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Direktor: Prof. Dr. Jens Ricke

Korrelation verschiedener radiologischer Untersuchungsverfahren und Verfahren der Lungenfunktionsuntersuchung bei Patienten mit zystischer Fibrose

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Vivien Laura Kratzer

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Berichterstatter:	Prof. Dr. Ullrich G. Mueller-Lisse
Mitberichterstatter:	Prof. Dr. Nikolaus Kneidinger
	Prof. Dr. Kathrin Kahnert
Mitbetreuung durch die promovierte Mitarbeiterin:	Dr. Hanna Zimmermann
Dekan:	Prof. Dr. Thomas Gudermann

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Abbreviations

BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CT	Computed tomography
CTDIvol	Volume computed tomography dose index
DLP	Dose length product
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
kVp	Peak kilovoltage
MDCT	Multidetector computed tomography
n	Size of a statistical sample
p	Probability value
PACS	Picture-archiving-and-communication-system
PFT	Pulmonary function test
r_s	Spearman's rank correlation coefficient
SD	Standard deviation
VC	Vital capacity

1. Abstracts

1.1 Abstract: Cross-sectional study

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease among the Caucasian population with the first pulmonary damages already occurring in early childhood. There is a very diverse course of disease during childhood and adolescence due to a varying degree of therapy adherence in that group. Therefore, a high variability of disease severity must be expected when treating CF patients in early adulthood.

To assess the actual, this study aims to evaluate the state of disease of young adults suffering from CF based on high-resolution computed tomography (HRCT) -examinations of the lungs and pulmonary function tests (PFTs) through a cross-sectional study.

The study used a dataset from 1998 to 2018 of ninety-one patients from age sixteen to twenty-two and was conducted in two steps. First, HRCT-examinations of the lungs were retrospectively evaluated by two observers (O1 and O2) using the Brody score to measure the degree of pulmonary damage. Second, the Brody score was correlated with the three spirometry parameters vital capacity (VC), forced expiratory volume in one second (FEV1), and the Tiffeneau index, as well as with the body-mass-index (BMI) and the genetic mutation.

Overall, the severity of pulmonary damages exhibited a wide range (Brody score ranging from 0 to 144 (O1) / 175 (O2)), with a high interobserver reproducibility (r_s=0.69). The associated PFTs presented a heterogeneous distribution as well. The Brody score showed an excellent correlation on a statistically highly significant level ($p<0.001$) with the three spirometry parameters VC (r_s=-0.75 (O1); r_s=-0.60 (O2)), FEV1 (r_s=-0.81 (O1); r_s=-0.69 (O2)), and the Tiffeneau index (r_s=0.68 (O1); r_s=0.67 (O2)), as well as with the BMI (r_s=-0.76 (O1); r_s=-0.67 (O2)). There was no statistically significant difference between male and female CF patients. A correlation between the Brody score and the genetic mutation status could not be found.

A promising avenue for future research would be analysing the causes of these vast differences in the state of disease, like, the influence of genetic mutations or the patient's compliance during childhood and teenage age.

1.2 Abstract: Cohort study

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease among the Caucasian population. As there is still no cure for CF, it is essential to prevent or at least delay pulmonary damage to conserve lung function. This aim can be achieved through regular monitoring using high-resolution computed tomography (HRCT) -examinations and pulmonary function tests (PFTs) to be able to intervene, if necessary, as soon as possible. Strict monitoring is especially essential in the case of young adults while getting more independent from their parents since they tend to have less disease knowledge than their parents. This often results in less therapy adherence which negatively influences the course of disease.

To evaluate whether there had been any changes in pulmonary damage within the first four years in CF patients after reaching adulthood, a retrospective cohort study was conducted.

The study used a dataset of twenty-nine patients having an HRCT-examination at the age of sixteen to twenty-two with a follow-up HRCT-examination after approximately four years and was conducted in three steps. First, the degree of pulmonary damage for the initial and the follow-up HRCT-examinations of the lungs was retrospectively evaluated by two observers (O1 and O2) using the Brody score. Second, the initial Brody score was correlated with the difference between the initial and the follow-up scores. Third, the associated spirometry parameters of the initial and the follow-up examinations were compared and correlated with the Brody score.

The results revealed a dependency between the magnitude of change in pulmonary damages within the four years and their initial state; the fewer pulmonary damages in the initial HRCT-examination, the bigger the increase of the pulmonary damages within the four-year period (r_s=-0.60 (O1) / r_s=-0.39 (O2)). This increase can be mainly ascribed to the sub-scores bronchiectasis, mucous plugging, and peribronchial thickening. Reduction of pulmonary damages was exclusively found in patients with a medium or high Brody score at the initial HRCT-examination. The spirometry parameters did not show a statistically significant change over the four years. There was no statistically significant correlation between the changes in the Brody score and the changes of the spirometry parameters ($p>0.05$). Statistically significant differences in the course of disease between male and female and Δ-F-508-homozygous and heterozygous CF patients could not be found.

Future research should focus on analysing the impact of different monitoring procedures between CF patients with initially low and high-grade disease severity.

2. Zusammenfassungen

2.1 Zusammenfassung: Querschnittstudie

Die Zystische Fibrose (CF) ist eine der häufigsten lebensbedrohlichen autosomal rezessiven Erkrankungen der kaukasischen Bevölkerung. Der Krankheitsverlauf während dem Kindes- und Jugendalter ist aufgrund der ungleichen Therapieadhärenz sehr unterschiedlich, sodass bei CF Patientinnen und Patienten im jungen Erwachsenenalter mit einer hohen Variabilität des Krankheitszustandes zu rechnen ist.

Vor diesem Hintergrund zielt diese Studie darauf ab, den Krankheitsstatus von jungen Erwachsenen mit CF anhand von hochauflösenden Computertomographie (HRCT) - Untersuchungen des Brustkorbs und Lungenfunktionsuntersuchungen (PFTs) mithilfe einer Querschnittstudie zu erforschen.

Hierfür wurde ein Datensatz aus den Jahren 1998 bis 2018 von einundneunzig CF Patientinnen und Patienten im Alter von sechszehn bis zweiundzwanzig Jahren in zwei Schritten ausgewertet. Zuerst wurden die HRCT-Untersuchungen des Thorax retrospektiv von zwei unabhängigen Betrachtern (O1 und O2) mithilfe des Brody Scores auf das Ausmaß pulmonaler Schäden ausgewertet. In einem zweiten Schritt wurden die Ergebnisse des Brody Scores mit den drei Lungenfunktionsparametern Vitalkapazität (VC), Einsekundenkapazität (FEV1), Tiffeneau-Index, dem Body-Mass-Index (BMI) und dem genetischen Mutationsstatus der CF Patientinnen und Patienten korreliert.

Insgesamt wurde eine große Bandbreite des Ausmaßes der pulmonalen Schäden gefunden (Brody Score Werte von 0 bis 144 (O1) / 175 (O2)). Die Brody Score Ergebnisse zeigten zudem eine hohe Reproduzierbarkeit zwischen den Betrachtern (r_s=0.69). Auch die zugehörigen PFTs zeigten eine heterogene Verteilung. Es wurden exzellente Korrelationen auf statistisch höchst signifikantem Niveau ($p<0.001$) zwischen den Brody Score Ergebnissen und den drei Lungenfunktionsparametern VC (r_s=-0.75 (O1); r_s=-0.60 (O2)), FEV1 (r_s=-0.81 (O1); r_s=-0.69 (O2)), Tiffeneau Index (r_s=0.68 (O1); r_s=0.67 (O2)), und dem BMI (r_s=-0.76 (O1); r_s=-0.67 (O2)) festgestellt. Ein statistisch signifikanter Unterschied zwischen männlichen und weiblichen CF Patientinnen und Patienten bestand nicht. Eine Korrelation zwischen den Brody Score Ergebnissen und dem genetischen Mutationsstatus konnte ebenfalls nicht festgestellt werden.

Zukünftig wäre zu erforschen, wie die große Bandbreite des Ausmaßes der pulmonalen Schäden zustande kommt, beispielweise welche Rolle hierbei der genetische Mutationsstatus oder auch die Compliance der CF Patientinnen und Patienten im Kindes- und Teenageralter spielt.

2.2 Zusammenfassung: Kohortenstudie

Die Zystische Fibrose (CF) ist eine der häufigsten lebensbedrohlichen autosomal rezessiven Erkrankungen der kaukasischen Bevölkerung. Da es bislang keine Heilung für die CF gibt, ist es essenziell das Voranschreiten pulmonaler Schäden zu verhindern oder zumindest zu verzögern, um die Lungenfunktion zu erhalten. Dies kann durch regelmäßige Kontrolluntersuchungen mit hochauflösenden Computertomographie (HRCT) -Untersuchungen des Brustkorbs und Lungenfunktionsuntersuchungen (PFTs) erreicht werden, um bei Bedarf zeitnah eingreifen zu können. Besonders bei jungen Erwachsenen, die sich in diesem Alter zunehmend von ihren Eltern unabhängig machen, ist eine strenge Überwachung besonders wichtig, da sie tendenziell weniger Wissen über ihre Krankheit besitzen als ihre Eltern. Dies kann zu einer sinkenden Therapieadhärenz führen, welche sich negativ auf den Krankheitsverlauf auswirken kann.

Vor diesem Hintergrund wurde mithilfe einer retrospektiven Kohorten-Studie untersucht, ob es innerhalb der ersten vier Jahre nach Erreichen des Erwachsenenalters zu Veränderungen der pulmonalen Schäden gekommen war.

Hierfür wurde ein Datensatz von neunundzwanzig CF Patientinnen und Patienten mit einer initialen HRCT-Untersuchung im Alter von sechszehn bis zweiundzwanzig und einer Kontroll-Untersuchung in einem Abstand von ungefähr vier Jahren herangezogen und in drei Schritten untersucht. Zuerst wurde das Ausmaß der pulmonalen Schäden in der initialen und der Kontroll-HRCT-Untersuchung des Brustkorbs anhand des Brody Scores retrospektiv von zwei unabhängigen Betrachtern (O1 und O2) bestimmt. In einem zweiten Schritt wurden die Veränderungen des Brody Scores zwischen der initialen und der Kontroll-HRCT-Untersuchung mit den initialen Brody Score Ergebnissen korreliert. Zuletzt wurden die zugehörigen Lungenfunktionsparameter der initialen und der Kontroll-Untersuchung verglichen und mit den Brody Score Ergebnissen korreliert.

Es wurde ein Zusammenhang zwischen dem Ausmaß der Veränderungen und dem Ausgangszustand gefunden; je weniger pulmonale Schäden in der initialen HRCT-Untersuchung vorhanden waren, desto größer war deren Anstieg innerhalb den Vierjahreszeitraums (r_s=-0.60 (O1) / r_s=-0.39 (O2)). Der Anstieg konnte hauptsächlich auf die Teil Scores Bronchiektasen, Mukusimpaktion und Bronchialwandverdickung zurückgeführt werden. Eine Verringerung der pulmonalen Schädigung konnte ausschließlich bei Patienten mit initial mittlerer und hoher pulmonaler Schädigung gefunden werden. Die Lungenfunktionsparameter zeigten weder eine statistisch signifikante Veränderung innerhalb des Vierjahreszeitraums, noch korrelierte deren Veränderung mit der Veränderung des Brody Scores ($p>0.05$). Der Krankheitsverlauf zwischen männlichen und weiblichen und zwischen Δ-F-508-homozygoten und heterozygoten CF Patientinnen und Patienten unterschied sich nicht.

Ein interessanter Ansatz für zukünftige Forschungen wäre, ob der Einsatz unterschiedlicher Überwachungsverfahren für CF Patientinnen und Patienten mit initial niedrigem und hohem Schweregrad der Erkrankung sinnvoll sein könnte.

3. Introduction

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease among the Caucasian population, with an incidence of 1 in 2,500 new-borns. In 2019, the European Cystic Fibrosis Society registered 50,902 CF patients in Europe, thereof 6,481 in Germany [1].

CF is caused by a genetic mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, located on chromosome 7, leading to an abnormal chloride channel function. Currently, 2,110 known genetic mutations are listed in the cystic fibrosis mutation database [2, 3]. The most common genetic mutation is ∆-F-508, found in two-thirds of CF patients in Europe and in over 70% of CF patients in Germany [4-6]. The chloride channel malfunction results in the accumulation of viscous luminal secretions in different organs, like the lungs, the gastrointestinal tract, the pancreas, sweat glands, and the ductus deferens in men. Common extrapulmonary symptoms are, to name a few, meconium ileus, pancreatic insufficiency, increased concentrations of sodium and chloride in sweat and male infertility [7, 8]. In the lungs, CF causes airway obstruction due to abnormal mucous and an increased vulnerability to pulmonary infections [9]. This results in a large spectrum of progressive pulmonary damages, which are still the primary cause of death in CF patients [8], resulting in a current life expectancy of 55 years for a new-born in Germany diagnosed with CF [10].

High-resolution computed tomography (HRCT) is particularly sensitive to detect those pulmonary changes at an early stage in which the pulmonary function is not yet impaired [11-13]. This is especially important as the first pulmonary damages occur at a very young age [9]. The most common pulmonary damages seen on computed tomography (CT) images are bronchiectasis and peribronchial thickening [14, 15], followed by mucous plugging and many others such as hyperinflation, ground-glass opacities, consolidations, bullae or cysts [16]. To monitor the pulmonary function of CF patients, regular pulmonary function tests (PFTs) are recommended, with vital capacity (VC), forced expiratory volume in one second (FEV1), and the Tiffeneau index being the most common and valuable parameters to evaluate the course of disease [17-19]. Nevertheless, the best method to monitor patients' pulmonary conditions is the combination of HRCT-examinations and PFTs [20, 21].

Monitoring the clinical status of CF patients is especially important since the course of the disease varies a lot and depends on optimal therapy adherence [22]. However, there are many barriers, especially for children and young adults, leading to less therapy adherence when growing older [23]. One huge barrier is time management since the daily treatments are complex and require much time [24-26]. Also, rising annual medical costs for CF treatments can become obstacles for some CF patients [27]. Other barriers can be simply forgetting to take the medication [25, 28], a lack of disease knowledge [29] or poor awareness of the consequences of non-adherence [26, 28]. However, also socio-psychological factors such as the feeling of losing their freedom [28] influence the therapy adherence of young adults [30]. Especially young adults tend to take higher risks, although being aware of the effect on their health, as shown in an online survey with participants aged eighteen to twenty-five [31].

Altogether, there are a lot of inter-individual differences in therapy adherence among young CF patients, so a high variability of the state of disease can be expected when the CF patients arrive in adolescence. Hence, this study aims to evaluate the state of disease of young adults suffering from CF through a cross-sectional study, resulting in the following research question:

Research question I: What is the state of disease of young adults suffering from cystic fibrosis based on HRCT-examinations of the lungs and PFTs?

As there is still no cure for CF, it is essential to prevent or at least delay pulmonary damage and conserve lung function. This aim can be achieved through regular monitoring to be able to intervene if necessary as soon as possible [32]. HRCT is a suitable measurement method for monitoring CF patients since it is more sensitive than PFTs in detecting the progress of pulmonary changes [18, 33-35]. However, there is currently no guideline on how or when to perform follow-up examinations. In Germany, there is currently an S2k guideline for “diagnosis of cystic fibrosis” [36] and an S3 guideline on “diagnostics and treatment in chronic infection with pseudomonas aeruginosa” [37]. Even though the best-practice guidelines issued by the “European Cystic Fibrosis Society” [38] mention the use of HRCT in some CF centres, it is not generally recommended. Still, many CF centres use routine HRCT-examinations for non-occasional status assessments and research purposes. For example, de Jong, P. A. et al. [33, 39] and Loeve, M., et al. [40] from the Netherlands chose two years, Fuchs, S. I., et al. [41] from Germany chose three years as their interval for follow-up CT-examinations. Helbich, T. H., et al. [42] from Austria even propose HRCT-examinations every six to eighteen months to react to pulmonary changes before they become irreversible. At the “Medizinische Klinik IV” at the “LMU Klinikum Innenstadt”, every patient over the age of eighteen is offered a follow-up HRCT-examination of the lungs once every four years to monitor the development of CF-related pulmonary damages [43].

When performing HRCT-examinations, especially on children and young adults, the risks of ionising radiation should not be overlooked. CF patients are exposed to a significantly higher radiation dose than the average population [44]. For comparison, the radiation dose of one HRCT-examination of the lungs can be up to 6,5 mSv [45], while the natural radiation dose of the population is about 4mSv per year. Even though the risk of developing cancer is only marginally increased [46-48], routine HRCT-examinations for monitoring HRCT should only be performed if there is a consequence for the CF patient and his treatment. Nevertheless, strict monitoring is essential in young adults while getting more independent from their parents since they tend to have less disease knowledge than their parents, resulting in less therapy adherence [29, 49]. So, a retrospective cohort-study was conducted to evaluate whether there had been any changes in pulmonary damages on HRCT-images and, if available, in the associated PFTs within the first four years after reaching adolescence with the following research question:

Research question II: What is the course of disease of CF patients in early adulthood within an interval of four years based on HRCT-examinations of the lungs and PFTs?

To answer the two research questions, CF patients with an HRCT-examination of the lungs at the age of sixteen to twenty-two and, if available, an associated PFT, were retrospectively recruited from the “Interdisziplinäres Mukoviszidose Zentrum des Klinikums der Universität München” and

were included in a cross-sectional study. Those CF patients with an additional follow-up HRCT-examination after approximately four years and, if available, an associated PFT, were included in a cohort-study.

The “Interdisziplinäres Mukoviszidose Zentrum des Klinikums der Universität München” is the largest one in Germany, treating 550 CF patients as of January 2022 [10, 50]. The centre consists of two departments: The “Christiane-Herzog-Ambulanz” at “Dr. von Haunersches Kinderspital” treats paediatric CF patients up to a maximum age of thirty years. Adult patients from the age of eighteen years on are treated at “Medizinische Klinik V” at the “LMU Klinikum Innenstadt” close by [50]. At the transition point from the paediatric to the adult department, an HRCT-examination of the lungs is usually performed [43]. It establishes an initial state of lung disease for future follow-up examinations since the paediatric department almost exclusively performs chest x-rays. In addition, as mentioned before, every patient over the age of eighteen is offered a follow-up HRCT-examinations of the lungs once every four years and a PFT once every six months. Additional HRCT-examinations are performed if there are indications of progress or aggravation [43].

To document the state of disease of the CF patients objectively, it is advisable to work with a standardized scoring system. Over time, several different CF-specific scoring systems were invented to evaluate the HRCT-scans, which were compared by de Jonget al. [51]. Among those, the Brody score notable stood out and was chosen for the evaluation of the HRCT-examinations for the two studies presented in this thesis. It involves all essential CF-specific pulmonary changes and presents excellent interobserver reproducibility [43, 51, 52]. It is applicable in children [11, 52, 53] and adult CF patients [43, 54], which is especially important since the patient collective of both studies is at the transition point from childhood to adulthood.

The Brody score was initially invented by Brody et al. [11] for incremental HRCT-scans of six-to-ten-year-old children suffering from CF. The Brody score is a weighted semi-quantitative, composite score with a theoretical range of 0 to 243 points and consists of five sub-scores: Bronchiectasis (range: 0 to 72 points), mucous plugging (range: 0 to 36 points), peribronchial thickening (range: 0 to 54 points), parenchymal opacity (range: 0 to 54 points), and hyperinflation (range: 0 to 27 points). Since combining different sub-scores with a maximum value, e.g., parenchymal opacities as consolidations, is not possible, the possible range for the Brody score is 0 to 207 points. The different pulmonary damages‘ presence, location, and extent is evaluated for the centre and the periphery of the upper, lower, and middle lobe (represented by the lingula on the left) of both lungs [11].

To answer the two research questions, this thesis is structured as follows: Following the introduction, the respective data sources and methodology of the cross-sectional study and the cohort study are presented. After reporting the results of the two studies, they are critically assessed and interpreted in a common discussion, considering the respective limitations of each study and the current state of medical research in the field.

4. Material and Methods

4.1 Study Design, Study Setting, and Patient Population

Two retrospective, mono-institutional studies were performed: A cross-sectional exploratory study and a cohort-study. The studies did not have a specific hypothesis to test, and sample-size calculation was not performed. Instead, all available data sets meeting the inclusion criteria of our institution, the "Interdisziplinäres Mukoviszidose Zentrum des Klinikums der Universität München", were utilised for analysis and exploration purposes. The development of the patient population is illustrated in Figure 1 below.

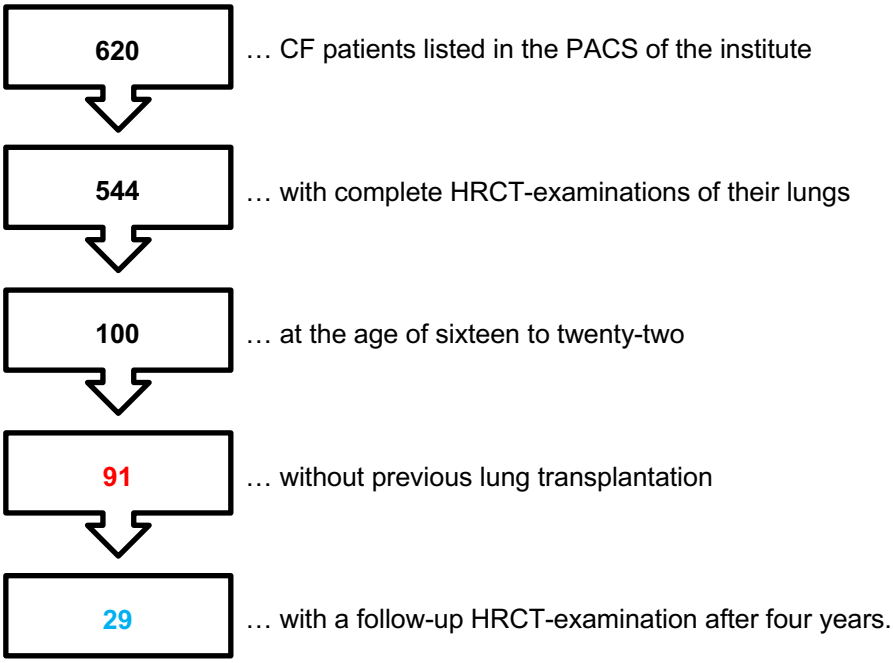


Figure 1: Flow chart of the patient population displaying the origin of the study size for the cross-sectional (91 patients, marked red) and the cohort study (29 patients, marked blue).

During the retrospective recruitment time, from September 1998 to March 2018, 620 patients with clinically or genetically established CF were listed in the institutional picture-archiving-and-communication-system (PACS). 544 of them had one or more HRCT-examinations of their lungs. Incomplete HRCT-examinations were excluded. Ninety-one had at least one HRCT-examination at the age of sixteen to twenty-two (range, 15.6 to 22.1 years) without previous lung transplantation. These patients were included in the monocentric, retrospective cross-sectional study. Twenty-nine of the CF patients in the cross-sectional study also had at least one follow-up HRCT-examination after four years (range, 2.9 to 5.3 years) without interval lung transplantation. These patients were included in the monocentric, retrospective cohort study.

The retrospective evaluation of the HRCT-images and the clinical data, such as spirometry and the genetic mutation, took place with the approval of the hospital ethics committee under the consecutive project number 294-10.

4.2 Variables and Outcomes

The primary outcome of the cross-sectional study was the lung morphology status of young adults suffering from CF aged sixteen to twenty-two years. In the cohort study, the primary outcome was the change of the lung morphology of these patients within a four-year period. To quantify the lung morphology status and its change, HRCT-examinations of the lung and PFTs were analysed. The Brody score, ranging from 0 to 207 points on a metric scale, was used to assess the HRCT-examinations. The interobserver reproducibility of the Brody score was a secondary outcome of the cross-sectional study. Secondary outcomes of both studies were the correlations between HRCT lung morphology and the spirometry parameters FEV1, VC, and the Tiffeneau-index. For reasons of comparability, percentage values instead of absolute values were used for the VC and the FEV1.

To minimise bias, the following precautions were taken: Two independent observers with varying levels of expertise scored the HRCT-examinations twice to reduce the impact of experience on the Brody score's outcome. To ensure that the lung morphology aligns with the lung function, the time interval between the HRCT-examinations and the PFTs for CF patients was limited to two days. This restriction was implemented considering the potential rapid deterioration of lung function due to factors like disease exacerbation.

The following variables were included in the analysis as potential confounders: age and gender of the CF patients, the CF-specific genetic mutation if available and the examination date of the initial and the follow-up HRCT-examination.

4.3 Data Sources and Measurements

4.3.1 HRCT protocol

The images were stored in DICOM format and were retrieved from the institutional PACS (Syngo, Siemens Healthineers AG, Erlangen, Germany). 110 of the 120 different HRCT-examinations included in the two studies were performed at "LMU Klinikum", using fifteen different clinical CT-scanners from 1998 to 2018. The remaining ten HRCT-examinations had been copied to PACS from data stores obtained from external hospitals and practices. The CT-scanner originated from the companies Philips Medical Systems DMC GmbH (Hamburg, Germany), GE Healthcare GmbH (Chicago, USA), Siemens AG (Munich, Germany), and Canon Medical Systems Corporation (Ōtawara, Japan). The slice thickness varied between 0.625 and 6.0 mm including a couple of incremental CTs. Table 7 and Table 8 in the Appendix show a complete overview of the different CT-scanners.

4.3.2 HRCT evaluation

120 different HRCT-examinations were used for the two studies, including ninety-one in the cross-sectional study and twenty-nine additional ones in the cohort study. Another thirty-eight HRCT-examinations of the lungs used for the study of a co-worker were added to the group since some data was shared. The resulting 158 HRCT-examinations were randomly assigned to thirty-two blocks, with thirty-one blocks including five HRCT-examinations each, and one block including three HRCT-examinations. After another review, ten HRCT-examinations from the co-worker's study were removed because of preceding lung transplantation. The remaining blocks consisted of twenty-two blocks with five, eight with four, and two with three HRCT-examinations each. Those thirty-two blocks were reviewed in random order by each of the two observers. For further evaluation, each patient was assigned a random ID number.

The remaining 148 HRCT-examinations were scored by each of the two independent observers (O1 and O2). O1 was an attending radiologist with nineteen years of post-fellowship experience, and O2 was a 4th-year medical student without experience in examining HRCT-examinations of the lungs. Before the evaluation, five HRCT-examinations of the lungs of patients suffering from cystic fibrosis, which were not part of any of the studies, were jointly evaluated by O1 and O2, based on the Brody scoring system [11].

For evaluation, HRCT-examinations were displayed in lung-window setting (centre, C, -600 Hounsfield-units, HU, window width, W, 1,600 HU) on two suitable 5k-PACS monitors, with axial and coronal images each displayed on the full-screen, side by side. The previously introduced Brody score was assigned independently by each O1 and O2, who remained unaware of each other's results. The results were recorded in customized scoring sheets in Microsoft Excel by another researcher who was not involved in the assessment. The template for the scoring sheets is provided in Table 9 in the Appendix.

4.3.3 PFTs and the genetic mutation status

After scoring the HRCT-examinations, pertinent clinical information (date of birth, gender, and genetic mutation status) for every patient was looked up in the hospital-information-system (HIS) and recorded if available. Afterwards, patient records were searched for PFTs obtained within two days of the HRCT-examination. If available, VC, FEV1, the Tiffeneau index (FEV1/FVC), and body weight and height were taken. The Body mass index (BMI) was calculated using the following formula:

$$BMI = \frac{weight\ (kg)}{height\ (m)^2}$$

4.4 Quantitative Variables and Statistical Methods

In all evaluations, the results were classified as statistically significant for $p<0.05$ and statistically highly significant for $p<0.001$. In the event of $p>0.05$, the results were classified as statistically insignificant.

4.4.1 Spearman's rank correlation coefficient

The Spearman rank correlation coefficient was chosen to assess the correlation between different values since a normal distribution could not be assumed. Spearman's rank correlation coefficient, also known as Spearman's ρ (rho) or r_s, is a non-parametric test to show the correlation between the ranks of two variables. It ranges between -1 and +1 and evaluates monotonic relationships [55] as opposed to Pearson's correlation which requires a linear relationship and a normal distribution of the values. Spearman's rank correlation coefficient is commonly used to compare two different examinations [e.g. 56] and to assess interobserver reproducibility [e.g. 57].

In the cross-sectional study, Spearman's rank correlation coefficient was used to correlate the following findings: The total Brody score with its respective sub-scores, with the age of the patients and with the dates of the HRCT-examinations. The total Brody score and its sub-scores with the spirometry parameters (VC, FEV1, Tiffeneau index) and the BMI. The total Brody score and its sub-scores scored by O1 with those scored by O2. Spearman's rank correlation coefficient was also used in the cohort study to correlate the Brody score changes with the initial Brody score and the changes of the spirometry parameters with the changes of the Brody score.

4.4.2 Wilcoxon signed-rank test

The Wilcoxon signed-rank test is a non-parametric test for paired samples. It identifies whether there is a difference in the mean ranks of the two samples [58]. The Wilcoxon signed-rank test was used to evaluate whether the Brody scores in the cross-sectional study were consistently higher for one of the two observers. In the cohort study, it was used to assess whether the Brody score and the spirometry parameters differed significantly between the initial and the follow-up examination.

4.4.3 Mann-Whitney-U-test (Wilcoxon rank-sum test)

To detect whether the gender or the genetic mutation status of the patients influenced the Brody score in the cross-sectional study and whether they influenced the changes of the Brody score in the cohort study, the Mann-Whitney-U-test was performed. It is a nonparametric test for two independent samples and is an alternative to the t-test, which requires a normal distribution [59]. The Mann-Whitney-U-test was chosen because a normal distribution of the values could not be assumed. Application examples for using the Mann-Whitney-U-test to identify the influence of gender are found in the studies by Bachettiet al. [60] and Kohet al. [61].

4.4.4 Bland-Altman-Plot

The Bland-Altman-Plot, also known as the mean-deviation-plot, was first introduced to medical statistics by Blandet al. [62]. It visualizes the agreement between two measurement methods, S_1 and S_2. and was chosen to visualise the interobserver reproducibility of the Brody score and its respective sub-scores. The average of the numerical results is displayed on the x-axis, while their difference is shown on the y-axis. The function formula for the graph is shown below:

$$S(x,y) = \left(\frac{S_1 + S_2}{2}, (S_1 - S_2)\right)$$

For a better visual interpretation, three supporting lines are added to the graph:

- the mean of the differences,
- the mean of the differences + 1,96 x SD of the mean difference
- the mean of the differences - 1,96 x SD of the mean difference.

The Bland-Altman-Plot visualises the deviation variation and shows systematic mistakes, such as if one method systematically returns higher measurements than the other [62, 63]. Bland Altman plots are commonly used to visualize the intra- and interobserver reproducibility of quantitative variables [e.g. 43, 64].

5. Results

5.1 Results of the Cross-sectional Study

5.1.1 Descriptive statistics of the CF patients in the cross-sectional study

The cross-sectional study included ninety-one patients aged sixteen to twenty-two years, with a balanced gender distribution. As displayed in Table 1, there was a slight difference in age between genders, whereby male patients were, on average, one-half-year younger than females. Among the seventy-two patients (79% of all) whose genetic mutations had been established, sixty-six (92% of seventy-two) presented at least one ∆-F-508 mutation. Almost 60% of ∆-F-508-mutation carriers were homozygotic, and about 40% were heterozygotic. In this context, the term "∆-F-508 heterozygotic" describes patients carrying two different CFTR mutations, one being the ∆-F-508 variant. Six patients had other established genetic mutations, e.g., G542X or G551D. In nineteen patients (21%), no genetic mutation analysis was found in the available patient record.

Table 1: Patient demographics in the cross-sectional study

		total	female	male
n		91	47	44
Age (years)	lowest	15.6	15.9	15.6
	highest	22.1	22.1	21.6
	mean	19.1	19.3	18.8
	median	19.3	19.8	19.1
Genetic mutation	∆-F-508 homozygote	39	21	18
	∆-F-508 heterozygote	27	12	15
	other	6	1	5
	unknown	19	13	6

As graphically illustrated in Figure 2, among the ninety-one patients having an HRCT-examination at the age of sixteen to twenty-two years (yellow circle), the genetic mutation was found in the patient records of seventy-two patients (blue circle). A PFT within two days of the HRCT-examination was performed in forty patients (red circle). A total of thirty-one patients exhibited both a recorded genetic mutation and pertinent PFT results (purple interface).

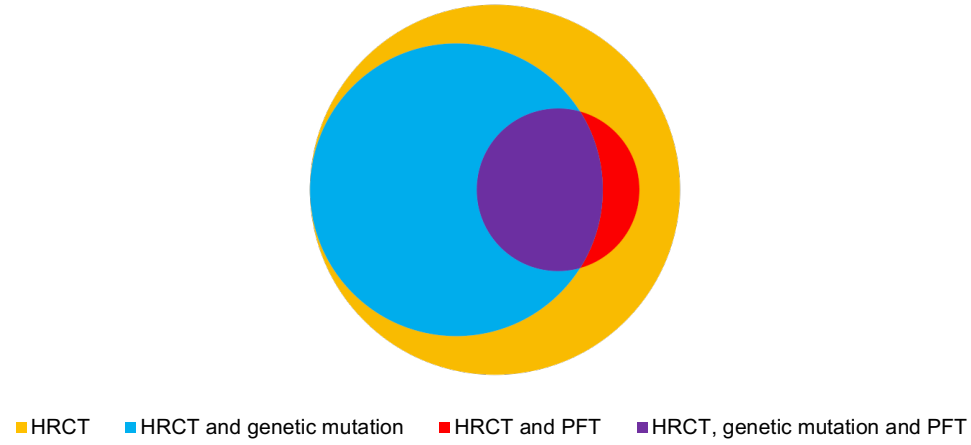


Figure 2: Venn diagram of the CF patients in the cross-sectional study.

5.1.2 The Brody score in the cross-sectional study

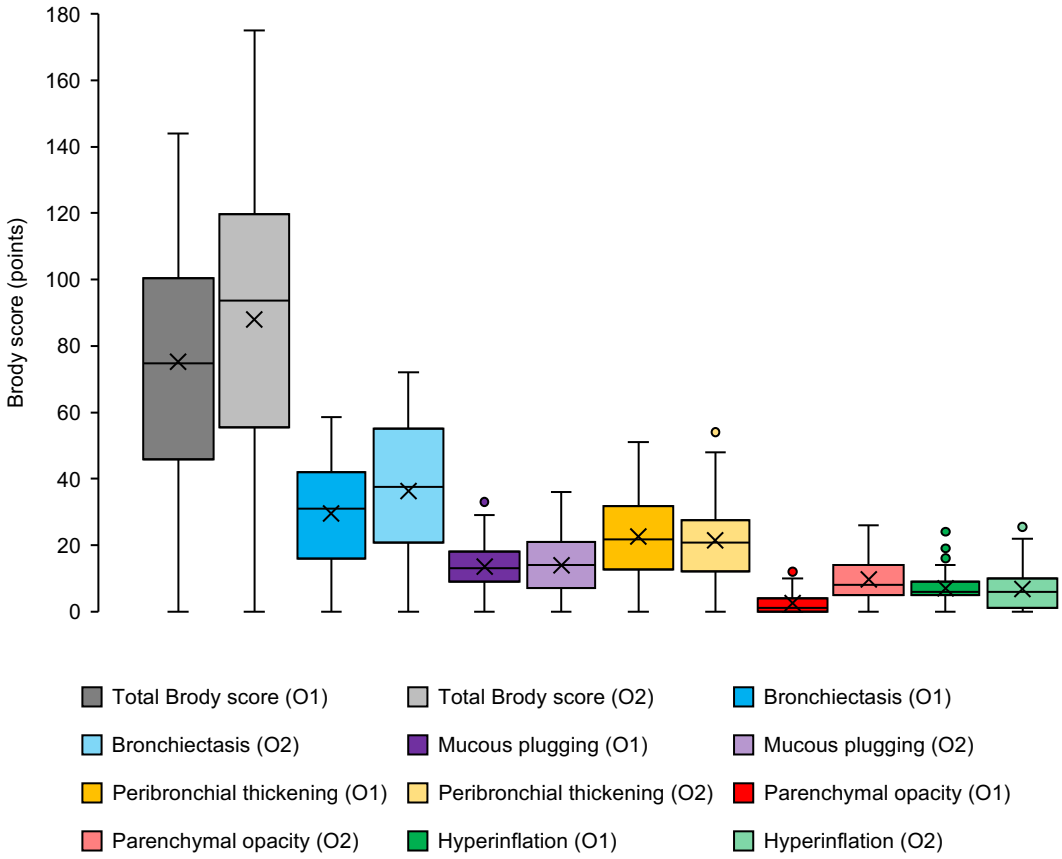


Figure 3: The Brody score in the cross-sectional study. The total Brody score (grey boxes) and its respective sub-scores for bronchiectasis (blue boxes), mucous plugging (purple boxes), peribronchial thickening (yellow boxes), parenchymal opacity (red boxes) and hyperinflation (green boxes) are shown in box-and-shisker-plots for each of the two observers, O1 and O2.

As displayed in Figure 3, a wide range of Brody scores was found (see Table 10 in the Appendix). The total Brody score scored by O1 ranged from 0 to 144 points, and from 0 to 175 points scored by O2. The possible maximum scoring result of 207 points was not reached. The entire possible ranges for the Brody sub-scores bronchiectasis, mucous plugging, peribronchial thickening and hyperinflation were only used by O2. The maximum scoring results of O1 for these sub-scores

were slightly lower. Even though a potential maximum of 54 points would have been possible, the highest parenchymal opacity sub-score was only 26 points from O2 and 12 points from O1.

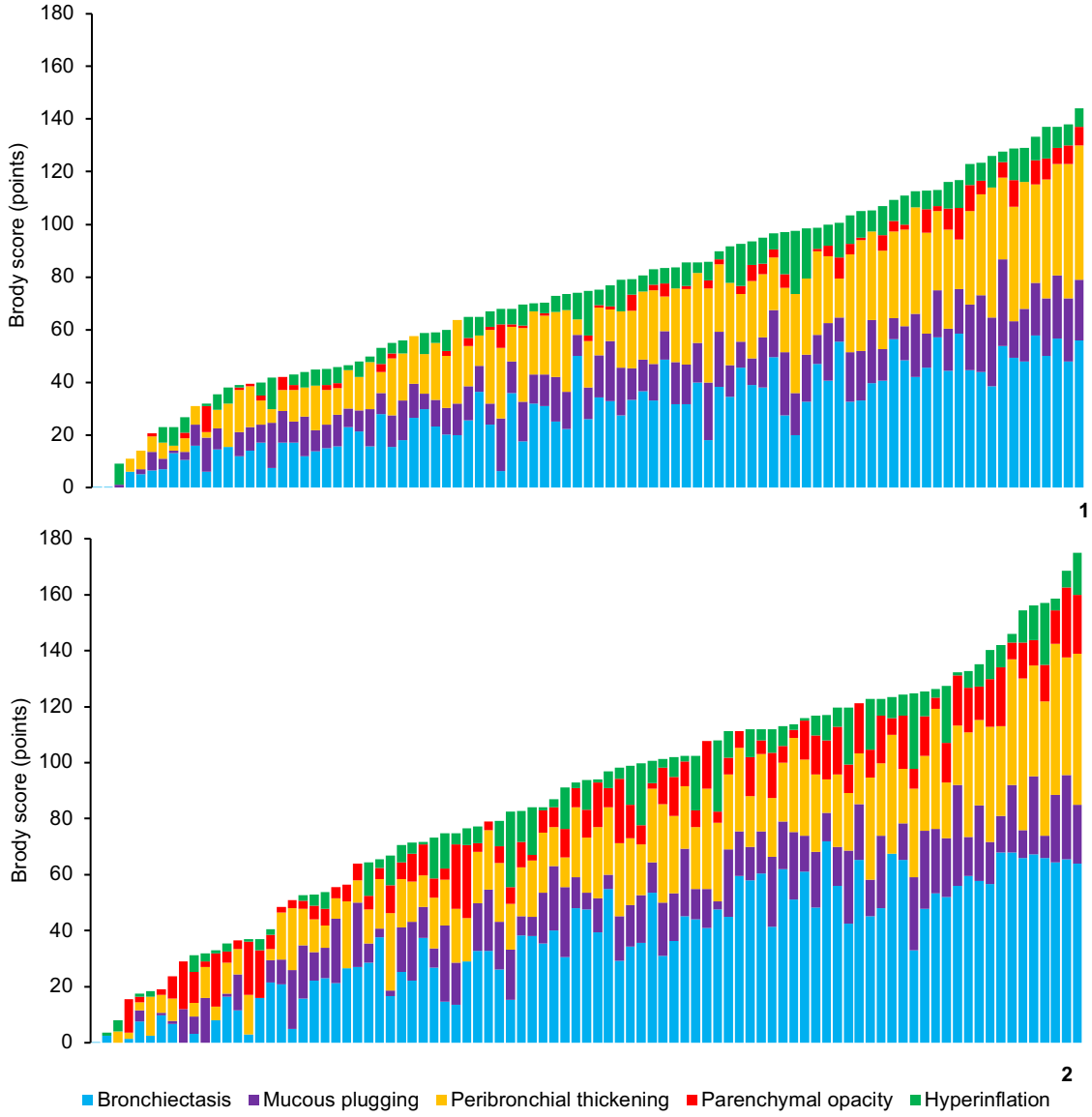


Figure 4: The composition of the total Brody score out of its five sub-scores in the cross-sectional study. The total Brody score composed of its respective sub-scores bronchiectasis (blue bars), mucous plugging (purple bars), peribronchial thickening (yellow bars), parenchymal opacity (red bars) and hyperinflation (green bars) is displayed on the x-axis in ascending order. **1** Brody score raised by O1 **2** Brody score raised by O2.

Figure 4 shows the composition of the total Brody scores. Each of the five sub-scores increased with a statistically highly significant correlation when the total Brody score rose (see Table 11 in the Appendix). The sub-scores for bronchiectasis and peribronchial thickening took the largest share of the total composite score. They also showed the best correlations with the total composite score (Spearman rank correlations, bronchiectasis: O1: r_s=0.90, O2: r_s=0.92; peribronchial thickening: O1: r_s=0.88, O2: r_s=0.85). The most significant difference between the Brody score from O1 and O2 was found in the parenchymal opacity sub-score. O2 assigned this sub-score in a higher proportion of patients as well as higher points in individual cases. Nevertheless, the Spearman rank correlation coefficients between the parenchymal opacity sub-score and the total Brody score were almost identical for O1 (r_s=0.50) and O2 (r_s=0.48).

5.1.3 Sample patients in the cross-sectional study

Figure 5 shows HRCT-images of a ∆-F-508 homozygote male CF sample patient at the age of 16.3 years as an example of low-grade disease severity with limited pulmonary changes.

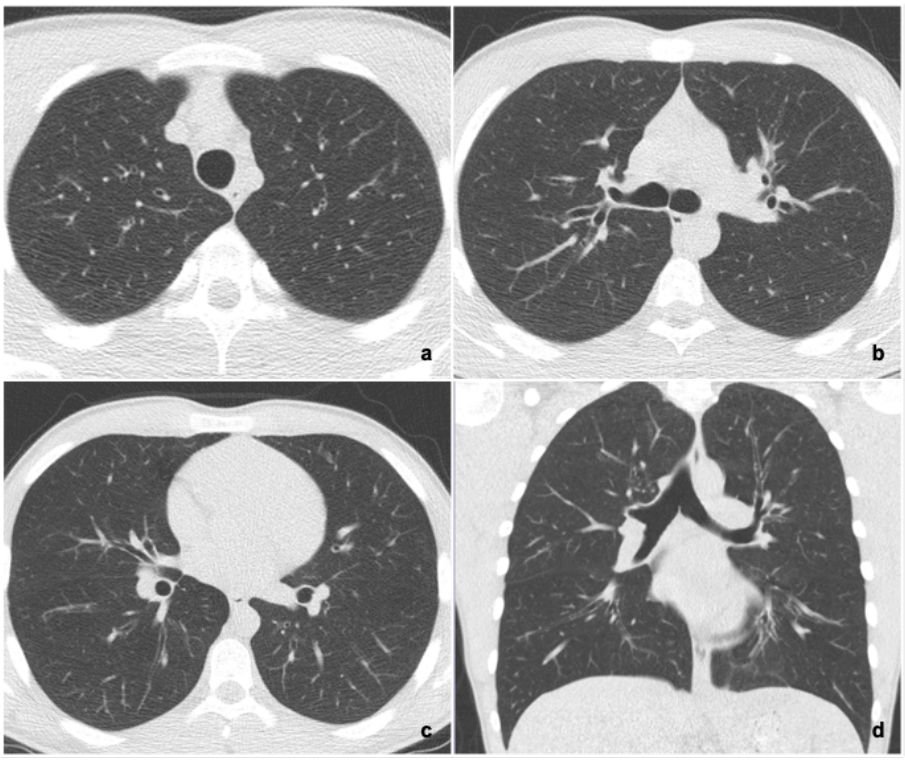


Figure 5: HRCT-images of a male CF sample patient with a low Brody score. a 5 cm above tracheal carina **b** at the level of tracheal carina **c** 5 cm below tracheal carina **d** coronal reconstruction showing the tracheal carina.

As displayed in Table 2, both observers assigned low values to the different sub-scores, resulting in a low total Brody score. The associated spirometry results were in the normal ranges for the patient's age and gender, with 95.7% for VC, 107.7% for FEV1, and a Tiffeneau index of 0.94.

Table 2: The Brody score of a CF sample patient with a low Brody score (see Fig. 5)

	O1	O2
Total Brody score	**11.00 points**	**18.50 points**
Bronchiectasis	6.00 points	2.50 points
Mucous plugging	0.00 points	0.00 points
Peribronchial thickening	5.00 points	14.00 points
Parenchymal opacity	0.00 points	0.00 points
Hyperinflation	0.00 points	2.00 points

For comparison, Figure 6 shows the HRCT-images of a patient with advanced CF-related lung disease, with advanced structural impairment of the lungs, resulting in a higher total Brody score. The patient was male, 20.1 years old, and ∆-F-508 heterozygous.

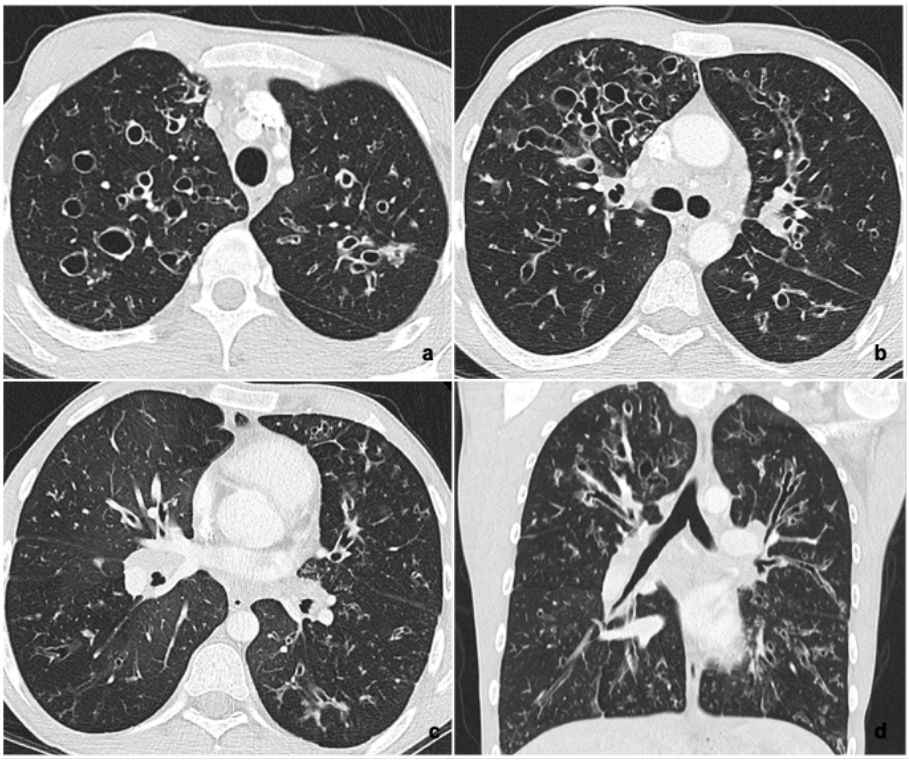


Figure 6: HRCT-images of a male CF sample patient with a high Brody score. a 5cm above tracheal carina **b** at the level of tracheal carina **c** 5cm below tracheal carina **d** coronal reconstruction showing the tracheal carina.

Unlike the sample patient in the first example above, this patient had high scoring results in all five sub-scores (see Table 3). The higher Brody score was associated with worse spirometry parameters compared to the first sample patient with a low Brody score, namely, 39.5% for VC and 23.5% for FEV1, with a Tiffeneau index of 0.49.

Table 3: The Brody score of a CF sample patient with a high Brody score (see Fig. 6)

	O1	O2
Total Brody score	**93.50 points**	**93.75 points**
Bronchiectasis	39.00 points	47.50 points
Mucous plugging	10.00 points	6.00 points
Peribronchial thickening	29.50 points	19.75 points
Parenchymal opacity	6.00 points	10.00 points
Hyperinflation	9.00 points	10.50 points

5.1.4 Interobserver reproducibility in the cross-sectional study

The Bland-Altman plot shown in Figure 7 visualizes the interobserver reproducibility of the Brody score. The results of the two observers showed a statistically highly significant correlation (Spearman rank correlations, r_s=0.69, p<0.001, n=91); however, with O2 raising higher scores than O1 (p<0.001, n= 87, Wilcoxon-test for matched pairs, considering ties). O2 raised, on average, 12.73 points higher scores than O1, with a maximum deviation of 84 points. The greater the total Brody score, the more significant the difference between O1 and O2.

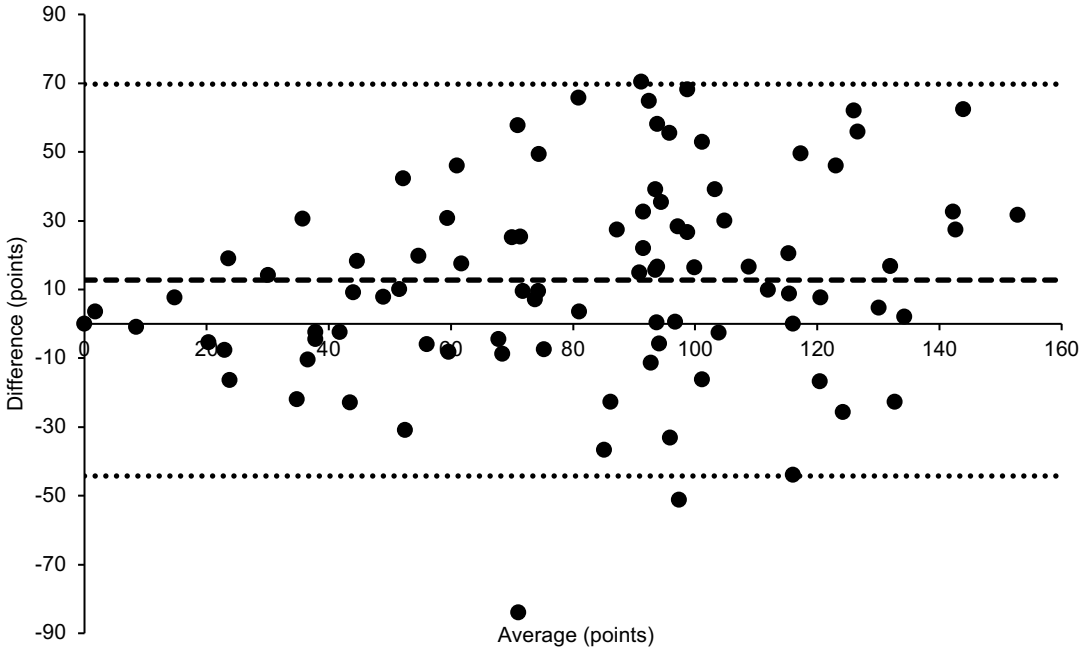
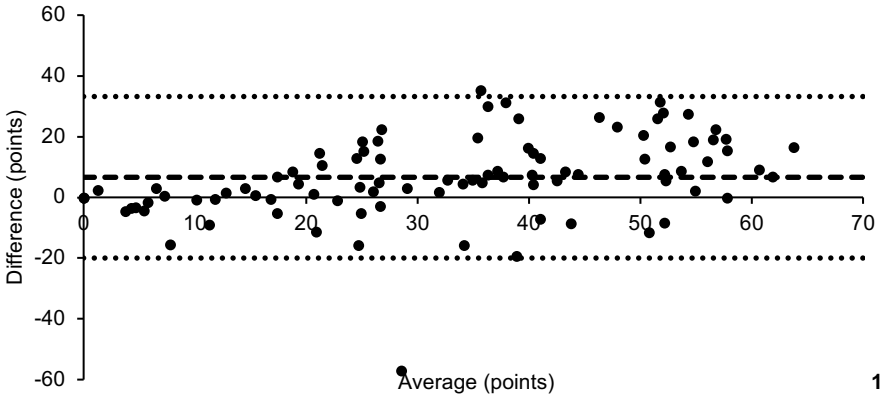
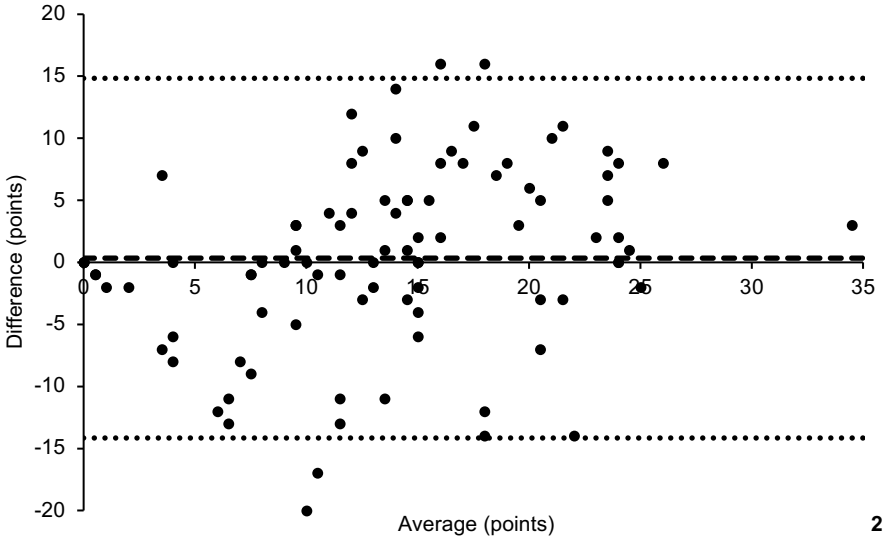


Figure 7: Interobserver reproducibility of the total Brody score in the cross-sectional study. The averages of the total Brody scores are displayed on the x-axis ((O1+O2)/2), and the difference of the total Brody score between O1 and O2 is displayed on the y-axis (O2-O1).

The Bland-Altman plots in Figure 8 visualise the interobserver reproducibility for each sub-score. As seen, there are systematic differences between the observers for the sub-scores on bronchiectasis and parenchymal opacity, respectively. O2 had higher scoring results in both sub-scores than O1 (bronchiectasis p<0.001, n= 87; parenchymal opacity p<0.001, n= 84; Wilcoxon-test for matched pairs, considering ties). Furthermore, the deviation increased when average scores increased, which is seen most clearly for the parenchymal opacity sub-score. The sub-scores on mucous plugging and peribronchial thickening showed an apparent spread, which mostly stayed within the limits of agreement. Especially for the hyperinflation sub-scores, large deviations were found around high average scoring results. There were no statistically significant differences between the observers for the sub-scores on mucous plugging, peribronchial thickening or hyperinflation (mucous plugging p>0.05, n= 79, rank sum: 1855,5, critical value: 1179; peribronchial thickening p>0.05, n= 87, rank sum: 1802,5, critical value: 1451; hyperinflation p>0.05, n= 80, rank sum: 1529,5, critical value: 1211; Wilcoxon-test for matched pairs, considering ties). For each sub-score of the Brody score, a statistically highly significant correlation was observed between the values of O1 and O2 (Spearman rank correlations, bronchiectasis r_s=0.77, mucous plugging r_s=0.55, peribronchial thickening r_s=0.49, parenchymal opacity r_s=0.46, hyperinflation r_s=0.37, each p<0.001, n=91).


Difference (points)
Average (points)
1


Difference (points)
Average (points)
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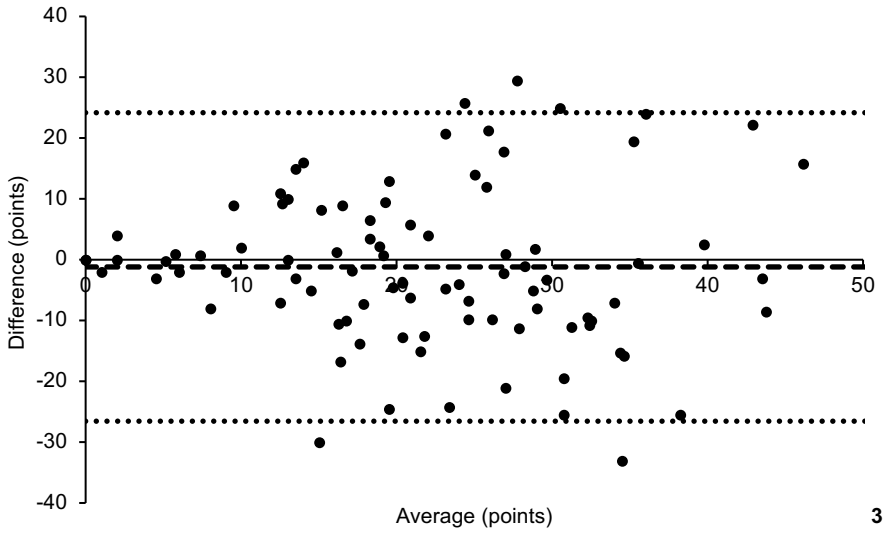
Difference (points)
Average (points)
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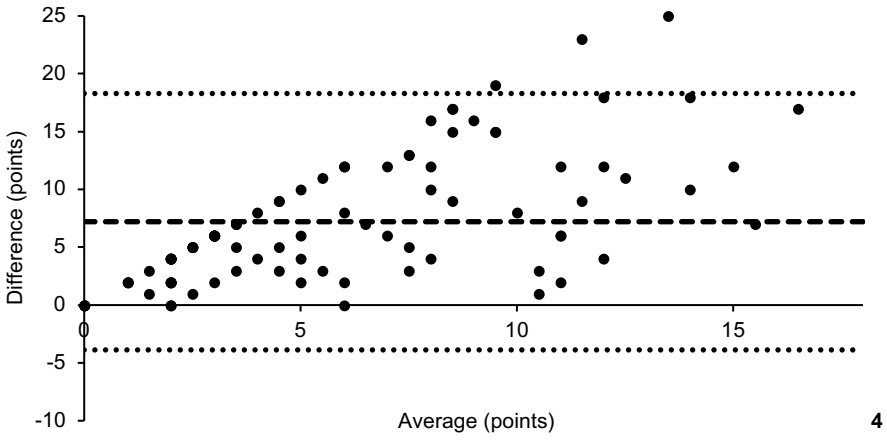
Difference (points)
Average (points)
4

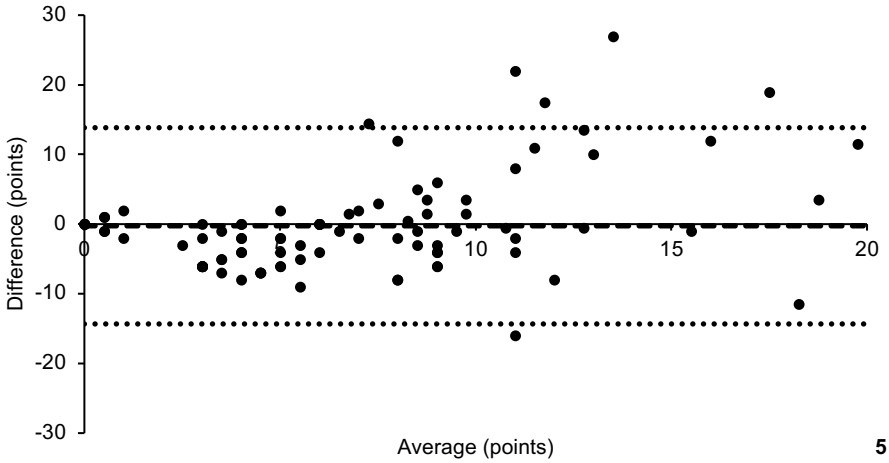

Figure 8: Interobserver reproducibility of the Brody sub-scores in the cross-sectional study. The averages of the Brody sub-score results are displayed on the x-axis ((O1+O2)/2), and the differences of the Brody sub-score results between O1 and O2 are displayed on the y-axis (O2-O1). **1** Bronchiectasis sub-score **2** Mucous plugging sub-score **3** Peribronchial thickening sub-score **4** Parenchymal opacity sub-score **5** Hyperinflation sub-score.

5.1.5 PFTs and the BMI in the cross-sectional study

Forty patients (twenty-one female, nineteen male) had a PFT within two days of their HRCT-examination. The spirometry parameters VC, FEV1, the Tiffeneau index and the BMI are displayed in Table 4.

Table 4: Spirometry parameters and the BMI in the cross-sectional study (n=40)

	Min.	Max.	Mean	Median	0.25	0.75
VC (%)	26.7	127.8	70.9	73.5	57.7	90.0
FEV1 (%)	17.7	116.0	61.6	62.6	42.9	83.5
FEV1/FVC	0.43	0.94	0.69	0.73	0.59	0.78
BMI (kg/m^2)	13.6	30.1	19.3	19.8	17.8	21.0

As with the Brody score, a wide range of PFT results and BMI were found, respectively. Only twelve CF patients had a normal FEV1 value (>80%). Eighteen patients had a Tiffeneau index <0.7, defined as pathological. Nineteen (47.5%) of the forty CF patients had a normal body mass index (BMI, 18.5 to 24.9 kg/m^2). Seventeen (42.5%) were underweight (BMI <18.5kg/m^2), three (7.5%) were overweight (BMI 25.0 to 29.9 kg/m^2), and one (2.5%) patient was adipose (BMI >30.0 kg/m^2).

Figure 9 visualises the correlation between the total Brody score and the spirometry parameters, VC and FEV1. The higher the Brody score, the lower the respective VC, FEV1 and Tiffeneau index results ($p<0.001$). Most Brody sub-scores also showed a statistically highly significant inverse correlation with the spirometry parameters, VC and FEV1, for both observers (for details, see Table 12 in the Appendix). The mucous plugging sub-score raised by O2 did not correlate

with the spirometry parameters, VC, FEV1, or the Tiffeneau index, and the parenchymal opacity sub-score raised by O1 did not correlate with the Tiffeneau index.

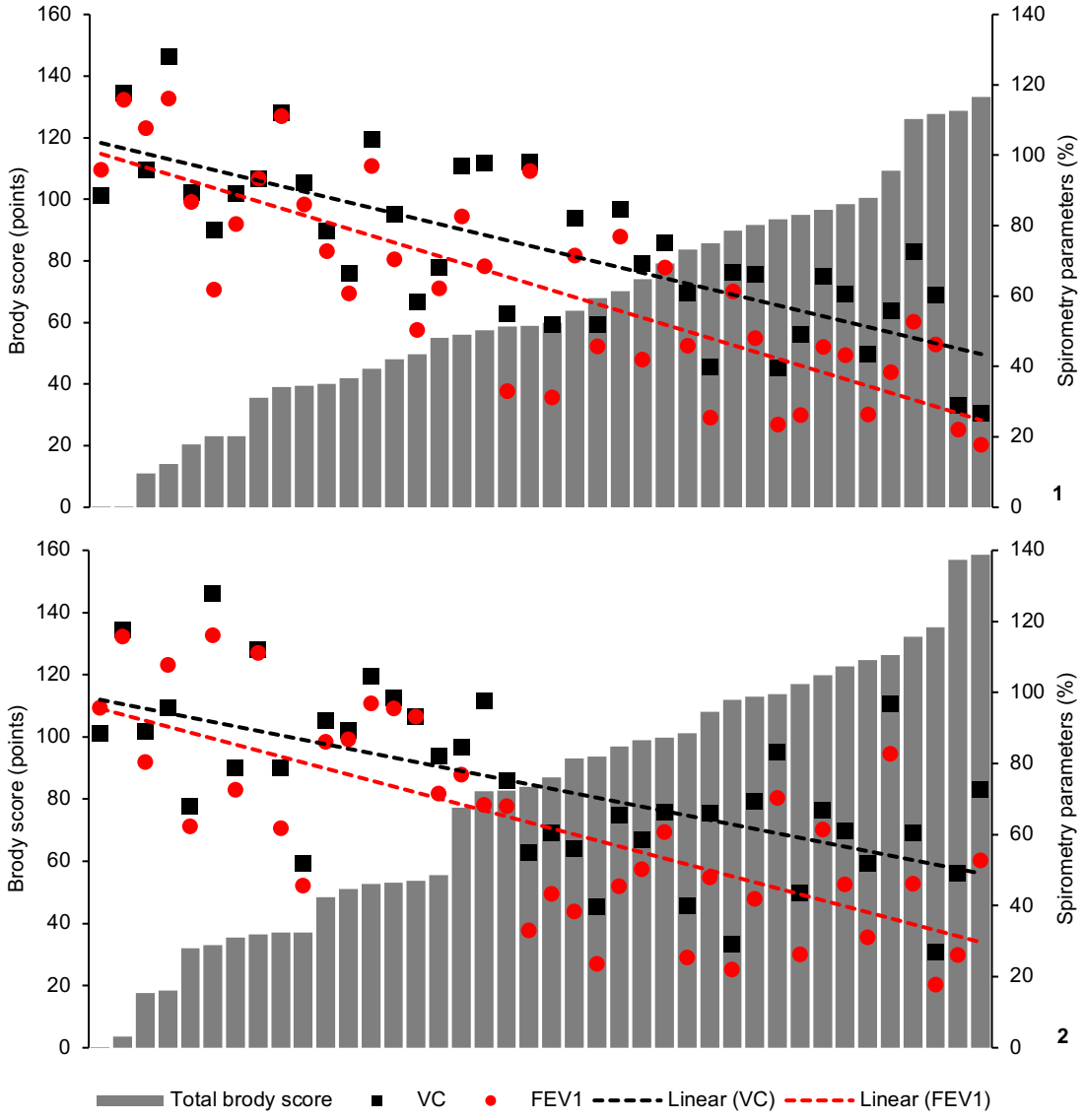

Figure 9: Correlation between the total Brody score and the spirometry parameters VC and FEV1 in the cross-sectional study. The total Brody score (grey bars) is displayed on the x-axis in ascending order, and the associated spirometry parameters VC (black squares) and FEV1 (red circles) are displayed on the y-axis. **1** Brody score raised by O1 (Spearman rank correlations, VC: r_s=-0.75; FEV1: r_s=-0.81) **2** Brody score raised by O2 (Spearman rank correlation, VC: r_s=-0.60; FEV1: r_s=-0.69).

A statistically highly significant correlation between the total Brody score and the BMI was found for both observers (Spearman rank correlations, O1: r_s=-0.76, O2: r_s=-0.67, both p<0.001, n=42). The higher the total Brody score of a patient, the lower the BMI at the time. This correlation also applied to the Brody sub-scores (for the exact Spearman rank correlation coefficients see Table 12 in the Appendix). The spirometry parameters also showed a statistically highly significant correlation with the BMI (Spearman rank correlations, VC: r_s=0.69, FEV1: r_s=0.72, p<0.001, n=42), where a higher BMI was associated with better spirometry parameters.

5.1.6 The influence of gender, age, the genetic mutation status, and the examination date in the cross-sectional study

Between the forty-four male and the forty-seven female patients, no statistically significant difference in the Brody score was found (Mann-Whitney-U-test, O1: U=914,5; p>0.05; rank sum females: 2281,5; n=47; rank sum males: 1904,5; n=44; critical value: 377; O2: U=930,5; p>0.05; rank sum females: 2265,5; n=47; rank sum males: 1920,5; n=44; critical value: 377). A complete overview of the Brody score per gender can be found in Table 13 in the Appendix. Within the group of patients having a PFT within two days, no statistically significant difference between the twenty-one female and the nineteen male patients was found for VC, FEV1 or the BMI (Mann-Whitney-U-test, VC: U=173; p>0.05; rank sum females: 457; n=21; rank sum males: 363; n=19; critical value: 126; FEV1: U=170; p>0.05; rank sum females: 460; n=21; rank sum males: 360; n=19; critical value: 126; BMI: U=171; p>0.05; rank sum females: 459; n=21; rank sum males: 361; n=19; critical value: 126). A statistically significant difference was observed for the Tiffeneau index, with the female patients having a slightly higher average value of 0.73 compared to the male patients, who had an average of 0.65 (Mann-Whitney-U-test, U=125; p<0.05; rank sum females: 505; n=21; rank sum males: 315; n=19, critical value: 126).

Within the cross-sectional study, neither the total Brody score (Spearman rank correlations, O1: r_s=0.10, p>0.05, n=91; O2: r_s=0.18, p>0.05, n=91) nor the BMI or the spirometry parameters correlated with the age of the patients (Spearman rank correlations, VC: r_s=0.08, p>0.05, n=40; FEV1: r_s=-0.17, p>0.05, n=40; FEV1/FVC: r_s=-0.18, p>0.05, n=40; BMI: r_s=-0.02, p>0.05, n=40). Also, the specific date of the examination, whether the HRCT-examination was performed at the beginning or at the end of the 20-year period that was examined, did not impact the height of the total Brody score (Spearman rank correlations, O1: r_s=0.01, p>0.05, n=91, O2: r_s=-0.03, p>0.05, n=91), the spirometry parameters or the BMI (Spearman rank correlations, VC: r_s=-0.06, p p>0.05, n=40; FEV1: r_s=-0.02, p>0.05, n=40; FEV1/FVC: r_s=-0.02, p>0.05, n=40; BMI: r_s=-0.02, p>0.05, n=40).

Figure 10 displays the Brody score divided according to the different genetic mutations of the CF patients. Due to the small sample size of patients with other genetic mutations (six patients), only the groups of ∆-F-508 homozygous and -heterozygous CF patients were compared. In both cases (scored by O1 and O2), no statistically significant difference between those two groups could be found (Mann-Whitney-U-test, O1: U=499; p>0.05; rank sum ∆-F-508 homozygous patients: 1298; n=39; rank sum ∆-F-508 heterozygous patients: 877; n=27; critical value: 204; O2: U= 490; p>0.05; rank sum ∆-F-508 homozygous patients: 1270; n=39; rank sum ∆-F-508 heterozygous patients: 894,5; n=27; critical value: 204).

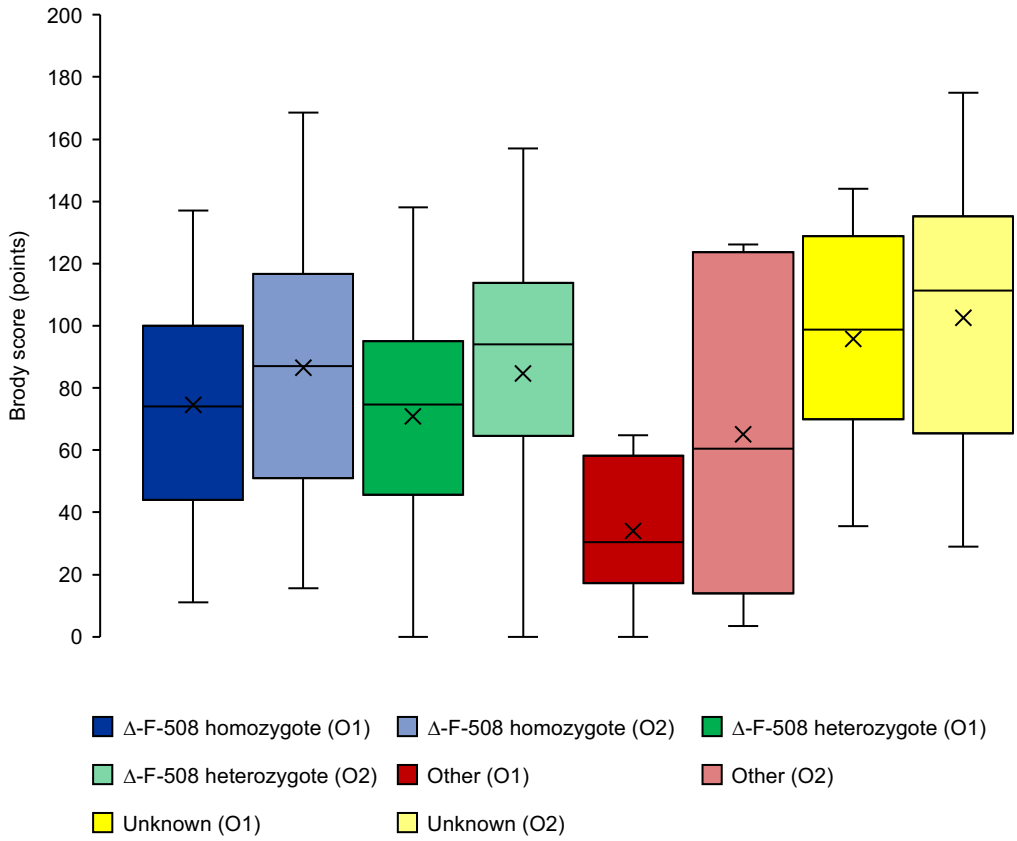

Figure 10: The influence of the genetic mutation on the Brody score in the cross-sectional study. The respective numbers of patients carrying the different genetic mutations were as follows: thirty-nine homozygous (blue boxes) and twenty-seven Δ-F-508 heterozygous (green boxes) carriers of the Δ-F-508 mutation, six patients with other genetic mutations (red boxes) and nineteen patients in whom the genetic mutation was unknown (yellow boxes). The different genetic mutations were shown in box-and-shisker plots for each of the two observers, O1 and O2.

5.2 Results of the Cohort Study

5.2.1 Descriptive Statistic of the CF patients in the cohort study

Eleven female and eighteen male CF patients were included in the retrospective cohort study. The age of the CF patients at the initial and the follow-up HRCT-examinations as well as the genetic mutation status is displayed in Table 5. There was no relevant difference in age between females and males. Twenty-six CF patients (90%) presented at least one ∆-F-508 mutation.

Table 5: Patient demographics in the cohort study

		total	female	male
n		29	11	18
Age at initial HRCT-examination (years)	lowest	15.6	15.9	15.6
	highest	21.3	21.3	21.1
	mean	18.8	18.6	18.8
	median	18.9	18.5	19.1
Age at follow-up HRCT-examination (years)	lowest	18.6	19.8	18.6
	highest	26.0	25.2	26.0
	mean	22.8	22.5	22.9
	median	23.4	23.2	23.4
Interval between initial and follow-up HRCT-examination (years)	lowest	2.9	2.9	2.9
	highest	5.3	4.9	5.3
	mean	4.0	3.9	4.1
	median	4.0	4.0	4.2
Genetic mutation	∆-F-508 homozygote	17	6	11
	∆-F-508 heterozygote	9	4	5
	other	1	0	1
	unknown	2	1	1

5.2.2 The Brody score in the cohort study

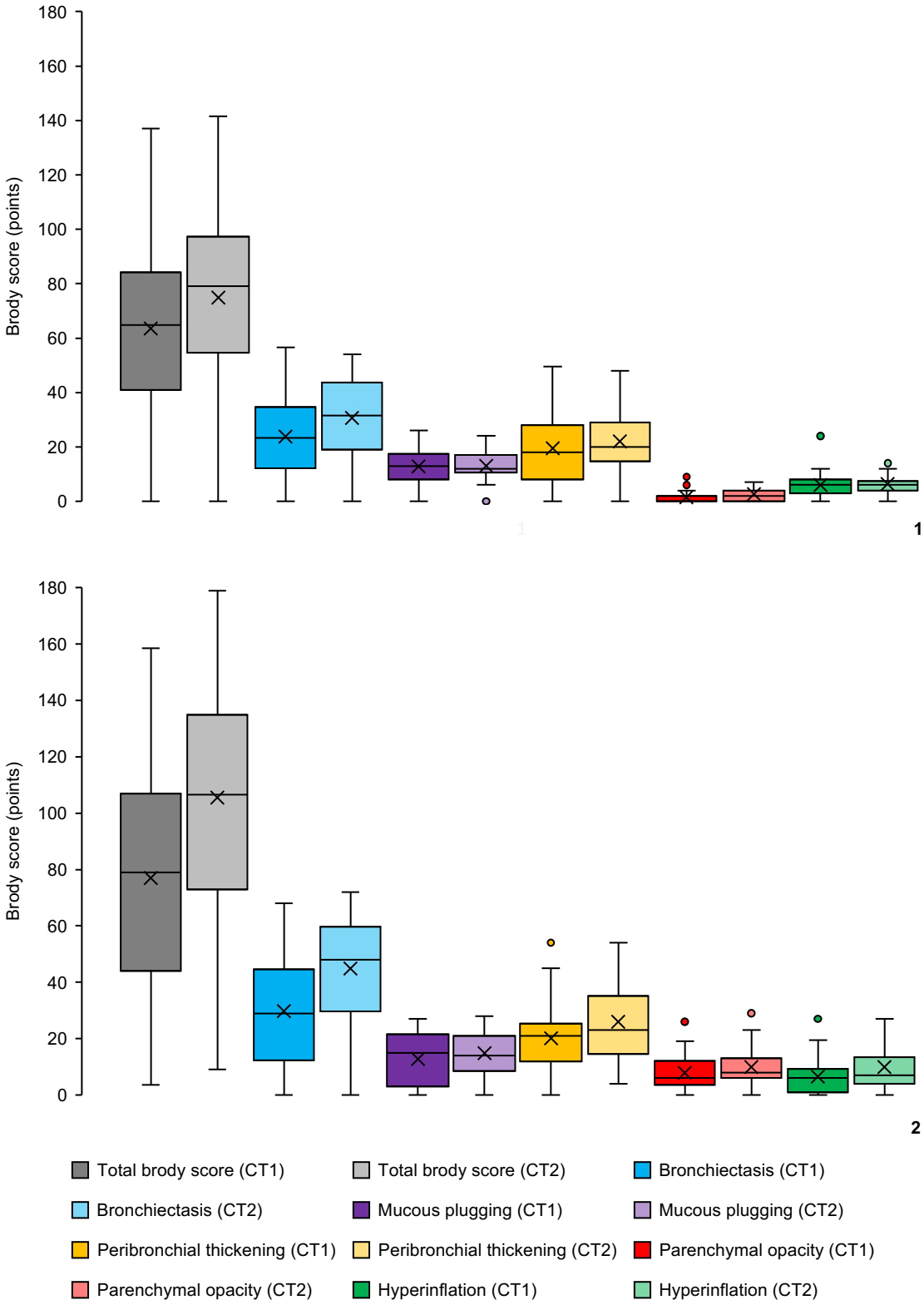

Figure 11: Comparison of the respective Brody scores of the initial and the follow-up HRCT-examinations. CT1 stands for the initial HRCT-examination performed at the age of sixteen to twenty-two years; CT2 stands for the follow-up HRCT-examination four years later. **1** Brody score raised by O1 **2** Brody score raised by O2. The total Brody score (grey boxes) and its respective sub-scores for bronchiectasis (blue boxes), mucous plugging (purple boxes), peribronchial thickening (yellow boxes), parenchymal opacity (red boxes), and hyperinflation (green boxes) are shown in box-and-shisker-plots for each of the two observers, O1 and O2.

As seen in Figure 11, the total Brody score presented a higher range and maximum values in the follow-up examination. The follow-up examination results were significantly higher than the initial examination results (O1 & O2: $p<0.001$, each, n= 29, Wilcoxon-test for matched pairs, no ties). The same change is also visible for the bronchiectasis sub-score (O1: $p<0.01$; O2: $p<0.001$, each, n= 28, Wilcoxon-test for matched pairs, considering ties). For the sub-scores peribronchial thickening and hyperinflation, a statistically significant increase was found only by O2 (O2: peribronchial thickening $p<0.05$, n= 29, hyperinflation: $p<0.05$, n= 26; O1: peribronchial thickening $p>0.05$, n= 29, rank sum: 163, critical value: 126, hyperinflation $p>0.05$, n= 23, rank sum: 148, critical value: 73, Wilcoxon-test for matched pairs, considering ties). The remaining sub-scores mucous plugging and parenchymal opacity did not show a statistically significant difference between the initial and follow-up examinations (O1: mucous plugging $p>0.05$, n= 28, rank sum: 211, critical value: 116, parenchymal opacity $p>0.05$, n= 22, rank sum: 85, critical value: 65; O2: mucous plugging $p>0.05$, n=27, rank sum: 173, critical value: 107, parenchymal opacity $p>0.05$, n= 28, rank sum: 175,5, critical value: 116, Wilcoxon-test for matched pairs, considering ties).

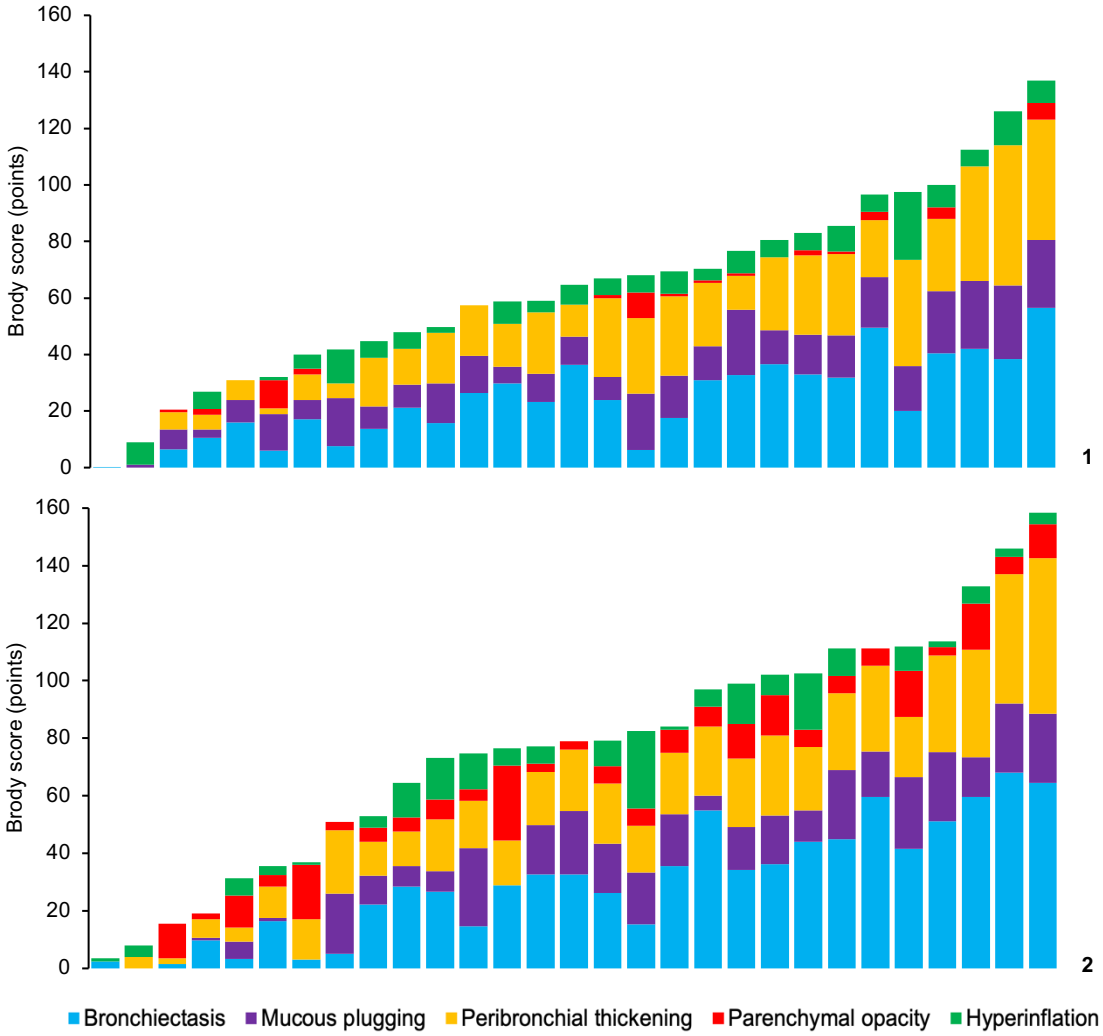

Figure 12: Composition of the respective total Brody scores and its five sub-scores for the initial HRCT-examinations as assessed by two independent observers (O1, O2). The total Brody score composed of its respective sub-scores bronchiectasis (blue bars), mucous plugging (purple bars), peribronchial thickening (yellow bars), parenchymal opacity (red bars), and hyperinflation (green bars) is displayed on the x-axis in ascending order. **1** Brody score raised by O1 **2** Brody score raised by O2.

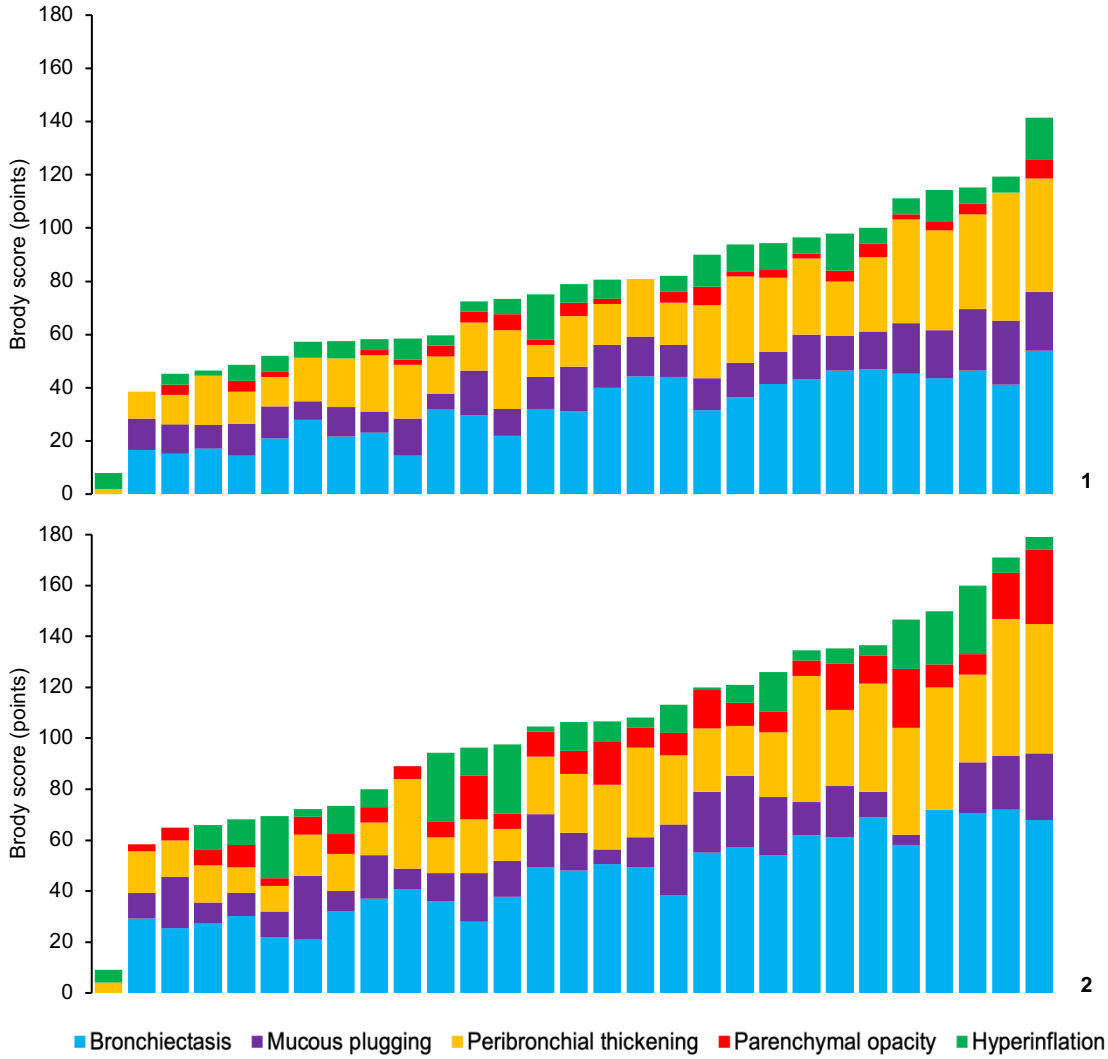

Figure 13: Composition of the respective total Brody scores and its five sub-scores for the follow-up HRCT-examinations as assessed by two independent observers (O1, O2). The total Brody score composed of its respective sub-scores bronchiectasis (blue bars), mucous plugging (purple bars), peribronchial thickening (yellow bars), parenchymal opacity (red bars), and hyperinflation (green bars) is displayed on the x-axis in ascending order. **1** Brody score raised by O1 **2** Brody score raised by O2.

Figure 12 and Figure 13 display the composition of the total Brody score out of its five sub-scores for the initial and the follow-up HRCT-examinations. It is noticeable that there are nearly no low scores in the follow-up examination compared to the initial examination. As seen in Figure 13, this is primarily due to the increase of the sub-scores bronchiectasis, mucous plugging, and peribronchial thickening. The exact values of the Brody score and its respective sub-scores for the initial and the follow-up HRCT-examination can be found in Table 14 and Table 15 in the Appendix.

In the scores raised by O1, nineteen patients showed an increase of their score by an average of 29.82 points, nine patients showed an average decrease of 19.19 points, and one patient had the same total Brody score in both examinations. For O2, there were twenty-two patients with an average increase of 41.11 points and seven patients with an average decrease of 10.96 points of their total Brody score. The exact values of the Brody score changes can be found in Table 16 in the Appendix.

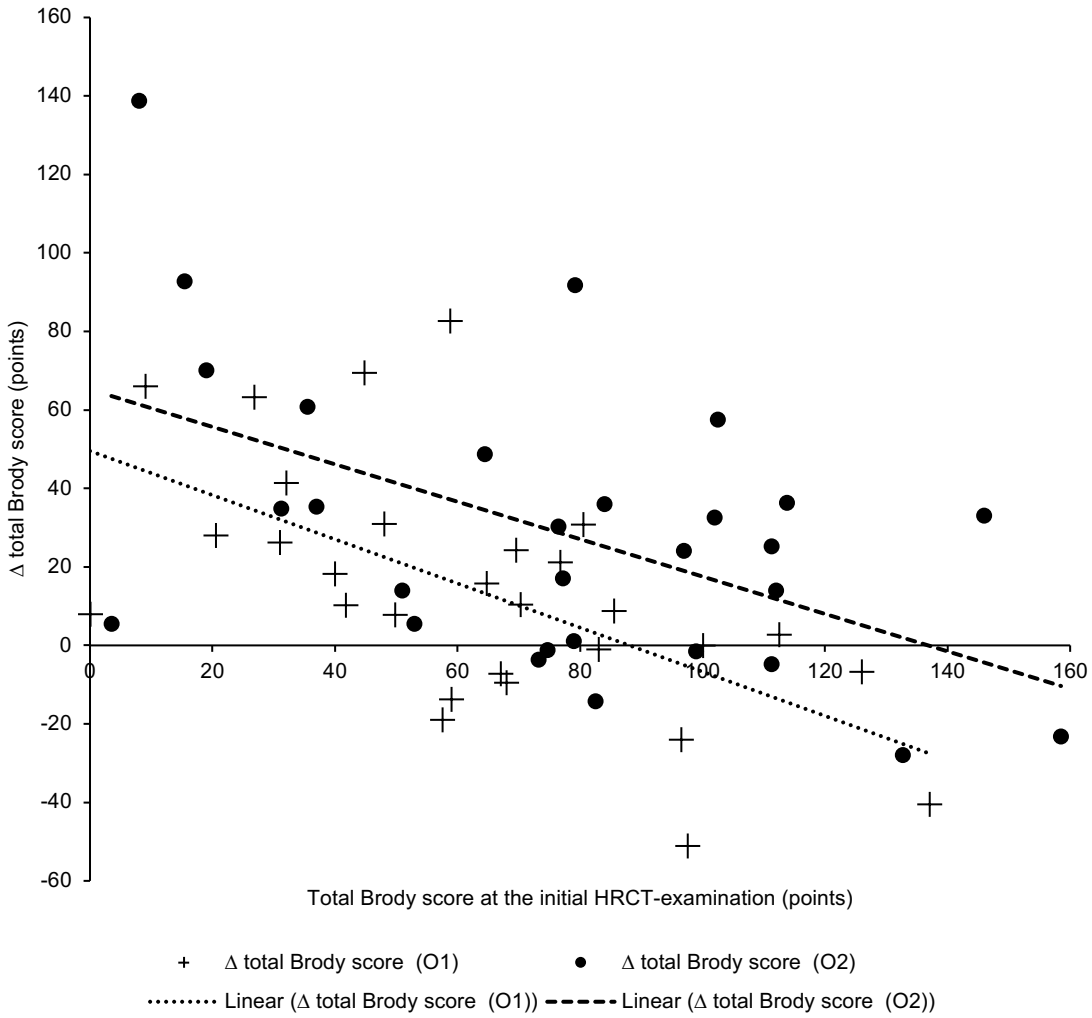

Figure 14: Total Brody score changes as a function of the initial total Brody score. The initial Brody scores are displayed on the x-axis, and the differences in Brody-scoring results between the subsequent and the initial HRCT-examination are displayed on the y-axis for O1 (black crosses) and O2 (black circles).

As Figure 14 graphically illustrates, the change of the Brody score is inversely correlated with the initial Brody score. The lower the initial score, the higher the increase in the Brody score (Spearman rank correlations, O1: r_s=-0.60, p<0.001, n=29; O2: r_s=-0.39, p<0.05, n=29). Decreases in the Brody score were only found in patients with a medium or high initial score. To investigate potential differences between patients with an initial low score and those with an initial high score, the group was divided into two subgroups based on the median value of the initial Brody score. The median value for the entire group was 64.75 points scored by O1 and 79 points scored by O2. The Mann-Whitney U test was used to examine the difference in Brody score changes between these subgroups. Notably, a significant difference in the Brody score change was observed only for O1 (Mann-Whitney-U-test, O1: U=46, p<0.05, rank sum CF patients with lower initial score: 269, n=14; rank sum CF patients with higher initial score: 166, n=15; critical value: 59; O2: U=73,5, p>0.05, rank sum CF patients with lower initial score: 241.5, n=14; rank sum CF patients with higher initial score:193.5, n=15; critical value: 59).

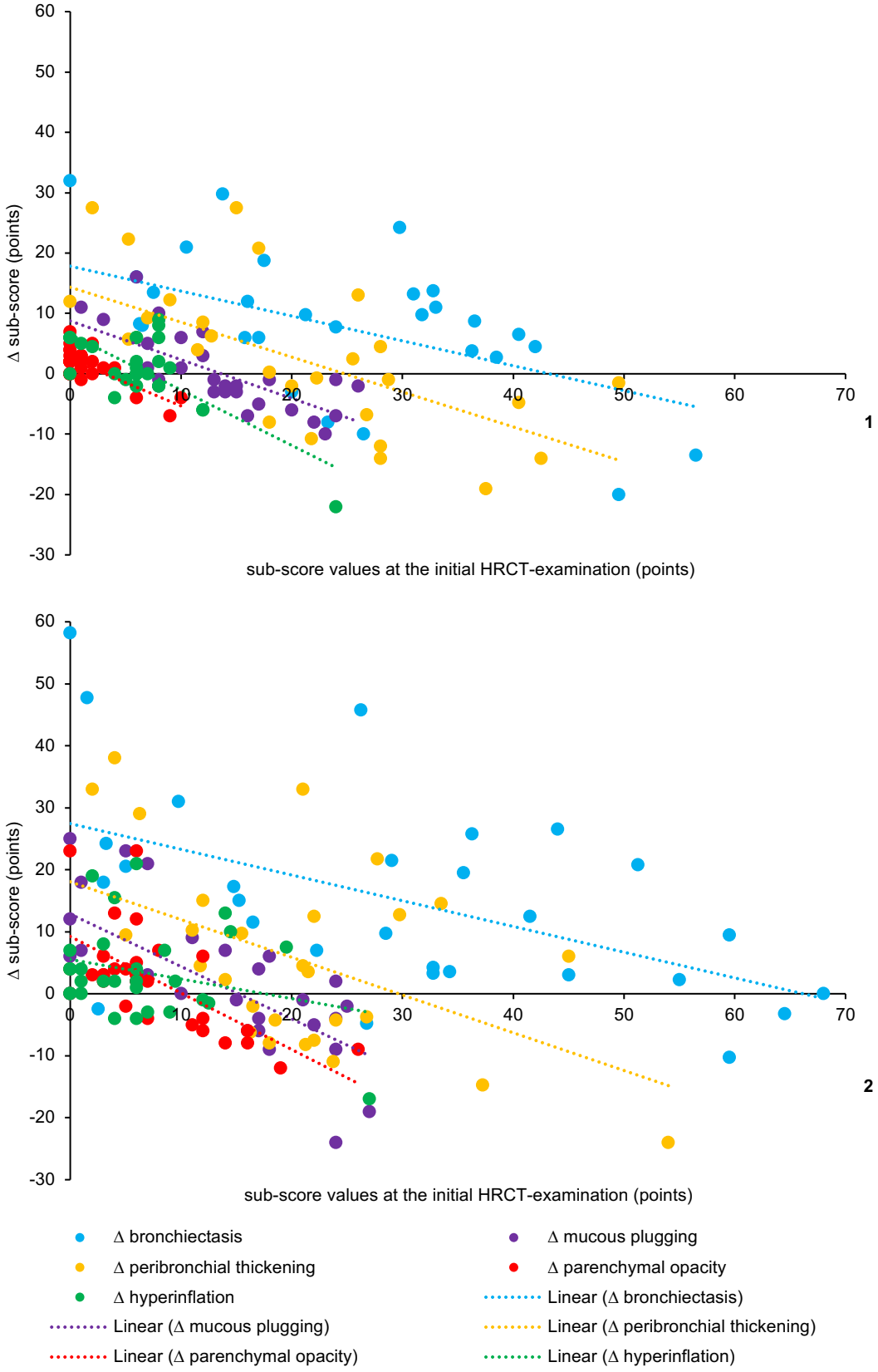

Figure 15: Brody sub-score changes as a function of the initial sub-score values. The initial Brody sub-score results for bronchiectasis (blue circles), mucous plugging (purple circles), peribronchial thickening (yellow circles), parenchymal opacity (red circles), and hyperinflation (green circles) are displayed on the x-axis. The differences in Brody sub-scoring results between the subsequent and the initial HRCT-examination are displayed on the y-axis **1** raised by O1 **2** raised by O2.

Figure 15 graphically illustrates the changes of the Brody sub-scores based on the initial sub-score values. The changes in the sub-scores on bronchiectasis (Spearman rank correlations, O1: r_s=-0.43, p<0.05, n=29; O2: r_s=-0.48, p<0.01, n=29), mucous plugging (Spearman rank correlations, O1: r_s=-0.77, p<0.001, n=29; O2: r_s=-0.72, p<0.001, n=29), peribronchial thickening (Spearman rank correlations, O2: r_s=-0.69, p<0.001, n=29; O2: r_s=-0.38, p<0.05, n=29), and, for O2 only, parenchymal opacity (Spearman rank correlations, O2: r_s=-0.49, p<0.01, n=29) inversely correlated with the initial sub-score values. The changes in the sub-scores on parenchymal opacity, raised by O1 (Spearman rank correlations, O1: r_s=-0.33, p>0.05, n=29), and hyperinflation (Spearman rank correlations, O1: r_s=-0.32, p>0.05, n=29; O2: r_s=-0.10, p>0.05, n=29) did not statistically significantly correlate with the initial sub-score values.

5.2.3 Sample patient in the cohort study

Figure 16 shows HRCT-images of a ∆-F-508 heterozygous female patient with advanced CF-related pulmonary damage. Structural impairments of the lungs were already apparent in the initial HRCT-examination.

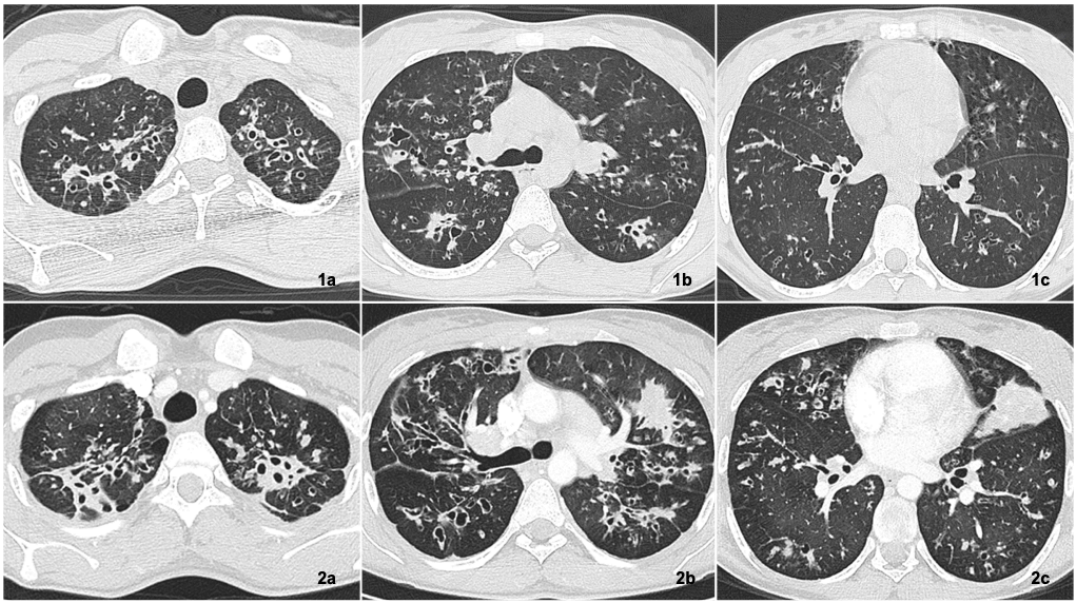

Figure 16: Example of changes of CF-related lung morphology over four years. Upper panel, **1** HRCT-images of a 20.1-year-old female CF sample patient **a** 5 cm above tracheal carina **b** at the level of tracheal carina **c** 5 cm below tracheal carina, lower panel, **2** CT scan of the same patient 4.0 years later at the age of 24.1 **a** 5 cm above tracheal carina **b** at the level of tracheal carina **c** 5 cm below tracheal carina.

O1 assigned a total Brody score of 58.75 points, while O2 allocated 84 points. The PFT results were 54.8% for VC, 33.0% for FEV1, and 0.52 for the Tiffeneau index. The follow-up examination after 4.0 years showed increased CF-related pulmonary changes, particularly bronchiectasis and peribronchial thickening. This worsening resulted in a total Brody score of 141.50 points by O1, more than a doubling of the initial Brody score (+141%), and 120 points by O2, corresponding to an increase of 43 % from the initial Brody score. Both observers found increases for all five sub-scores (see Table 6). The vital capacity slightly worsened over time with 50.8%. The Tiffeneau index stayed almost unchanged at 0.56. The FEV1, though, improved with 51.1%.

Table 6: The Brody score for the initial and the follow-up HRCT-examination and its change of a female CF sample patient (see Fig. 16)

		initial HRCT-examination	follow-up HRCT-examination	change
Total Brody score	O1	58.75	141.50	82.75
	O2	84.00	120.00	36.00
Bronchiectasis	O1	29.75	54.00	24.25
	O2	35.50	55.00	19.50
Mucous plugging	O1	6.00	22.00	16.00
	O2	18.00	24.00	6.00
Peribronchial thickening	O1	15.00	42.50	27.50
	O2	21.50	25.00	3.50
Parenchymal opacity	O1	0.00	7.00	7.00
	O2	8.00	15.00	7.00
Hyperinflation	O1	8.00	16.00	8.00
	O2	1.00	1.00	0.00

5.2.4 PFTs and the BMI in the cohort study

Among the twenty-nine patients in the cohort study, twelve (41%) had a PFT within two days of their initial HRCT-examination, and twenty-three (79%) within two days of their follow-up HRCT-examination, respectively. Table 17 and Table 18 in the Appendix show a complete overview of the respective spirometry parameters for the initial and the follow-up HRCT-examination.

The spirometry parameters VC and FEV1 correlated inversely with the total Brody score for the initial and the follow-up examination, graphically illustrated in Figure 17 and Figure 18. The Spearman's rank correlation coefficients for the correlations between the total Brody score, the spirometry parameters VC and FEV1, the Tiffeneau index, and the BMI can be found in Table 19 in the Appendix. Among those twelve patients, who had a PFT within two days of each the initial and the follow-up HRCT-examination, seven patients showed a worsening, and five patients showed an improvement of their spirometry parameters. One half had a lower, and the other half had a higher BMI at the follow-up examination. There was no statistically significant change of the spirometry parameters over time (VC: $p>0.05$, $n= 12$, rank sum: 33, critical value: 13; FEV1: $p>0.05$, $n= 12$, rank sum: 33, critical value: 13, Wilcoxon-test for matched pairs, no ties). Table 20 shows a complete overview of the change of the spirometry parameters, including the BMI, in the Appendix.

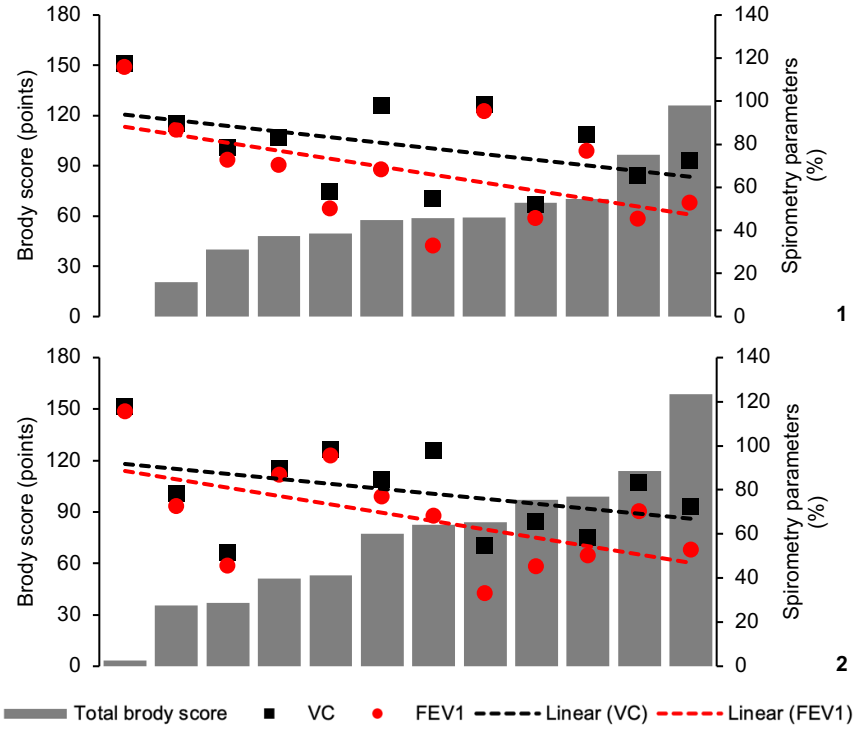

Figure 17: Associated spirometry parameters at the respective time of the initial HRCT-examination. The total Brody score (grey bars) is displayed on the x-axis in ascending order, and the associated spirometry parameters VC (black squares) and FEV1 (red circles) are displayed on the y-axis. **1** Brody score raised by O1 **2** Brody score raised by O2**.**

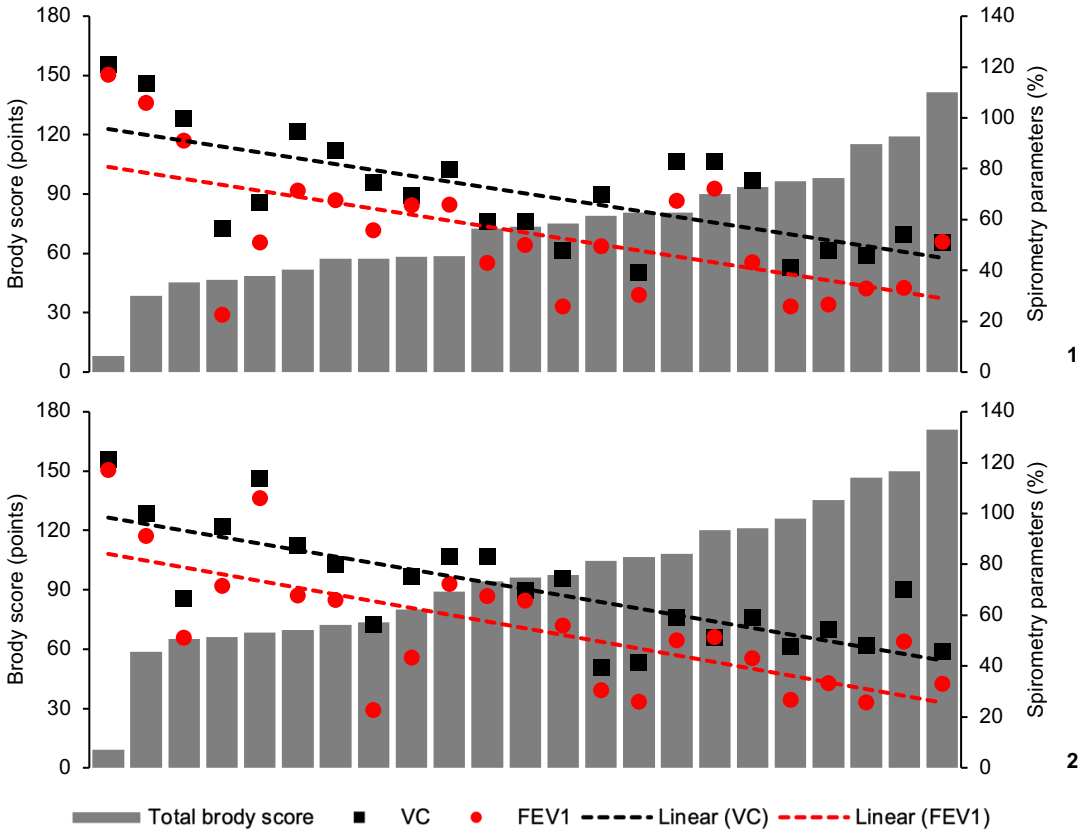

Figure 18: Associated spirometry parameters at the respective time of the follow-up HRCT-examination. The total Brody score (grey bars) is displayed on the x-axis in ascending order, and the associated spirometry parameters VC (black squares) and FEV1 (red circles) are displayed on the y-axis. **1** Brody score raised by O1 **2** Brody score raised by O2**.**

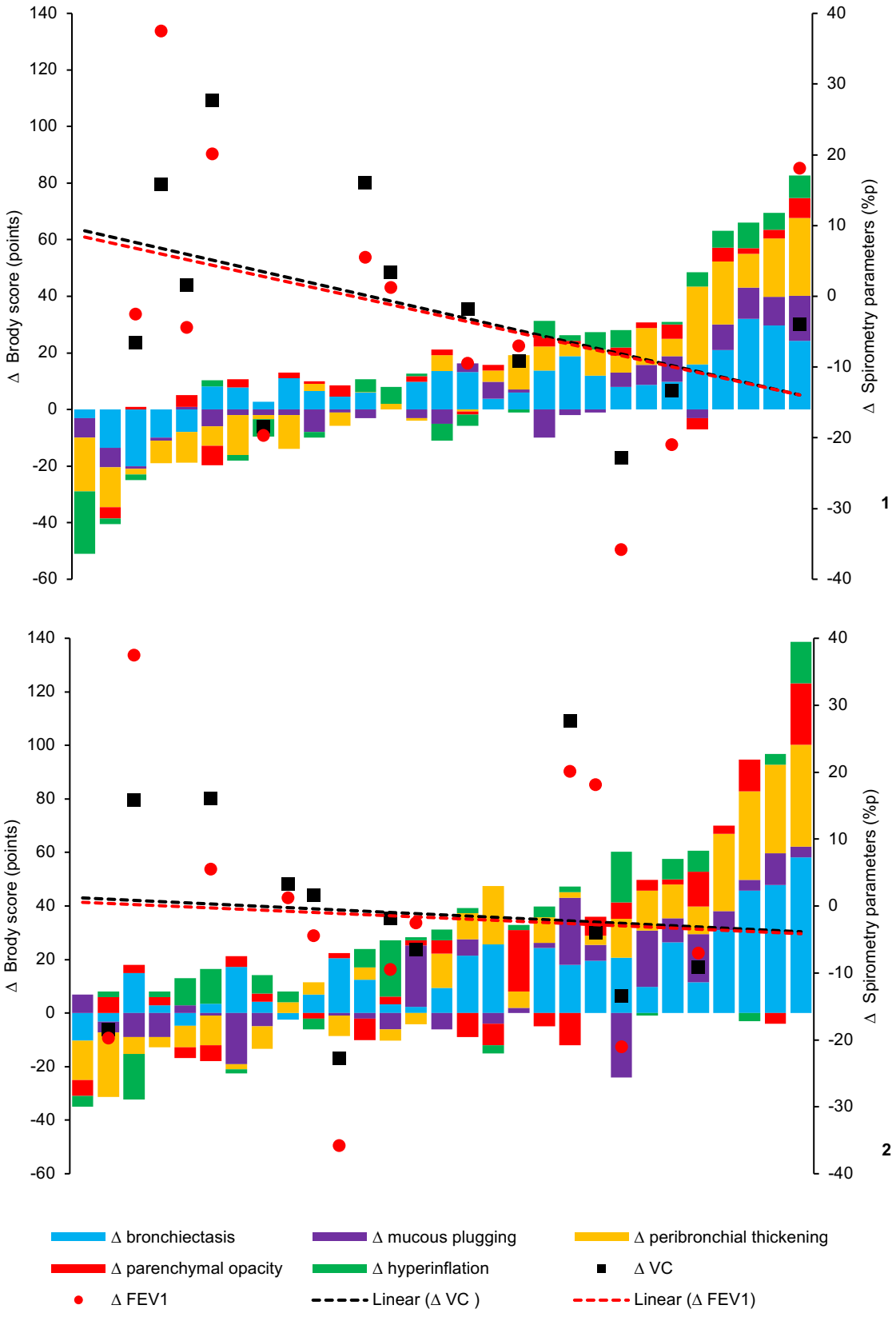

Figure 19: Brody score chances with the associated changes of the spirometry parameters VC and FEV1. The Brody score changes are displayed on the x-axis in ascending order with, if available, the associated changes of the spirometry parameters VC (black squares) and FEV1 (red circles). **1** Brody score raised by O1 **2** Brody score raised by O2.

Figure 19 illustrates the changes of the total Brody score out of its respective sub-scores, together with the associated changes of the spirometry parameters, VC and FEV1, if available. The increase of the total Brody score depends primarily on the increase of the sub-scores bronchiectasis, mucous plugging, and peribronchial thickening. The decrease of some of the total Brody scores can be mainly ascribed to the decrease of the sub-scores mucous plugging and peribronchial thickening, as well as the sub-score bronchiectasis for those scored by O1. There was no statistically significant correlation between the change of the Brody score and the change of the spirometry parameters, neither for the VC (Spearman rank correlations, O1: r_s=0.45, p>0.05, n=12; O2: r_s=0.22, p>0.05, n=12) nor for the FEV1 (Spearman rank correlations, O1: r_s=0.42, p>0.05, n=12; O2: r_s=0.13, p>0.05, n=12), nor for the Tiffeneau index (Spearman rank correlations, O1: r_s=-0.27, p>0.05, n=12; O2: r_s=0.10, p>0.05, n=12).

5.2.5 The influence of gender, the genetic mutation status, and the examination date in the cohort study

There were no statistically significant differences in Brody score changes between men and women (Mann-Whitney-U-test, O1: U=62; p>0.05; rank sum females: 202; n=11; rank sum males: 233; n=18, critical value: 55; O2: U=83,5; p>0.05; rank sum females: 180,5; n=11; rank sum males: 254,5; n=18, critical value: 55) or between ∆-F-508-homozygous and heterozygous CF patients (Mann-Whitney-U-test, O1: U=53; p>0.05; rank sum ∆-F-508 homozygous patients: 206; n=17; rank sum ∆-F-508 heterozygous patients: 145; n=9, critical value: 39; O2: U= 61; p>0.05; rank sum ∆-F-508 homozygous patients: 214; n=17; rank sum ∆-F-508 heterozygous patients: 137; n=9, critical value: 39). Also, the magnitude of change was not dependent on the date of the initial HRCT-examination (Spearman rank correlations, O1: r_s=0.06, p>0.05, n=29; O2: r_s=0.20, p>0.05, n=29).

6. Discussion

6.1 The state of disease of young adults suffering from CF

The retrospective cross-sectional study revealed a wide range of pulmonary damages on HRCT-images of the lungs in young adult CF patients, with the Brody score ranging between 0 and 144 (O1) / 175 (O2) points. The associated spirometry parameters VC, FEV1 and the Tiffeneau presented a heterogenous distribution as well. The BMI and the associated spirometry parameters VC, FEV1 and the Tiffeneau index showed excellent correlations with the Brody score on a statistically highly significant level ($p<0.001$). The disease severity did not depend on the CF patients' gender or genetic mutation status.

The patient collective of the cross-sectional study is unique since no other study ever solely focused on young adults. Most studies only concentrate on young children [15, 65, 66] or adult patients aged 17 or 18 and above with no upper limit [15, 67]. With ninety-one patients, the patient collective is comparably large considering the small age range from sixteen to twenty-two years [65, 66]. All in all, the patient collective appears to be a representative cross-section of general CF patients. As in many other studies [42, 67], the gender distribution was close to 50:50 since cystic fibrosis is independent of gender. 92% of the CF patients with a known genetic mutation status were homozygote or heterozygote carriers of the ∆-F-508 mutation, which is a typical distribution for Germany and other European countries [4-6, 67]. Also, it is common that over 80% of adult CF patients exhibit an abnormal FEV1 [67].

As expected, a high variability of the state of disease was found within the group of young adult CF patients. This heterogeneity is not only common in adult CF patients [68] but was already observed in young children aged one to six [65]. Potential confounding by age or the HRCT-examination date was eliminated through statistical testing. The high variability of the state of disease could be ascribed to inter-individual differences in therapy adherence among young CF patients since the course of the disease depends mainly on optimal therapy adherence [22]. Another influence might be the difference in socioeconomic status of the CF patients with a higher socioeconomic status being linked to a longer median survival [69-72]. Comparing the groups of ∆-F-508 homozygous and -heterozygous CF patients, a significant influence of the genetic mutation status on the state of disease was not detected. Similar results were also found in previous studies, where the genetic mutation status appeared to have only little or no effect on the state of disease [15, 73]. In accordance with the available studies, the gender of the CF patients revealed no influence on the state of disease considering HRCTs and PFTs [74-78].

In the evaluation of the HRCT-examinations using the Brody score, the most frequent pulmonary changes were bronchiectasis, followed by peribronchial thickening and mucous plugging. This is consistent with the results of many other studies using the Brody score or other HRCT scoring systems [14, 15, 21, 65, 79-83]. However, bronchiectasis is not only the most frequent but also the most important pulmonary change in predicting the quality of life of CF patients [79, 80, 84]. Among all Brody subscores, bronchiectasis also presented the best correlations with spirometry

parameters VC, FEV1 and the Tiffeneau index on statistically highly significant levels ($p<0.001$) [82, 85]. Nevertheless, almost all Brody subscores as well as the composite total Brody score correlated with the PFT results, which has already been proven in several other studies [11, 15, 18, 19, 21, 54, 82, 85, 86]. Since the state of disease of CF patients can change rapidly due to exacerbations or pulmonary infections, associated PFTs were only considered when performed within two days of the HRCT-examination to minimize potential bias.

A secondary outcome of the cross-sectional study was the interobserver reproducibility of the Brody score. Excellent interobserver reproducibility was found as already proven in several studies [34, 43, 52]. Equal interobserver reproducibility can also be found when comparing the scores of qualified with nonqualified observers [87] as happened in this study. These findings do not only support the Brody score as an adequate scoring system but also objectify this study's scoring results and make them more reliable.

6.2 The course of disease of CF patients in early adulthood

The retrospective cohort study revealed a high dependency between the initial state of disease and the magnitude of change in pulmonary damages of young adult CF patients within four years. While CF patients with advanced structural impairment of their lungs at their initial HRCT-examination showed little progress or even improvements, CF patients with initially low-grade disease severity and limited pulmonary changes showed a strong progression of their pulmonary damages. The associated spirometry parameters did not show a statistically significant change over the four years. The course of disease did not depend on the gender or the genetic mutation status of the CF patients.

Monitoring the course of disease in young adult CF patients is especially interesting since they are situated at the transition point from paediatric to adult healthcare. This transition is a very vulnerable chapter in the lives of CF patients and can strongly influence the future course of disease [88-91]. Especially since young adults tend to have less disease knowledge than their parents as well as poor awareness of the consequences of risky behaviour, getting more independent from their parents might have a negative effect on their future course of disease [26, 28, 29, 31, 49]. When comparing the initial and the follow-up HRCT-examinations of those young adults, an inverse correlation was found between the initial state of disease and the magnitude of change in pulmonary damage. Potential confounding by age or the HRCT-examination date in this study was eliminated through statistical testing. This inverse correlation between the initial state of disease and the magnitude of change could be explained by the fact, that patients suffering from fewer symptoms tend to have lower therapy adherence than patients with higher disease severity [28].

When comparing the initial and the follow-up HRCT examinations, bronchiectasis, followed by peribronchial thickening and mucous plugging, played the biggest role in the progression of pulmonary damages, both in CF patients with initially low-grade and high-grade disease severity [33, 90, 92]. As with the total Brody score, the subscores bronchiectasis, peribronchial thickening and mucous plugging revealed an inverse correlation between their initial appearance and their

magnitude of change. Improvements in pulmonary changes were exclusively found in patients with initially high-grade disease severity and were mostly ascribed less presence or less severe appearance of bronchiectasis, peribronchial thickening, and mucous plugging.

Improvements in the subscore bronchiectasis were not found in the same patients by the two observers. Therefore, it cannot be assumed that there was a real improvement, but rather individual errors in scoring [43]. Although improvements in the appearance of bronchiectasis have already been found in other studies [33], these results must be viewed very critically, as bronchiectasis by definition represents irreversible pulmonary damage [33]. Improvements in the subscores peribronchial thickening and mucous plugging may have resulted from the possibility, that the initial HRCT-examination may have taken place during pulmonary infections or acute aggravation [85]. This possible bias cannot be excluded since the purpose of the HRCT-examinations was not considered during the selection process.

As in many other studies, the cohort study revealed no significant change of the spirometry parameters VC, FEV1, or the Tiffeneau index despite significant changes in pulmonary damages seen on HRCT-examinations [33, 39, 90, 92-95]. Some patients even showed improvements in PFTs despite progressive pulmonary damage [17, 33]. This could be explained by the fact, that HRCT is known to be more sensitive in detecting pulmonary changes than PFTs [11-13, 18, 33-35]. For that reason, HRCT-examinations play a significant role in monitoring CF patients [16].

Most studies describe a strong progression of pulmonary damages in female CF patients with consecutive higher mortality, which is mostly ascribed to less therapy adherence in female CF patients [79, 90, 96, 97]. However, this study did not reveal a significant difference in the course of disease between men and women. This lack of conformity might be ascribed to the comparably small patient collective including only twenty-nine patients. The unequal distribution with 62% of the CF patients in the cohort study being male might also be held accountable. A few studies describe a connection between the magnitude of change in pulmonary damage and the genetic mutation status of CF patients [97-99]. This dependency could not be determined despite the high proportion of known mutations in the cohort study (93%). Again, this divergence might be ascribed to the comparably small patient collective.

6.3 Limitations

The cross-sectional and the cohort study are beset with five limitations.

First, the external validity of the results from the cross-sectional and the cohort study is limited since the patient collectives of both studies originated from a single centre, the “Interdisziplinäres Mukoviszidose Zentrum des Klinikums der Universität München”, in Germany. Even though the centre is the largest one of its kind in Germany [10, 50], the results can only be applied to CF patients within similar healthcare systems since the socioeconomic state influences therapy adherence, disease severity and mortality of CF patients [70-72].

Second, during the retrospective recruiting time from 1998 to 2018, the CT images were obtained from various CT scanners with varying slice thicknesses, including some multidetector computed

tomography (MDCT) and incremental CT images. Due to the different CT scanners and protocols over the years, there is a wide range of radiation exposure values, which is why statistical values like median, mean, and standard deviations could not be determined. In the more recent HRCT-examinations, the radiation dose was kept as low as possible without quality loss [100-102]. A significant influence of the different CT scanners or slice thicknesses on the study results is not assumed since other studies on patients suffering from different pulmonary damaging diseases revealed a high intermodal reproducibility [103, 104]. However, a certain influence of the different device technologies on the quality of CT images and thus the image evaluation cannot be ruled out.

Third, the purpose of the HRCT-examinations was not considered during the selection process for both studies. Ideally, the HRCT-examinations were intended to serve as an initial state of pulmonary disease and as a routine follow-up. However, the HRCT-examination could also have been performed due to pulmonary infections or acute aggravation. These possible biases were not considered in the evaluation.

Fourth, small changes in the total brody score and its subscores might be linked to inaccuracies caused by the observers, despite a high intra-observer reproducibility [43]. This can explain the small improvements of the subscore bronchiectasis, which by definition is an irreversible pulmonary damage [33].

Last, the size of the patient collective in the cohort study might have been influenced by the fact that additional HRCT-examinations are usually performed if there are indications of progress or aggravation [43]. Therefore, CF patients with a more rapid progression of their disease might have needed another HRCT-examination within less than three years, shifting the whole 4-year follow-up cycle. This would not satisfy the inclusion criteria of the second examination being within 2.9 to 5.3 years after the initial HRCT-examination. Such a scenario could also influence the results of the cohort study as CF patients with a more rapid disease progression might not be included.

7. Conclusion

Overall, the studies at hand show that young adult CF patients exhibit a wide range of pulmonary damages on HRCT-images as well as a heterogeneous distribution of the associated spirometry parameters. While CF patients with initially high-grade disease severity showed little progress or even improvements, those with initially low-grade disease severity showed a strong progression of their pulmonary damages. The associated spirometry parameters did not show a statistically significant change. Neither the disease severity nor the course of disease did depend on the CF patients' gender or genetic mutation status.

For clinical practice, treating physicians should be aware of a heterogeneous state of disease among young adult CF patients transferring to adult healthcare. When monitoring CF patients, those with comparably low-grade disease severity should not be disregarded, as rapid deterioration of their state of disease must be expected.

Future research should focus on analysing the possible influences of the genetic mutation status as well as the patient's compliance during childhood on the resulting state of disease. Lastly, the impact of different monitoring procedures between CF patients with initially low and high-grade disease severity should be analysed.

8. References

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9. Appendix

Table 7: CT scanners applied overtime at "LMU Klinikum"

Model	Manufacturer	n	Period	Slice thickness (mm)	kVp (kV)	Tube current (mA)	Exposure (C/kg)	Convolution kernel	CTDIvol (mGy)	DLP (mGy*cm)
Tomoscan M/EG	Philips	2	03/1999 - 03/2000	2.0 - 10.0	120 - 130	30 - 40		BF10, VBF4		
SOMATOM Volume Zoom	Siemens	2	11/1999 - 01/2003	1,25 - 5,0	120 - 140	35	10	B50s, B40f	1.14	39
MX8000	Philips	15	11/1999 - 10/2006	1.3 - 5.0	90 - 120	30 - 342	10-190	C, D		
Aura	Philips	32	07/2002 - 05/2013	1.0 - 10.0	120 - 130	40 - 100	40 -100	AT0, AE+2, AT+2		
SOMATOM Sensation 16	Siemens	3	02/2003 - 10/2009	1.0 - 6.0	120	35 - 218	15 - 109	B30f, B40f, B50f	1.2 - 8.1	38 - 304
SOMATOM Sensation 64	Siemens	4	04/2006 - 07/2009	0.75 - 1.0	120	103 - 554	42 -197	B70f, O	4.2 - 13.1	137 - 432
SOMATOM Definition	Siemens	1	04/2007	5,0	120	190	67	B30f	4,3	157
Diamond Select Brilliance 64	Philips	36	12/2007 - 02/2013	1.5 - 3.0	120	31 - 70	15 - 30	L, YA	0.9 - 1.9	31.4 - 78.7
LightSpeed VCT	GE	1	07/2009	0,625	120	40	1	LUNG	1,68	59,89
SOMATOM Definition AS+	Siemens	1	03/2011	3,0	120	127	90	B60f	4,57	160
SOMATOM Definition Flash	Siemens	1	04/2013	4,0	100	77	64	I30f/3	4,19	270
Optima 660	GE	9	04/2013 - 03/2018	0.625 - 2.50	100 - 120	12 - 40	0	LUNG	0.64 - 1.61	20.7 - 61.0
Discovery CT750 HD	GE	1	01/2014	2,5	120	86	2	LUNG	3.28	127,17
SOMATOM Definition Edge	Siemens	1	09/2014	3,0	120	212	88	I50f/3	5,95	162
SOMATOM Definition AS	Siemens	1	10/2014	1,5	100	111	92	I70f/2	3,18	374

Table 8: CT scanners applied in external radiology department

Model	Manufacturer	n	Period	Slice thickness (mm)	kVp (kV)	Tube current (mA)	Exposure (C/kg)	Convolution kernel	CTDIvol (mGy)	DLP (mGy*cm)
SOMATOM (Edge) Plus 24	Siemens	1	09/1998	4.0	137	275				
SOMATOM Sensation 16	Siemens	1	01/2009	2.0	120	126	57	B60f		
SOMATOM Emotion 6	Siemens	1	04/2011	2.5	130	250	150	B70s	7,19	289,56
SOMATOM	Siemens	1	05/2011	5.0	110	27	16	B80s	1,3	37
SOMATOM Sensation 64	Siemens	2	09/2013 - 10/2013	1.0 - 5.0	100 - 120	42 - 57	15 - 20	B70f	1,15	38
Aquilion	Canon	1	10/2013	1.0	120	40	20	FC35	2,6	
SOMATOM Definition AS	Siemens	1	05/2014	1.0	120	252	105	I70f/2	5,9	224
SOMATOM Definition AS	Siemens	1	10/2014	3.0	80	43	23	I40f/3	0,49	14
SOMATOM Emotion 6	Siemens	1	08/2015	5.0	130	62	46	B31s	7,54	387

Table 9: HRCT Scoring system (adapted from Brody, A.S., et al. [11])

Bronchiectasis score (range, 0 - 12)	=	Extend of bronchiectasis in central lung 0 = none 1 = 1/3 – 2/3 of lobe 2 ≥ 2/3 of lobe	+	Extend of bronchiectasis in peripheral lung 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	x	Average bronchiectasis size multiplier Average multiplier size 0.5 = 0 1 = 1 1.5 = 1.25 2 = 1.5 2.5 = 1.75 3 = 2	
Where average bronchiectasis size	=	Size of largest dilatated bronchus 1 ≤ 2x 2 = 2x – 3x 3 ≥ 2x	+	Average size of dilated bronchi 1 ≤ 2x 2 = 2x – 3x 3 ≥ 3x	÷	2	
Mucous plugging score (range, 0 - 6)	=	Extend of mucous plugging in central lung 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	+	Extend of mucous plugging in peripheral lung 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe			
Peribronchial thickening score (range, 0 - 9)	=	Extend of peribronchial thickening in central lung 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	+	Extend of peribronchial thickening in peripheral lung 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	x	Severity of peribronchial thickening 1 = mild 1.25 = moderate 1.5 = severe	
Parenchyma score (range, 0 - 9)	=	Extend of dense parenchymal opacity 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	+	Extend of ground-glass opacity 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	+	Extend of cysts or bullae 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	
Hyperinflation score (range, 0 - 4.5)	=	Extend of air trapping 0 = none 1 = 1/3 of lobe 2 = 1/3 – 2/3 of lobe 3 ≥ 2/3 of lobe	x	Appearance of air trapping 1 = subsegmental 1.5 = segmental or larger			

"range" refers to the respective minimum and maximum scores attainable for each individual lung lobe.

Table 10: The Brody score in the cross-sectional study (n=91)

		Min.	Max.	Mean	Median	0.25	0.75
Total Brody score	O1	0.00	144.00	75.18	74.75	56.00	118.38
(range, 0 - 207)	O2	0.00	175.00	87.91	93.75	46.13	100.25
Bronchiectasis	O1	0.00	58.50	29.59	31.00	21.00	54.25
(range, 0 - 72)	O2	0.00	72.00	36.21	37.50	16.50	41.25
Mucous plugging	O1	0.00	33.00	13.48	13.00	9.00	18.00
(range, 0 - 36)	O2	0.00	36.00	13.82	14.00	7.00	21.00
Peribronchial thickening	O1	0.00	51.00	22.60	21.75	12.88	31.50
(range, 0 - 54)	O2	0.00	54.00	21.41	20.75	12.50	27.50
Parenchymal opacity	O1	0.00	12.00	2.46	1.00	0.00	4.00
(range, 0 - 54)	O2	0.00	26.00	9.67	8.00	5.00	14.00
Hyperinflation	O1	0.00	24.00	7.04	7.00	5.00	9.00
(range, 0 - 27)	O2	0.00	27.00	6.80	6.00	1.00	9.75

Table 11: Correlations between the total Brody score and its respective sub-scores in the cross-sectional study (n=91)

	O1	O2
Bronchiectasis	r_s=0.90, p<0.001	r_s=0.92, p<0.001
Mucous plugging	r_s=0.76, p<0.001	r_s=0.56, p<0.001
Peribronchial thickening	r_s=0.88, p<0.001	r_s=0.85, p<0.001
Parenchymal opacity	r_s=0.50, p<0.001	r_s=0.48, p<0.001
Hyperinflation	r_s=0.63, p<0.001	r_s=0.50, p<0.001

Table 12: Correlation between the Brody score and its respective sub-scores with the different spirometry parameters, vital capacity (VC), forced expiratory volume in one second (FEV1), and the Tiffeneau index (FEV1/FVC), and with the body mass index (BMI) in the cross-sectional study (n=40)

		VC	FEV1	FEV1/FVC	BMI
Total Brody score	O1	r_s=-0.75 p<0.001	r_s=-0.81 p<0.001	r_s=0.68 p<0.001	r_s=-0.76 p<0.001
	O2	r_s=-0.60 p<0.001	r_s=-0.69 p<0.001	r_s=-0.67 p<0.001	r_s=-0.67 p<0.001
Bronchiectasis	O1	r_s=-0.64 p<0.001	r_s=-0.74 p<0.001	r_s=-0.71 p<0.001	r_s=-0.70 p<0.001
	O2	r_s=-0.59 p<0.001	r_s=-0.69 p<0.001	r_s=-0.68 p<0.001	r_s=-0.58 p<0.001
Mucous plugging	O1	r_s=-0.52 p<0.001	r_s=-0.54 p<0.001	r_s=-0.39 p<0.05	r_s=-0.64 p<0.001
	O2	r_s=-0.23 p>0.05	r_s=-0.29 p>0.05	r_s=-0.28 p>0.05	r_s=-0.55 p<0.001
Peribronchial thickening	O1	r_s=-0.60 p<0.001	r_s=-0.61 p<0.001	r_s=-0.45 p<0.005	r_s=-0.68 p<0.001
	O2	r_s=-0.51 p<0.001	r_s=-0.58 p<0.001	r_s=-0.58 p<0.001	r_s=-0.59 p<0.001
Parenchymal opacity	O1	r_s=-0.60 p<0.001	r_s=-0.52 p<0.001	r_s=-0.25 p>0.05	r_s=-0.58 p<0.001
	O2	r_s=-0.62 p<0.001	r_s=-0.63 p<0.001	r_s=-0.50 p<0.005	r_s=-0.49 p<0.01
Hyperinflation	O1	r_s=-0.66 p<0.001	r_s=-0.75 p<0.001	r_s=-0.71 p<0.001	r_s=-0.39 p<0.05
	O2	r_s=-0.44 p<0.01	r_s=-0.52 p<0.001	r_s=-0.53 p<0.001	r_s=-0.37 p<0.05

Table 13: The Brody score per gender in the cross-sectional study (n=91)

		Min.	Max.	Mean	Median	0.25	0.75
Male patients (n=47)	O1	0.00	137.00	71.36	71.88	42.50	97.38
	O2	2.50	158.50	84.40	92.13	58.75	112.00
Female patients (n=44)	O1	0.00	144.00	78.75	79.25	55.00	105.25
	O2	0.00	175.00	91.20	98.25	53.75	122.75

Table 14: The Brody score in the cohort study: initial HRCT-examination (n=29)

		Min.	Max.	Mean	Median	0.25	0.75
Total Brody score	O1	0.00	137.00	63.91	64.75	41.75	83.00
(range, 0 - 207)	O2	3.50	158.50	76.92	79.00	51.00	102.50
Bronchiectasis	O1	0.00	56.50	23.78	23.25	13.75	33.00
(range, 0 - 72)	O2	0.00	68.00	29.79	29.00	14.75	44.00
Mucous plugging	O1	0.00	26.00	12.90	13.00	8.00	17.00
(range, 0 - 36)	O2	0.00	27.00	12.79	15.00	5.00	21.00
Peribronchial thickening	O1	0.00	49.50	19.44	18.00	9.00	28.00
(range, 0 - 54)	O2	0.00	54.00	20.04	21.00	12.00	24.00
Parenchymal opacity	O1	0.00	10.00	1.52	0.00	0.00	2.00
(range, 0 - 54)	O2	0.00	26.00	7.86	6.43	4.00	12.00
Hyperinflation	O1	0.00	24.00	6.28	6.00	4.00	8.00
(range, 0 - 27)	O2	0.00	27.00	6.43	6.00	1.00	9.00

Table 15: The Brody score in the cohort study: follow-up HRCT-examination (n=29)

		Min.	Max.	Mean	Median	0.25	0.75
Total Brody score	O1	8.00	141.50	77.49	79.00	57.50	96.50
(range, 0 - 207)	O2	9.00	179.00	105.47	106.50	73.50	134.50
Bronchiectasis	O1	0.00	54.00	31.80	31.75	21.75	43.50
(range, 0 - 72)	O2	0.00	72.00	44.88	48.00	30.25	58.25
Mucous plugging	O1	0.00	24.00	13.38	12.00	11.00	17.00
(range, 0 - 36)	O2	0.00	28.00	14.83	14.00	9.00	21.00
Peribronchial thickening	O1	2.00	48.00	22.53	20.00	15.50	28.50
(range, 0 - 54)	O2	4.00	54.00	25.90	23.00	14.50	35.00
Parenchymal opacity	O1	0.00	7.00	2.76	2.00	2.00	4.00
(range, 0 - 54)	O2	0.00	29.00	9.93	8.00	6.00	11.00
Hyperinflation	O1	0.00	17.00	7.02	6.00	6.00	8.00
(range, 0 - 27)	O2	0.00	27.00	9.93	7.00	4.00	11.50

Table 16: Change of the total Brody score and its respective sub-scores in the cohort study (n=29)

		Min.	Max.	Mean	Median	0.25	0.75
Total Brody score	O1	-51.00	82.75	13.58	10.25	-6.75	28.00
	O2	-23.25	138.75	28.54	25.25	1.00	36.25
Bronchiectasis	O1	-20.00	32.00	8.02	8.25	3.75	13.50
	O2	-10.25	58.25	15.09	12.50	3.25	21.50
Mucous plugging	O1	-10.00	16.00	0.48	-1.00	-3.00	5.00
	O2	-24.00	25.00	2.03	2.00	-4.00	7.00
Peribronchial thickening	O1	-19.00	27.50	3.09	2.50	-4.75	9.25
	O2	-24.00	38.00	5.85	4.50	-4-25	12.75
Parenchymal opacity	O1	-7.00	7.00	1.24	2.00	0.00	3.00
	O2	-12.00	23.00	2.07	3.00	-4.00	5.00
Hyperinflation	O1	-22.00	9.00	0.74	0.00	-2.00	6.00
	O2	-17.00	21.00	3.50	2.00	0.00	7.00

Table 17: Spirometry parameters in the cohort study: initial examination (n=12)

	Min.	Max.	Mean	Median	0.25	0.75
VC (%)	51.8	117.7	79.3	80.9	63.7	91.4
FEV1 (%)	33.0	115.7	67.7	69.3	49.1	79.3
FEV1/FVC	0.52	0.82	0.70	0.74	0.59	0.77
BMI (kg/m^2)	16.6	26.6	20.0	19.6	18.0	20.6

Table 18: Spirometry parameters in the cohort study: follow-up examination (n=23)

	Min.	Max.	Mean	Median	0.25	0.75
VC (%)	39.0	121.0	70.3	69.4	52.5	82.8
FEV1 (%)	22.5	116.9	54.9	50.9	32.9	67.4
FEV1/FVC	0.33	0.80	0.62	0.62	0.54	0.73
BMI (kg/m^2)	15.7	26.2	19.4	18.6	18.0	19.9

Table 19: Correlations between the Brody score, the spirometry parameters, and the BMI in the cohort study

		VC	FEV1	FEV1/FVC	BMI
initial examination (n=12)	O1	r_s=-0.43 p>0.05	r_s=-0.51 p>0.05	r_s=-0.54 p>0.05	r_s=-0.48 p>0.05
	O2	r_s=-0.36 p>0.05	r_s=-0.53 p>0.05	r_s=-0.65 p>0.05	r_s=-0.58 p<0.05
follow-up examination (n=23)	O1	r_s=-0.65 p<0.001	r_s=-0.51 p<0.05	r_s=-0.44 p<0.05	r_s=-0.39 p>0.05
	O2	r_s=-0.75 p<0.001	r_s=-0.69 p<0.001	r_s=-0.51 p<0.05	r_s=-0.41 p<0.05

Table 20: Change of the spirometry parameters between the initial and the follow-up examination in the cohort study (n=12)

	Min.	Max.	Mean	Median	0.25	0.75
initial VC (%)	51.8	117.7	79.3	80.9	63.7	91.4
follow-up VC (%)	39.0	121.0	70.3	69.4	52.5	82.8
Δ VC (%p)	-22.8	27.7	-1.0	-2.9	-10.2	6.4
initial FEV1 (%)	33.0	115.7	67.7	69.3	49.1	79.3
follow-up FEV1 (%)	22.5	116.9	54.9	50.9	32.9	67.4
Δ FEV1 (%p)	-35.8	37.5	-1.5	-3.5	-12.1	8.7
initial FEV1/FVC	0.52	0.82	0.70	0.74	0.59	0.77
follow-up FEV1/FVC	0.50	0.80	0.67	0.69	0.61	0.74
Δ FEV1/FVC	-0.15	0.18	-0.03	-0.03	-0.10	0.02
initial BMI (kg/m^2)	16.6	26.6	20.0	19.6	18.0	20.6
follow-up BMI (kg/m^2)	15.7	26.2	19.4	18.6	18.0	19.9
Δ BMI (kg/m^2)	-2.0	1.1	-0.2	0.0	-0.9	0.5

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Affidavit

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

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selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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