Letter to Editor

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Utility of the 6-minute walk test and health-related quality of life questionnaires in granulomatous and lymphocytic interstitial lung disease

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ABSTRACT

Introduction: Granulomatous lymphocytic interstitial lung disease (GLILD) is a non-infectious complication affecting 10-20% of patients with common variable immunodeficiency disorders. Exercise capacity in GLILD patients, who often report shortness of breath during exercise, has not been previously evaluated. This study aimed to assess the utility of the six-minute walk test (6MWT) as an outcome measure in GLILD. It also evaluated reproducibility and effectiveness of King's Brief ILD Questionnaire (K-BILD) questionnaire in capturing the multidimensional impact of GLILD on quality of life.

Methods: This was an observational prospective cohort study. The 6MWT and questionnaires were conducted at baseline and two follow-ups. The 6MWT was performed according to ERS/ATS guidelines. The utility was evaluated by correlating the 6MWT measures (walked distance (6MWD) and distance-saturation product (DSP)) with clinical parameters and health-related quality of life (HRQOL) questionnaires. Reproducibility was assessed using the Intraclass Correlation Coefficient.

Results: Thirteen participants (54% male, median age 45 (IQR 38- 62) years) were included. The median 6MWT distance was 457 meters. DSP was the only measure strongly correlated with FVC% and FEV_1%, and it showed stronger correlations with clinical measures than 6MWD. The 6MWT has good 6-month and one year reproducibility. Finally, K-BILD appeared to be a useful tool for assessing HRQOL in patients with GLILD, who often have multi-system involvement.

Conclusion: Our findings highlight the potential of the 6MWT as a useful measure to assess GLILD. The 6MWT and K-BILD correlations with clinical parameters suggest utility in assessing disease severity and monitoring patients' physical functioning.

Key words: Granulomatous lymphocytic interstitial lung disease, common variable immunodeficiency disorders, 6-minute walk test

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Dear Editor,

Granulomatous lymphocytic interstitial lung disease (GLILD) is a non-infectious complication affecting 10-20% of patients with common variable immunodeficiency disorders (CVID). GLILD is known as a manifestation of immune dysregulation in CVID and is associated with increased morbidity and mortality[1]. It is characterized by lymphocytic infiltration and/ or granulomatous inflammation within the lung parenchyma [2]. Typical radiological findings include ground-glass opacities, consolidation, nodules, and interlobular septal thickening, while the most common histological features are lymphoid interstitial pneumonia, follicular bronchiolitis, and non-caseating granulomas [3, 4]. GLILD frequently coexists with other systemic manifestations of CVID including splenomegaly, lymphadenopathy, and autoimmune complications [1].

The diagnosis and management of GLILD is a challenge due to the heterogeneity of the disease and the lack of evidence-based guidelines. Currently, the evaluation of GLILD relies on high-resolution computed tomography (HRCT), pulmonary function tests (PFTs), and supporting laboratory tests with or without biopsy [5]. However, these measures are limited by the need for specialised equipment, skilled personnel, patient cooperation, and can be costly and time-consuming, making them less accessible in some settings. Additionally, the extrapulmonary complications in CVID that involve multiple organs can significantly impact quality of life in these patients. Therefore, understanding the contribution of respiratory disease can be challenging, and current assessment tools may not fully capture the broader impact of GLILD on patients' lives.

Evaluating functional capacity using the 6-minute walk test (6MWT) could be beneficial in the evaluation of GLILD. 6MWT is a well-established, accessible tool used to measure patients' functional capacity, track disease progression, evaluate therapeutic efficacy, and as a predictor of morbidity and mortality of patients with various cardiac and pulmonary conditions [6]. In addition to functional measures, health-related quality of life (HRQOL) assessment is critical for understanding the broader impact of GLILD. Therefore, this study aimed to assess the utility of the 6MWT and King's Brief ILD Questionnaire (K-BILD) in GLILD patients, exploring correlations with clinical measures, reproducibility over time, and potential as tools for disease monitoring and treatment evaluation.

Methods

We conducted a prospective cohort study involving all adult patients with confirmed GLILD and CVID, recruited from the respiratory-immunology clinic at the Royal Free Hospital in London. Due to the rarity of the disease, we recruited all GLILD patients who were followed at our hospital, with recruitment starting in July 2021 and ending in January 2024. Participants met the following inclusion criteria: age ≥18 years, confirmed CVID diagnosis per international consensus guidelines [7], and GLILD based on local guideline including HRCT findings and, where indicated, video-assisted thoracoscopic lung biopsy. Exclusion criteria included recent respiratory infection, inability to perform the 6MWT, and resting oxygen saturation <88% on room air.

The 6MWT was conducted at baseline, within six months, and one year, following European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [6]. Participants completed the test on a 30-meter flat, indoor track. Key outcome measures included the six-minute walk distance (6MWD) and the distance-saturation product (DSP), which integrates both the distance walked and the lowest

oxygen saturation level recorded during the test [8]. DSP was calculated as 6MWD * (lowest SpO_2 during the test/100); 90% = 0.9, for example. The unit is m%. BORG dyspnea score was recorded pre- and post-test.

HRQOL was assessed at baseline using the K-BILD, a validated ILD-specific questionnaire that evaluates psychological well-being, breathlessness and activities, and chest symptoms [9]. Other tools included the 36-Item Short Form Survey (SF-36) [10], Fatigue Assessment Scale (FAS) [11], and Medical Research Council (MRC) dyspnoea scale [12].

Patients' demographic and clinical data, including lung function parameters were retrieved from medical records. Frequencies and percentages are used to represent categorical data, whereas median and interquartile range (IQR) are used to express continuous data. Based on the distribution of the data, assessed using visual inspection of histograms and the Shapiro–Wilk test, either Pearson's or Spearman's rank correlation coefficient was used to evaluate the relationship between the 6MWT measures and other variables. The correlations were classified as follows: very strong > 0.80, strong > 0.60, moderate > 0.40, and weak < 0.39. Intraclass correlation coefficients (ICCs) were calculated to assess the reproducibility of repeated measurements.

Results

Sixteen GLILD patients were seen at our clinic during recruitment, with three excluded due to limited time, inability to walk, or learning disability. We included 13 patients, out of whom 10 completed the first follow-up and 6 completed the second. Seven (54%) of were male, with a median age of 45 (IQR 38- 62) years and a median body mass index (BMI) of 22 (IQR 20–25) kg/m^2. Eight (57%) of the participants were prescribed systemic GLILD therapy.

For every comparison between 6MWT measures and clinical variables, the strongest correlation was with DSP, and most of these correlations were statistically significant, (Table 1). Notably, DSP demonstrated the only strong correlations with FVC% (r = 0.70, p = 0.03) and FEV_1% (r = 0.72, p = 0.03) compared to other 6MWD metrics. The reproducibility of 6MWT was excellent with ICC values of 0.96 (95% CI: 0.59-0.97, p=0.003) at six months and 0.95 (95% CI: 0.69-0.99, p<0.001) at one year.

K-BILD scores provided additional insights into HRQOL. The total K-BILD score correlated strongly with DSP (r = 0.67, p <0.05), total SF-36 scores (r = 0.762, r^2 = 0.58), while FAS scores were inversely correlated (r = - 0.833, r^2 = 0.69). Reproducibility of K-BILD was similarly high, with ICCs of 0.94 (95% CI: 0.75 - 0.98, p<0.001) at six months and 0.95 (95% CI: 0.80 - 0.99, p<0.001) at one year.

Discussion

Several studies have documented the prognostic significance of the 6MWT in ILD, particularly in idiopathic pulmonary fibrosis (IPF). However, the utility of the 6MWT has not been previously reported in GLILD. Therefore, we explored the utility of the 6MWT as a clinical measure in GLILD. Our results suggest that the DSP shows stronger correlations with clinical measures than other 6MWD metrics; and that the 6MWT showed good longitudinal reproducibility in our cohort. Finally, results showed that K-BILD may be a useful measure of respiratory-related HRQOL in patients with GLILD.

The correlations between the 6MWT and other clinical parameters highlight the effects of lung disease on patients' physical functioning in real-life scenarios. Variability in these correlations across studies of chronic lung diseases likely reflects differences in disease physiology, study methodologies, and population sizes. For example, in IPF, weak correlations have been reported between the 6MWD and pulmonary function measures, including FEV_1%, FVC%, $FEF_{25–75}$%, and VC% [13, 14], as well as a strong negative correlation with the MRC breathlessness scale [15]. In contrast to these findings, our baseline results revealed no association between the 6MWD and lung function parameters. This lack of correlation may be due to the variability of PFT patterns among our patients, as not all individuals with GLILD exhibit restrictive lung function. Additionally, the variability in disease severity among the included patients may have further contributed to the absence of a clear relationship.

Table 1. Correlations between 6MWD and DSP with clinical measures.

	6MWD		DSP	
	r_s	p-value	r_s	p-value
PFT				
FVC%	0.58	0.09	0.70	**0.03**
FEV_1%	0.57	0.11	0.72	**0.03**
FEV_1/FVC	0.05	0.90	0.20	0.61
DL_{CO}%	0.41	0.32	0.48	0.23
K-BILD				
Psychological	0.64	**0.02**	0.60*	**0.03**
Breathlessness and activities	0.65	**0.02**	0.75	**0.003**
Chest symptoms	0.57	**0.04**	0.58*	**0.04**
Total	0.59*	**0.04**	0.67*	**0.01**
SF-36				
Physical functioning	0.58	**0.04**	0.66	**0.01**
Limitations physical health	0.20	0.51	0.28	0.34
limitations due to emotional problems	0.31	0.29	0.32	0.28
Energy/fatigue	0.22	0.48	0.35	0.24
Emotional well-being	0.19	0.54	0.25	0.41
Social functioning	0.26	0.40	0.34	0.25
Pain	0.23	0.15	0.50	0.08
General health	0.20	0.51	0.27	0.37
FAS	-0.53	0.07	-0.58*	**0.04**
VAS	-0.54	0.07	-0.62	**0.03**
MRC	-0.83	<**0.001**	-0.87	<**0.001**
Post-BORG				
Dyspnoea	-0.65	**0.02**	-0.73	**0.004**
Fatigue	-0.49	0.09	-0.62	**0.03**

6MWD: 6-minute walk distance and DSP: distance-saturation product. * Pearson (r) Correlation Coefficients.

Interestingly, across every comparative analysis between 6MWT measures and clinical variables, DSP consistently displayed the strongest correlations. This observation likely reflects the composite nature of DSP, which integrates walking distance and oxygen desaturation, thereby capturing several physiological dimensions of exercise limitation. In GLILD, where various physiological mechanisms contribute to impairment, a composite index such as DSP may demonstrate greater sensitivity than distance alone.

The reproducibility of 6MWT metrics over time supports their integration into routine clinical assessments. These findings are consistent with studies in IPF, which report ICCs ranging from 0.83 to 0.98 over similar intervals [6, 16]. While very high ICC values were observed at six months and one year, interpretation of ICCs as measures of reproducibility in GLILD should be made cautiously. Given that GLILD is a heterogeneous and potentially progressive condition, longitudinal variability may reflect true disease or treatment -related changes rather than measurement error alone. Therefore, the high ICCs in our cohort likely represent both measurement stability and underlying disease dynamics, particularly given the small sample size.

K-BILD appeared to be a useful tool for assessing HRQOL in GLILD. It had a 2-week test-retest reliability with an ICC range from 0.89 to 0.93 [9, 17]. However, no study has evaluated the long-term reproducibility. Here, we reported excellent 6-month and one-year reproducibility of K-BILD in our small GLILD population. K-BILD strong correlations with functional measures and excellent reproducibility over one year support its potential applicability in this rare disease population. By capturing psychological, physical, and symptomatic domains, K-BILD complements traditional clinical measures, providing a comprehensive view of disease impact.

The study is limited by its small sample size and single-center design, which may reduce generalizability. Additionally, the inclusion of patients who regularly attend clinical appointments may introduce selection bias, as these individuals may differ in characteristics such as symptom severity from those who do not attend regularly. Finally, logistical constraints during the COVID-19 pandemic prevented same-day PFT and 6MWT assessments for some participants.

In conclusion, the lack of well-established parameters that define what constitutes "normal" in CVID versus CVID with GLILD represents a key limitation in evaluating disease impact. This distinction is challenging due to the variable presentations of CVID and the additional complexity introduced by GLILD, which can significantly affect pulmonary function and overall health. The results of our study suggested that 6MWT and especially DSP may have potential as a sensitive marker for evaluating physical limitations and tracking disease progression in patients with GLILD. While the 6MWT is not a substitutes for traditional assessments, such as HRCT and PFT, it offers a practical approach to monitoring the impact of GLILD.

References

1. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immun 2004;114(2):415-21.
2. Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. J Aller Cl Imm-Pract 2017;5(4):938-45.
3. Tanaka N, Kim JS, Bates CA, Brown KK, Cool CD, Newell JD, et al. Lung diseases in patients with common variable immunodeficiency: Chest radiographic, and computed tomographic findings. J Comput Assist Tomo 2006;30(5):828-38.
4. Dhalla F, Lochlainn DJM, Chapel H, Patel SY. Histology of Interstitial Lung Disease in Common Variable Immune Deficiency. Front Immunol 2020;11:605187.
5. Bintalib HM, van de Ven A, Jacob J, Davidsen JR, Fevang B, Hanitsch LG, et al. Diagnostic testing for interstitial lung disease in common variable immunodeficiency: a systematic review. Front Immunol 2023;14:1190235.
6. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44(6):1428-46.
7. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. J Aller Cl Imm-Pract 2016;4(1):38-59.
8. Lettieri CJ, Nathan SD, Browning RF, Barnett SD, Ahmad S, Shorr AF. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Resp Med 2006;100(10):1734-41.
9. Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, Desai SR, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax 2012;67(9):804-10.
10. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med 2016;4:2050312116671725.
11. Hendriks C, Drent M, Elfferich M, De Vries J. The Fatigue Assessment Scale: quality and availability in sarcoidosis and other diseases. Curr Opin Pulm Med 2018;24(5):495-503.
12. Stenton C. The MRC breathlessness scale. Occup Med (Lond), 2008;58(3):226-7.
13. Mura M, Ferretti A, Ferro O, Zompatori M, Cavalli A, Schiavina M, et al. Functional predictors of exertional dyspnea, 6-min walking distance and HRCT fibrosis score in idiopathic pulmonary fibrosis. Respiration 2006;73(4):495-502.
14. Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Resp Med 2009;103(1):117-23.
15. Kozu R, Jenkins S, Senjyu H. Evaluation of activity limitation in patients with idiopathic pulmonary fibrosis grouped according to Medical Research Council dyspnea grade. Arch Phys Med Rehab 2014;95(5):950-5.

16. Eaton T, Young P, Milne D, Wells AU. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005;171(10):1150-7.

17. Prior TS, Hilberg O, Shaker SB, Davidsen JR, Hoyer N, Birring SS, et al. Validation of the King's Brief Interstitial Lung Disease questionnaire in Idiopathic Pulmonary Fibrosis. BMC Pulm Med 2019;19(1):255.

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