[9] muscle mass,[10-12] and adiposity[13] are promising for phenotyping.[14] In contrast, airway alterations have been studied extensively, while the use of extrapulmonary morphology on CT images has been limited to the association with symptoms and QoL in asthma.[15,16] Rhinosinitis is the vital pathophysiology to interact with asthma.[17] Recently, sinusitis changes have been evaluated by CT using the Lund-Mackey scoring system (LMS) score, a CT scoring scale, in the course of treatment with biologics in patients with asthma. We also utilized LMS

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Abbreviations used

AFD: Airway fractal dimension
AQLQ: Asthma Quality of Life Questionnaire
BMI: Body mass index
COPD: Chronic obstructive pulmonary disease
CT: Computed tomography
DLCO: Diffusion capacity of carbon monoxide in lungs
ESM: Erector spinae muscle
FENO: Fractional exhaled nitric oxide
FEV_1: Forced expiratory volume in 1 second
Hi-CARAT: Hokkaido-based Investigative Cohort Analysis for Refractory Asthma
ICS: Inhaled corticosteroids
LAV: Low attenuation volume
%LAV: Ratio of LAV with threshold of −950 Hounsfield Unit to total lung volume
LMS: Lund-Mackey scoring system
OCS: Oral corticosteroids
QoL: Quality of life
VF: Abdominal visceral fat

to explore the association of sinus pathology with lung function and systemic or airway type 2 inflammation in nonsmokers and smokers with asthma.[18] The interaction between the upper and lower airway supports the concept of one airway and one disease. Eosinophilic rhinosinusitis, which often requires intensive therapy (eg, oral corticosteroids [OCS] or biologics), is often observed as a comorbidity in patients with severe asthma and may impair asthma-related QoL.[19,20] However, whether LMS score affects QoL independently of intra- or extrapulmonary CT indices is unclear.

Increased abdominal visceral fat on CT images have been correlated with impaired asthma QoL questionnaire (AQLQ) scores in both male and female patients.[5] A high fat mass index relative to free fat mass index and loss of muscle strength have also been reported to be associated with impaired AQLQ scores.[21,22] Furthermore, sarcopenia[23] and sarcopenic obesity, characterized by low muscle mass and high fat mass, were found to deteriorate activities of daily living. Studies have shown that the erector spinae and pectoral muscles serve as radiologic prognostic biomarkers in COPD,[9,12] which suggests that quantitative assessment of specific muscles may broaden our insight into asthma's pathophysiology. A combined fat and muscle index may serve as a QoL-related biomarker for asthma.

This study aimed to examine whether a high adiposity to muscle index (visceral fat/erector spinae muscle [VF/ESM]) and high LMS score are correlated with impaired QoL score, regardless of the severity of the airway and parenchyma lesions assessed by CT in patients with asthma across the spectrum of disease severity.

METHODS

Participants

All patients with asthma included in the Hokkaido-based Investigative Cohort Analysis for Refractory Asthma (Hi-CARAT)[18,24] were eligible for inclusion in this study. The Hi-CARAT study was approved by the ethics committee of Hokkaido University Hospital (approval 009-0205) and registered with the University Hospital Medical Information Network Clinical Trials Registry system (UMIN-CTR, ID 000003254; center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000003917). Initially, we recruited patients with severe asthma diagnosed by respiratory physicians between February 2010 and September 2012 at Hokkaido University Hospital and 29 other affiliated hospitals and clinics.

We also recruited additional patients with mild to moderate asthma between March 2011 and September 2012. Their disease had been in stable condition for at least 6 months and did not require high doses of ICS or OCSs. Diagnosis of severe asthma was based on the 2000 American Thoracic Society criteria for refractory asthma,[18] with slight modifications, as we describe here. Major characteristics to diagnose asthma were as follows:

1. To achieve asthma control, patient requires treatment with continuous or near-continuous (>50% of year) OCS receipt.
2. To achieve asthma control, patient requires treatment with high-dose ICS.

ICS doses were modified because of differences in their availability in Japan, as follows: fluticasone ≥800 μg; budesonide ≥1200 μg; ciclesonide ≥600 μg; mometasone furoate ≥600 μg; salmeterol, inafoate fluticasone propionate ≥1000 μg; and budesonide/formoterol fumarate dihydrate dihydrate ≥960 μg.

Minor characteristics were as follows:

1. Requirement for daily treatment with controller medication in addition to ICS (eg, long-acting β-agonist, theophylline, leukotriene antagonist).
2. Asthma symptoms that require short-acting β-agonist receipt on daily or near-daily basis.
3. Persistent airway obstruction (forced expiratory volume in 1 second [FEV_1] of <80% predicted; diurnal peak expiratory flow variability >20%).
4. One or more urgent care clinic visits for asthma per year.
5. Three or more OCS "bursts" per year.
6. Prompt deterioration with <25% reduction in OCS or ICS dose.
7. Near-fatal asthma event in past.

The definition of severe asthma required one or both major and two minor criteria.

Coordinators trained to run clinical trials reviewed participants' prescriptions for the year before study entry and recorded ICS doses, OCS receipt, and hospitalizations. They also recorded pack years of tobacco at the time of study entry.

AQLQ assessment and hospitalization

Asthma-related QoL of all patients was assessed using the Japanese version of the AQLQ (S)[25] at the initial visit. Permission to use the Japanese version of the AQLQ (S) was obtained from Elizabeth F. Juniper (McMaster University, Hamilton, Ontario, Canada).[26] The AQLQ (S) is split into 4 categories comprising 32 items: activity limitations (11 items), symptoms (12 items), emotional functioning (5 items), and exposure to environmental stimuli (4 items). Each item was scored on a scale of 1 (most impaired condition) to 7 (least impaired condition). The patients rated all items according to their subjective assessment of asthma-related QoL over the preceding 2 weeks. The total AQLQ (S) score was obtained by averaging the scores for 32 items.[27] The history of asthma-related hospitalization in the preceding year was assessed during the initial visit.

Atopy

Atopy was defined as having a positive specific IgE (>1.01 lumicount) for at least one common inhaled allergen and/or multiple antigen simultaneous test.

Quantitative CT

Among the 213 patients with asthma, 190 underwent CT examinations with a 64-detector array (Aquilion Multi, TSX-101A/6A; Toshiba Medical Systems, Tochigi, Japan) at Hokkaido University Hospital.[27]

Extrapulmonary indices of VF, ESM, and LMS

Abdominal visceral fat. In addition to chest and sinus CT images, consecutive abdominal CT images were acquired at the level of the third lumbar vertebra with the patient supine. The Fat Scan software program Ziostation 2 (Ziosoft, Tokyo, Japan)[5] was used to determine the VF area on the CT image.

Erector spinae muscle. The cross-sectional areas of the ESM were assessed on the axial mediastinal images acquired at the level of the lower margin of the 12th thoracic vertebra reconstructed using kernel FC 03 with SYNAPSE VINCENT (FUJIFILM Medical, Tokyo, Japan).[11] The ESM was identified and manually traced in both lungs, yielding the cross-sectional muscle mass area sum. Both muscles were distinguished using −50 and 90 HU. Interobserver variation on the assessment of ESM was examined by K.S. and N.W., with randomly selected 40 (20 male and 20 female subjects) anonymized CT data sets.

Lund-Mackey scoring system. An otolaryngologist (Y.N.) reviewed and scored the sinus CT images using the LMS.[17,18] A score of 0 (completely aerated), 1 (partially opacified), or 2 (completely opacified) was assigned to each of the 5 sinus complexes: maxillary, anterior/posterior ethmoidal, sphenoidal, and frontal. A score of 0 (unobstructed) or 2 (obstructed) was assigned to the ostiomeatal complex. Sinus CT images were scored on a scale of 0 to 24.

Intrapulmonary indices of low attenuation volume and airway fractal dimension

SYNAPSE VINCENT was used to perform a quantitative assessment of the emphysematous regions. The ratio of low attenuation volume (LAV) with a threshold of −950 HU to total lung volume (%LAV) was considered an index of parenchymal disease. As reported in previous studies, the airway fractal dimension (AFD) was calculated using the box-counting method[28,29] to quantify the entire airway structure. A low AFD, which may represent airway alterations (such as remodeling and mucus secretion), indicates decreased complexity of the airway tree.

Pulmonary function tests

Chestac (Chest MI, Tokyo, Japan) was used to evaluate carbon monoxide's spirometry and diffusion capacity in the lungs (DLCO). Maintenance and calibration were performed according to the guidelines published by the Japanese Respiratory Society.[30] The best FEV_1 and forced vital capacity measured during spirometry were recorded according to Japanese Respiratory Society guidelines. DLCO was assessed immediately after prebronchodilator spirometry by a single-breath method. DLCO was corrected using hemoglobin according to the European Respiratory Society/American Thoracic Society guidelines.[31] The prediction equation of Burrows et al[32] was adopted.

Lung volumes (total lung capacity, functional residual capacity, and residual volume) were assessed using multiple breaths in the helium closed-circuit method. These volumes were expressed as percentages of the predicted values using the prediction equations formulated by Nishida et al.[33]

Fractional exhaled nitric oxide

Fractional exhaled nitric oxide (FENO) concentrations were measured with a NIOX MINO monitor (Circassia, Solna, Sweden) according to American Thoracic Society guidelines.[34]

Statistical analysis

The association between extra- and intrapulmonary indices was assessed by Spearman correlation coefficients and compared between male and female participants by Wilcoxon test. The participants were divided into the high (highest quartile) and low (other quartiles) VF/ESM groups according to the value of VF/ESM, LMS, VF, and ESM to determine the features defined by each extrapulmonary index. Anthropometric indices; smoking status; severity and duration of asthma; FENO; IgE; receipt of ICS and OCS; pulmonary function tests results; eosinophil and neutrophil count in blood; AQLQ (S) scores; and frequency of exacerbation during the preceding year in male and female participants and in high/low VF/ESM and LMS groups were compared by Student *t* test, Wilcoxon test, or chi-square test. Multiple regression analysis was performed to evaluate the associations of the AQLQ (S) scores after adjusting for the intra- and extrapulmonary CT indices for age, sex (in analysis of all participants), body mass index (BMI), pack years of tobacco, and eosinophil count in blood in the analysis of all the participants and the subgroup analysis of male and female participants. Despite the collinearity, BMI was included as a covariate to differentiate the impact of VF/ESM on AQLQ from that of BMI. We examined interobserver variability in evaluating ESM by using intraclass correlations that used the CT data set of 40 participants (20 male and 20 female). All statistical analyses were performed by JMP 16.0 software (SAS Institute, Cary, NC).

RESULTS

Among the 213 patients with asthma eligible for study inclusion, 5 patients underwent CT examination with a different scanner, and 24 patients lacked CT data that could be analyzed to determine the parenchymal and airway indices. In 21 patients, a slice at the caudal end of the 12th thoracic vertebra was not included, so the ESM assessment was not applicable (see Fig E1 in this article's Online Repository at www.jaci-global.org). Thus, 163 patients comprised 63 male and 100 female subjects, 61 smokers and 102 nonsmokers, and 105 patients with severe asthma and 58 patients with mild to moderate asthma (see Table E1 in the Online Repository). Significant differences were observed between male and female participants in terms of smoking status and serum IgE levels (Table E1).

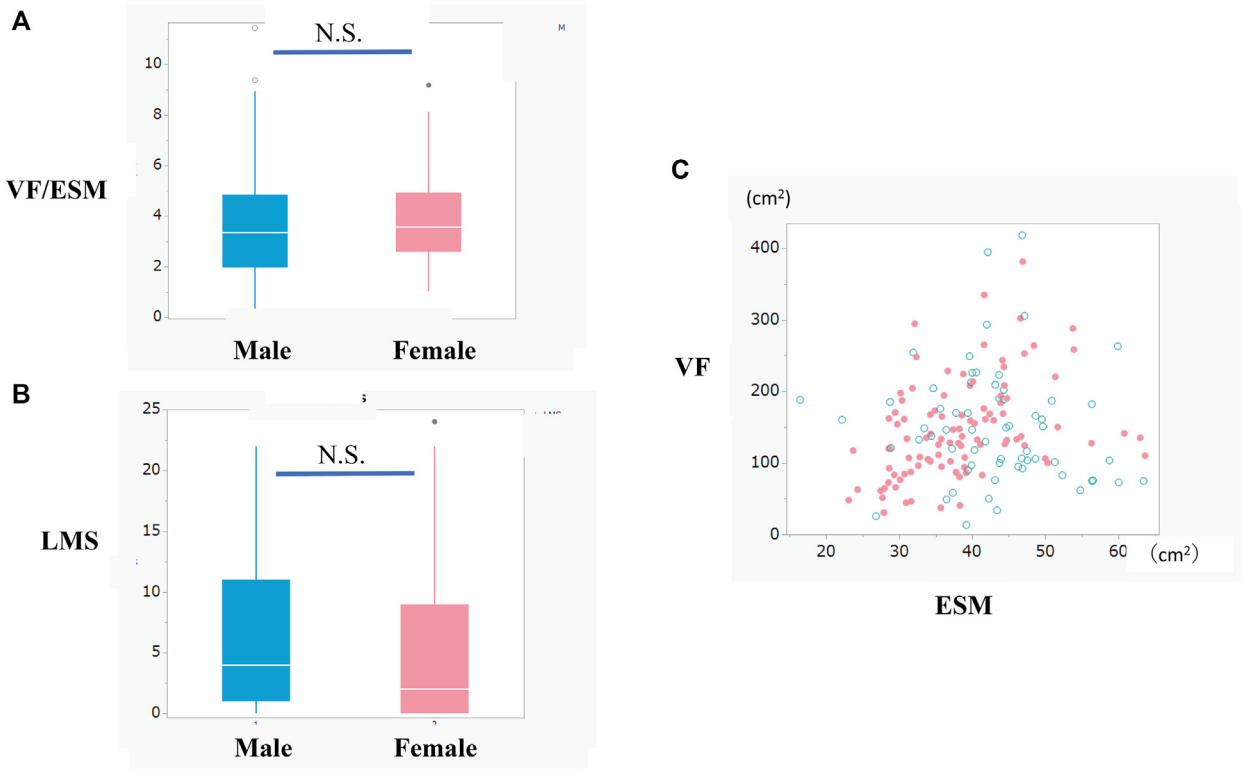

FIG 1. VF, ESM, and LMS in male and female participants. Positive association was observed between VF and ESM in female participants. VF/ESM and LMS scores did not differ significantly between male and female participants. *Open circles* indicate male participants; *solid circles,* female participants.

ESM, VF, and LMS in male and female participants

No significant differences were observed between the male and female participants in terms of VF/ESM (mean [standard deviation] for male participants, 3.71 [2.27]; female participants, 3.81 [1.64]; $P = .34$; Fig 1, *A*), VF (149.6 [80.4] cm^2, 146.1 [68.7] cm^2; $P = .95$; see Table E2 in the Online Repository at www.jaci-global.org) and LMS scores (male participants, 6.33 [6.15]; female participants, 5.29 [5.99]; $P = .95$; Fig 1, *B*). However, the ESM mass was higher in male versus female participants (male participants, 43.0 [9.00] cm^2; female participants, 38.4 [8.36] cm^2; $P < .001$; Table E2). Fig 1, *C,* shows the positive correlation between VF and ESM mass in female participants. Notably, no such correlation was observed in male participants (male participants: $\rho = -0.143$, $P = .264$; female participants: $\rho = 0.461$, $P < .001$). Intraclass correlation coefficient on the evaluation of ESM was 0.96 with CT scans of 40 patients.

Increased LMS scores were correlated with low AFD, suggesting association of more severe sinusitis findings on CT with more narrowed airways. This correlation was found in female participants ($\rho = 0.38$, $P < .01$) but not in male participants ($\rho = 0.05$, $P = .71$). Meanwhile, an increase in VF/ESM was associated with low %LAV in female participants ($\rho = -0.23$, $P = .02$; see Table E3 in the Online Repository at www.jaci-global.org).

Comparisons between high and low VF/ESM and high and low LMS groups

Regarding the analysis of all the participants shown in Table I, BMI, prevalence of severe asthma, ICS dose, and blood neutrophil count were higher in the high VF/ESM group compared to the low VF/ESM group. In contrast, FENO, IgE, and blood eosinophil count were higher in the high LMS group compared to the low LMS group (Table I). AQLQ was significantly lower in the high VF/ESM group (5.00 [1.04]) than that of the low VF/ESM group (5.87 [0.93]). Also, AQLQ was significantly lower in the high LMS group (5.42 [1.04]) than that of the low LMS group (5.73 [1.01]), respectively (Fig 2).

Table II and Table E4 in the Online Repository at www.jaci-global.org show comparisons between high/low VF/ESM and high/low LMS groups in male and female participants. BMI, prevalence of severe asthma, and blood neutrophil count were higher, and AQLQ scores were lower in the male and female participants in the high VF/ESM group than those in the low VF/ESM group (AQLQ (S) high/low group, numbers in brackets are SDs: male, 5.24 [0.74]/5.99 [1.05]; female: 4.87 [1.17]/5.79 [0.85]; see Fig E2 in the Online Repository). FENO level and blood eosinophil count were higher in the high LMS group than in the low LMS group (Table E4). However, there was no significant difference in AQLQ between high and low LMS groups in male and female participants (high/low group: male, 5.56 [0.99]/5.90 [1.04]; female, 5.32 [0.09]/5.63 [0.99]; Fig E2).

Multivariate analysis of association between extrapulmonary CT indices and AQLQ (S)

High VF/ESM in all the participants (95% confidence interval), −0.43 (−0.61, −0.25) and male (−0.33 (−0.63, −0.03)) and female (−0.58 (−0.71, −0.24)) participants and high LMS scores in all the participants (−0.22 (−0.41, −0.03)), and female participants (−0.28 (−0.52, −0.04))

TABLE I. Characteristics of 2 study group cohorts

Characteristic	High VF/ESM	Low VF/ESM	*P*
Subjects in cohort, no. (%)	40 (37.5)	123 (39.0)	.86
Age (years)	64 (53.3, 68.8)	64 (54, 71)	.47
BMI (kg/m^2)	26.8 (24.0, 29.7)	23.5 (21.0, 26.4)	<.01
PY, no. (%)	16 (40.0)	45 (36.6)	.70
Severe, no. (%)	35 (87.5)	70 (56.9)	<.01
Asthma duration (years)	19.5 (8.5, 30.5)	16 (7, 29)	.37
Atopy, no. (%)	22 (55.0)	88 (71.5)	.06
IgE (IU/mL)	108.3 (31.3, 345.1)	189.9 (68.2, 474.9)	.08
FENO (ppb)	32 (17.5, 56.5)	28 (15, 48)	.52
ICS dose (μg)	1500 (1275, 1600)	1500 (450, 1500)	<.01
OCS, no. (%)	12 (30.0)	24 (19.5)	.18
%FEV$_1$ (%)	99.9 (18.8)	109.7 (24.7)	.02
FEV$_1$/FVC (%)	67.0 (11.6)	68.2 (12.3)	.58
%DLCO (%)	96.3 (18.3)	107.2 (23.2)	.01
%K_{CO} (%)	110.1 (19.8)	108.4 (23.5)	.65
RV/TLC (%)	36.1 (5.1)	36.8 (7.1)	.56
%TLC (%)	108.4 (12.3)	114.3 (14.1)	.08
Eosinophils (μL)	353 (85.3, 542)	216 (112, 427)	.68
Neutrophils (μL)	5037.7 (4039.8, 6234.8)	3525 (2856, 4543)	<.01

FVC, Forced vital capacity; K_{CO}, transfer coefficient of carbon monoxide in lungs; *PY,* pack years; *RV,* residual volume; *TLC,* total lung capacity. When there are 2 numbers in parentheses, the first number is the number of participants who are positive to the item, followed by percentage of the participants who are positive to the corresponding item.

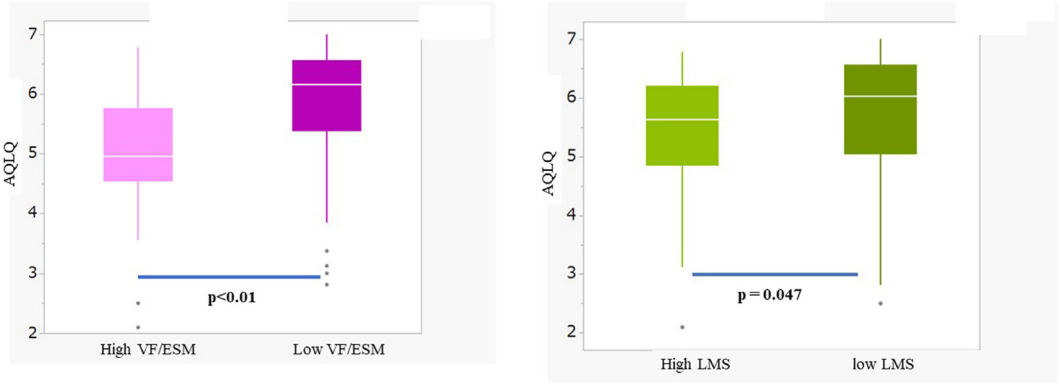

FIG 2. AQLQ (S) scores in high/low VF/ESM and high/low LMS groups. AQLQ (S) scores were significantly lower in high VF/ESM group *(left)* and high LMS group *(right)* than low VF/ESM group and low LMS group.

were associated with low AQLQ scores after adjusting for age, BMI, smoking status, blood eosinophil count, and intrapulmonary CT indices (Fig 3, and see Figs E3 and E4 in the Online Repository at www.jaci-global.org). Either VF or ESM was not associated with AQLQ (S) in the multivariate analysis with the same covariates, including LMS, in the analysis of all the participants as well as the male and female subgroups (Fig 3, Fig E3, Fig E4). Notably, the association of VF/ESM with the AQLQ (S) scores was the strongest among all the CT-derived indices in the analysis of all participants and the male and female subgroups.

Associations of high VF/ESM with asthma-related hospitalization in preceding year

The number of male participants hospitalized for asthma-related causes was higher in the high VF/ESM group than in the low VF/ESM group ($P = .01$) (Table III).

DISCUSSION

This study revealed that an increased VF/ESM and high LMS were associated with impaired AQLQ (S) scores. In contrast, VF and ESM mass showed no association with AQLQ (S) scores after adjusting for intrapulmonary disease and LMS. Higher LMS scores were associated with low AFD, which might better reveal the interaction of deteriorated sinusitis and airway remodeling in female participants. Increased VF/ESM in male and female participants and increased LMS scores in female participants were related to the AQLQ (S) scores; this result was independent of age, BMI, pack years of tobacco, blood eosinophil count, and intrapulmonary indices of airway and parenchymal disease on CT. Notably, high VF/ESM may be associated with higher neutrophil count in blood of both male and female participants.

Increased VF/ESM is correlated with asthma severity and asthma-related poor QoL in male and female participants, irrespective of the severity of airway and parenchymal diseases. A previous study showed that high-fat mass index/free relative to

TABLE II. Characteristics of high and low VF/ESM group by sex

Participant sex	Characteristic	VF/ESM high	VF/ESM low	*P*
Male	No. of subjects	16	47	
	Age (years)	62 (54.5-67.8)	64.1 (53-73)	.38
	BMI (kg/m^2)	25.3 (24.2-27.0)	22.9 (20.9-25.8)	.02
	PY10, no. (%)	13 (81.2)	30 (63.8)	.18
	Severe, no. (%)	14 (87.5)	26 (55.3)	.01
	Asthma duration (years)	21 (8.8-28.5)	16 (9-25)	.47
	Atopy, no. (%)	10 (62.5)	37 (78.7)	.21
	IgE (IU/mL)	235.8 (79.3-562.6)	300.4 (131.2-601.9)	.55
	FENO (ppb)	22.5 (17.5-40.8)	19 (12-61)	.15
	ICS dose (μg)	1500 (1200-1600)	1200 (400-1500)	.08
	OCS, no. (%)	6 (37.5)	11 (23.4)	.28
	%FEV$_1$ (%)	109 (20.9)	122.3 (27.1)	.08
	FEV$_1$/FVC (%)	60.5 (10.5)	65.1 (12.2)	.17
	%DLCO (%)	104.7 (20.0)	118.2 (25.1)	.06
	%K_{CO} (%)	95.9 (16.5)	99.9 (20.4)	.14
	RV/TLC (%)	34.2 (4.9)	34.7 (6.9)	.92
	%TLC (%)	109.1 (12.4)	112.0 (14.1)	.94
	Eosinophils (μL)	133 (64.8-432.8)	250 (146-498)	.14
	Neutrophils (μL)	5098.5 (3349.5-6449.0)	3505.5 (2801.4-4529)	.01
Female	No. of subjects	25	75	
	Age (years)	64 (52.5-70)	63 (54-71)	.76
	BMI (kg/m^2)	28.3 (23.7-30.7)	24.1 (21.0-27.2)	<.01
	PY10, no. (%)	4 (16.0)	14 (18.7)	.76
	Severe, no. (%)	21 (84.0)	44 (58.7)	.02
	Asthma duration (years)	16 (7.5-34.5)	15 (7-29)	.71
	Atopy, no. (%)	13 (52.0)	50 (66.7)	.19
	IgE (IU/mL)	65.3 (21-219.3)	147.6 (46.8-358.2)	.06
	FENO (ppb)	37 (19-69.5)	26 (13-42)	.09
	ICS dose (μg)	1500 (1350-1600)	1500 (600-1550)	.02
	OCS, no. (%)	6 (24.0)	13 (17.3)	.32
	%FEV$_1$ (%)	94.8 (15.3)	91.6 (19.5)	.12
	FEV$_1$/FVC (%)	71.4 (10.2)	70.1 (12.1)	.72
	%DLCO (%)	91.8 (15.6)	100.1 (19.1)	.05
	%K_{CO} (%)	119.2 (13.7)	113.8 (24.1)	.13
	RV/TLC (%)	37.1 (4.9)	38.2 (7.1)	.31
	%TLC (%)	107.8 (12.3)	116.0 (14.0)	.03
	Eosinophils (μL)	476 (109-603)	211 (112-427)	.14
	Neutrophils (μL)	4989.6 (4041.3-6151)	3555.0 (2905.7-4647.5)	<.01

FVC, Forced vital capacity; *K_{CO},* transfer coefficient of carbon monoxide in lungs; *PY,* pack years; *RV,* residual volume; *TLC,* total lung capacity.

fat mass index was associated with administering higher doses of ICS, poorer lung function, and lower physical activity. The findings of this study were consistent with the traits associated with poor clinical outcomes.[21,35,36] The association of high VF/ESM with AQLQ (S) scores was strongest among the intra- and extrapulmonary CT-derived indices, which emphasize the clinical impact of high adiposity and low muscle mass in patients with any combination of airway and parenchymal diseases.

ESM showed no correlation with impaired asthma-related QoL in male or female participants; however, ESM is an established CT-based prognostic biomarker for COPD.[37] Increased VF/ESM, indicating decrease in muscle mass relative to adiposity, was correlated with worsening of QoL after adjusting for BMI and frequent incidence of asthma-related hospitalization during the preceding year in male participants. These observations indicate that an imbalance between muscle mass and adiposity, rather than the cross-sectional area of muscle, may be correlated with a decrease in activity and exacerbation; however, causality could not be addressed because of the study's cross-sectional nature. A previous study reported that a low free fat mass index is associated with poor exercise capacity. In contrast, impaired muscle strength is associated with poor asthma control, impaired QoL,[38] and higher incidence of emergency department visits.[22] This finding indicates the differential roles of muscle mass and strength in asthma.

The quantitative assessment of adiposity or muscle can determine the specific traits of the region of interest, which may be the therapeutic or interventional target. Conversely, BMI varies among the ratio of adiposity to muscle. Symptom scores and pulmonary function tests are affected by the concomitant pathophysiology, which may not aid in ascertaining the cause of the corresponding impairments. Moreover, the relationships among intra- and extrapulmonary indices might be addressed. A decrease in VF/ESM was correlated with a high %LAV in female participants, whereas a decrease in ESM mass was correlated with a high %LAV in patients with COPD.[39] This finding demonstrates that emphysema-induced systemic inflammation decreases adiposity and muscle masses. Age can also affect body composition. Thus, future studies should explore the clinical roles of muscles and adiposity in elderly patients with asthma.

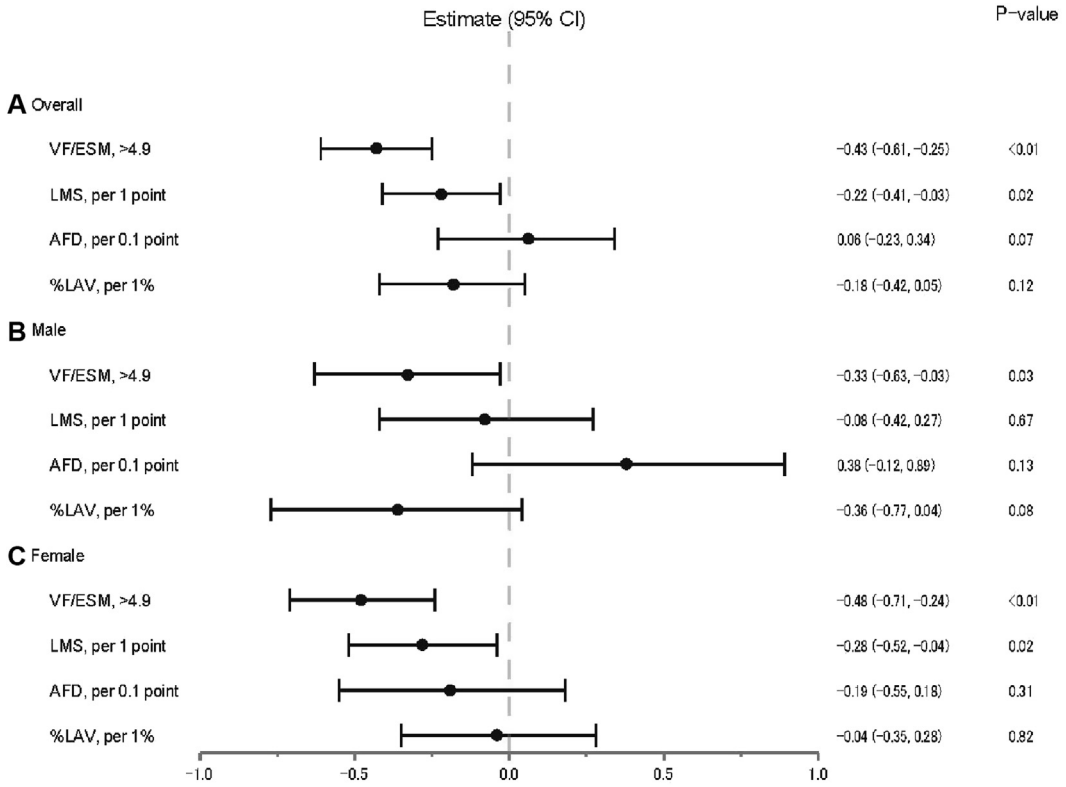

FIG 3. Relationships of VF/ESM, LMS, and intrapulmonary indices with AQLQ (S). High VF/ESM and high LMS were associated with impaired AQLQ after adjustment for intrapulmonary indices, age, sex, BMI, pack years of tobacco, and blood eosinophil count in all participants. Correlation of VF/ESM with AQLQ was confirmed by subanalysis of male and female participants.

TABLE III. Rate of hospitalization in previous year

Sex	High VF/ESM, no. (%)	Low VF/ESM, no. (%)	*P*
Male	4 (25.0)	1 (7.9)	.01
Female	4 (16.0)	9 (12.0)	.61

The correlation between low AFD (which may reflect airway diseases), high LMS score, and severe sinus-related CT findings in female participants verified the concept of one airway and one disease, which shares type 2 inflammation. A previous study reported that female patients have smaller airway luminal areas than male patients, after adjusting for height and total lung capacity, and have a more prominent effect on pulmonary function, worse symptoms, QoL, 6-minute-walk distance, and mortality, with a unit change in airway narrowing.[40] The findings of this study indicate the presence of a triad of airway diseases, sinusitis observed at CT, and impaired AQLQ scores in female patients, which is consistent with the findings of previous studies. A high LMS score was correlated with airflow obstruction in nonsmokers but not in smokers with asthma in a previous study.[18] However, an association was observed between the LMS scores and impaired AQLQ (S) scores in female participants, irrespective of pack years of tobacco in this study. Thus, the morphologic association between the upper and lower airways and AQLQ (S) scores should be elucidated considering sex, airway size, and smoking.

Novel therapies, especially those targeting type 2 inflammation, have improved asthma control in some patients. The non–type 2 phenotype can tolerate these unmet needs. A recent report proposed that a low free fat mass index. was related to a high leukocyte count in blood; however, no correlation was observed between free fat mass index. and eosinophil count in blood of patients with asthma.[21] Another study also reported that high VF was correlated with neutrophilia, impaired QoL, and frequent exacerbations.[41] This study has broadened the insight into adiposity or imbalanced body composition and inflammation, indicating that patients in the high VF/ESM group had higher neutrophil count in the blood than those in the low VF/ESM group. Moreover, increased VF/ESM was correlated with impaired AQLQ (S) scores, independent of eosinophil count in blood. Hence, the pathophysiology associated with high abdominal VF, which does not depend on type 2 inflammation, may require physical therapy to maintain activity and total control of asthma.

This study has several limitations. First, it was not a large-scale study. However, some patients with mild to severe asthma and some patients with and without smoking history were included. Moreover, almost none of the patients received therapy with biologic agents, which can significantly alter asthma's pathophysiology and clinical course. Second, longitudinal CT data were lacking; thus, there is no basis to support the benefit of the interventional approach for ameliorating body composition. Future studies should therefore confirm the robustness of VF/

ESM, VF, and ESM relationships with AQLQ (S) scores using longitudinal data sets.

In conclusion, increased abdominal VF relative to the ESM and severity of sinusitis on CT images showed associations with impaired asthma-related QoL, independent of intrapulmonary indices on CT, age, smoking status, BMI, and blood eosinophil count. These findings may broaden the insight into treatable traits, which may lead to the amelioration of the total control of asthma.

DISCLOSURE STATEMENT

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