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Quantitative computed tomography applied to interstitial lung diseases

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ABSTRACT

Objectives: To evaluate a new image marker that retrieves information from computed tomography (CT) density histograms, with respect to classification properties between different lung parenchyma groups. Furthermore, to conduct a comparison of the new image marker with conventional markers.

Materials and methods: Density histograms from 220 different subjects (normal = 71; emphysema = 73; fibrotic = 76) were used to compare the conventionally applied emphysema index (EI), 15^{th} percentile value (PV), mean value (MV), variance (V), skewness (S), kurtosis (K), with a new histogram's functional shape (HFS) method. Multinomial logistic regression (MLR) analyses was performed to calculate predictions of different lung parenchyma group membership using the individual methods, as well as combinations thereof, as covariates. Overall correct assigned subjects (OCA), sensitivity (sens), specificity (spec), and Nagelkerke's pseudo R^2 (NR^2) effect size were estimated. NR^2 was used to set up a ranking list of the different methods.

Results: MLR indicates the highest classification power (OCA of 92%; sens 0.95; spec 0.89; NR^2 0.95) when all histogram analyses methods were applied together in the MLR. Highest classification power among individually applied methods was found using the HFS concept (OCA 86%; sens 0.93; spec 0.79; NR^2 0.80). Conventional methods achieved lower classification potential on their own: EI (OCA 69%; sens 0.95; spec 0.26; NR^2 0.52); PV (OCA 69%; sens 0.90; spec 0.37; NR^2 0.57); MV (OCA 65%; sens 0.71; spec 0.58; NR^2 0.61); V (OCA 66%; sens 0.72; spec 0.53; NR^2 0.66); S (OCA 65%; sens 0.88; spec 0.26; NR^2 0.55); and K (OCA 63%; sens 0.90; spec 0.16; NR^2 0.48).

Conclusion: The HFS method, which was so far applied to a CT bone density curve analysis, is also a remarkable information extraction tool for lung density histograms. Presumably, being a principle mathematical approach, the HFS method can extract valuable health related information also from histograms from complete different areas.

1. Introduction

With the recent introduction of radiomics [1,2] into the field of radiology reliable techniques for quantitative image markers obtained additional interest. The motivation to explore new image features is to enrich conventional methods to maximize information extraction from image data, so that additional knowledge is generated, which can potentially improve the diagnosis accuracy for patients. In the diagnostics of interstitial lung diseases, many image markers analyze frequency distributions of Hounsfield units (HU) of computed tomography (CT) images. Such markers are for instance the emphysema index (EI) [3–7], percentile value (PV) [8,9], mean value (MV), variance (V), skewness (S), and kurtosis (K) [10–12]. A recently developed density curve analysis method is the histogram's functional shape (HFS) method, which describes the shape of a transformed CT density histogram by using nonlinear function fits [13]. This HFS method was applied so far in an age-at-death estimation project in forensic medicine, were it appeared as a very helpful tool to extract age related information from CT density curves of skull caps.

In this study, it is at first investigated if the HFS method can retrieve useful information of CT lung density curves that enable a classification between the lung morphology groups normal, emphysema, and fibrosis.

At second, an image marker competition is set up where the EI, PV, MV, V, S, K, and HFS methods are evaluated with respect to their classification capabilities to attribute subjects to one of the three named lung parenchyma groups. Multinomial logistic regression (MLR) is used to calculate the classification predictions for the different lung morphology groups, where the covariates of the MLR are based on the EI,

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PV, MV, V, S, K, and HFS results [13–18]. The degree of correct or false attributed subjects, sensitivity, and specificity are estimated. A judgment of the classification properties of the various methods is performed, evaluating 21 different MLR models, which used the individual image marker methods, as well as combinations thereof, as covariates in the MLR. Results of a “test” (n = 158 subjects) and a “validation group” (n = 62) are compared on the basis of the ranking performance in the MLR model competition.

The hypothesis behind this study is that the HFS method is capable to improve the information extraction from CT density curves in the context of interstitial lung diseases. It is assumed that the rather novel HFS concept enriches existing image marker concepts, and that it can be used as helpful additional radiomic image marker. Twenty one MLR model calculations are reported in detail so that the reader can judge the classification properties of each model precisely. Seven MLR model calculations show the seven different image markers studied individually; 14 MLR models present combinations of image marker evaluations, so that potential synergistic effects between image markers can be found. Hence, the general purpose of this study is the improvement of numerical tools that can extract health related information from density histograms and that can serve as image markers in radiomics analyses.

2. Materials and methods

2.1. Patients

The retrospective study was approved by the local ethic committee of the University. Written consent of patients was waved. Patient data were selected from January 2011 to April 2016 using the University’s Radiological Information System and Picture Archiving and Communication System. A database search was performed to reveal 158 patients of a “test group‘ (98 men; 60 women; overall mean age 60 ± 15 years) and of 62 patients of a “validation group“ (33 men; 29 women; overall mean age 62 ± 16 years) in whom a CT of the thorax was performed and with a radiologically confirmed diagnoses of one of the following inclusion criteria: normal lung parenchyma, emphysema, or fibrosis. Patient data were attributed randomly to the “test” and the ‘validation group’. Two radiologists (one with 10 years of experience, one with 20 years of experience) attributed the data sets in concordance to the different patient groups. “Normal’ was diagnosed by the absence of any visible pulmonary abnormality or pathology of macroscopic pulmonary structures (bronchial, pleural, large vessels) or small structures as distribution of tissue, vessels or air. ‘Emphysema’ was diagnosed according to the definitions of centrilobular, panlobular, and paraseptal emphysema. Other diseases, leading to low-attenuation patterns (missing lung destruction, mosaic perfusion, cystic lung diseases), were carefully excluded. The diagnosis of fibrosis was based on the clinical suspicion of an idiopathic interstitial pneumonia (IIP) or lung fibrosis with known etiology and radiological criteria of fibrosis. According to the classification of the American Thoracic Society and the European Thoracic Society of IIP, only patterns of major IIP with fibrotic morphology as non-specific interstitial pneumonia (NSIP) and idiopathic pulmonary fibrosis (usual interstitial pneumonia (UIP)-pattern) were included. Non-fibrotic IIP (smoke related as respiratory bronchiolitis - interstitial lung disease and desquamative interstitial pneumonia, and (sub-) acute IIP (acute interstitial pneumonia or cryptogenic organizing pneumonia), rare IIP (lymphocytic interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis), as well as non-classifiable diseases, were not included in the study. Cases of lung fibrosis with known etiology (i.e. drug-toxicity, asbestosis, collagenosis) with typical patterns of UIP or NSIP were included in the study. Patients with combined pulmonary fibrosis and emphysema were excluded. Table 1 shows the gender and age distribution of the different lung parenchyma groups.

2.2. CT imaging

Imaging was performed with a 64- or a 40- section multidetector CT scanner (Somatom Force (Dual Source; 29 examinations from test and validation group) or Somatom Definition AS; 191 examinations from test and validation group; Siemens Medical Systems, Erlangen, Germany). The following protocol was used: supine position, head first; deep inspiration; range: apex to diaphragm; 120 kV; tube current was adjusted depending on body weight: < 75 kg: 25 mAs; > 75 kg: 45 mAs on the 64 MSCT; and 50 mAs on the 40 MSCT; pitch 1.2; slice reconstruction thickness 1 mm. On both scanners image reconstructions were performed using filtered back projection kernel B50f into a 512 × 512 voxel matrix.

2.3. Lung segmentation

The software package MEVIS Pulmo 3D (Version 3.6.1, Fraunhofer MEVIS, Bremen, Germany), was used for the lung segmentation and the density histogram calculation, which was defined as frequency of voxels as function of HU [19,20].

2.4. Image marker calculations

All image marker methods were implemented in a computer program, using the image analysis software IDL®, Version 8.4, Exelis Visual Information Solutions, Boulder, CO, USA.

2.4.1. EI concept

The percent EI was calculated as follows from the density histogram data of a segmented lung:

$$EI = \frac{\text{number of voxels having a HU} \leq -950}{\text{number of voxels of the complete HU range}} * 100.$$

2.4.2. PV concept

PV is defined as the HU value that corresponds to the value of 0.15 on the y-axis of a normalized cumulative lung density histogram, which corresponds to the 15$^{\text{th}}$ percentile value.

2.4.3. MV, V, S and K concepts

The standard statistics parameters MV, V, S, and K were estimated using the “MOMENT” function of the IDL program package. This function was applied to the density histogram’s data as input.

2.4.4. HFS concept

At first, a cumulative histogram was calculated from the density histogram from the MEVIS Pulmo 3D lung segmentation results. Next, the cumulative frequencies of the histogram were normalized to 1. These calculations define a normalized cumulative histogram with values in the range from 0 to 1 on the frequency-axis, which is the y-axis. This axis is labeled “normalized frequency” on later shown line graphs, Fig. 1. The original HU-scale, the x-axis, of the density histogram laid in the range from −1024 to 150 HU. This scale was shifted so that it began at a value of 0, which is labeled “shifted HU” on the resulting line graphs. Henceforth, such normalized and x-axis shifted cumulated histograms are called “transformed histograms”.

After that, a transformed histogram was fitted to a logistic growth function, which was introduced by Verhulst [21].

$$\mathbf{y} = \frac{1}{A_0 A_1^{\mathbf{x}} + A_2} \tag{1}$$

Here, **y** corresponds to the normalized cumulative frequency of a transformed histogram, **x** are the shifted HU values, and A_0, A_1, and A_2 are the fit-parameters. To enable the estimation of the fit-parameters, a curve fit algorithm needs initial values of the fit-parameters, so that it can optimize the fitted function to the measured transformed histogram