Quantitative computed tomographic imaging–based clustering differentiates asthmatic subgroups with distinctive clinical phenotypes

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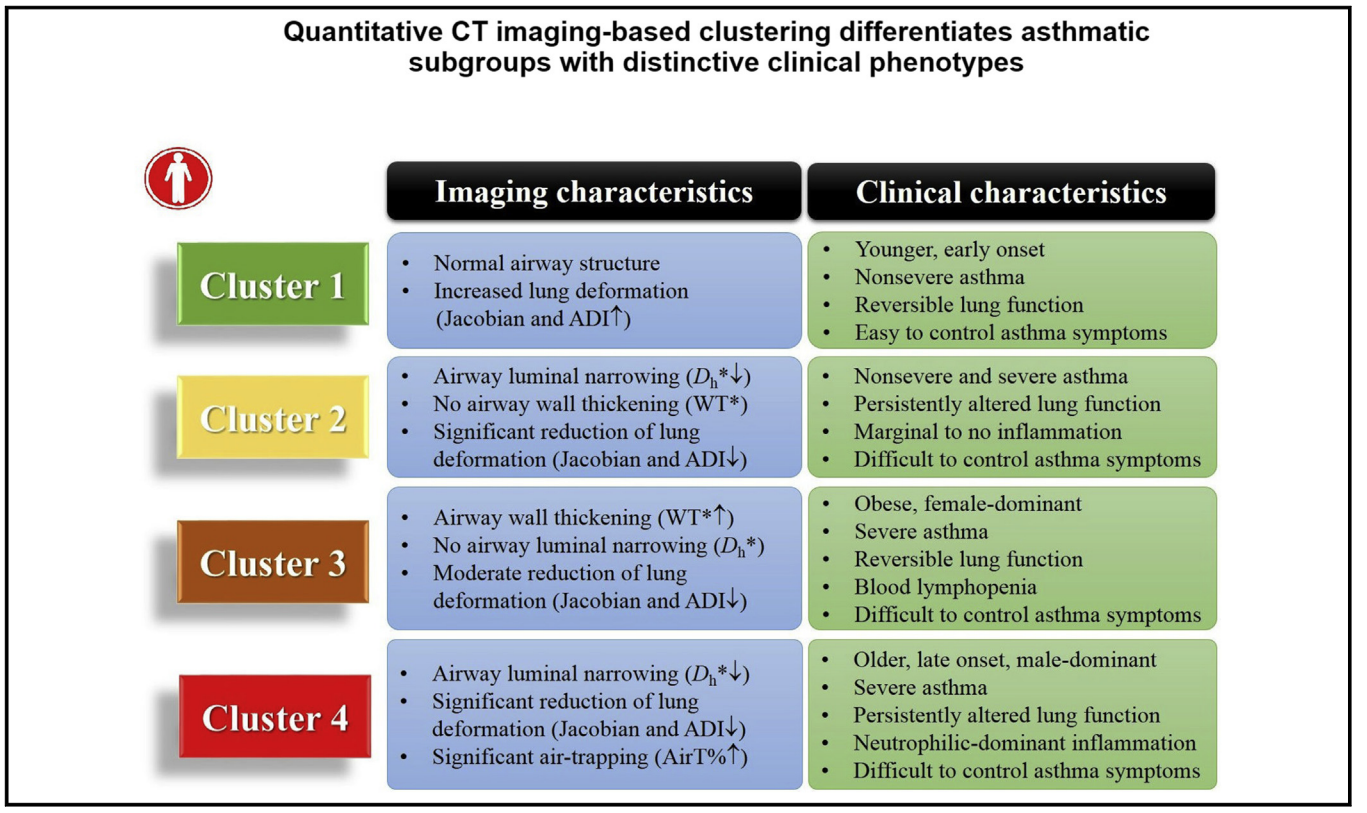
GRAPHICAL ABSTRACT



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Background: Imaging variables, including airway diameter, wall thickness, and air trapping, have been found to be important metrics when differentiating patients with severe asthma from those with nonsevere asthma and healthy subjects.

Objective: The objective of this study was to identify imaging-based clusters and to explore the association of the clusters with existing clinical metrics.

Methods: We performed an imaging-based cluster analysis using quantitative computed tomography–based structural and functional variables extracted from the respective inspiration and expiration scans of 248 asthmatic patients. The imaging-based metrics included a broader set of multiscale variables, such as inspiratory airway dimension, expiratory air trapping, and registration-based lung deformation (inspiration vs expiration). Asthma subgroups derived from a clustering method were associated with subject demographics, questionnaire results, medication history, and biomarker variables.

Results: Cluster 1 was composed of younger patients with early-onset nonsevere asthma and reversible airflow obstruction and normal airway structure. Cluster 2 was composed of patients with a mix of patients with nonsevere and severe asthma with marginal inflammation who exhibited airway luminal narrowing without wall thickening. Clusters 3 and 4 were dominated by patients with severe asthma. Cluster 3 patients were obese female patients with reversible airflow obstruction who exhibited airway wall thickening without airway narrowing. Cluster 4 patients were late-onset older male subjects with persistent airflow obstruction who exhibited significant air trapping and reduced regional deformation. Cluster 3 and 4 patients also showed decreased lymphocyte and increased neutrophil counts, respectively.

Conclusions: Four image-based clusters were identified and shown to be correlated with clinical characteristics. Such clustering serves to differentiate asthma subgroups that can be used as a basis for the development of new therapies. (J Allergy Clin Immunol 2017;140:690-700.)

Key words: *Computed tomography, image processing, severe asthma, air trapping, image registration, luminal narrowing, wall thickening, airway circularity, cluster analysis, neutrophilic asthma*

Abbreviations used

ACQ: Asthma Control Questionnaire
ACT: Asthma Control Test
ADI: Anisotropic deformation index
AirT%: Air-trapping percentage (residual gas at expiration)
AQLQ: Asthma Quality of Life Questionnaire
BAL: Bronchoalveolar lavage
BMI: Body mass index
BronInt: Right intermediate bronchus
Cr: Airway luminal circularity
D_h: Hydraulic luminal diameter
FRC: Functional residual capacity
ICS: Inhaled corticosteroid
LA: Airway luminal area
OCS: Oral corticosteroid
PCA: Principal component analysis
PFT: Pulmonary function test
QCT: Quantitative computed tomography
RMB: Right main bronchus
SARP: Severe Asthma Research Program
sLLL: Subgrouped left lower lobe with branches of LB6 and LB8 to LB10
sLUL: Subgrouped left upper lobe with branches of LB1 to LB5
sRLL: Subgrouped right lower lobe with branches of RB6 to RB10
sRML: Subgrouped right middle lobe with branches of RB4 to RB5
sRUL: Subgrouped right upper lobe with branches of RB1 to RB3
TA: Airway total area
θ: Bifurcation angle
TLC: Total lung capacity
ΔV_{air}^{F}: Lobar fraction of air volume change between TLC and FRC
WA%: Airway wall area percentage (ie, the ratio of wall area to total area)
WT: Airway wall thickness

As a multicenter study of severe asthma, the Severe Asthma Research Program (SARP) has established genetic, environmental, and clinical variables for characterization of asthma phenotypes, leading to a better understanding of asthma pathology.[1-6] For instance, Moore et al[2] have used only clinical variables in a cluster analysis to derive clinical clusters. Their study has also defined "simple" clinical clusters (80% accuracy of original clusters) with only 3 factors, including age of asthma onset and prebronchodilator and postbronchodilator FEV_1. Moore et al[7] recently performed another cluster analysis using inflammatory biomarkers in addition to clinical characteristics, leading to 4 asthma subgroups. Although quantitative computed tomography (QCT) of the lungs has been an important component of SARP, imaging variables have not been explored as the basis for identifying patient clusters. Only a limited set of available QCT metrics has been exploited, with not only SARP but also most of the multicenter studies incorporating QCT of the lungs. In this context the objective of this study was to develop imaging-based asthma clusters using a variety of imaging-based variables reflecting airway and parenchymal pathologies at multiscale levels.

Multiscale imaging-based cluster analysis uses a set of QCT-based segmental airway (local scale) and lung and lobar-based (global scale) density and shape-based variables[8-10] to identify clinically meaningful patient clusters. The rationale behind multiscale imaging-based cluster analysis is that structural and functional alterations can occur regionally, globally, or both. Thus it is necessary to analyze variables at multiple scales to capture a wide spectrum of disease states. QCT[11-18] has identified structural and functional variables that, in isolation, distinguish patients with severe asthma from healthy subjects and those with nonsevere asthma and further correlate with physiologic and clinical parameters. For instance, it has been found that airway luminal area (LA)[19] decreases and airway wall area percentage (WA%)[20] and air-trapping percentage (AirT%)[21,22] increase mostly in patients with severe asthma, showing significant correlations with FEV_1. The observed structural and functional alterations are aligned with the pathophysiology of asthma, such as airway narrowing, chronic inflammation, small-airway disease, and reduced elastic recoil.[23,24] A strength of imaging in the study of asthma is its ability to extract regional measurements because obstruction has been shown to be regionally heterogeneous.[21,25] In addition, these noninvasively acquired imaging biomarkers can be followed for the longitudinal assessment of therapies directed against bronchial wall thickening and air trapping.