Evaluation of the learning effect on the 6-min walk distance in adults with long COVID

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To the Editor:

At the time of writing this letter, worldwide >770 million people had a laboratory-confirmed coronavirus disease 2019 (COVID-19) infection, a condition caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Long-term effects of COVID-19 are referred to as long COVID and include fatigue, dyspnoea, muscle weakness, anxiety, depression and sleep difficulties [2]. The National Institute of Health and Care Excellence (NICE) has defined long COVID as "signs and symptoms that develop during or after an infection consistent with COVID-19, that continue for more than four weeks and are not explained by an alternative diagnosis" [3]. Given that it is a multifactorial condition that can persist for months, the NICE guideline recommends integrated multidisciplinary rehabilitation services in the management of long COVID.

Since long COVID can lead to increased fatigue and decreased exercise capacity [4], the 6-min walk test (6MWT) is an often-used outcome parameter in clinical trials including patients with long COVID. The 6MWT is a valid tool, with a good test–retest reliability to test patients' functional exercise capacity, to evaluate the response of a therapeutic intervention or to assess prognosis [5]. Guidelines in chronic respiratory disease report a significant learning effect and therefore advise performing a practice test. More specifically, patients with COPD showed a pooled mean improvement on the second 6MWT of 26.3 m, and patients with asthma had a learning effect of 18 m (95% CI 11–24 m) [5, 6]. It is not yet known whether a similar learning effect exists in patients with long COVID. As overexertion can lead to a worsening of symptoms in this population, it is important to carefully consider whether a practice walk is needed [7]. With this research we aimed to investigate whether a learning effect on the 6-min walk distance (6MWD) is present in patients with long COVID.

Baseline data of 51 patients that were enrolled in the randomised controlled PuRe-COVID trial (clinicaltrials.gov identifier NCT05244044) [8] were used for analysis. Patients were included between April 2022 and June 2023 in two hospitals in Belgium: Antwerp University Hospital (UZA, Edegem) and Ziekenhuis Oost-Limburg (ZOL, Genk). Ethical approval was obtained from both institutional review boards (UZA: 2022–3067, ZOL: Z-2022–01) and patients gave informed consent at inclusion. Adult patients (aged ⩾18 years) were eligible if they had the post-COVID-19 status of ⩾6 weeks with persistent COVID-19-related symptoms, based on the following criteria: COPD Assessment Test score ⩾10 [9, 10] and/or modified Medical Research Council dyspnoea scale ⩾2 [9, 11] and/or Checklist Individual Strength–fatigue ⩾36 [12, 13] and/or post-COVID-19 Functional Status ⩾2 [14].

Two 6MWTs were performed on the same day, according to American Thoracic Society/European Respiratory Society standards [15], in a straight hospital corridor of 50 m with a minimum of 30 min between both tests. All tests were undertaken by a trained investigator. A standard operating procedure was used with standardised phrases for explaining the goal of the test (walk as far as possible) and for encouragement, which were given each minute. Rating of perceived exertion (RPE) and dyspnoea (RPD), using the modified Borg scale (range 0–10), was captured before and immediately at the end of the test.

Data are presented as either mean±SD or median (interquartile range (IQR)), as appropriate. The 6MWD, post-RPE and post-RPD between the two measuring times were compared through a paired samples t-test,

Shareable abstract (@ERSpublications)
There was no learning effect found on 6-min walk distance (6MWD) in patients with long COVID, performing a 6-min walk test twice. However, considerable variation in the difference between the two 6MWDs was observed: only 51% showed an increase. https://bit.ly/3H70G1r

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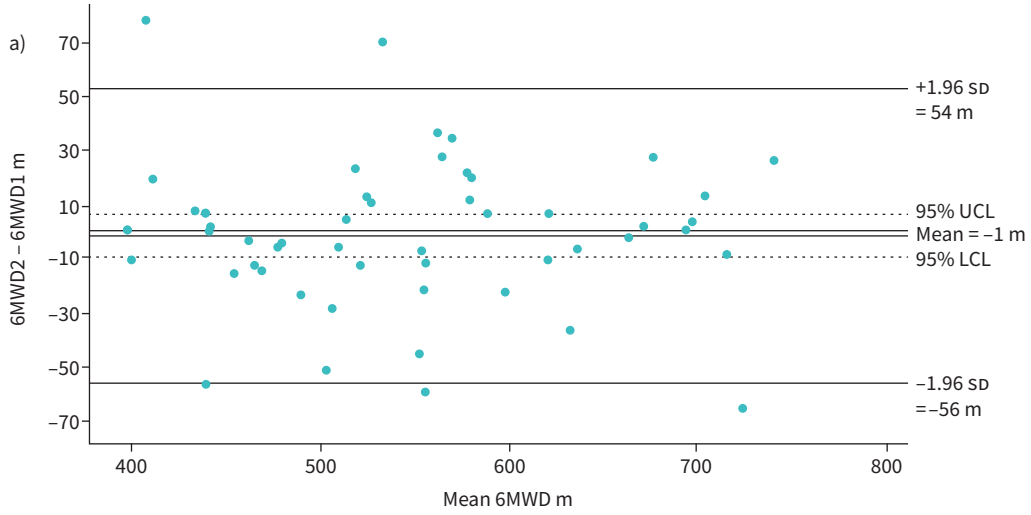
a)



b)

Participants	51
Female	33 (64.7)
Age years	50±12
BMI kg·m^{-2}	27.5±4.9
Smoking status never/current/former	35 (69)/4 (8)/12 (23)
Time since COVID-19 infection days	333 (222–594)
Charlson Comorbidity Index	1 (0–2)
Hospital admission during acute COVID-19	4 (7.8)
Length of hospital stay during acute COVID-19 days	7±2.8
FEV_1 % predicted	98.1±13.6
FEV_1/FVC ratio %	79.8±6.4
CAT score (points)	19.6±6.9
CIS fatigue (points)	47.4±6.8
mMRC (grade)	1 (1.0–2.0)
PCFS (grade)	2 (2.0–3.0)

FIGURE 1 a) Bland–Altman plot of 6-min walk distance (6MWD); b) participant characteristics. Data are presented as n, n (%), mean±SD or median (interquartile range). UCL: upper class limits; LCL: lower class limits; BMI: body mass index; COVID-19: coronavirus disease 2019; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; CAT: COPD Assessment Test; CIS: Checklist Individual Strength; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status scale.

using SPSS (version 28.0; IBM, Armonk, NY, USA). The Spearman correlation between the time interval between both tests and the difference between both 6MWDs (test 2 − test 1) was calculated. Associations between patient characteristics and the difference between both 6MWD were also considered. The two-way random intraclass correlation coefficient (ICC) with single measures and the Bland–Altman plot was used to assess the test–retest reliability of the 6MWT.

51 patients were recruited (figure 1). Patients performed a first 6MWT with a mean±SD 6MWD of 548 ±95 m, median (IQR) RPE of 3.0 (2.0–6.0) and RPD of 4.0 (3.0–7.0). During the second 6MWT (with a median time interval of 91 min between both tests, minimum 37 min and maximum 176 min) they had a 6MWD of 547±94 m, RPE of 4.0 (3.0–5.0) and RPD of 4.0 (3.0–6.0). The mean change between the two consecutive 6MWDs was −1 m (95% CI −9–7 m; p=0.83). There was a mean change for RPE of 0.3 (−0.1–0.7; p=0.14) and for RPD of −0.1 (−0.5–0.2; p=0.47). Only 26 (51%) patients performed better during their second 6MWD, while 25 (49%) patients performed less well (figure 1). Four (8%) patients showed a >30.5 m increase (the suggested minimal clinical important difference for 6MWD for patients with cardiopulmonary diseases [16]), while six patients (12%) showed a >30.5 m decrease. The limits of agreement between the two 6MWTs ranged from −55.7 m to 54.0 m. The test–retest reliability between both 6MWTs was excellent (ICC 0.96, 0.93–0.98; p<0.001). No significant associations were found

between the patient characteristics and the difference between both 6MWDs. However, there was a statistically significant positive association (r=0.35, p=0.02) between the time interval between both tests and the difference between both 6MWD, suggesting that a longer time interval tends to coincide with an increase of 6MWD in the second test compared to the first test.

While relevant differences are observed between two walk tests in individual patients, a systematic increase in 6MWD (indicating a learning effect) was not found. This is in contrast with the learning effect seen in other chronic respiratory diseases or even in healthy subjects [6, 17, 18]. Only half of them (51%) increased their second 6MWT; this in contrast with patients with COPD where this is 82% [17] and 73% in patients with asthma [6].

It is not clear yet why almost half of the patients with long COVID decreased their second 6MWD. A possible explanation could be that some patients suffer from post-exertional malaise (PEM), which is an important and debilitating symptom in this population [7]. PEM is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12–48 h after activity, but may be immediate, and lasting for days or even weeks [19]. It might be that the effect of overexertion overrules a possible learning effect. We could assume that if patients suffer from fatigue, their RPE would be higher at the start of their second 6MWD. While in the whole group the baseline RPE did not differ between the first and second tests (1.8±1.9 *versus* 2.0±2.0, p=0.57), in the group of patients who decreased their second 6MWD (n=25), baseline RPE was statistically significantly higher at the start of the second test (1.8±1.1 (first) *versus* 2.4±1.6 (second), p=0.04). Another hypothesis for the decrease in 6MWD could be a lack of motivation, due to the extended test battery they needed to perform in light of their participation in the PuRe-COVID study. Lack of motivation and PEM in relation to 6MWT were not investigated in this study and could be incorporated in future research studies on learning curve in the 6MWT.

In conclusion, no significant learning effect was observed in patients with long COVID. However, considerable heterogeneity between the two 6MWDs was observed in individual patients, and a learning effect cannot be ruled out in a subgroup of them. These findings may have implications in clinical practice or in designing studies using the 6MWD as an outcome measure in patients with long COVID. Further studies are required, as our results suggest that a subgroup of patients might deteriorate at a second test, which may improve if a longer time window between the two tests is considered.

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