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Title

The spectrum of structural abnormalities on CT scans from CF patients with severe advanced lung disease.

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ABSTRACT

Rationale: In cystic fibrosis (CF), lung disease is the predominant cause of morbidity and mortality. Little is known about the spectrum of structural abnormalities on computed tomography (CT) scans from CF patients with severe advanced lung disease (SALD). No specific CT scoring system for SALD is available.

Objectives: To design a quantitative CT scoring system for SALD, to determine the spectrum of structural abnormalities in patients with SALD, and to correlate the SALD system with an existing scoring system for mild CF lung disease and pulmonary function tests (PFTs).

Methods: 57 CF patients contributed one CT made during screening for lung transplantation. For the SALD system, lung tissue was divided into 4 components: infection/inflammation (including bronchiectasis, airway wall thickening, mucus and consolidations) air trapping/hypoperfusion, bulla/cysts, and normal/hyperperfused tissue. The volume proportion of the components was estimated on a 0-100% scale, mean volumes for the whole lung were computed. Scores were correlated with Brody-II scores and PFTs.

Results: The SALD system identified a wide spectrum of structural abnormalities ranging from predominantly infection/inflammation to predominantly air trapping/hypoperfusion. SALD infection/inflammation scores correlated with Brody-II scores (r_s 0.36 to 0.64) and SALD normal/hyperperfusion scores correlated with FEV_1 (r_s = 0.37). Reproducibility for both systems was good.

Conclusions: We developed a CT scoring system to characterize the structural abnormalities in patients with SALD. A wide spectrum was observed in SALD ranging from predominantly air trapping to predominantly infection/inflammation-related changes. This spectrum may have clinical implications for patients with SALD.

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INTRODUCTION

Since the first description of cystic fibrosis (CF) in 1938, patients' life expectancy has greatly improved. Thanks to better treatment that curbs progression of pulmonary disease (1, 2), life expectancy is now around 40 years (3), and over 40% of CF patients are adults (4). Nevertheless, most patients still develop Severe Advanced Lung Disease (SALD), the predominant cause of mortality in CF.

Little is known about the structural abnormalities in SALD, as few pathology studies are available. These studies used lung specimens from transplant and/or autopsy procedures to describe the structural changes in SALD (5-7). To the best of our knowledge, no systematic studies have investigated SALD *in vivo*. Routine chest computed tomography (CT) scans from CF patients made for screening for lung transplantation may be used for this purpose. Knowledge on the structural changes in SALD is important, as it may indicate which structural abnormalities in CF lung disease can lead to SALD and hence, have to be monitored and treated in patients with early disease to prevent progression to SALD. Furthermore, it may give more insight in clinical differences and outcomes in patients with SALD. When SALD has established, lung transplantation is often the only treatment option left. To date, it has been a major challenge to determine which SALD patients have the highest risk of dying, and are thus most in need of a lung transplant. This is reflected in reported mortality estimates for patients awaiting transplantation, which range from 15% to 40% (8-10). Currently used prediction models for waiting list survival in these patients include clinical parameters, but no information on lung structure. CT may add important information to these prediction models, as it was proven to be more sensitive to detect and monitor CF lung disease than pulmonary function tests (PFTs) (1, 11-13). We speculate that the patient's clinical outcome may be impacted by the type of structural lung abnormality observed on CT. Our hypothesis is that, based on our clinical impression, a spectrum of abnormalities can be observed in SALD, ranging from predominantly infection/inflammation-associated changes such as consolidations and bronchiectases to hypoventilation-associated changes such as air trapping and hypoperfusion.

To test this hypothesis, a scoring method is needed to quantify the structural abnormalities in SALD in a systematic, objective and time-efficient fashion. Current scoring systems, such as the Brody-II system, are reproducible (14), but were primarily designed to quantify early and moderately advanced disease (11, 15, 16). For the CT scans of patients with SALD, a dedicated SALD scoring system may be more sensitive to detect differences in disease spectrum between patients.
Therefore, we aimed to 1) design a CT scoring system for the CT abnormalities of patients with SALD; 2) correlate this new system with the Brody-II system and PFTs, and 3) investigate the spectrum of structural abnormalities on CT scans of CF patients with SALD.

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METHODS

Study population

In this retrospective study, data from patients with a confirmed diagnosis of CF and screened for lung transplantation between 2001-2005 was collected in three transplant centers. Patients were only included when screening data, including a chest CT scan, was available. Patient characteristics are defined in the online supplement. Screening criteria were based on internationally used recommendations (8, 17-20), although one center (center 3 in analysis) used a forced expiratory capacity in 1 second (FEV_1) of < 25% for males and FEV_1 < 40% for females. The review boards of all three participating centers approved the study protocol and waived informed consent.

CT scanning procedures and scoring

Lung structure was evaluated with CT scans. Eight CT scanners (characteristics in online supplement) were used in this study. CT scans were anonymised before evaluation and analysed in random order. A single experienced observer scored all scans using the Brody-II scoring system (11) and a newly developed SALD scoring system. Reproducibility within and between observers was determined for both systems. Within observer agreement was tested by re-scoring a random subset of 25 scans. For between-observer agreement analysis, an independent experienced second observer scored a random subset of 25 scans. Both observers were blinded for clinical data and outcome of the patients.

Brody-II scoring system

This system evaluates bronchiectasis, airway wall thickening, mucus plugging and opacities on inspiratory images and air trapping on expiratory images (11). As expiratory images were lacking in 45/57 patients, the maximal possible total Brody-II score (207 points) was reduced by the air trapping score (27 points), thus changing the upper limit to 180 points. To enable direct comparison, scores were recalculated and expressed as percentages of the maximal possible score on a scale of 0 (no disease) to 100 (maximal lung disease).

SALD scoring system

The development of the SALD system is described in the online supplement. In brief, the SALD score aims to divide the total lung volume into 4 mutually-exclusive and comprehensive components of lung morphology, each assessed on a 0-100% scale. Three components indicate abnormalities: 1) infection/inflammation, which includes bronchiectasis, airway wall thickening, mucus and consolidations, 2) air trapping/hypoperfusion, and 3) bulla/cysts. The fourth category, normal/hyperperfused tissue, reflects parenchyma that is normal or hyperperfused due to a redistribution of blood caused by perfusion defects. This tissue is still thought to contribute to normal gas exchange. For all CT slices (1 slice per 10 mm), the observer estimated the percentage of total lung area to be assigned to each component. Then, for each component separately, the volume estimates from all slices were summated and the sum was divided by the number of slices to obtain mean volume estimates. High scores for the first three categories reflect a high volume of structurally changed lung tissue and thus, severe disease. A high score for the normal/hyperperfusion component reflects a high volume of relatively normal lung tissue. Thus, in the SALD system, all lung tissue was assigned to one or more of the four SALD components, with these four component scores adding up to 100%.

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Therefore, the SALD scoring system consist of only four component scores and does not compute a total score.

Statistical analysis

For continuous and categorical variables, the Kruskal-Wallis and Chi-square test were used in the comparison of baseline characteristics between the centres. Correlations between SALD and Brody-II score and between CT scores and PFTs were investigated using Spearman's correlation coefficients (r_s). Reproducibility for both scoring systems was evaluated using intraclass-correlation coefficients (ICC) and Bland-Altman plots. Although no universally applicable standards are available for what constitutes poor, fair or good reliability (21), we considered ICC values between 0.4 and 0.6, 0.6 and 0.8, and 0.80 or greater to represent moderate, good and very good agreement. SPSS version 14.0 for Windows was used for all statistical analyses. Results are displayed as median (range) unless defined otherwise. $P < 0.05$ was considered significant.

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RESULTS

Data was collected from 57 consecutive patients. No significant differences in patient characteristics were observed between the centers, except for some components of the Brody-II system (Table I). SALD component scores for bulla/cysts were excluded in further analyses, since this item was only present in 11/57 (19%) patients.

Table I Patient characteristics and CT scores for the study cohorts in the three transplant centres

Center	**1**	**2**	**3**	***Total***
N	10	12	35	*57*
Males	5 (50%)	8 (67%)	21 (60%)	*34 (60%)*
Age (years)	28.5 (16-38)	32.2 (16-49)	24.4 (17-53)	*26.7 (16-53)*
BMI (kg/m^2)†	19.5 (16-26)	20.0 (18-22)	19.0 (15-27)	*19.0 (15-27)*
Pancreatic insufficiency	8 (80%)	10 (83%)	34 (97%)	*52 (91%)*
Diabetes Mellitus	5 (50%)	3 (25%)	9 (26%)	*17 (30%)*
Microbiology				
P. aeruginosa	10 (100%)	11 (92%)	32 (92%)	*53 (93%)*
B. cepacia Complex	0	2 (17%)	2 (6%)	*4 (7%)*
FEV_1 (% predicted)‡	24 (19-34)	26 (15-38)	27 (13-45)	*26 (13-45)*
FVC (% predicted)*	43 (25-70)	42 (29-67)	43 (24-89)	*42 (24-89)*
Brody-II scores				
Total score	40 (32-60)	48 (33-59)	34 (17-52)	*37 (17-60)*
Bronchiectasis	44 (29-57)	60 (35-72)	36 (25-60)	*41 (25-72)*
Mucus plugging	31 (25-47)	16 (8-42)	19 (0-42)	*25 (0-47)*
Airway wall thickening	31 (19-63)	54 (26-69)	35 (15-60)	*36 (15-69)*
Opacities	11 (6-26)	15 (7-26)	9 (0-22)	*11 (0-26)*
SALD scores				
Infection/inflammation	24 (17-30)	23 (17-41)	23 (9-43)	*24 (9-43)*
Air trapping /hypoperfusion	48 (27-61)	36 (28-68)	43 (24-61)	*43 (24-68)*
Bulla/cysts	0 (0-11)	4.5 (0-39)	0 (0-13)	*0 (0-39)*
Normal/hyperperfusion	29 (21-43)	31 (10-46)	31 (20-51)	*30 (10-51)*

Data are given as patient numbers (%) or as median (range).
† Body Mass Index
‡Forced expiratory volume in 1 second

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*Forced vital capacity

CT scoring systems

Between and within observer agreement

Between and within observer agreement for both scoring systems was good with most ICC values near or above 0.80 (Table II). Bland-Altman plots showed that differences between the observers were independent of the magnitude of the scores in either scoring system (online supplement).

Table II Between and within observer agreement expressed as intraclass correlation coefficients for the Brody-II and SALD scoring system

Type of scoring system	Within observer agreement	Between observer agreement
Brody-II scoring system		
Total score	*0.77*	*0.80*
Bronchiectasis	0.79	0.65
Mucus plugging	0.77	0.79
Airway wall thickening	0.56	0.73
Opacities	0.77	0.61
SALD scoring system		
Infection/inflammation	0.89	0.77
Air trapping/hypoperfusion	0.88	0.70
Bulla/cyst	0.99	0.98
Normal/hyperperfusion	0.71	0.68

SALD spectrum

Although all scans showed the SALD components infection/inflammation, air trapping/hypoperfusion and normal/hyperperfusion, there was a striking difference in the extent in which these abnormalities were present (Figure I and E5 online supplement). Thus, a SALD spectrum could be distinguished ranging from predominantly infection/inflammation to predominantly air trapping/hypoperfusion (Figure II).

Correlation SALD system – Brody-II system

Positive correlations were found between the SALD infection/inflammation score and the total Brody-II score (r_s =0.64 p<0.001; Figure III) as well as with each of the Brody-II component scores: bronchiectasis (r_s=0.59 p<0.001), airway wall thickening (r_s=0.62 p<0.001), mucus plugging (r_s=0.50 p<0.001) and opacities (r_s=0.36 p=0.006). No significant correlations were found between the SALD

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normal/hyperperfusion score and the total Brody-II score or any of the component scores.

Correlation CT scores – PFTs

Total Brody-II score correlated, albeit weakly, with forced vital capacity (FVC) (r_s = -0.28 p=0.035, Figure IV) but not with forced expiratory volume in 1 second (FEV_1). None of the Brody-II component scores correlated with FEV_1, and only the component score airway wall thickening correlated with FVC (r_s = - 0.31 p=0.018). None of the SALD components correlated with FVC, and only the normal/hyperperfusion score correlated with FEV_1 (r_s =0.37 p=0.005, Figure IV).

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DISCUSSION

To our knowledge, this is the first study in CF that systematically describes the structural abnormalities on CT scans from CF patients with SALD screened for lung transplantation. The most important finding of this study is the wide disease spectrum that was identified in patients with SALD in vivo, using the newly developed SALD scoring system. On one end of the spectrum, patients had predominantly infection/inflammation-related changes, on the other end predominantly air trapping/hypoperfusion. The observed structural abnormalities have been described in pathology studies, which revealed the presence of inflammation, atelectasis, bronchiestasis, fibrosis, cyst formation, airway wall thickening, and a substantial loss of cartilage (5-7). In these pathology studies, it was well recognized that these abnormalities were unevenly distributed throughout the lung. However, whether substantial differences in disease spectrum between patients could be observed was not studied.

Infection/inflammation, which included bronchiectasis, was found to be an important disease component in SALD. The importance of bronchiectasis in CF has been well recognized (22-24). Hence, prevention of bronchiectasis is an important treatment target in patients with SALD. A striking observation is the finding that air trapping is another important disease component in many patients with SALD. In some patients, it was clearly the predominant morphological substrate for their severely impaired lung function. Air trapping has been observed early in the disease process of CF (25, 26). In a small randomized controlled study, it was shown that treatment with dornase alpha in patients with mild to moderately severe CF lung disease reduced air trapping on CT and improved peripheral airway obstruction (27). These results suggest that air trapping may be reversible when treated early. Clearly, this warrants further investigation.

Our observation is not only important in terms of prevention of SALD, but can also be relevant for the management of patients with SALD. We feel that more tailored treatment of the subtypes in SALD at an earlier stage of the disease has the potential to reduce mortality and improve the quality of life. It is likely that the therapeutic strategy for SALD patients with predominantly bronchiectasis should be different from that of patients with predominantly air trapping. Whether air trapping in CF patients with SALD is reversible is unknown. To the best of our knowledge, no systematic therapeutic studies have been performed in CF patients with SALD with the aim to reduce the severity of air trapping. The effect of dornase alpha in CF patients with advanced disease has been studied, air trapping however was not included as an endpoint (28). This needs to be further investigated in clinical studies. In addition, we think that the CT information of SALD patients may improve patient selection for lung transplantation. Currently used selection criteria comprise predicted forced expiratory volume in 1 second (FEV_1) < 30%, rapid respiratory deterioration with predicted FEV_1 > 30%, $PaCO_2$ > 50 mmHg and/or PaO_2 < 55 mmHg on room air, and/or females <18 years of age with FEV_1 > 30% and rapid deterioration (8, 17-20). Several studies have aimed to identify better predictors of survival, but remarkably, CT related parameters were never evaluated (8, 17, 18). It has been suggested that patients with SALD and predominantly infection/inflammation-related changes on their CT have a poorer prognosis than patients with predominantly air trapping/hypoperfusion (29). If so, the SALD score infection/inflammation may be able to contribute to

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survival prediction models independent of lung function-related parameters. A large multi-center study is currently ongoing to investigate this further.

Correlating CT scores with PFT parameters revealed only one significant association, i.e. between the SALD air trapping/hypoperfusion score and FEV_1. None of the Brody component scores correlated significantly with FEV_1. A likely explanation is the limited range in FEV_1 in this cohort (from 13- to 45%-predicted), and / or the limited sample size. These correlations will be further investigated in our large multi-center study.

In this study, the reproducibility of the SALD scoring system in the evaluation of SALD-related structural abnormalities was comparable to that of the Brody-II scoring system. However, there are several reasons why we consider the SALD scoring system to be more attractive for further development than the Brody score. First, the SALD system is probably easier to automate than the Brody system, as it is based on differentiation between areas with high density (infection/inflammation) and low density (air trapping). This in contrast to the Brody-II system, which is based on pattern recognition, and therefore difficult to automate. Automated analysis can likely further improve the SALD system's reproducibility. A challenge for the automated approach however, will be the range of CT scanners and scan protocols used in transplant centers, which likely affects density parameters. The semi-quantitative scoring systems used in this study are less sensitive for technical differences than currently available automated systems (30). A short term option to improve the precision of the SALD system is to use a digital grid to estimate the volume of the components, a method shown feasible for volumes of air trapping (31). Second, the SALD system is easier to learn than the Brody-II system. The latter requires estimating severity of lesions, has more components, and requires classifying abnormalities per lobe. Third, SALD scores are continuous variables representing the volume of abnormal lung tissue involved in infection/inflammation, air trapping, and normal tissue. Hence, it is easy to understand what the scores mean. This in contrast to the Brody scores, which are computed of scores for severity and extent of an abnormality. This makes it complicated to understand what the scores mean for the patient.

The development of an automated method for the SALD system is important. Currently, the most important drawback for the clinical use of the current SALD system is its time-consuming nature. The SALD system requires 45-60 minutes to score a single CT examination while the Brody-II system requires only 20 minutes. An automated approach can make the SALD scoring more time-efficient and therefore, more accessible for clinical use. Currently, we would recommend using the SALD scoring system solely to evaluate SALD CT scans. It provides insight into the predominant features of the abnormalities on the CT scans. This system has not yet been validated, however, for patients with mild to moderately advanced lung disease. Our next step, therefore, will be to further validate the SALD system in a large cohort and to study correlations between SALD scores and clinical outcome. In this analysis, we may include the observation of bullae/cysts in the air trapping/ hypofusion component, since this reflects lung tissue not contributing to gas exchange, and which likely shows little inflammatory changes.

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This study has a few limitations. First, we used CTs that were obtained with 8 different CT scanners and scanning protocols. This may have introduced some bias related to differences in resolution and density distribution. However, we consider it unlikely that this should have affected observation of the substantial differences in disease spectrum present in the patients. Before scoring, images were assessed on image resolution and movement artefacts. All were found to be of sufficient quality for scoring, with good reproducibility, so we may assume that the use of different scanners was non-differential. In addition, manual semi-quantitative scoring systems generally are thought to be less sensitive to differences between CTs and protocols (30, 32). Second, the correlations between the components of the two scoring systems were limited by the absence of air trapping scores since expiratory scans were only available in 12/57 patients (21%). Evidently, expiratory images were not routinely included in the screening protocols before 2005. The absence of expiratory images likely had more impact on the Brody-II scores than on the SALD scores, as air trapping in the Brody system was completely excluded. The SALD component air trapping/hypoperfusion most likely included areas that would have been classified as air trapping on expiratory images. Third, we cannot be sure that the morphological features on CT adequately reflect the histology of these abnormalities. Several studies have shown correlations between CT morphology and histologic findings, although none of them included CF patients (33-35). However, a study in idiopathic pulmonary fibrosis patients showed that chronic cystic lesions, including bronchiectasis, correlated well with histology. This in contrast to ground glass opacities and consolidations on CT, that failed to correlate with histologic specimens (33). Additional correlative studies using CT scans and histology from CF patients could address this issue.

In summary, we designed a CT scoring system specifically for CF patients with SALD and tested this retrospectively on 57 CT scans made during screening for lung transplantation. The new SALD system is reproducible, and able to identify a wide spectrum of structural abnormalities in SALD. A striking finding was that air trapping/hypoperfusion was an important component of SALD, in addition to inflammation/infection (including bronchiectasis). Differences in disease spectrum may have implications for prognosis and treatment of CF patient with SALD. Our next step will be to link the SALD scores to clinical outcome, to determine the minimal important difference of changes in the component scores

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Figure I Distribution of the SALD component scores. CT scans from lung transplant screening were scored according to the SALD criteria. A SALD spectrum was identified in which the dark grey bars represent the lung volume scored as hypoperfused tissue, the white bars infection/inflammation; the light grey bars normal/hyperperfused tissue; and the black bars bulla or cysts. Patients are sorted according to their air trapping/hypoperfusion component. The figure sorted for the infection/inflammation component can be found in the online supplement.

Figure II Illustration of the SALD spectrum. Images show the spectrum of SALD-related changes in lung morphology and SALD component scores for each image. These range from infection/inflammation-related changes such as bronchiectasis (black arrows) to air trapping / hypoperfusion (white arrows). Image A shows predominantly bronchiectasis, image B shows a mix of bronchiectasis and air trapping / hypoperfusion, and image C displays minimal bronchiectasis but extensive air trapping and hypoperfusion.

Figure III Figure showing the correlation between the SALD infection/inflammation score and the total Brody-II score.

Figure IV Correlation between CT scores and lung function parameters. Plot A shows the correlation between the total Brody-II score and the forced vital capacity (FVC), while plot B displays the correlation between the SALD air trapping/hypoperfusion score and the forced expiratory volume in 1 second (FEV_1).

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Supplementary material for the online depository.

Patient characteristics

Diagnosis of CF followed from clinical CF features, positive sweat test, and/or the presence of two CF mutations. Age was defined as 'age at the time of the screening CT scan'. Pancreatic exocrine insufficiency was defined as maintenance treatment with pancreatic enzyme. Diabetes mellitus was defined by the use of subcutaneous insulin by the patient. This was obtained by chart review. A patient was considered chronically infected with a given micro-organism when it was cultured from three or more different sputum samples in the six months preceding screening. The following international used guidelines were used to determine the moment of screening for patients:

- Predicted forced expiratory volume in 1 second (FEV_1) < 30%
- Rapid respiratory deterioration with predicted FEV_1 > 30%
- $PaCO_2$ > 50 mmHg and/or PaO_2 < 55 mmHg on room air, and/or
- Females under the age of 18 years with FEV_1 > 30% and rapid deterioration (1-5).

Computed Tomography (CT) scanning protocols

Lung structure was evaluated using CT scans. In this multi centre study, 8 different CT scanners were used during the screening period.

In center one, three multi slice scanners were used (Sensation 16, Emotion 16 and Volume zoom, Siemens AG Medical Solutions, Forchheim, Germany). Scans were obtained using a beam current of maximally 390 mA, and dose modulation was used in two of the three scanners. The rotation time was 0.5-0.6 seconds, and the beam potential 110-120 kV. Scans were obtained from lung apex to base at intervals varying from 1.2-5.0 mm using 1.0-5.0 mm thick slices.

In center two, one single slice CT scanner (SR7000, Philips Medical Systems, Best, the Netherlands) and two multi-slice scanners (Brilliance 16 and the MX8000, Philips Medical Systems) were used throughout the study period. Scans were obtained using a beam current of 250 mA for the single slice scanner, and dose modulation was applied in the multi scanner protocol. The exposure time ranged from 0.5-1.0 seconds, and the beam potential was 120 kV for all three scanners. Scans were made from lung apex to lung base at 5-10 mm intervals using 1.0-5.0 mm thick slices.

In center three, a single slice CT scanner (Hi speed ZXi, GE Medical Systems, Milwaukee, WI, USA) was used up to October 2004, and a multislice CT scanner after October 2004 (Light Speed 16 Pro, GE Medical Systems). Scans were obtained using a beam current of 300-700 mA, a rotation time of 0.5-1.0s, and a beam potential of 140 kV from lung apex to base at 10 mm intervals using 1.25 mm thick slices.

Since different transplant centers use different scanners and scanning protocols, image quality was likely to vary. Therefore, the quality of the CTs was assessed before scoring. This was done by scrolling through the scan and determining whether the quality was sufficient for scoring. CT scans with severe movement artefacts were excluded from analysis.

CT scoring

Development of the SALD scoring system

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In order to define tissue/morphology categories for use in the SALD scoring system, a panel consisting of a pediatric radiologist, a pediatric pulmonologist, and a PhD student systematically evaluated a random set of 10 CT scans acquired from CF patients during lung transplant screening. They classified the most prevalent structural abnormalities on these CT scans into 5 categories: 1) infection/inflammation; 2) air trapping and/or hypoperfused tissue; 3) hyperperfusion; 4) bullae or cysts, and 5) normal lung tissue, which formed the basis of the SALD scoring system.
Two independent observers tested this concept categorization on 10 CT's. This pilot indicated that clear distinction between areas of hyperperfusion areas of normal tissue was difficult to make. As the experts felt that hyperperfusion does not necessarily negatively influence lung function, these categories were combined into a single category 'normal/hyperperfusion' into which all tissue with functional gas exchange would fall. The final SALD scoring system therefore incorporated 4 categories — three components indicating abnormalities: 1) infection/inflammation, 2) air trapping/hypo perfusion, and 3) bulla/cysts; and one component reflecting tissue with a normal contribution to gas exchange: normal/hyperperfused tissue. The category infection/inflammation includes area with bronchiectasis, bronchial wall thickening, atelectasis, ground glass, consolidations, and mucus plugging (Figure E1). The definitions for these items are according to Brody et al (6). The category air trapping/hypoperfusion (Figure E2) includes areas with a lower density than normal lung tissue, which are thought to represent poorly ventilated and hypoperfused parenchyma (7-9). The category bulla/cysts (Figure E3) represents areas of apparent parenchymal destruction thought to have no association with inflammation and no contribution to gas exchange. Both bulla and cysts are defined as more or less round, air-filled parenchymal spaces with well-defined walls and a diameter of more than 1 cm. Neither has an identifiable connection to the bronchial tree. A cyst has a wall thickness of more than 1 mm and a bulla of less than 1 mm (10). The last category covers areas likely to contribute to gas exchange, including normal and hyperperfused tissue (Figure E2). Hyperperfusion appears on CT as areas with a higher density than normal lung parenchyma, and is considered a secondary effect related to areas of hypoperfusion.

After definition of the categories, we decided on a scoring system based on relative volume, and tested 2 methods to estimate the relative volume, each on 25 scans using 2 independent observers with respectively 1 and 4 years experience in scoring chest CT scans. For both methods the left and right lung were scored separately, and for both methods, all lung tissue was completely and exclusively divided over the SALD categories, so that the component scores added up to 100% by definition.

In the first method, the observer scrolls through the entire lung using all available slices and then directly estimates the volume of tissue in each category for the entire lung (the "scroll and score method"). In the second method, the observer estimates the percentage lung area in each category on each individual slice, which are averaged to determine the final SALD component score (the "single slice method"). For the single-slice method, we scored one image from each 10 mm interval; hence, not all available slices were scored. In the case of scans using a 10-mm interval, we did score all

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slices, while only every second slice was scored in scans using a 5-mm interval, and so on. Each image was scored independently and in random order. The precision level of each method was investigated by establishing the means and standard error of the means for each component. The Wilcoxon signed rank test was used to compare the methods. The single slice method was more precise and better reproducible. Therefore, only results obtained by that method are displayed in the results section.

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Figure E1 Illustration of the SALD category infection/inflammation. Shown is a CT scan of a CF patient with SALD. The areas in the right lung which would be scored as SALD 'infection/inflammation' are outlined in black and include abnormalities such as bronchiectasis (white arrow), bronchial wall thickening (grey arrow) and mucus plugging (black arrow).

Figure E2 CT slice of a CF patient with SALD illustrating the SALD categories air trapping/hypoperfusion and normal/hyperperfusion. Areas which are hypodense due to air trapping and hypo perfusion are circled in black. Normal and hyperperfused lung parenchyma is circled in white.

Figure E3 CT image to illustrate the SALD category cysts/bulla. Shown is a CT scan of a CF patient with SALD. The arrows indicate the bullae in the left lung of this patient.

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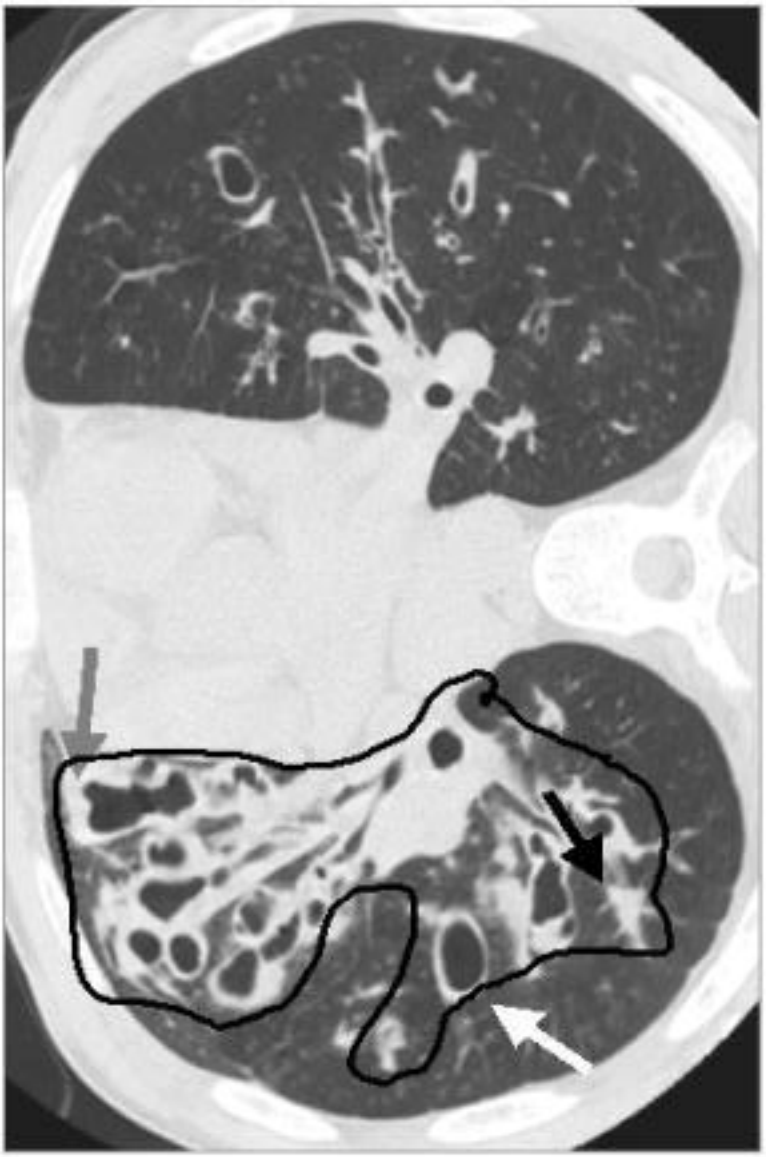

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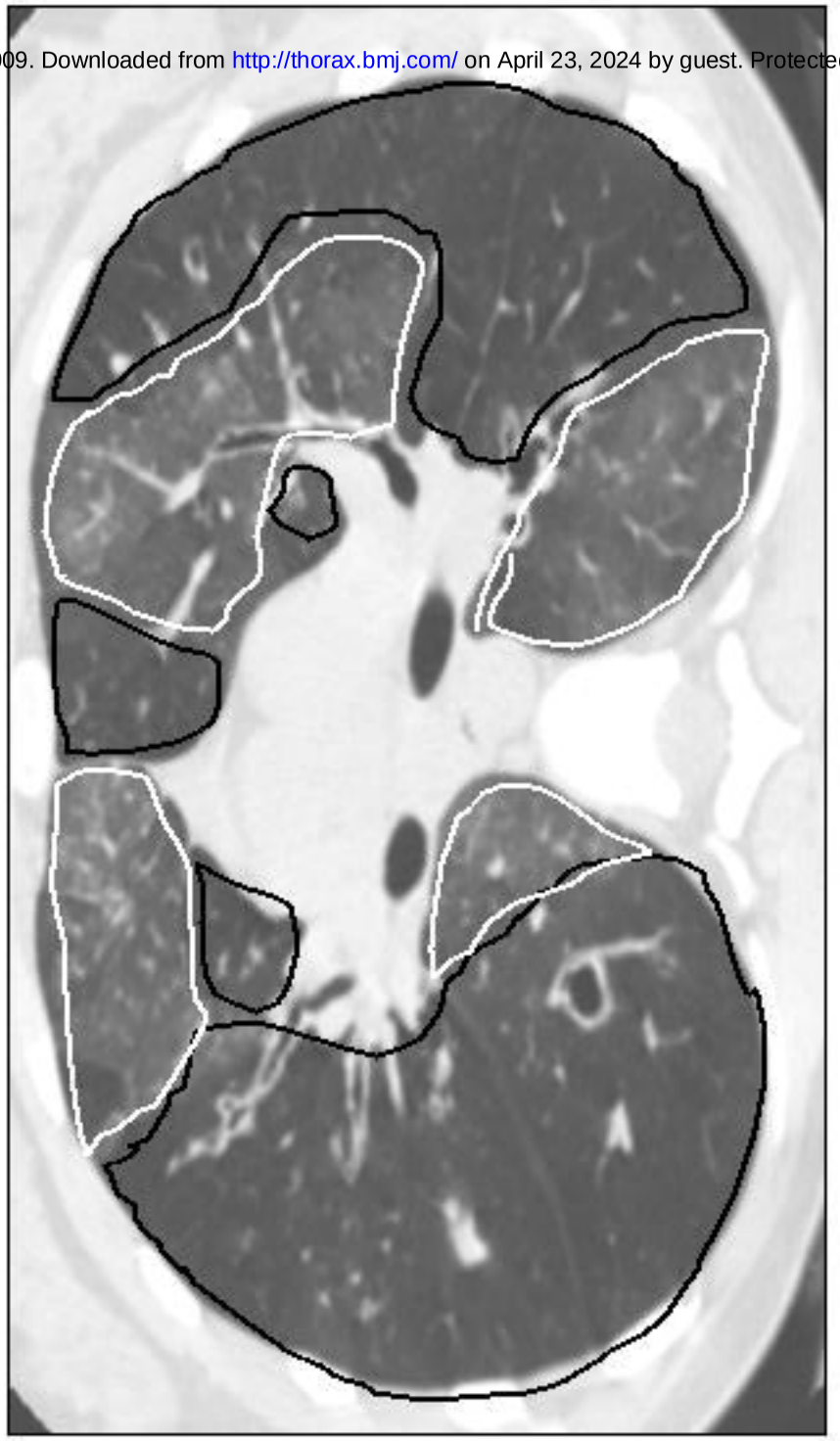

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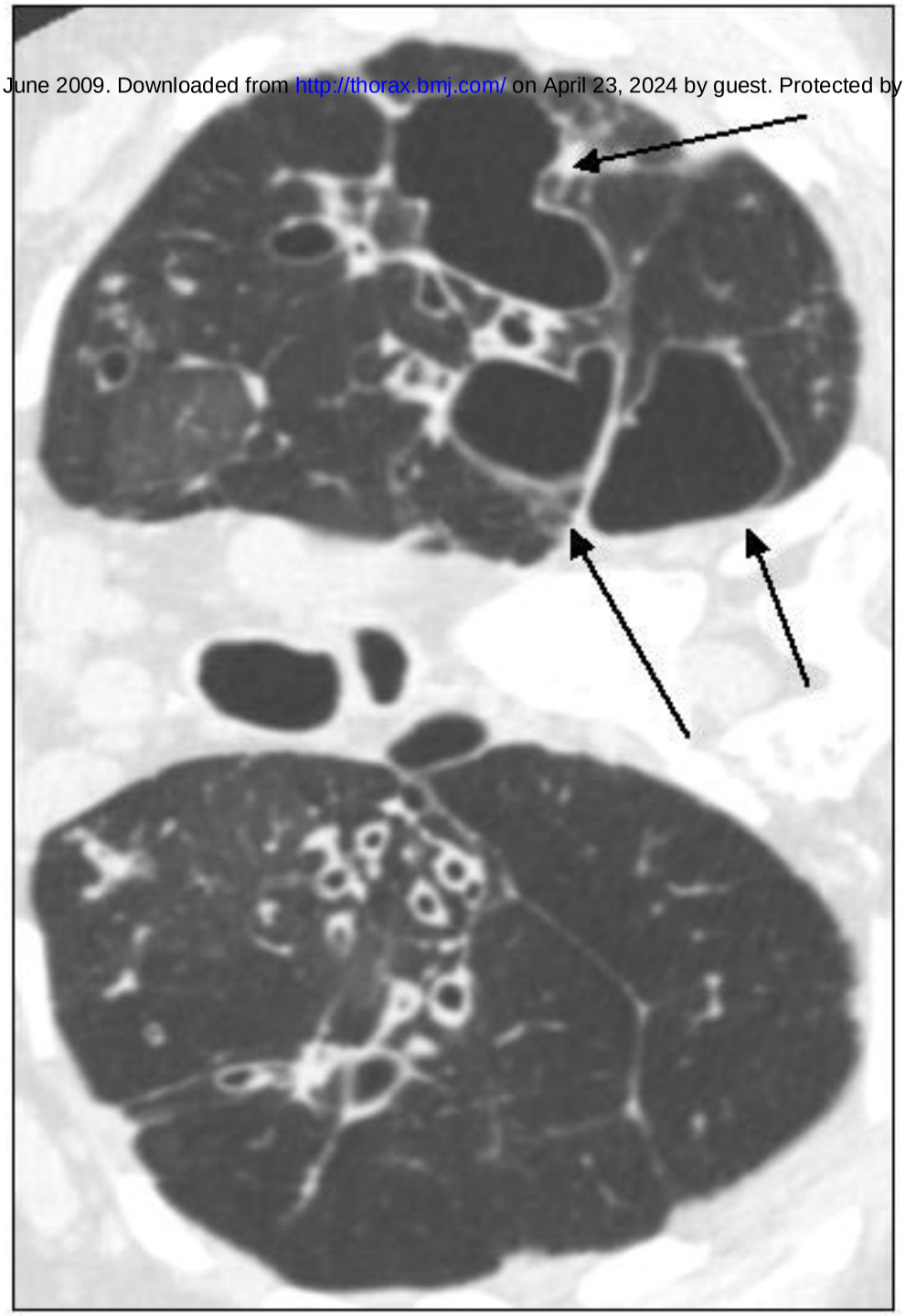

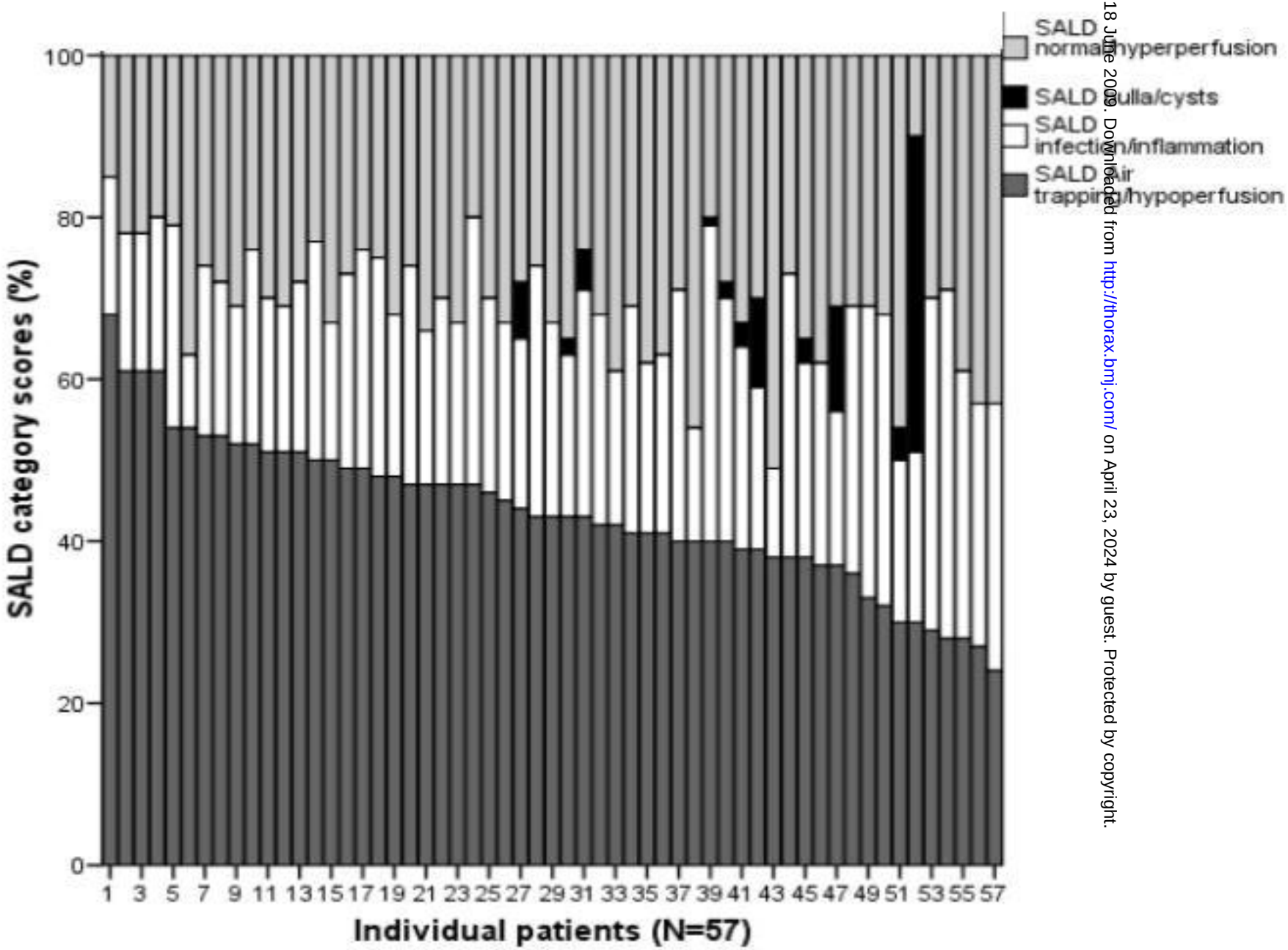

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SALD category scores

Infection/inflammation:	35%
Air trapping/hypoperfusion:	30%
Normal/hyperperfusion:	35%
Bulla/cysts:	0%

SALD category scores

Infection/inflammation:	15%
Air trapping/hypoperfusion:	25%
Normal/hyperperfusion:	60%
Bulla/cysts:	0%

SALD category scores

Infection/inflammation:	5%
Air trapping/hypoperfusion:	70%
Normal/hyperperfusion:	25%
Bulla/cysts:	0%

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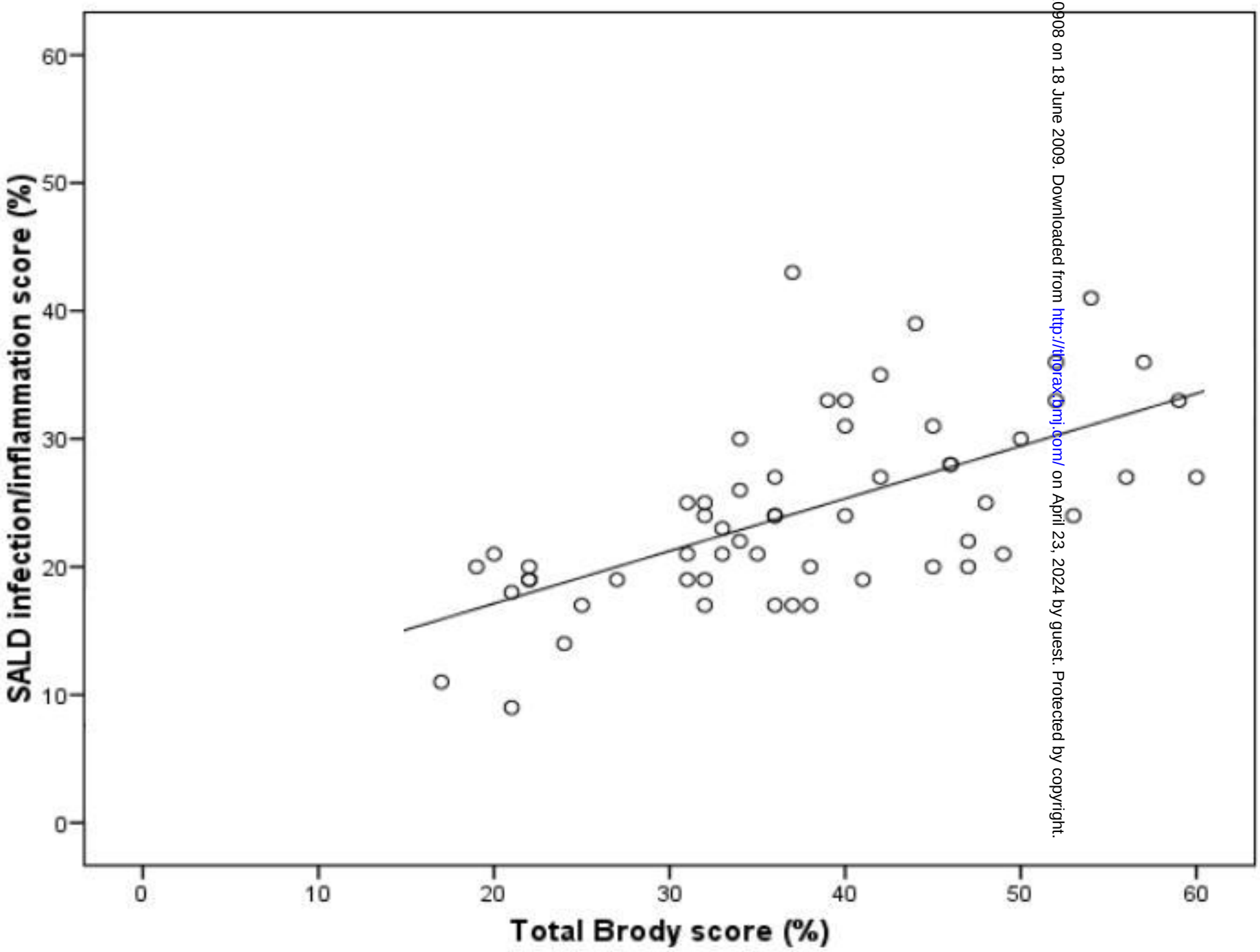

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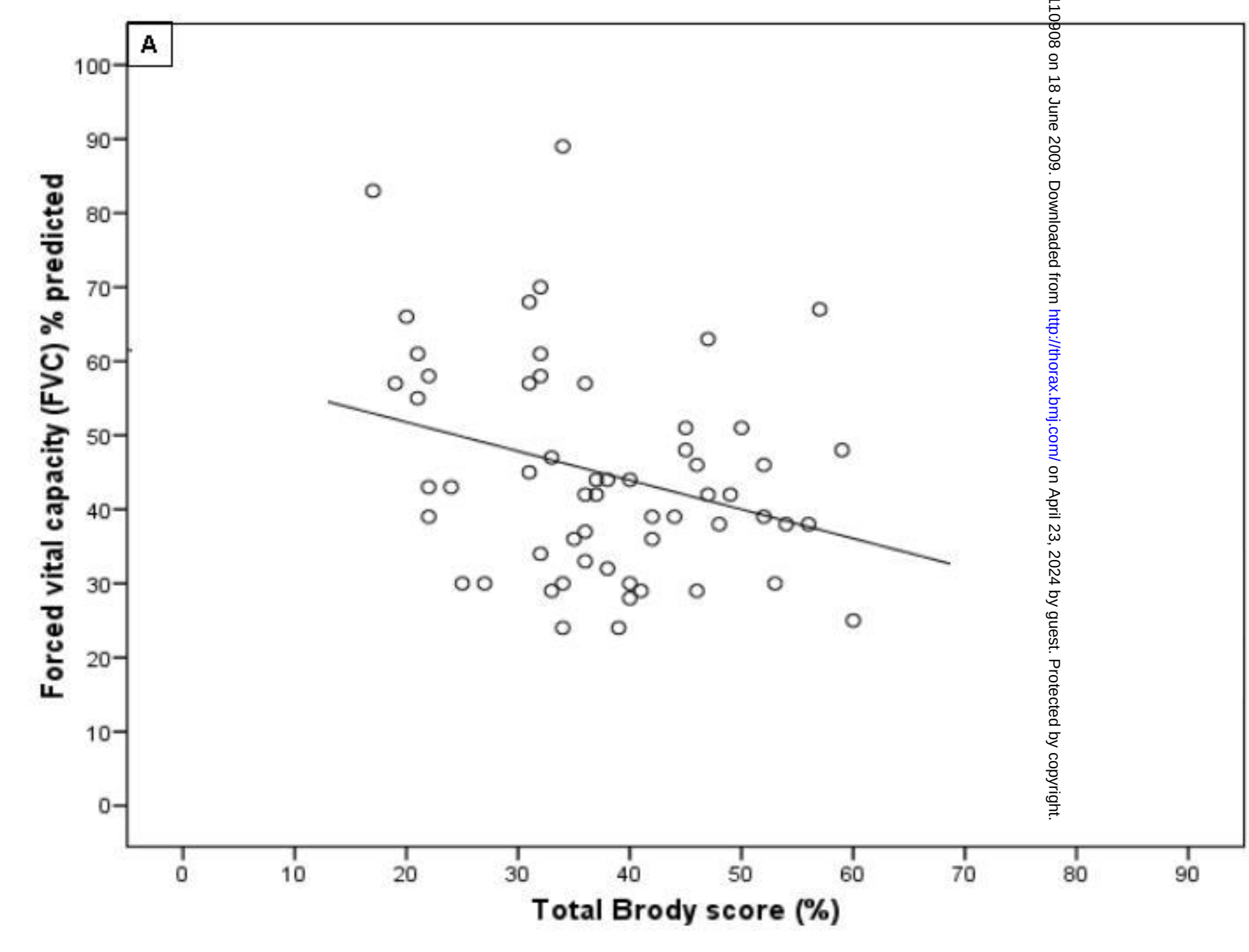

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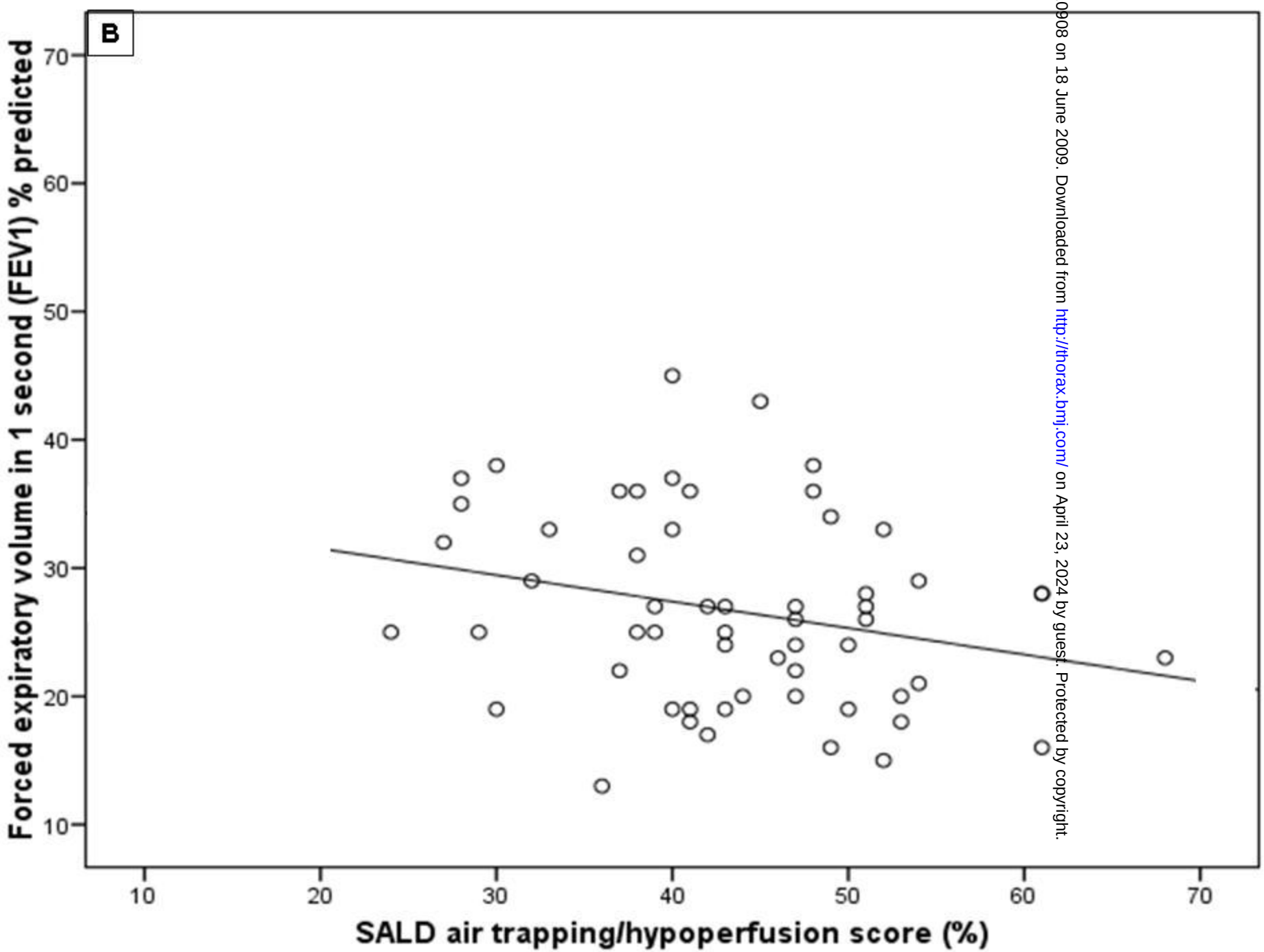

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