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Transbronchial lung cryobiopsy: prospective safety evaluation and 90-day mortality after a standardized examination protocol

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Abstract

Background: Transbronchial lung cryobiopsy (TBLC) is a new method of bronchoscopic tissue sampling in patients with unclear diffuse parenchymal lung disease (DPLD). While not the gold standard, TBLC has a good diagnostic correlation with surgical lung biopsy, and retrospective analyses of peri-interventional complications and mortality are promising. However, prospective reports on 90-day mortality are lacking.

Objectives: This study addresses morbidity and 30- and 90-day mortality in TBLC after a standardized protocol.

Methods: In this prospective study, 75 patients with DPLD requiring tissue sampling were included. A standardized protocol (including prophylactic use of an endobronchial balloon, postinterventional observation, and minimum sampling requirements) was used in all patients. Adverse events (pneumothorax, bronchial bleeding, premature discontinuation, prolonged monitoring at ICU, and fatal outcome) and 30- and 90-day mortality rates were recorded.

Results: A total of 308 cryobiopsies were performed in 75 patients. Peri- and postinterventional pneumothorax were observed in 20% (9.3% mild and 10.7% moderate with the necessity of chest drainage), and bronchial bleeding was found in 29.3% (22.7% moderate and 6.7% severe). Total lung capacity below normal value was associated with the risk of pneumothorax ($p = 0.009$), and diffusion limitation for carbon monoxide below normal value was associated with the risk of bronchial bleeding ($p = 0.044$). No fatal events were observed within 30 days, and the 90-day mortality rate was 1.3%, but not related to the procedure itself.

Conclusion: As it gradually becomes the invasive procedure of choice in unclear DPLD, TBLC is a safe procedure with a low 30- and 90-day mortality.

Trial registration ID: DRKS00026746 (German Clinical Trial Register)

Keywords: cryobiopsy, mortality, safety

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Introduction

Diffuse parenchymal lung disease (DPLD) comprises a heterogeneous group of conditions with variable natural history, pathologic and radiologic characteristics, and treatment options and responses. Multidisciplinary discussion (MDD) based on comprehensive clinical, serological, and radiological data is used to define the underlying interstitial lung disease subtype.[1–3] However, in up to 30% of cases, the clinical findings and high-resolution CT results are not sufficient to allow a confident clinical diagnosis requiring surgical lung biopsy (SLB) for histopathological evaluation.[4] However, SLB in DPLD has been associated with substantial risks, including significant in-hospital mortality (16% for non-elective patients and 1.7% for elective patients).[5–7] Overall, 30-day mortality

was reported from the case series to be 1.5–4.5%[8] and 2.4% from a large European database.[6] Although mortality risk might be lower in experienced centers, this invasive technique should always be considered in an overall view since many patients have advancing age, comorbid disease, and limited cardiopulmonary reserve.

Transbronchial lung cryobiopsy (TBLC) has emerged as an alternative diagnostic technique and has been proposed as a safer and less invasive alternative to SLB for diagnosing DPLD. Compared to SLB, TLCB represents a potentially cost-saving and less-time consuming approach.[8,9] The superior health resource use and acceptable diagnostic yield compared to SLB have been shown recently, which advantages TBLC over SLB in a considerable number of patients.[10–12] Using an elaborated design, Troy *et al.* enrolled 65 patients with uncertain DPLD and took samples with TBLC and SLB. They showed 70.8% histopathologic agreement (CI = 0.55–0.86), and for TBLC with high or definitive diagnostic confidence at MDD, 95% were concordant with SLB diagnosis.[10] Moreover, TBLC already finds utilization in diagnosing non-interstitial diseases such as malignant or infectious diseases, with satisfying diagnostic certainty.[13,14]

As a relatively new technique, suggestions for indications, contraindications, and patient selection have recently been formulated and reviewed by Hetzel *et al.* based on current evidence and expert suggestions.[15] Key points of the procedural aspects include using general anesthesia or deep sedation and fluoroscopic guidance of the advancing cryoprobe with biopsies in the subpleural area (1 cm from the visceral pleura) to reduce the risk of bleeding.[16] TBLC from two different segments of an affected lung lobe has been associated with a 33% increased diagnostic yield compared to biopsy from only one segment without significant differences in complications.[9] The prophylactic use of a Fogarty balloon or bronchial blocker with immediate inflation after TBLC prevents blood from entering the central areas in case of significant bleeding. A postprocedural chest X-ray should be performed to assess the occurrence of pneumothorax.[15] Based on the known risk of transbronchial biopsies in general and TBLC in particular, it seems prudent to follow a standardized approach to increase patient safety.

Between 2009 and 2021, at least 30 studies evaluated the diagnostic yield and safety outcomes of TBLC in DPLD. However, very few had a prospective design, and less than half of the studies reported 30-day mortality. Pooled analyses estimated mortality rates post-TBLC as 0.1–2.7%, with exacerbations of idiopathic pulmonary fibrosis (IPF) as a leading cause of death.[1,8,17] For 90-day mortality, only one letter to the editor with retrospective US data shows a mortality rate of 1.67% (3 of 189 patients).[18] The all-cause 30-day mortality in this study was 25% for inpatient procedures (two of eight total inpatients) and 1.1% for outpatient procedures. These findings were higher than the meta-analyzed reports of procedural mortality rates of 0.1–0.3%, raising concerns about safety in advanced DPLD.[18,19] The authors concluded that all patients who died at 30 days had poor baseline lung function, and the occurrence of bleeding also predicted a higher risk of mortality. However, two patients died of unknown causes on days 29 and 74.

For long-term survival, Pannu *et al.* retrospectively analyzed the median 5-year survival of different diagnostic approaches in DPLD, comparing only TBLC, SLB, and HRCT, and found a significant difference if the histopathologic evaluation was included in MDD. Furthermore, TBLC showed a trend toward increased survival compared to SLB.[20] European data on 90-day mortality are lacking.

Reported complication rates of TBLC vary considerably, and the two most common complications are pneumothorax and bleeding. Overall, pneumothorax risk was reported to be 6%, with a 3% risk of chest drain insertion.[21] More recent meta-analyses estimate the overall pneumothorax risk to be closer to 10%.[1,8] Bleeding risk is more difficult to quantify, as there is no internationally accepted severity scale. Pooled analyses of studies reporting moderate and severe bleeding estimated a risk of 4.9–39%.[8,22,23]

Based on the above, we decided to perform a prospective study to evaluate the peri-interventional complications and the 30- and 90-day mortality rates after TBLC for the histological diagnosis of DPLD. Therefore, we used a standardized procedure protocol based on the recommendations of Hetzel *et al.*[15]

Methods

Study population

Patients with radiologically proven DPLD requiring a histological examination for further evaluation were included in this study. All patients were above 18 years of age. Exclusion criteria included any possible bleeding disorders [international normalized ratio (INR) $>$ 1.3, partial thromboplastin time (PTT) above the normal range, and thrombocytopenia $<$ 100.000/µl], treatment with thienopyridines, oxygen saturation below 90% after delivery of oxygen at a maximum flow rate of 2 liters per minute, pre-existing severe cardiac diseases (e.g. unstable angina pectoris, myocardial infarction, and decompensated cardiac insufficiency), or known echocardiographically measured pulmonary hypertension with a systolic pulmonary artery pressure greater than 50 mmHg. While treatment with phenprocoumon, clopidogrel, and other new antiplatelet drugs had to be stopped peri-interventionally, treatment with acetylsalicylic acid could be continued.

The study design and protocol were approved by the local ethics authority (Ethic Committee of the FederalStateLowerAustria,GS1-EK-1/182-2018). Furthermore, all patients gave their written informed consent for participation.

Bronchoscopy

Bronchoscopy was performed flexibly under general anesthesia in all patients. A rigid tube or laryngeal mask was used, depending on the operator's choice and pre-interventional evaluation of bleeding risk. Jet ventilation was used in all patients, and for the laryngeal mask, a 'Veres adapter' was used to connect it to jet ventilation.[24] When using rigid tubes, deep sedation was necessary. According to local standards, all patients were continuously monitored during the intervention, including continuous oxygen saturation, ECG monitoring, and repeated non-invasive blood pressure monitoring.

Tissue sampling and bronchoalveolary lavage

At least two tissue biopsies from at least two lung segments of the area of interest, guided by a pre-procedure high-resolution CT thorax, were taken using a 2.4-mm outer diameter cryoprobe. All cryobiopsies were taken in the distal part of the lung parenchyma with fluoroscopic guidance, usually in the most affected areas but with avoidance of the most densely fibrotic lung parenchyma. In all patients, a prophylactic endobronchial blocker or Fogarty balloon was inserted and prophylactically inflated with 3–4 ml of air after every biopsy to control possible bleeding. Bronchial blockers or balloons were tested for leaks before the procedure.[25] All interventions were performed by one of two experienced interventional operators.

Bronchoalveolary lavage (BAL) was performed before tissue biopsy. For the BAL procedure, 200 ml of prewarmed 0.9% saline was instilled into the lobe of interest and then gently aspirated.

Peri-interventional bleeding was defined as *moderate* (use of interventions such as vasoconstrictive drugs) or *severe* (use of transient tamponade with gauze, additional prolonged monitoring or intensive care therapy after the procedure, discontinuation of the procedure due to bleeding, or fatal outcome) following Hetzel *et al.*[23]

A chest X-ray was performed 2 h after the end of the procedure or immediately if unexplained oxygen desaturation, persistent cough, and/or thoracic pain were present. Pneumothorax was defined as *mild* if no chest drainage was necessary and pneumothorax resolved spontaneously, or *moderate* if a chest tube was indicated due to the size of the pneumothorax (i.e. large pleural gap along the entire length of lateral chest wall, or shift of mediastinum) and/or symptoms of the patient.

All patients were further clinically monitored for a minimum of 18 h and then discharged if no complication occurred. Follow-up included physical examination and lung function testing 1 month and at least a second physical examination 3 months after the procedure.

Pathologic evaluation and diagnosis

All TBLC specimens were evaluated by one of two expert pathologists for lung histology. BAL fluids were analyzed for total; differential cell counts and the CD4/CD8 ratio was calculated. If the erythrocyte count in BAL fluids exceeded 1000/ml, further diagnostic evaluations were not performed. The final diagnosis for each patient was achieved through an MDD, according to guidelines.[1,26]

Table 1. Characteristics of the patients.

Variable	
Number of patients	75
Female, n (%)	36 (48)
Male, n (%)	39 (52)
BMI, mean (SD)	27.7 (±5.0)
Age at bronchoscopy, median (interquartile range)	60 (48–69)
Thrombocytes (1000/µl), mean (SD)	285 (±84.5)
Activated partial thromboplastin time in seconds, mean (SD)	29.6 (±3.2)
CRP (mg/dl), mean (SD)	0.98 (±2.92)
Lung function parameters before TBLC	
FVC (L), mean (SD)	3.36 (±1.0)
FVC (% pred.), mean (SD)	85.8 (±16.7)
FEV1 (L), mean (SD)	2.58 (±0.83)
FEV1 (% pred.), mean (SD)	83.4 (±18.3)
TLC (L), mean (SD)	5.22 (±1.20)
TLC (% pred.), mean (SD)	89.5 (±19.7)
DLCO (% pred.), mean (SD)	67.0 (±17.8)

BMI, body mass index; CRP, C-reactive protein; DLCO, diffusion limitation for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; SD, standard deviation; TBLC, transbronchial lung cryobiopsy; TLC, total lung capacity.

Statistics

All statistical data were analyzed using IBM SPSS Statistics software, version 23 (SPSS, IBM Corporation, Armonk, NY). Continuous variables were calculated as mean and standard deviation, or median and range. Categorical variables were calculated as absolute numbers and percentages. The rate of adverse events, the mortality rate at 30 and 90 days, and the frequency of definite or probable or definite DPLD diagnosis were analyzed in all patients. A chi-square test or Fisher's exact test was used for categorical variables. All tests were two-sided, and differences were considered statistically significant if p was less than 0.05.

Results

During the 36-month study period, 75 patients were included in the study, with 48% female patients. The median age was 60 years, the mean body mass index (BMI) was 27.7 kg/m^2, and mean levels of thrombocytes and activated PTT in seconds were within normal values. Lung function testing before bronchoscopy showed mean values of total lung capacity (TLC) and forced vital capacity (FVC) at the lower normal range, with mean values of 91.1% and 86.6%, respectively. However, standard deviations for both values were high, reflecting that many of the patients with unclear DPLD already showed restrictive lung function pattern. Furthermore, mean diffusion limitation for carbon monoxide (DLCO) was already below normal values (65.7%), which is frequently observed early in the development of DPLD. In our study, 74.6% (n = 56) showed a DLCO below 80% (Table 1).

Two cryobiopsies from at least two lung segments were mandatory per protocol; therefore, the mean number of TBLC per patient was 4.1 (Table 2). For rigid bronchoscopy (n = 10, 13.3%), the patients received deep sedation. Most procedures were performed using a laryngeal mask (n = 63, 84.0%) and general anesthesia, or flexible endotracheal intubation (n = 2, 2.7%) and general anesthesia. The right lower lobe was the most frequently used location for TBLC (45.2%) since it is convenient for access and placing a bronchial blocker or balloon, and DPLD frequently starts in the lower regions of the lungs. Therefore, the upper lobes were only used in 3.9% (left upper lobe) and 8.6% (right upper lobe). In 29 patients (38.7%), TBLC was performed in more than one lobe. Mean procedural time (= time of insertion of the bronchoscope until the end of bronchoscopy) was 24 min. BAL was performed in all patients, and the most frequent differential cytology profile was found for lymphocytic BAL (49.3%), reflecting that hypersensitivity pneumonia (fibrotic n = 11, nonfibrotic n = 1) and sarcoidosis (n = 8) were among the most frequently diagnosed DPLD in this study (shown in Table 2).

Evaluation of peri- and postoperative complications showed peri- and postinterventional pneumothorax (observed within 18 h after the procedure) in 15 patients (20%). Of those, in eight patients (10.7%), drainage was indicated. In seven other patients (9.3%), mild pneumothorax resolved without intervention. Bronchial bleeding was more often observed than pneumothorax, with moderate bleeding in 22.7% (n = 17) and severe bleeding in 6.7% (n = 5). In one patient

(1.3%), severe bleeding led to premature discontinuation of the procedure due to the necessity of instillation of gauze, with additional prolonged monitoring in the intensive care unit after the procedure. Within 30 days, none of the study patients died, and one patient experienced hemoptysis 10 days after TBLC. This patient was later diagnosed with amiodarone-induced lung injury, and hemoptysis was most probably caused by anticoagulation therapy and resolved without further intervention. One patient died within 90 days after TBLC (56 days after the procedure). The final diagnosis in this patient was lung adenocarcinoma, and the cause of death was rapid tumor progression. One patient developed a pneumothorax 22 and 68 days after TBLC (shown in Table 3). This patient also had periinterventional pneumothorax and needed drainage in all cases. His final diagnosis was advanced pulmonary Langerhans cell histiocytosis, and he was later referred for lung transplantation.

Using Fisher's exact test, patients' characteristics, bronchoscopic interventions, and final diagnosis were evaluated as possible risk factors for periinterventional TBLC adverse events. We found that patients with a baseline TLC $< 80\%$ significantly had a pneumothorax more often during and after TBLC ($p = 0.009$). Furthermore, patients with reduced DLCO $< 80\%$ significantly had moderate and severe bronchial bleeding more often during the TBLC procedure ($p = 0.044$). Age was suggested to be another possible risk factor for peri-and postinterventional adverse events after TBLC.[23] However, in our study, no significant difference was found in patients older or younger than 75 years of age (shown in Table 4).

After discussion of the histopathological results in an MDD, the final diagnosis of the study population revealed fibrotic hypersensitivity pneumonitis in 11 patients (14.7%), followed by IPF in 9 patients (IPF, 12.0%), sarcoidosis and respiratory-bronchiolitis interstitial lung disease (RB-ILD) in 8 patients each (10.7%), and unclassifiable DPLD in 7 patients (9.3%). Less frequently, non-specific interstitial pneumonia (NSIP, n = 6), rheumatoid arthritis interstitial lung disease (RA-ILD, n = 6), connective tissue interstitial lung disease (CTD-ILD, n = 5), cryptogen organizing pneumonia (n = 4), alveolar lung carcinoma (n = 3), and others were found (shown in Table 5).

Table 2. Bronchoscopic interventions.

Variable	
Total number of TBLC	308
Mean number of TBLC per patient	4.1
Procedure time (min), mean (SD)	24 (±12.5)
Sedation, n (%)	
General anesthesia	65 (86.7)
Deep sedation	10 (13.3)
Intubation technique, n (%)	
Rigid bronchoscope	10 (13.3)
Endotracheal tube	2 (2.7)
Laryngeal mask	63 (84.0)
Location of TBLC, n (%)	
Right upper lobe	9 (8.6)
Middle lobe	29 (27.9)
Right lower lobe	47 (45.2)
Left upper lobe	4 (3.9)
Left lower lobe	15 (14.4)
BAL result	
Total cell count per ml, median (range)	408 (59–1211)
Neutrophilic BAL, n (%)	19 (25.3)
Lymphocytic BAL, n (%)	37 (49.3)
Eosinophilic BAL, n (%)	9 (12.0)
BAL cell count in normal ranges, n (%)	10 (13.3)

BAL, bronchoalveolary lavage; SD, standard deviation; TBLC, transbronchial lung cryobiopsy.

Discussion

This is the first study evaluating the safety of TBLC in Austria, and the first prospective study evaluating 30- and 90-day mortality after TBLC in Europe.

With a mortality of 1.3% after 90 days and no deaths within 30 days after TBLC, we confirmed that TBLC is a safe diagnostic procedure for DPLD, especially when compared to SLB (30-day mortality up to 4.5%).[27] Our present data

Table 3. Peri- and postinterventional adverse events after transbronchial lung cryobiopsy.

	n (%)
Pneumothorax	15 (20.0)
Mild (no intervention)	7 (9.3)
Moderate (drainage)	8 (10.7)
Bronchial bleeding	22 (29.3)
Moderate	17 (22.7)
Severe	5 (6.7)
Premature discontinuation of procedure	1 (1.3)
ICU admission post-bronchoscopy	1 (1.3)
Hemoptysis post-bronchoscopy	1 (1.3)
Pneumothorax after dismission	
Within 30 days	1 (1.3)
Within 90 days	1 (1.3)
ICU admission within 90 days	1 (1.3)
Mortality within 30 days	0
Mortality within 90 days	1 (1.3)

ICU, intensive care unit.

confirm a previous report from US data on 189 patients, with a 90-day mortality rate of 1.67%.[28] Furthermore, in our study, the observed case of fatal outcome 56 days after TBLC was assigned to the rapidly progressing neoplastic disease of this patient rather than to TBLC.

TBLC inherits a higher risk for pneumothorax, especially bronchial bleeding, than other bronchoscopic biopsy techniques.[23] Therefore, it should be applied in experienced centers, and published recommendations about patient selection, safety techniques during the procedure (e.g. prophylactic balloon placement), and postinterventional observation should be fulfilled.[15] In our study, we used the suggestions of the Ravenna Cryobiopsy Working Group, published by Hetzel *et al.*[15] We observed a pneumothorax in 20%, with the need for chest drainage in around half of the cases (53.3%), based on size and/or symptoms of the patient. Moderate to severe bronchial bleeding was observed in 29.3% of TBLC cases, supporting the high value of a prophylactic endobronchial balloon during TBLC. Thus, only in one patient did the bleeding induce premature discontinuation and admission to the intensive care unit for further treatment. Our observations of pneumothorax are slightly higher than reports in the

Table 4. Risk factors for peri-interventional pneumothorax and bronchial bleeding in transbronchial lung cryobiopsy.

	Pneumothorax			Bronchial bleeding		
	None	Mild/moderate	*p*-value[a]	None	Moderate/severe	*p*-value[a]
All, n (%)	60 (80.0)	15 (20.0)		53 (70.7)	22 (29.3)	
Age, years						
⩾75	8	3	0.683	7	4	0.721
<75	52	12		46	18	
TLC, %						
<80	13	9	0.009	15	15	0.785
>80	47	6		38	7	
DLCO, %						
<80	44	12	0.747	36	20	0.044
>80	16	3		17	2	

DLCO, diffusion limitation for carbon monoxide; TLC, total lung capacity.
[a]Fisher's exact test was applied.

Table 5. Final diagnosis according to multidisciplinary discussion.

	n (%)
Fibrotic hypersensitivity pneumonitis	11 (14.7)
Idiopathic pulmonary fibrosis	9 (12.0)
Respiratory-bronchiolitis interstitial lung disease	8 (10.7)
Sarcoidosis	8 (10.7)
Unclassifiable DPLD	7 (9.3)
Non-specific interstitial lung disease	6 (8.0)
Rheumatoid-arthritis interstitial lung disease	6 (8.0)
Connective tissue interstitial lung disease	5 (6.6)
Cryptogen organizing pneumonia	4 (5.3)
Alveolary lung carcinoma (adenocarcinoma)	3 (4.0)
Desquamative interstitial pneumonia	2 (2.6)
Nonfibrotic hypersensitivity pneumonitis	1 (1.3)
Langerhans cell hystiocytosis	1 (1.3)
Eosinophilic granulomatosis with polyangiitis	1 (1.3)
Radiation-induced organizing pneumonia	1 (1.3)
Drug-induced ILD (Amiodaron)	1 (1.3)
Behcet's disease	1 (1.3)

DPLD, diffuse parenchymal lung disease; ILD, interstitial lung disease.
Percentages may not total 100% because of rounding.

literature, but the risk for chest drainage (overall 10.7% in our study) was similar to previous reports.[1,8] Furthermore, our data reports of severe bronchial bleeding (6.7%) parallels previous reports.[8,22,23]

We could also identify TLC below the normal value as a significant risk factor for a pneumothorax event, reflecting that patients with advanced DPLD burden have a higher risk due to progressing fibrotic lung changes. Furthermore, we found a significantly higher bleeding risk for patients with diffusion limitations. These findings underline the need to carefully evaluate the patients' initial lung function before performing TBLC to estimate peri-interventional risk.

However, since mortality rates were very low, and the adverse events of TBLC are manageable in an expert center, our results support the recommendation to use TBLC in patients with unclear DPLD (after MDD) ahead of SLB, where all patients experience intraoperative pneumothorax and a postoperative chest tube, and peri-and postoperative mortality reports are clinically relevant (in-hospital mortality up to 16%).[5] Nevertheless, we must admit that our study was not designed to directly compare TBLC *versus* SLB, and such comparisons are difficult due to many possible variables affecting each diagnostic procedure.

One limitation of our study was the sample size and its monocentric design. Although we prospectively collected data since 2018, we experienced fewer patients assigned for diagnostic evaluation of DPLD during the COVID-19 pandemic, which was probably caused by a general reluctance of

patients to seek medical evaluation of chronic symptoms. Furthermore, two experienced interventional operators performed all biopsies, and the risk of morbidity or mortality might be increased in less-trained investigators or less experienced centers. Therefore, we suggest confirming our data in larger multicenter trials using a standardized protocol among all study sites.

Conclusion

Our study has shown that TBLC is associated with a low 30- and 90-day mortality risk. The study results suggested reduced baseline lung function as a risk factor for pneumothorax and bronchial bleeding, supporting the necessity of careful patient selection, training, and standardized interventional processes, including precautions for bleeding control. These findings should be further evaluated in prospective multicenter studies.

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Author contributions

Klaus Hackner: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Writing – original draft.

Antonia Stadler: Data curation; Project administration; Writing – review & editing.

Felix Schragel: Data curation; Writing – review & editing.

Valerie Klamminger: Data curation; Investigation; Writing – review & editing.

Bahil Ghanim: Formal analysis; Writing – review & editing.

Alexander Varga: Data curation; Investigation; Writing – review & editing.

Peter Errhalt: Conceptualization; Methodology; Project administration; Supervision; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement

The study was performed following the World Medical Association Declaration of Helsinki. The study design and protocol were reviewed and approved by the local ethics authority (Ethic Committee of the Federal State Lower Austria, GS1-EK-1/182-2018). All patients gave their written informed consent for participation.

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Data availability statement

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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