**Automated MR-based Lung Volume Segmentation in Population-based Whole-Body MR Imaging: Correlation with Clinical Characteristics, Pulmonary Function Testing and Obstructive Lung Disease**

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**Key Points**

* Although whole-body MRI often does not include dedicated lung sequences, lung volume can be automatically derived using dedicated segmentation algorithms
* Lung volume derived from whole-body MRI correlates with typical predictors and risk factors of respiratory function including smoking and represents about 65% of total lung capacity and 125% of the functional residual capacity
* Lung volume derived from whole-body MRI is independently associated with residual volume and the ratio of forced expiratory volume in 1 second to forced vital capacity and may allow detection of obstructive lung disease

**Key words (MESH):**

Magnetic Resonance Imaging, Whole Body Imaging, Computer-Assisted Image Analysis, Pulmonary Function Test, Obstructive Lung Disease

**Abbreviations:**

|  |  |
| --- | --- |
| AUC | Area under the curve |
| BMI | Body mass index |
| BSA | Body surface area |
| CAT | COPD Assessment Test |
| COPD | Chronic obstructive pulmonary disease |
| CT | Computed tomography |
| FEF25-75 | Forced expiratory flow between 25% and 75% of FVC |
| FEV1 | Forced expiratory volume in one second |
| FRC | Functional residual capacity |
| FVC | Forced vital capacity |
| MRI | Magnetic resonance imaging |
| PFT | Pulmonary function testing |
| ROC | Receiver operating characteristic |
| RV | Residual volume |
| TLC | Total lung capacity |
| TLCO | Transfer factor of the lung for carbon monoxide |
| VA | Alveolar volume |

**ABSTRACT**

**Objectives:** Whole-body MR imaging is increasingly utilized. Although dedicated lung sequences are often not included, the chest is typically imaged and lung volumes can be derived. Our objective was to determine the clinical utility of lung volumes derived from non-dedicated MRI sequences in the population-based KORA-FF4 cohort study.

**Methods:** A total of 400 subjects (56.4±9.2years, 57.6% males) underwent whole-body MRI including a coronal T1-DIXON-VIBE sequence in inspiration breath-hold, originally acquired for fat quantification. Based on MRI, lung volumes were derived using an automated framework and related to common predictors, pulmonary function tests (PFT; spirometry and/or pulmonary gas exchange, n=214) and obstructive lung disease.

**Results:** MRI-based lung volume was 4.0±1.1L, which was 64.8±14.9% of the predicted total lung capacity (TLC) and 124.4±27.9% of the predicted functional residual capacity. In multivariate analysis, it was positively associated with age, male, current smoking, and height. Among PFT indices, MRI-based lung volume correlated best with TLC, alveolar volume (VA), and residual volume (RV; r=0.57 each), while it was negatively correlated to FEV1/FVC (r=0.36) and transfer factor for carbon monoxide (r=0.16). Combining the strongest PFT parameters, RV and FEV1/FVC remained independently and incrementally associated with MRI-based lung volume (β=0.50, p=0.04 and β=-0.02, p=0.02, respectively) explaining 32% of the variability. For the identification of subjects with obstructive lung disease, height-indexed MRI-based lung volume yielded an AUC of 0.673-0.654.

**Conclusion:** Lung volume derived from non-dedicated whole-body MRI is independently associated with RV and FEV1/FVC, after accounting for well-known predictors and typical risk factors of respiratory function. Furthermore, its moderate accuracy for the detection of obstructive lung disease indicates it may be a promising tool to assess pulmonary health in whole-body imaging when pulmonary function tests are not available.

# **INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality; in 2015, about 3.2 million deaths worldwide were estimated to be associated with COPD, making it one of the most common causes of death [1]. Economic costs attributable to COPD and its sequelae amounted to $32.1 billion in 2010, in the US alone [2]. In view of still limited therapeutic options, early detection and treatment are crucial for slowing down disease progression and decreasing the number of exacerbations and hospitalizations [3; 4].

Pulmonary function testing (PFT) plays a crucial role in the diagnosis, severity estimation, and monitoring of COPD; it is the basis for the assessment of lung function [5]. Beyond respiratory symptoms and a history of exposure, a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) below 0.7 is the cornerstone of COPD diagnosis [6]. Beside PFT, imaging plays a more significant role in assessing, grading, and monitoring of pulmonary disease. The mainstay of lung imaging is classical computed tomography (CT). However, magnetic resonance imaging (MRI) has become a reliable, radiation-free alternative in research and clinical settings. It is the preferred imaging modality, when repetitive scans are necessary, e.g. in cystic fibrosis [7], infectious diseases, and in immunosuppressed patients [8]. In 1998, Gierada et al. were the first showing that MR measurements are as accurate as CT measurements to determine lung volumes in patients with emphysema [9]. Furthermore, MR imaging could be used to detect paradoxical diaphragmatic motion in patients with emphysema [10]. Another group included subjects with pulmonary emphysema as well as patients undergoing lung volumes reduction surgery, to prove that dynamic breathing MRI in comparison to xenon-133 single-photon emission CT is feasible to noninvasively assess impaired respiratory mechanisms [11; 12].

Recently, other studies have been conducted using dedicated, non-clinical, helium-enhanced MR scanning. Such complex MR scans are moderately correlated with selected PFT values (r=-0.61 with percentage predicted transfer factor of the lung for carbon monoxide (TLCO); r=0.47 with percentage predicted functional residual capacity [FRC]) and revealed strongly associated with COPD [13]. However, helium-enhanced scans are more cost-intensive, time-consuming and only available at specialized centers.

Whole-body MRI today has a broad and increasing spectrum of applications [14]. Typical uses for whole body MRI include oncological diseases, e.g. lymphoma [15], multiple myeloma [16], and musculoskeletal applications such as rheumatoid arthritis [17]. It is also increasingly employed in children, as well as adults, given the lack of radiation [18], high tissue contrast - even without contrast agents, and the low rate of side effects. For the same reason, whole-body MR imaging is offered as a screening tool for patients with defined risk factors like genetic disorders [19] or for check-up examinations [20].

Besides these clinical applications, whole-body MR imaging is increasingly used in population-based cohort studies to derive imaging-based risk markers such as e.g. visceral adipose tissue, and in novel Radiomics aimed at subclinical states and personalized medicine [21]. Two large ongoing population-based imaging studies are the UK-Biobank aiming for 100,000 and the German National Cohort aiming for 30,000 whole-body MR exams [22; 23]. However, these two MR protocols do not include dedicated MR lung sequence. Nevertheless, the lungs are part of the fields imaged, and thus may enable a degree of assessment. There is some evidence that non-dedicated MR imaging of the lung may provide useful insights in lung and its diseases [24].

Thus, our objective was first, to examine the feasibility of deriving lung volumes automatically from whole-body MR data as acquired in a population-based cohort, and second, to assess the correlation of MR-based lung volume with PFT parameters. In a secondary, explorative analysis we sought to evaluate the association with obstructive lung disease.

**METHODS**

*Study Design and Population*

The study was designed as a prospective case-control study nested in a cohort from the “Cooperative Health Research in the Region of Augsburg” (KORA). As described elsewhere, KORA is a longitudinal, epidemiological cohort study with several follow-up examinations representing a broad sample from the general population in the region of Augsburg, Germany [25]. As part of the FF4 follow-up examination, subjects were enrolled in an MRI sub-study (n=400) if no contraindications to either MRI or gadolinium contrast administration existed [26]. In addition, a subset underwent PFT also as part of the FF4 examination. The study was approved by the institutional review board of the medical faculty of Ludwig-Maximilian University Munich, and all participants gave their written informed consent.

*Clinical Characteristics*

The KORA FF4 examination took place between June 2013 and September 2014 at the KORA study center [26]. Presence of obstructive lung disease was defined as FEV1/FVC <70% or as a self-reported physician diagnosis of COPD/emphysema. For subjects with self-reported COPD/emphysema, the standardized COPD Assessment Test (CAT) was performed and information regarding disease exacerbation within the last 12 months was collected [27]. Anthropometric data and information on smoking history, number of pack-years, as well as further diagnoses such as prediabetes, diabetes, hypertension were collected in a standardized fashion as part of the KORA study design as described elsewhere [25; 26].

*Whole-Body MR Imaging*

As described previously, whole-body MRI scans were performed with a 3 Tesla MR system (Magnetom Skyra, Siemens Healthcare) [26]. The whole-body MRI protocol comprised sequences covering the entire body (from neck to below hip) for tissue/organ quantification but also included sequences dedicated to a particular organ such as for cardiac or brain. The lung was covered by a 2-point DIXON T1 sequence in submaximal inspirational breath hold with an acquisition time of 15 s, coronal acquired with a slice thickness of 3 mm. A further parameter of this sequence was a field of view of 488 x 716, a matrix of 256 x 256, a repetition time of 4.06 ms and an echo time of 1.26 ms.

*MR Image Analysis for Lung Volumes*

The analysis was performed in a blinded fashion by an automated framework, which was outlined in detail by Ivanovska et al. [28]. The lung segmentation algorithm consisted of the following steps: (1) Correction of intensity inhomogeneities, (2) Pre-extraction of a coarse region of interest containing the airways, (3) Segmentation of the bilateral lung and trachea regions, (4) Trachea extraction and lung separation (right and left lung), and (5) Lung region refinement. Pulmonary vessels outside the mediastinal contours were included in the lung region (see example in **Appendix E1**). After the automated processing of the whole set of MRI scans, the results have been visually checked by an independent reader, unaware of the clinical covariates. High-quality outputs of the aforementioned framework could thus be verified.

*Pulmonary Function Test (PFT)*

Pulmonary function parameters vary with age, standing height, sex and ethnicity. Therefore, all test results including TLC and FRC were compared to predicted values according to the Global Lung Function Initiative [29]. Lower and upper limits of normal were appropriate for the individuals being tested.

Pulmonary function tests were performed in line with the American Thoracic Society and European Respiratory Society recommendations [30; 31]. PFT parameters were categorized into three groups: (1) “Volumes” comprising residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC), alveolar volume (VA), and FVC; (2) “Obstruction” comprising FEV1/FVC (%), forced expiratory flow between 25% and 75% of FVC (FEF25-75, in l/s) and (3) “Gas Exchange” covering TLCO and TLCO/VA. Airflow limitation in subjects with FEV1/FVC<70% was further classified into spirometric grades based on the percentage of predicted FEV1 using prebronchodilator values following modified GOLD criteria (grade 1 as FEV1≥80% predicted (“mild”), grade 2 as 50%≤FEV1<80% (“moderate”), grade 3 as 30%≤FEV1<50% (“severe”), grade 4 as FEV1<30% (“very severe”)) [6].

Flow-volume curves were obtained using a pneumotachograph-type spirometer (MasterScope, Jaeger). Subjects performed at least 3 and up to 8 spirometric maneuvers to obtain a minimum of two acceptable and reproducible values. TLCO was determined using the single-breath technique. Subjects performed a maximum of 5 trials to achieve a minimum of two acceptable and reproducible values with an effective breath hold time within 10±2 seconds according to ATS/ERS recommendations [32]. TLCO results were adjusted for hemoglobin obtained from blood samples collected on the day of the physical examination in the study center [33].

*Statistical Analysis*

Continuous variables were summarized as means and standard deviations and categorical variables as counts and percentages. Differences between subgroups were assessed by t-test or chi2-test and correlation using Pearson correlation coefficients.

Associations between clinical characteristics and MR-based lung volume were evaluated by linear regression analysis estimating β-coefficients with 95% confidence intervals for unadjusted, age and sex-adjusted and fully adjusted models. The fully adjusted model included age and sex plus all co-variables (body mass index (BMI), height, weight, body surface area (BSA), smoking status, pack-years, diabetes status, HbA1c, hypertension) with p<0.10 in univariate analysis, in case of co-linearity parameters with variance inflation factor >10 were stepwise removed. The same model was used to assess the association of clinical characteristics with PFT parameters. Further, PFT parameters were associated with MR-based lung volume separately in age- and sex-adjusted and fully adjusted linear regression models. In a final model, best-associated PFT parameters from each PFT parameter group (volumes, obstruction and gas exchange) were included simultaneously together with clinical characteristics to predict MR-based lung volume. R2 was used as a goodness of fit statistic and served as a measure of how much variance of the outcome variable was explained by exposure variables included in the statistical model. Total adjusted r2 was calculated to evaluate the fit of the overall model and partial r2 was calculated to evaluate the proportion of explained variance by each single exposure variable in the model. Normal distributions of residuals were checked graphically.

Receiver operating characteristic (ROC) curves for detecting obstructive disease (either defined by past medical history or by FEV1/FVC<0.70) were calculated separately for MR-based lung volume and RV as derived from PFT. Area under the curve (AUC) values were compared by Likelihood-ratio test.

A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata 14.1 (Stata Corporation).

**RESULTS**

A total of 400 subjects without a clinical history of cardiovascular disease underwent whole-body MR imaging. Complete results regarding MR-based lung volumes were derived automatically from 396 subjects (**Figure 1**). Four subjects had to be excluded because of inadequate image quality. Patients´ characteristics are shown in **Table 1**. Briefly, the cohort consists of middle-aged subjects (56.4±9.2 years) with a slightly higher number of males than females. 20.0% were current smokers and additional 43.4% former smokers; the number of pack-years of current and former smokers was 12.9±18.8. In 26% of these subjects, the number of pack-years was beyond 20. A self-reported physician diagnosis of COPD and/or emphysema was present in 21 participants (5.3%). Mean CAT score in these patients was 11.5±6.5; 5 subjects reported ≥1 exacerbation within the last 12 months, in 3 subjects requiring hospitalization or emergency department visit. PFT was performed in 214 subjects, this subset was on average older (58.2±5.7 vs. 54.2±11.7 years, p<0.001), and had a higher percentage of COPD (7.9% vs. 2.2%, p=0.01) compared to subjects without PFT data; all other patients´ characteristics did not differ (**Table 1**). Average TLC was 6.24±1.23L, FRC 2.86±0.68L, and RV 2.13±0.39L while 22.4% had a FEV1/FVC<70%. Of subjects with FEV1/FVC<70% (n=48), 75% had an airflow limitation of spirometric grade 1 and 25% of spirometric grade 2, higher spirometric grades were not observed.

*MR-based Lung Volumes and Correlation with Clinical Characteristics*

Based on the whole-body MR scan, total lung volume was 4.0±1.1 L; on average, the right lung volume was larger than the left lung volume (2.18±0.59 L and 1.82±0.54 L, p<0.001 respectively). Overall, the MR-derived lung volume corresponded to 64.8±14.9% of TLC and 124.4±27.9% of the FRC predicted from reference equations.

As expected, MR-derived lung volumes were significantly higher in males than in females (all p<0.001; **Figure 2**), and correlated positively with different anthropometric measures including height, weight, and BSA (**Table 2**). Otherwise, MR-based lung volumes were significantly higher in current smokers compared to never-smokers (4.25±1.11 vs. 3.80±1.20 L, p=0.007), and correlated positively with pack-years (r=0.22, p<0.001). In contrast, traditional cardiovascular risk factors including hypertension did not correlate with MR-based lung volume. In multivariate analysis, MR-based lung volume was positively associated with age, current smoking, male sex, and body height, and inversely with BMI (**Table 2**). These associations did not differ if using only right or left lung volume (data not shown).

*Correlation between MR-based Lung Volumes and Pulmonary Function Testing*

Using PFT parameters as a reference standard, MR-based total lung volume correlated best with TLC (r=0.57), VA (r=0.57), and RV (r=0.57), followed by FVC, FRC, and TLCO (**Figure 3**) while FEV1/FVC and TLCO/VA were negatively correlated with MR-based total lung volume. No significant correlation was observed for FEF25-75 with MR‑based total lung volume (p=0.51; **Figure 3**). Comparing the association pattern of predictors and MR-based lung volume, it was more similar to the pattern of “PFT Volumes” as compared to “PFT Obstruction” and “PFT Gas Exchange” (**Figure 4**).

In linear regression with adjustment for predictors, MR-based lung volume was most strongly associated with RV in the group of “PFT Volumes,” with FEV1/FVC in the group “PFT Obstruction”, and with TLCO/VA in the group of “PFT Gas Exchange” (**Table 3**). Including these three PFT-parameters in a combined, multivariate model, RV and FEV1/FVC were independently and incrementally associated with MR-lung volume, while TLCO/VA became not significant (**Table 4**). Altogether, the model explained 43% of the variability of the MR data (32% without co-variates) while the partial r2 was slightly higher for FEV1/FVC than for RV (0.026 vs. 0.022, respectively). The association of PFT-derived parameter with MR-based total lung volume did not improve replacing RV in the multivariate model by TLC or FVC (data not shown).

*MR-based Lung Volumes between subjects with and without Obstructive Lung Disease*

Of the entire cohort, 21 subjects (5.3%) reported a physician diagnosis of COPD (n=20) or emphysema (n=1). In the PFT subgroup, 48 subjects (22.4%) had FEV1/FVC <70% (FEV1/FVC 63.8±6.6%). In both groups, subjects with airflow obstruction (defined by self-reported diagnosis or FEV1/FVC<0.70) had higher MR-based lung volumes than those without (**Figure 5**).

MR-based lung volume (indexed by height) yielded an AUC of 0.673 for FEV1/FVC <70% and 0.654 for COPD/emphysema diagnosis. Compared to PFT-derived RV, MR-based lung volume was slightly more sensitive but less specific, however without significant difference in AUC (**Figure 6**; 0.688 vs. 0.673, p=0.72). At a predefined sensitivity of 75% for FEV1/FVC <70%, the corresponding specificity was 49% at a cut-off of 2.17 L/m for height-adjusted, MR-based total lung volume.

**DISCUSSION**

In our cohort of subjects without a history of cardiovascular disease drawn from a general population, lung volume derived from non-dedicated MRI sequences was feasible and associated with traditional pulmonary risk factors including smoking status and pack-years. Furthermore, as being well established [29], MR-based lung volume was positively associated with age, sex, and height. In addition, an inverse relationship with BMI was observed, most likely due to the fact, that in the supine position, abdominal pressure on the thorax/lung increases with increasing abdominal adiposity. MR-based lung volume represented, on average, two-thirds of predicted TLC and about a quarter more (124%) than the predicted FRC – due to the applied procedure - and was independently associated with PFT measures of increased RV but also of reduced FEV1/FVC as a measure for obstructive airway disease. Accordingly, MR-based lung volume showed discriminative value for COPD.

COPD is a major medical challenge due to its high morbidity and mortality. This is expected to increase over the coming decades [34]. The main problem in the work-up of COPD patients is the lack of tools enabling early detection, as diagnosis usually occurs when lung capacity has already been reduced by at least 50% [35; 36]. On the other hand, early treatment can prevent disease progression and improve quality of life [37]. Therefore, having new methods for early detection of COPD, preferably in a subclinical phase, is key to managing the disease burden. Previous studies assessing lung volume from non-dedicated whole-body imaging were commonly based on CT imaging [24]. Alternatively, dedicated lung MR imaging is available, which carries no radiation burden, but is technically challenging due to the lower quantity of protons in lung tissue and the loss of signal caused by field inhomogeneity between water and air [38]. Dedicated lung protocols have been developed to overcome these limitations – such as hyperpolarized helium used as an aerosol to further increase MRI signal in dedicated lung imaging [39]. However, for several reasons, such specialized protocols are often not available in whole-body MRI. Today, whole-body MRI is routinely performed in wide clinical settings. It is increasingly used in screening examinations and epidemiological investigations. Thus, large amounts of lung data are being generated that have so far been underutilized for the assessment of the lung.

In our study, MR-based lung volume reflected two-thirds of predicted TLC and about a quarter more than the predicted FRC. Several factors may explain the discrepancies between MR-based lung volumes and the predicted values of TLC and FRC. First, MR-based lung volumes were acquired with a standard breathing instruction for MRI “breath out, breath in and hold your breath”. A few previous studies have shown that breathing instruction routinely used for MR or CT imaging may reflect a submaximal inspiration in contrast to TLC which is based on maximal inspiration and FRC which is defined as the remaining volume at the end of tidal expiration [40; 41]. Second, MR-based values are derived in supine position compared to prone positioning in PFT, on which the predicted values of TLC and FRC are predicated on.

Further, MRI-derived lung volume demonstrated the strongest independent association with residual volume and FEV1/FVC. Whereas FEV1/FVC is the classical parameter for the definition of airway obstruction, residual volume is considered a marker for hyperinflation in obstructive lung diseases. In COPD patients, RV is of unique prognostic value [42]. For the correlation of MR-derived with PFT-derived lung volumes, our study, using non-dedicated whole-body MRI, revealed results comparable to findings by Matin et al. using dedicated, helium-enhanced MR lung imaging (correlation to FRC: r=0.53 vs. r=0.47 for non-dedicated vs. dedicated MR lung imaging; correlation to FEV1/FVC: r=-0.36 vs. r=‑0.37 or non-dedicated vs. dedicated MR lung imaging) [13]. In contrast, dedicated helium-enhanced MR lung imaging showed better correlation with PFT gas exchange parameters, such as TLCO (r=0.40 vs. r=0.61 for non-dedicated vs. dedicated MRI) [13]. This is expected, since helium-enhanced MRI is based on diffusion-weighted imaging, and is therefore a measurement of Brownian motion of the HE atoms independent of lung volumes [43].

Certain limitations warrant mention. First, our sample size is relatively small with a limited number of clinically diagnosed COPD and the cohort does not include subjects with severe COPD. Although the sample is drawn from a general population, it may have limited generalizability. Second, only patients without the history of cardiovascular disease were included in the study, although there is a well-described relationship between COPD and cardiovascular disease including an overlap of common risk factors between both. Consequently, the prevalence of these risk factors among patients without COPD may have been artificially low in our study cohort, which potentially further increased the discriminatory power of these risk factors in our data.

Our study - an epidemiological cohort - introduces the possibility of deriving lung volumes based on a short, non for lung imaging dedicated T1-Dixon sequence, which is further associated with traditional risk factors and COPD. Although PFT and dedicated MR lung imaging remain the gold standard, this kind of imaging analysis can be applied to large samples as part of population-based cohort studies or personal screening exams without the necessity of specific breathing maneuvers and thus only low requirements for participant cooperation. In such settings, measuring lung volumes derived from MRI potentially identifies a significant portion of patients requiring a functional diagnostic work-up for obstructive lung disease. Automatic procession of the MRI data is critical for acceptance in clinical routine. The automated framework used in this study enables rapid calculation of MR-based lung volume data that can be readily assessed and reported. We further show that MR-based lung volume derived by non-dedicated imaging is associated with typical risk factors for COPD/emphysema, like tobacco use, age, and body-height [44; 45]. Furthermore, there is an inverse correlation with BMI, which can be protective against exacerbations and the diagnosis of emphysema-type COPD [46; 47]. Further research is necessary to verify these initial results. Therefore larger, more generalizable studies using cohorts such as the German Nation Cohort or the UK Biobank are needed.

**CONCLUSION**

Lung volumes calculated automatically from non-dedicated whole-body MR imaging range between the values of functional residual capacity and total lung capacity derived from pulmonary function tests in our epidemiological setting. Due to its independent association with residual volume and the FEV1/FVC ratio as well as its moderate accuracy for the detection of obstructive lung disease, it is a potentially promising parameter to assess pulmonary health in whole-body imaging when pulmonary function tests are not available.

**TABLES**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All Subjects with MR-based Lung Measures** | **Without PFT Results** | **With PFT Results** |
| N | 396 | 182 | 214 |
| Age (years) | 56.4 (9.2) | 54.2 (11.7) | 58.2 (5.7)\*\*\*\* |
| Sex (men) | 228 (57.6%) | 102 (56.0%) | 126 (58.9%) |
| Height (cm) | 171.6 (9.7) | 171.6 (9.6) | 171.6 (9.9) |
| Weight (kg) | 83.0 (16.6) | 81.7 (16.9) | 84.1 (16.3) |
| BMI (kg/m2) | 28.1 (4.9) | 27.7 (5.1) | 28.5 (4.8) |
| Body surface area (m2) | 1.95 (0.22) | 1.94 (0.22) | 1.96 (0.22) |
| Smoking status |  |  |  |
| Never-Smoker | 145 (36.6%) | 67 (36.8%) | 78 (36.5%) |
| Ex-Smoker | 172 (43.4%) | 82 (45.1%) | 90 (42.1%) |
| Current-Smoker | 79 (20.0%) | 33 (18.1%) | 46 (21.5%) |
| Cigarette smoking (py) | 12.9 (18.8) | 12.7 (18.0) | 13.0 (19.4) |
| Diabetes Status |  |  |  |
| Normal | 241 (60.9%) | 120 (65.9%) | 121 (56.5%) |
| Prediabetes | 101 (25.5%) | 40 (22%) | 61 (28.5%) |
| Diabetes | 54 (13.6%) | 22 (12.1%) | 32 (15.0%) |
| HbA1c (%) | 5.58 (0.74) | 5.51 (0.82) | 5.63 (0.6) |
| Hypertension | 136 (34.3%) | 54 (29.7%) | 82 (38.3%) |
| Clinical History Of  COPD and Emphysema | 21 (5.3%) | 4 (2.2%) | 17 (7.9%)\* |
| CAT Score | 11.5 (6.5) | 11.8 (9.5) | 11.4 (6.0) |
| Exacerbation within the last 12 months | 5 (23.8%) | 1 (25%) | 4 (23.5%) |
| Exacerbation requiring hospitalization/ED visit within the last 12 months | 3 (14.3%) | 1 (25%) | 2 (11.8%) |
| ***MR-based Lung Measures*** |  |  |  |
| Total Lung Volume (L) | 4.00 (1.11) | 3.96 (1.06) | 4.04 (1.15) |
| % of expected FRC | 124.4 (27.9) | 124.0 (27.5) | 124.7 (28.3) |
| % of expected TLC | 64.8 (14.9) | 64.6 (15.0) | 65.1 (14.8) |
| Left Lung Volume (L) | 1.82 (0.54) | 1.80 (0.52) | 1.84 (0.56) |
| Right Lung Volume (L) | 2.18 (0.59) | 2.16 (0.56) | 2.20 (0.61) |
| ***Pulmonary Function Test (PFT)*** |  |  |  |
| RV (L) | N/A | N/A | 2.13 (0.39) |
| FRC (L) | N/A | N/A | 2.86 (0.68) |
| AV (L) | N/A | N/A | 6.06 (1.21) |
| TLC (L) | N/A | N/A | 6.24 (1.23) |
| FVC (L) | N/A | N/A | 4.19 (1.04) |
| FEV1/FVC (%) | N/A | N/A | 74.8 (7.6) |
| FEV1/FVC <70% | N/A | N/A | 48 (22.4%) |
| FEF25-75 (L/s) | N/A | N/A | 2.48 (0.95) |
| TLCO (mmol/min/kPa) | N/A | N/A | 8.47 (1.97) |
| TLCO/VA (mmol/min/kPa/l) | N/A | N/A | 1.40 (0.19) |

**Table 1: Characteristics of the entire study sample and used subgroups.** Data are given as mean (standard deviation) for continuous variables, and count (percentage) for categorical variables. Differences between the subgroups with and without PFT are indicated by \* for p<0.05, and \*\*\*\* for p<0.0001.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Univariate Associations** | | **Associations adjusted  for Age and Gender** | | **Fully adjusted Associations** | |
|  | β  (95%CI) | p-value | β  (95%CI) | p-value | β  (95%CI) | p-value |
| Age (years) | 0.005 (-0.007;0.017) | 0.41 | 0.006 (0.004;0.016) | 0.27 | 0.016 (0.005;0.027) | 0.005 |
| Sex (men) | 1.17 (0.98;1.36) | <0.001 | 1.17 (0.98;1.36) | <0.001 | 0.64 (0.37;0.92) | <0.001 |
| BMI (kg/m2) | -0.03 (-0.05;-0.01) | 0.004 | -0.04 (-0.06;-0.02) | <0.001 | -0.04 (-0.06;-0.02) | <0.001 |
| Height (cm) | 0.06 (0.05;0.07) | <0.001 | 0.04 (0.03;0.06) | <0.001 | 0.04 (0.02;0.05) | <0.001 |
| Weight (kg) | 0.01 (0.00;0.02) | 0.001 | -0.01 (-0.01;0.00) | 0.025 |  |  |
| BSA (m2) | 1.63 (1.15;2.11) | <0.001 | -0.08 (-0.66;0.5) | 0.790 |  |  |
| Smoking status |  |  |  |  |  |  |
| Never-Smoker | Ref. |  | Ref. |  | Ref. |  |
| Ex-Smoker | 0.26 (0.01;0.5) | 0.04 | 0.11 (-0.1;0.32) | 0.31 | 0.16 (-0.04;0.36) | 0.12 |
| Current-Smoker | 0.44 (0.14;0.75) | 0.004 | 0.41 (0.15;0.67) | 0.002 | 0.41 (0.17;0.66) | 0.001 |
| Cigarette smoking (py) | 0.012 (0.006;0.018) | <0.001 | 0.006 (0;0.011) | 0.03 | \*\*\* | \*\*\* |
| Diabetes Status |  |  |  |  |  |  |
| Normal | Ref. |  | Ref. |  | Ref. |  |
| Prediabetes | 0.31 (0.06;0.57) | 0.02 | 0.13 (-0.10;0.36) | 0.26 | 0.31 (0.08;0.53) | 0.009 |
| Diabetes | 0.21 (-0.12;0.54) | 0.21 | -0.10 (-0.40;0.19) | 0.49 | 0.10 (-0.19;0.39) | 0.50 |
| HbA1c | -0.03 (-0.18;0.12) | 0.71 | -0.06 (-0.19;0.07) | 0.38 |  |  |
| Hypertension | -0.02 (-0.25;0.21) | 0.89 | 0.15 (-0.06;0.36) | 0.16 |  |  |

**Table 2: Association of MR Lung Volume to Clinical Characteristics.** The fully adjusted model included age and gender plus all co-variates with p<0.10 in univariate analysis, in case of collinearity the weaker parameter was removed. \*\*\* because of collinearity not included in the fully adjusted model.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| MR-derived Total Lung Volume (l)  N=214 | | | | |
|  | | β (95%CI) | p-value | |
| **Model 1 - adjusted for age and sex** | | | | |
| **PFT volumes** | RV (L) | 1.09 (0.71 - 1.47) | <0.001 | | |
| FRC (L) | 0.61 (0.39 - 0.83) | <0.001 | | |
| TLC (L) | 0.41 (0.24 - 0.58) | <0.001 | | |
| VA (L) | 0.41 (0.24 - 0.58) | <0.001 | | |
| FVC (L) | 0.39 (0.19 - 0.59) | <0.001 | | |
| **PFT obstruction** | FEV1/FVC (%) | -0.04 (-0.06 - (-0.02)) | <0.001 | | |
| FEF25-75 (L/s) | -0.12 (-0.26 - 0.03) | 0.11 | | |
| **PFT gas exchange** | TLCO (mmol/min/kPa) | 0.03 (-0.08 - 0.13) | 0.61 | | |
| TLCO/VA (mmol/min/kPa/l) | -1.31 (-1.99 - (-0.63)) | <0.001 | | |
| **Model 2 - Adjusted for age, sex, height, weight, smoking status** | | | | |
| **PFT volumes** | RV (L) | 0.75 (0.32 - 1.18) | | 0.001 | |
| FRC (L) | 0.40 (0.10 - 0.71) | | 0.01 | |
| TLC (L) | 0.25 (0.04 - 0.47) | | 0.02 | |
| VA (L) | 0.25 (0.04 - 0.47) | | 0.02 | |
| FVC (L) | 0.20 (-0.04 - 0.44) | | 0.11 | |
| **PFT obstruction** | FEV1/FVC (%) | -0.03 (-0.05 - (-0.02)) | | <0.001 | |
| FEF25-75 (L/s) | -0.13 (-0.28 - 0.01) | | 0.07 | |
| **PFT gas exchange** | TLCO (mmol/min/kPa) | 0 (-0.11 - 0.11) | | 0.95 | |
| TLCO/VA (mmol/min/kPa/l) | -0.72 (-1.47 - 0.03) | | 0.06 | |

**Table 3: Associations between Parameters derived from Pulmonary Function Test and MR-derived Total Lung Volume.** Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, height, weight, and smoking status**.** β-coefficients were obtained from linear regression.

|  |  |  |  |
| --- | --- | --- | --- |
| **PFT Parameters** | **β (95%CI)** | **p-value** | **Partial r2** |
| RV (L) | 0.50 (0.03; 0.97) | 0.04 | 0.022 |
| FEV1/FVC (%) | -0.022 (-0.041; -0.003) | 0.02 | 0.026 |
| TLCO/VA | -0.42 (-1.17; 0.33) | 0.27 | 0.006 |

**Table 4: Multivariate Model of PFT Parameters predicting MR-based Lung Volume.** Total adjusted r2 of the final model was 0.43. Only the strongest parameter of each of the PFT groups “Volume”, “Obstruction” “Gas Exchange” was included in the model. The model was developed including the following co-variates: age, gender, height, weight, and smoking status.

**FIGURE LEGEND**

**Figure 1: Lung Volume Segmentation on Non-dedicated Whole-Body MR Imaging.** Using a typical T1-DIXON-VIBE sequence as used for fat quantification on Whole-Body MR studies, lung volumes were derived for the right and left lung using an in-house developed software algorithm.

**Figure 2: Boxplot of MR-based Lung Volume stratified by Gender**

**Figure 3: Correlation between MR-based Lung Volume and PFT (Pulmonary Functional Test) Results.** ThePFTparameters were stratified into 3 groups: (A) “PFT Volumes” comprising RV, FRC, TLC, VA and FVC; (B) “PFT Obstruction” comprising FEV1/FVC (%), FEF25-75 (l/s); (C) “PFT Gas Exchange” covering TLCO and TLCO/VA.

**Figure 4: Association Pattern between Clinical Predictors and MR-based Lung Volume vs. Clinical Predictors and PFT Parameters.** Derived associations were stratified as following; + = positive significant; (+) = positive, but non-significant; - = negative significant; () = negative, but non-significant correlation. The underlying table with all beta-estimates and p-values is located in the **Appendix E2**.

**Figure 5: Difference of MR-based Lung Volume between subjects with and without Obstructive Disease.** Left image for definition based on PFT (FEV1/FVC<0.70), right image for a clinical definition as history of COPD or Emphysema.

**Figure 6: AUC-ROC plot of MR-based Total Lung Volume for detecting FEV1/FVC<0.70;** MR-based lung volume was corrected for body height.

**APPENDIX**

**Appendix E1:** An example illustrating the lung segmentation at the hilus (A: coronal, B: axial). Pulmonary vessels outside the mediastinal contours were included in the lung region. The segmented region of interest was shaded dark-green for the right lung and bright-green for the left lung.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **MR based lung volume** | | **Pulmonary Function Test (PFT)** | | | | | | | | | | | | | | | | | |
|  | **RV (l)** | | **FRC (l)** | | **TLC (l)** | | **VA (l)** | | **FVC (l)** | | **FEV1/FVC (%)** | | **FEF25-75 (L/s)** | | **TLCO (mmol/min/kPa)** | | **TLCO/VA (mmol/min/kPa/l)** | |
|  | **ß** | **P** | **ß** | **P** | **ß** | **P** | **ß** | **P** | **ß** | **P** | **ß** | **P** | **ß** | **P** | **ß** | **P** | **ß** | **P** | **ß** | **p** |
| **Age** | 0.02  (0;0.04) | 0.056 | 0.01  (0;0.01) | 0.035 | -0.01 (-0.02;0) | 0.043 | -0.03  (-0.05;-0.02) | <0.001 | -0.03  (-0.05;-0.02) | <0.001 | -0.04  (-0.05;-0.03) | <0.001 | -0.11  (-0.29;0.07) | 0.214 | -0.04  (-0.06;-0.02) | 0.001 | -0.09  (-0.12;-0.06) | <0.001 | -0.01  (-0.01;0) | <0.001 |
| **Gender** | 0.73 (0.33;1.13) | <0.001 | 0.17 (0.05;0.29) | 0.007 | 0.27 (0.09;0.44) | 0.004 | 0.89 (0.64;1.14) | <0.001 | 0.89 (0.63;1.14) | <0.001 | 0.72 (0.49;0.95) | <0.001 | -3.12  (-6.33;0.09) | 0.057 | 0.02  (-0.36;0.4) | 0.924 | 1.73 (1.23;2.24) | <0.001 | 0.07 (0;0.14) | 0.058 |
| **Height** | 0.04 (0.02;0.06) | <0.001 | 0.02 (0.01;0.03) | <0.001 | 0.03 (0.02;0.04) | <0.001 | 0.06 (0.05;0.08) | <0.001 | 0.06 (0.05;0.08) | <0.001 | 0.05 (0.04;0.06) | <0.001 | -0.02  (-0.18;0.14) | 0.797 | 0.03 (0.01;0.05) | 0.007 | 0.07 (0.04;0.09) | <0.001 | 0  (-0.01;0) | 0.124 |
| **Never Smoker** | Ref. |  | Ref. |  | Ref. |  | Ref. |  | Ref. |  | Ref. |  | Ref. |  | Ref. |  | Ref. |  | Ref. |  |
| **Ex-Smoker** | 0.18  (-0.1;0.47) | 0.202 | -0.01  (-0.09;0.08) | 0.883 | 0.02  (-0.1;0.15) | 0.705 | 0.04  (-0.14;0.21) | 0.701 | 0.03  (-0.15;0.21) | 0.704 | 0.05  (-0.11;0.21) | 0.562 | -0.49  (-2.76;1.78) | 0.67 | 0.03  (-0.24;0.3) | 0.847 | -0.22  (-0.58;0.13) | 0.216 | -0.05  (-0.1;0) | 0.063 |
| **Current-Smoker** | 0.35 (0.01;0.68) | 0.044 | 0.1  (0;0.21) | 0.048 | 0.17 (0.02;0.32) | 0.027 | -0.1  (-0.32;0.11) | 0.346 | -0.1  (-0.32;0.11) | 0.342 | -0.19  (-0.39;0) | 0.047 | -3.05  (-5.75;-0.36) | 0.026 | -0.43  (-0.75;-0.11) | 0.009 | -1.02  (-1.44;-0.6) | <0.001 | -0.15  (-0.21;-0.09) | <0.001 |
| **BMI** | -0.04  (-0.06;-0.01) | 0.008 | -0.02  (-0.02;-0.01) | <0.001 | -0.06  (-0.07;-0.05) | <0.001 | -0.04  (-0.06;-0.03) | <0.001 | -0.05  (-0.07;-0.03) | <0.001 | -0.04  (-0.05;-0.02) | <0.001 | 0.3 (0.09;0.52) | 0.007 | 0.02  (-0.01;0.04) | 0.233 | 0  (-0.04;0.03) | 0.936 | 0.01 (0.01;0.02) | <0.001 |

**Appendix E2: Multivariate Associations between clinical variables, MRI based lung volume and spirometry values (N=214).**

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