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Long-term course of bronchial inflammation and pulmonary function testing in children with postinfectious bronchiolitis obliterans

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Abstract

Rationale: Postinfectious bronchiolitis obliterans (PIBO) is a rare, chronic respiratory condition, which follows an acute insult due to a severe infection of the lower airways.

Objectives: The objective of this study was to investigate the long-term course of bronchial inflammation and pulmonary function testing in children with PIBO.

Methods: Medical charts of 21 children with PIBO were analyzed retrospectively at the Children's University Hospital Frankfurt/Main Germany. Pulmonary function tests (PFTs) with an interval of at least 1 month were studied between 2002 and 2019. A total of 382 PFTs were analyzed retrospectively and per year, the two best PFTs, in total 217, were evaluated. Additionally, 56 sputum analysis were assessed and the sputum neutrophils were evaluated.

Results: The evaluation of the 217 PFTs showed a decrease in FEV1 with a loss of 1.07% and a loss in *z* score of −0.075 per year. FEV1/FVC decreased by 1.44 per year. FVC remained stable, showing a nonsignificant increase by 0.006 in *z* score per year. However, FEV1 and FVC in L increased significantly with FEV1 0.032 L per cm and FVC 0.048 L/cm in height. Sputum neutrophils showed a significant increase of 2.12% per year.

Conclusion: Our results demonstrated that in patients with PIBO pulmonary function decreased significantly showing persistent obstruction over an average follow-up period of 8 years. However, persistent lung growth was revealed. In addition, pulmonary inflammation persisted clearly showing an increasing amount of neutrophils in induced sputum. Patients did not present with a general susceptibility to respiratory infections.

Silvija P. Jerkic and Sinem Koc-Günel have contributed equally to this publication.

KEYWORDS
body plethysmography, chronic inflammation, lung function, postinfectious bronchiolitis obliterans

1 | INTRODUCTION

Postinfectious bronchiolitis obliterans (PIBO) is a rare, chronic disease which is caused by an initial insult to the lower airways.[1] The injury to the lower respiratory tract can be caused by various pathogens such as adenovirus, influenza, measles, respiratory syncytial virus, and mycoplasma pneumonia.[2] In previous studies, patients with PIBO have been reported mainly among certain populations in Argentina,[3] Chile,[4] Turkey,[5] and in Canada.[6] However, there is an increasing number of reports from Europe[7] and South Korea[8] who have reported small cohorts of patients with PIBO. Rationale for such a variable prevalence may suggest genetic predisposition.[9] Furthermore, nutrition, health care provision and various serotypes of the causative agent may influence the development of PIBO, too.[10]

PIBO is considered to be a rare disease characterized by persistent airway obstruction with functional and radiological evidence of small airway disease.[11] However, its incidence is possibly more frequent than expected due to variable nomenclature and an initial presentation which does not differ from severe bronchiolitis.

Clinically, these patients present with persistent tachypnea, crackles, wheezing, and hypoxemia after the causative insult.[12] In addition, the pulmonary function tests (PFT) show a fixed airway obstruction with decreased forced expiratory volume (FEV1), reduced FEV1/VC and reduced end-expiratory flow (MEF25).[13,14] Hyperinflation is indicated by an increased residual volume (RV) and an increased functional residual capacity (RV/TL). In addition, there is typically no or little response to bronchodilation.[14] In high-resolution chest CT (HRCT) the pathognomonic finding in PIBO is variation in the density of alveolar lung tissue called mosaic attenuation which occurs from alveolar hyperinflation and hypoxic vasoconstriction of the effected lungs.[11,15]

There are case series which describe the short follow-up outcome of patients with PIBO.[4,7] However, little is known about the long-term follow-up of PFTs, the lung growth and the pulmonary inflammatory process in patients with PIBO. A study by Colom et al.[16] in Argentina showed severely impaired PFTs characterized by obstruction and air-trapping during a 12-years follow-up period which slowly improved during childhood. In addition, a long-term follow-up of children with chronic bronchiolitis obliterans syndrome (BOS) revealed lung growth in these patients despite severely impaired PFTs.[17]

Previous studies have indicated that after the initial insult, the repair process to the lower airways is severely altered.[11] A persistent inflammatory process might be an important part of the disease process. A short-term study by Eckrich et al.[7] has revealed an increased number of persistent neutrophils in sputum samples of patients with PIBO over 4 weeks. Furthermore, a study with 11 patients revealed persistent neutrophilic inflammation several years after disease onset.[14]

The aim of this study was to investigate the long-term course of PFTs in a cohort of European patients with PIBO and to determine the long-term pulmonary inflammatory process in these patients.

2 | MATERIAL AND METHODS

2.1 | Patient setting

In this retrospective cohort study, 21 patients, who have been diagnosed with PIBO and who have been followed-up between 2002 and 2019 at the Division of Allergy, Pulmonology and Cystic Fibrosis at the Children's University Hospital Frankfurt/Main, Germany, were included. All 21 patients were identified by the register of our specialist clinic for rare lung diseases and were known to the authors.

The Children's University Hospital is a tertiary center associated with the Goethe University Frankfurt and takes referrals from all over the country. The study was approved by the Ethics Committee of the Goethe University Frankfurt (number 116/16) and patients' consent was waived.

PIBO was defined as followed[1]: history of a severe respiratory infection,[2] persistent respiratory symptoms such as tachypnea, cough, wheezing, exercise intolerance, and hypoxemia,[3] impaired lung function with evidence of airway obstruction with FEV1 < 75% and[4] new onset of changes on HRCT such as mosaic patterns, air trapping and bronchial wall thickening.

Medical data was collected from the patients' electronical charts (Medistar) which included routine clinical visits at least two times a year and additional consultations such as upon sudden deterioration. All 21 patients performed two or more PFTs per year with a gap of at least 1 month. In addition, 18 patients provided induced sputum for analysis, with 13 of them in at least 2 different years.

2.2 | Pulmonary function test

PFTs (spirometry and body-plethysmography) were performed by body plethysmograph (CareFusion) according to the recommendations of the American Thoracic Society[18] and the European Respiratory Society.[19] The following measurements were obtained: FVC, FEV1, FEV1/FVC, RV, and RV/TLC.

2.3 | Sputum collection, processing, and cell analysis

Sputum collection was performed and analyzed as previously described.[20,21] Sputum was obtained by incremental inhalation of 3%, 4%, and 5% saline solution every 7 min.

The obtained sputum was quantified, and sputum plugs were selected from the samples. Then, 4× 0.1% (weight/volume) dithiothreitol DTT) was added, and the samples were processed on ice for 15 min followed by subsequent addition of 2× weight/volume of phosphate-buffered saline. After each sample was centrifuged for 10 min at 790*g*, the supernatants were removed by pipette and stored at −80°C until further protein analyses. The slides used to analyze cellular differentiation were generated from these samples. Four hundred cells per slide were identified using the Leucodiff 800plus instrument (Instrumentation Laboratory), and the percentages of neutrophils, lymphocytes, eosinophils, and macrophages were quantified.

2.4 | Statistical analysis

Changes in PFTs and sputum neutrophil percentages were evaluated by a longitudinal panel data analysis using generalized linear mixed effect models calculated through R (nlme library), with random effects specified at the level of the individual. Data were analyzed using RStudio 1.0.153, © 2009-2016 RStudio, Inc. (The R Foundation for Statistical Computing), Numbers (macOS; Apple Inc.) and GraphPad Prism 5.0 (GraphPad Software Inc.). Statistical significance was assumed at $p < .05$. *Z* scores were calculated using the calculator of the Global Lung Function Initiative (http://gligastransfer.org.au/calcs/spiro.html).

3 | RESULTS

Twenty-one patients with PIBO were included in this study. The diagnosis of PIBO was based on three criteria[1]: clinical history of severe respiratory infection in a previously healthy patient (21/21). As pathogens, mycoplasma was diagnosed in 3/21 patients, adenovirus in 2/21, RSV in 2/21, H1N1 in 1/21 and 13/21 patients remained unclear (Table 1).[2] Evidence of airway obstruction with no or small response to bronchodilation based on PFTs (21/21) and,[3] air trapping and/or mosaic pattern on HRCT (21/21).

3.1 | Pulmonary function tests

A total of 382 PFTs were analyzed and the two best PFTs per year were selected. Best PFT was defined as PFT with the largest FEV1 which was recorded after examining the data from all of the usuable curves.[22]

TABLE 1 Study population of patients with PIBO

Number	21
Male/female	14/7
Age at diagnosis	8–180 months
Infectious insult	21/21
Adenovirus	2/21
Mycoplasma	3/21
RSV	2/21
H1N1	1/21
Unknown	13/21
CT scan with mosaic perfusion	21/21
Duration of follow-up	12–192 months

In total, 217 PFTs were evaluated. The average follow-up period of the patients was 8 years with a range of 1–16 years.

Average loss of FEV1/FVC was significant by 1.44% per year ($p < .0001$) (Figure 1A).

The analysis of *z* scores of FEV1 showed a significant decrease in FEV1 by 0.075 per year ($p < .0001$) (Figure 2A) and an

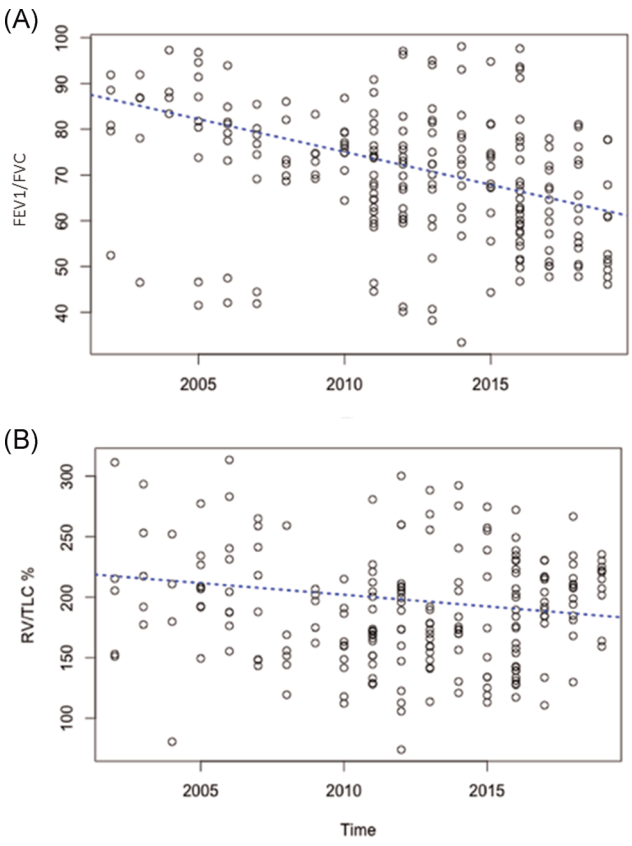


FIGURE 1 Longitudinal panel data analysis using generalized linear mixed effects models. (A) FEV1/FVC shows a decrease of 1.44% per year; $p < .0001$. (B) RV/TLC% shows a decrease 1.92% per year; $p < .0001$ [Color figure can be viewed at wileyonlinelibrary.com]

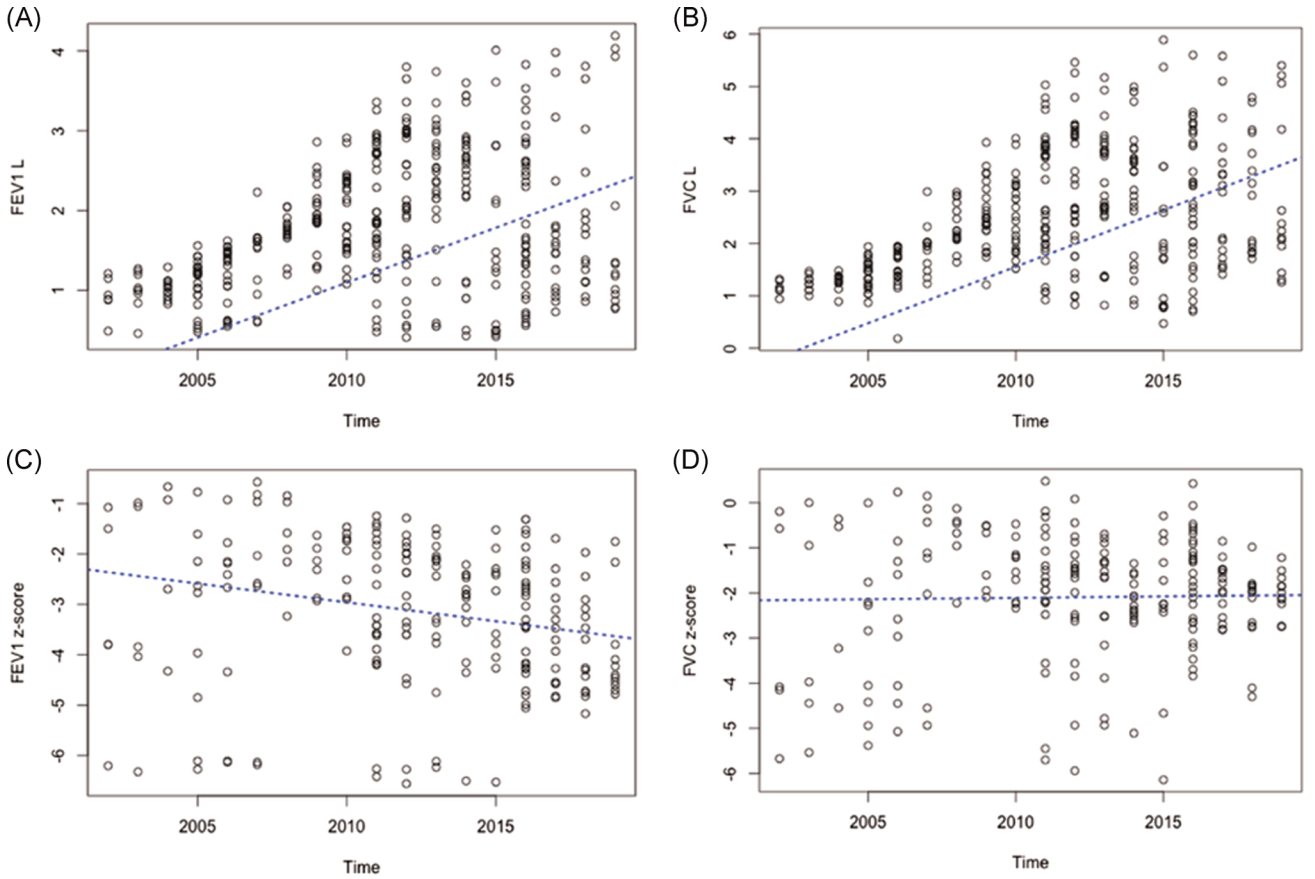
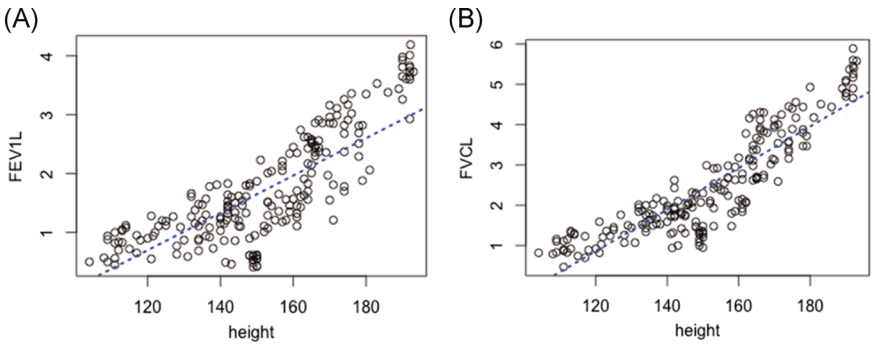


FIGURE 2 Longitudinal panel data analysis using generalized linear mixed effects models. (A) FEV1L shows an increase of 0.11 L per year; $p < .0001$. (B) FVC L shows an increase of 0.18 L per year; $p < .0001$. (C) *Z* score of FEV1 shows a decrease by −0.075 per year; $p < .0001$. (D) *Z* score of FVC shows an increase by 0.006 per year; $p = .6267$ [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Longitudinal panel data analysis using generalized linear mixed effects models (A) FEV1 in L increases by 0.032 L per cm of height; $p < .0001$. (B) FVC in L increases by 0.051 L per cm height; $p < .0001$ [Color figure can be viewed at wileyonlinelibrary.com]



insignificant increase by 0.006 in FVC per year ($p = .63$) (Figure 2B). VC max% was stable with a slightly significant increase of 0.56% per year ($p = .004$). Furthermore, a significant decrease of 1.92% of RV/TLC% ($p < .0001$) (Figure 1B) was observed per year accompanied by a stable rate of R tot% of 1.80% per year ($p = .25$).

PFTs in absolute numbers showed the following results. A yearly increase of 0.11 L in FEV1 ($p < .0001$) (Figure 2C) and a yearly increase of 0.18 L in VC max L ($p < .0001$) were observed. FVC showed a significant increase of 0.18 L per year ($p < .0001$) (Figure 2D). Rot kPa/L decreased significantly by 0.02 L per year ($p < .01$).

However, FEV1 in L and FVC in L were analyzed in relation to growth showing an increase in FEV1 by 0.032 L per cm of height (Figure 3A). This increase is significant with $p < .0001$. FVC increased by 0.051 L per cm of height which is likewise significant with $p < .0001$ (Figure 3B).

The analysis of FEV1% pred. and FVC% pred. was concordant with the results of the *z* score analysis of FEV1 and FVC.

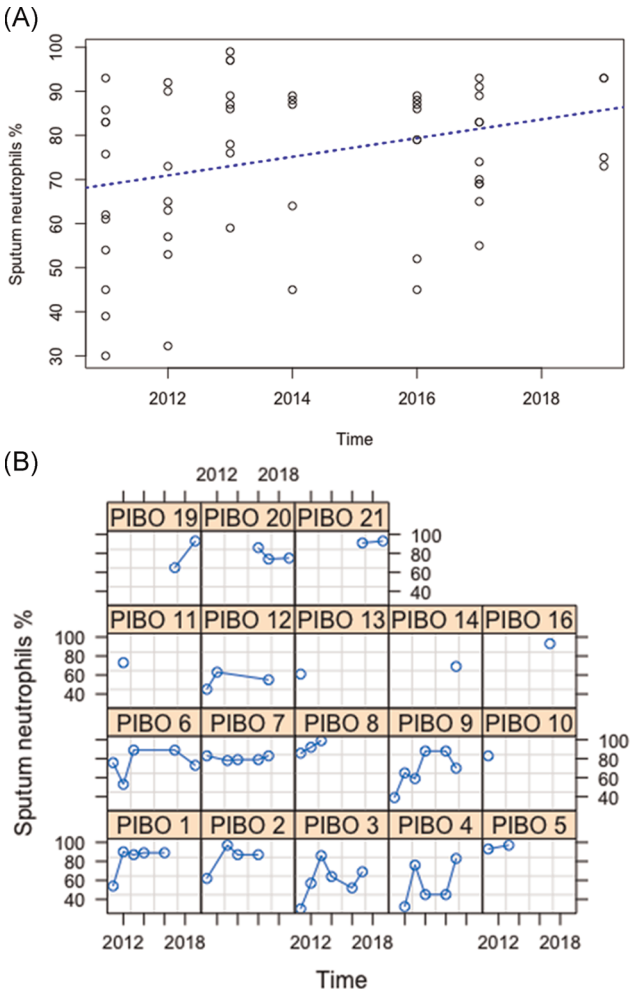


FIGURE 4 Longitudinal panel data analysis using generalized linear mixed effects models. (A) Neutrophils % shows an increase of 2.12% per year. The increase is significant with $p = .0144$. (B) Sputum neutrophil percentage of individual patients over time [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Sputum neutrophils

Patients with one or more sputum samples were included. In 18 patients, a total of 56 sputum samples were analyzed. The median follow-up period was 3 years, range 1–6 years.

Sputum cell composition analysis showed a persistent neutrophilic cell pattern with a significant increase of 2.12% per year with $p < .05$ (Figure 4A). Sputum neutrophils of every individual are shown in Figure 4B.

4 | DISCUSSION

PIBO is a rare, chronic disease which presents with an impaired lung function, decreased exercise tolerance, frequent chest exacerbations and a decreased quality of life needing a life-long medical management.[23–25]

In our study, patients with PIBO showed significantly impaired PFTs with fixed bronchial obstruction and air trapping throughout an average follow-up period of 8 years. Although their PFTs remained impaired, the cohort remained stable with no increase of hospital admissions over time.

As described in other studies, PFTs of all patients showed a characteristic pattern of a severe and fixed bronchial obstruction, increased airway resistance, and persistent air trapping.[23] The long-term analysis of these PFTs revealed persistent lung function impairment with a significant loss in FEV1% pred. of 1.07% per year. This is in contrast with Colom who has shown a stabilization in FEV1% pred. as well as an increase in FVC% pred. over a follow-up period of 12 years.[16,24] However, this could be attributed to a longer follow-up period, a bigger patient cohort and a difference in etiological and genetical factors. It is supposable that the perpetuating neutrophilic inflammation persists for several years. Subsequently, the neutrophilic inflammation results into irreversible, fibrotic changes of the airway epithelium, and ends in a fixed, mixed pattern expressed on PFTs. In our cohort, we showed continuous decrease in RV/TLC % indicating partial reduction of trapped air which could refer to some benefit of the broncho-dilative and anti-inflammatory therapy and which points toward a constant growth of vital capacity.[25] There has been some evidence that early in the course of the disease, airway obstruction responds to treatment with systemic corticosteroids despite the presence of neutrophilic inflammation.[26]

It is important to note that all patients presented with a significant yearly increase measured in absolute values of 0.11 L in FEV1 and of 0.18 L in FVC demonstrating continuous lung growth. In relation to their growth, these results revealed an increase of 32 ml per cm height in FEV1 and an increase of 51 ml per cm height in FVC. These findings indicate that after the severe insult, regular lung growth is clearly hindered. However, these children catch up with time and generate development of lung parenchyma which exceeds airway growth. The natural course of lung function parameters in childhood and adolescence has been described by Quanjer et al.[27] showing the natural outgrowth of FVC in relation to FEV1. While in adolescence the number of alveoli increases, the diameter of airways is proportionally limited.[28,29] In view of this, other factors than PFTs, such as exercise intolerance, chest exacerbations, and nutritional status, need to be included in the follow-up assessment of patients with PIBO.

In our study, patients remained in a good nutritional status. Although the nutritional requirements are generally high due to the increased respiratory work, this is likely to be caused by high nutritional intake in a cohort of patients with a similar socioeconomical background and in a setting of a highly developed health care system. Overall growth remains essential in patients with chronic lung disease as it improves lung function and quality of life in general.

Previous studies in patients with PIBO have shown increased neutrophilic inflammation in BAL samples which persisted over the follow-up period indicating persistent, nonresolving inflammation.[14,16] In our study, our patients showed a persistent increase of neutrophilic inflammation by 2.12% per year. The sputum

samples were collected regularly in times of nonexacerbation. Therefore, sputum neutrophilia in our patients is likely to present a chronic, nonresolving inflammatory airway process rather than an ongoing infection. These findings are in concordance with previous studies.[14] In addition, calprotectin which is released by neutrophils, has been shown to be significantly increased in patients with PIBO.[30] Persistent airway neutrophils and their pathomechanistic mediators such as interleukin-8 have been shown to play a major role in various small airway diseases such as COPD, cystic fibrosis, and BOS after HSCT.[7,32-34] This underlines the importance of understanding the role of the neutrophilic dominance and its mediators in the process of small airway disease in PIBO, especially as such mediators could serve as potential marker and therapeutic target.[35,36]

The clinical pattern of PIBO can vary. Not all patients with PIBO are diagnosed promptly after the initial insult to the lungs. Especially patients with some bronchodilator response may have been diagnosed with nonallergic asthma. Therefore, it remains unclear what percentage of initially mild PIBO is mislabeled for example as asthma, COPD, or other obstructive diseases of unknown origin.[37] Therefore, and in view of the persistent inflammatory process, it is important that PIBO is considered as differential diagnosis in any age. Thus, PIBO should be considered in young adulthood, especially when a history of smoking or other inhaled pollutant is missing.

5 | CONCLUSION

Long-term pulmonary function follow-up in PIBO shows a constant impairment as well as persistent neutrophilic inflammation in the lungs. The management of PIBO patients requires continuous follow up beyond adolescence. Further investigations are needed to distinguish the triggers of neutrophilic inflammation and its resolution in the airways of patients with PIBO.

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AUTHOR CONTRIBUTIONS

Eva Herrmann: formal analysis (equal); methodology (equal); resources (equal); software (equal); validation (equal). **Lia Kriszeleit**: data curation (equal); investigation (equal); methodology (equal); resources (equal). **Jonas Eckrich**: data curation (equal); investigation (equal); methodology (equal); resources (equal). **Ralf Schubert**: conceptualization (equal); formal analysis (equal); methodology (equal); project administration (equal); software (equal); supervision (equal); validation (equal); visualization (equal). **Stefan Zielen**: conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); visualization (equal).

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SUPPORTING INFORMATION

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