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Lung outcomes and related risk factors in patients after SARS-CoV-2 infection: a hospitalised single-centre cohort from Johannesburg, South Africa

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Summary

Background Sequelae post-SARS-CoV-2 infection, including lung and functional impairment, pose a significant challenge post-recovery. We explored the burden and risk factors for post-COVID-19 sequelae in an African population with prevalent comorbidities including tuberculosis (TB) and HIV.

Methods We conducted an observational cohort study on hospitalised adults with confirmed SARS-CoV-2 infection from 20 March to 06 October 2021 at Chris Hani Baragwanath Academic Hospital, South Africa. We collected data on comorbidities, and COVID-19 severity using the World Health Organization (WHO) clinical progression scale. Prospectively, we followed up all participants within 40-days post-discharge to assess body mass index (BMI), COVID-19 symptoms and quality of life using St George's Respiratory Questionnaire (SGRQ), 6-min walking-test (6MWT), and spirometry. A subsequent in-depth visit assessed plethysmography, diffusing capacity for the lung for carbon monoxide (DLCO), and high-resolution chest-CT.

Findings We followed up 111 participants, where 65.8% were female, median age 50.5 years, and predominantly black-African (92.8%). Relevant comorbidities included TB disease (18.9%) and HIV infection (36%). SGRQ total scores were elevated in 78.9%, median 6MWT distance was reduced at 300 m (IQR 210–400), and nearly half (49.5%) exhibited spirometry findings below the lower limit of normal (LLN). In-depth pulmonary assessment for 61 participants revealed abnormalities in total lung capacity (31.6% <80% predicted), DLCO (53.4% <80% predicted), and chest-CT (86.7% abnormal). Significant risk factors for individual abnormal outcomes, adjusted for age and sex, were TB disease, HIV with CD4 <200 cells/mm^3, BMI <18.5 kg/m^2 and >35 kg/m^2, and initial COVID-19 severity.

Interpretation This study demonstrates substantial lung and functional morbidity within the first weeks post-COVID-19, particularly in individuals with pre-existing comorbidities including TB, HIV, and low or high BMI. Chest-CT and DLCO show best early potential at reflecting COVID-19-related pathologies.

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Keywords: Long-COVID; COVID-19; Post-COVID-19; Tuberculosis; HIV; Africa

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Research in context

Evidence before this study

We searched PubMed for any research on the long-term consequences of COVID-19 published from 01 May 2020 to 30 November 2023 using the following search terms: "post-COVID-19 condition" OR "long-COVID" OR "post-COVID-19 complications" OR "COVID-19 sequelae" OR "post-acute COVID-19 syndrome" OR "post-acute sequelae of COVID-19" OR "PASC" OR "post-acute sequelae of SARS-CoV-2" OR "long-term COVID-19 complications"; AND "TB" OR "tuberculosis" OR "HIV" OR "risk factors"; OR "lung outcomes" OR "respiratory outcomes" OR "lung function" OR "pulmonary complications". We found few studies reporting on symptoms related to long-term consequences of COVID-19 in African countries and no studies reporting in-depth lung and functional outcomes in an African cohort with a high prevalence of TB and HIV comorbidity. Additionally, few studies reported on the risk factors for post-COVID-19 sequelae, where age, initial COVID-19 severity, female sex and pre-existing comorbidities were recognised as potential risk factors. As a result, it became apparent that research is needed to provide descriptions and definitions of post-COVID-19 sequelae in the African context, and to particularly assess the impact of pre-existing comorbidities such as TB and HIV.

Added value of this study

We found a high morbidity burden within the first six weeks post-hospitalisation for COVID-19, where TB disease history (18.9%) and HIV infection (36%) were prevalent. We found chest-CT showed the highest abnormality (86.7%), followed by symptom burden, impact on quality of life and functional impairment as measured by St George's Respiratory Questionnaire (78.9% elevated scores) and 6-min walking-test (66.3% walked less than 350 m). We additionally found substantial lung function impact as evidenced by spirometry abnormalities in half the participants, impaired DLCO in 53.4%, and reduced total lung capacity in 31.6%. Our findings supported the notion that COVID-19 results in a fibrotic lung phenotype. We found that pre-existing comorbidities including TB and HIV were associated with worse outcomes, as well as being underweight (BMI <18.5 kg/m^2) or morbidly obese (BMI >35 kg/m^2) and the initial COVID-19 severity.

Implications of all the available evidence

This evidence is relevant for clinicians and healthcare providers to understand the prevalent pathologies and associated morbidity burden post-COVID-19, and that those with pre-existing comorbidities have a higher risk for abnormal findings and should therefore be screened for these. This insight could guide the development of context-specific standardised diagnostic and management algorithms and the allocation of healthcare services related to post-COVID-19 care. Further longitudinal data to track sequelae progression is important to determine the impact of underlying comorbidities and the potential for recovery.

Introduction

Emerging evidence highlights longer term sequelae post-SARS-CoV-2 infection. Recognised features include respiratory compromise and early pulmonary fibrosis with persistent dyspnoea, lung function and chest imaging abnormalities, and overall decreased quality of life (QoL); termed "long-COVID" or "Post-acute Sequelae of COVID-19" or "PASC". A review by Groff and colleagues,[1] revealed 54% of patients reporting at least one symptom of PASC six months post-COVID-19, with further evidence of persistent sequelae up to 12 months post-COVID-19.[1,2] The prevalence and characterisation of post-COVID-19 sequelae in African countries is poorly described. In a recent systematic review on post-COVID-19 sequelae in African countries by Müller and colleagues, the prevalence ranged from 2% to 86%, where potential risk factors had high variability and included female sex, increasing age, non-Black ethnicity, severity of acute COVID-19 and pre-existing comorbidities.[3] Interestingly, tuberculosis (TB) and human immunodeficiency virus (HIV) were not found to be associated with increased risk of post-COVID-19 sequelae, which warrants further investigation given their high prevalence in African countries.[3] Scarcity of data on post-COVID-19 sequelae, their characterisation and impact on quality of life in African populations poses a gap in understanding.

While prior TB, current TB, or HIV infection appears to increase the risk of severe and fatal COVID-19, evidence remains scarce.[4] COVID-19 mortality rates in African countries have been low compared to most high burden countries, suggesting a unique disease burden.[5] However, South Africa has been an outlier, recording just over four million cases (4,092,483) and 100,000 deaths (102,595), the highest cumulative number of cases in Africa, as of 01 February 2023.[6,7]

South Africa has a high TB burden, with approximately 852 cases (95% CI 679–1026) per 100,000 population and has almost double the prevalence in people living with HIV (PLWHIV) at 1734 cases (95% CI 1219–2249) per 100,000 population.[8] Concurrently, resource allocation challenges in low- and middle-income countries, such as South Africa, pose a further strain on the health system. With the potential added burden of post-COVID-19 sequelae in these populations, the understanding of the interplay with

pre-existing comorbidities may identify and guide the management of high-risk groups post-COVID-19.[4] Prioritising resources based on disease burden is pivotal to effective strategies. Considering the concerted efforts to combat COVID-19 and TB, with treatment provision and vaccination, more people survive these infections. Consequently, more people are living with the long-term health sequelae.[9,10] We sought to determine the physiological, functional, and quality of life outcomes post-COVID-19 hospitalisation, and the impact of potential risk factors, such as TB and HIV coinfection on post-COVID-19 sequelae.

Methods

Study design, site and participants

We conducted an explorative observational study in a post-hospitalisation cohort at Chris Hani Baragwanath Academic Hospital, a government-funded tertiary facility in Johannesburg, South Africa. Our primary objective was to describe lung outcomes post-SARS-CoV-2 infection and the potential risk factors for severe outcomes. We recruited hospitalised participants with confirmed SARS-CoV-2 infection, aged 18–70 years from 20 March to 22 September 2021, with first participant enrolled on 23 March 2021 and last participant followed up on 06 October 2021. All those at discharge from COVID-19 wards, were invited to participate. Those who were imprisoned, pregnant, or had a severe uncontrolled medical or psychiatric condition were excluded from the study. Potential information bias, e.g. for misdiagnosis of COVID-19, was mitigated by referring to hospital records, and pulmonary outcome measurements were standardised and strictly adherent to international guidelines. Selection bias was mitigated by inviting all patients on day of discharge from COVID-19 wards to participate.

Procedures

Retrospective data collection

We collected demographic- (age, sex), behavioural (smoking history), and hospitalisation data on COVID-19 treatment (medications, complications and oxygen or ventilation requirements) summarising severity with the World Health Organization (WHO) clinical progression scale.[11] Pre-existing comorbidities were verified through self-report and medical records.

Prospective data collection

We scheduled all follow-up visits within 40 days of discharge, with a subset of participants completing further in-depth investigation (including body plethysmography, DLCO-diffusion capacity measurement and chest computed tomography scan [CT-scan]). This subset of in-depth analysed participants was sampled systematically after the tenth enrolled participant, until approximately half of the total projected cohort completed all three in-depth investigations, with the participants' voluntary agreement for the additional investigations. We applied in all participants the St George's Respiratory Questionnaire (SGRQ), a weighted questionnaire to assess health related QoL in respiratory illness, where a total score above seven is abnormal.[12,13] We calculated the body mass index (BMI), and an HIV test (INSTI rapid) was done with consent if HIV status was unknown or negative. We collected blood samples for interferon-gamma release assay (IGRA), CD4 count if HIV positive, and where indicated by WHO four-symptom screen or by the opinion of the clinician, sputum samples to screen for active TB (Xpert MTB/RIF assay). We conducted 6-min walking-test (6MWT) in the study clinic, following European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, expressed in metres (m), with a distance less than 350 m considered abnormal.[14,15]

Lung function testing. We conducted on-site spirometry according to ERS/ATS guidelines[16] (EasyOne Connect PC software, Easy-On ultrasonic PC spirometer). For FEV1 (forced expiratory volume in the first second), FVC (forced vital capacity) and FEV1/FVC-ratio, absolute values, values for percentage of predicted (% pred) and z-scores, based on Global Lung Initiative (GLI) references for the ethnic category "other", were reported.[17] Definitions used were: obstruction as FEV1/FVC-ratio below lower limit of normal (LLN) with normal FVC, restriction as FVC below LLN and preserved FEV1/FVC-ratio, and mixed as having both FEV1/FVC-ratio and FVC below LLN.[16,17] A professional pulmonology team at a study-partner site conducted plethysmography, further spirometry and diffusing capacity testing of the lungs for carbon monoxide (DLCO) in the in-depth cohort, where TLC (total lung capacity), IC (inspiratory capacity), RV/TLC-ratio (residual volume to total lung capacity ratio), and DLCO were measured and recorded as absolute values and %pred, adjusted for ethnicity group "other".[17] A value of <80% pred was considered abnormal.[16] Further details on respiratory assessments are included in Annex 1.

Chest-CT scan. For the in-depth cohort, high-resolution non-contrasted chest-CT scans, using 64-slice Bright Speed (GE Health Optima CT 660, USA), were performed in supine and prone position with maximal inspiration, under 120 kV and 220 mA. Images were reconstructed at 0.625 mm slice thickness and were reported by two radiology specialists. Features recorded included ground glass opacities (GGO), consolidation, linear opacity, septal thickening and/or reticulation, crazy-paving pattern, pleural thickening, bronchiectasis, cavities, honeycombing and lymphadenopathy and were grouped into COVID-related abnormalities (see Annex 2), TB-related abnormalities and other lung abnormalities.

Data collection and statistical analysis

Data were captured into an OpenClinica (version 3.1, OpenClinica LLC, Needham, MA) database to allow for real-time data validation and quality control. All statistical analyses were done using Stata software (v. 17, StataCorp, College Station, TX). Descriptive analyses used medians and inter-quartile ranges (IQR) to summarize continuous variables and absolute numbers and percentages for categorical variables. To assess associations of potential risk factors with the outcomes, we used uni- and multivariable Poisson regression with robust variance estimates to estimate risk ratios (RRs) and their 95% confidence intervals (CIs)[18] and to adjust for potential confounders such as age and sex. A p-value below 0.05 was considered statistically significant. Missing data were handled by correction or pairwise deletion.

Ethical considerations

This study was approved by the University of the Witwatersrand Human Research Ethics Committee (Wits HREC) (ethics ref: 200912) and funded by the Bavarian State Ministry of Science and Arts. All participants gave written informed consent prior to participation.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results

We screened 157 patients, where 154 enrolled in hospital between 23 March and 22 September 2021. We completed retrospective data collection for the hospitalisation period in all enrolled participants, and 111 out of 154 came for post-hospitalisation follow-up (Fig. 1). The in-depth cohort had 61/111 participants who completed

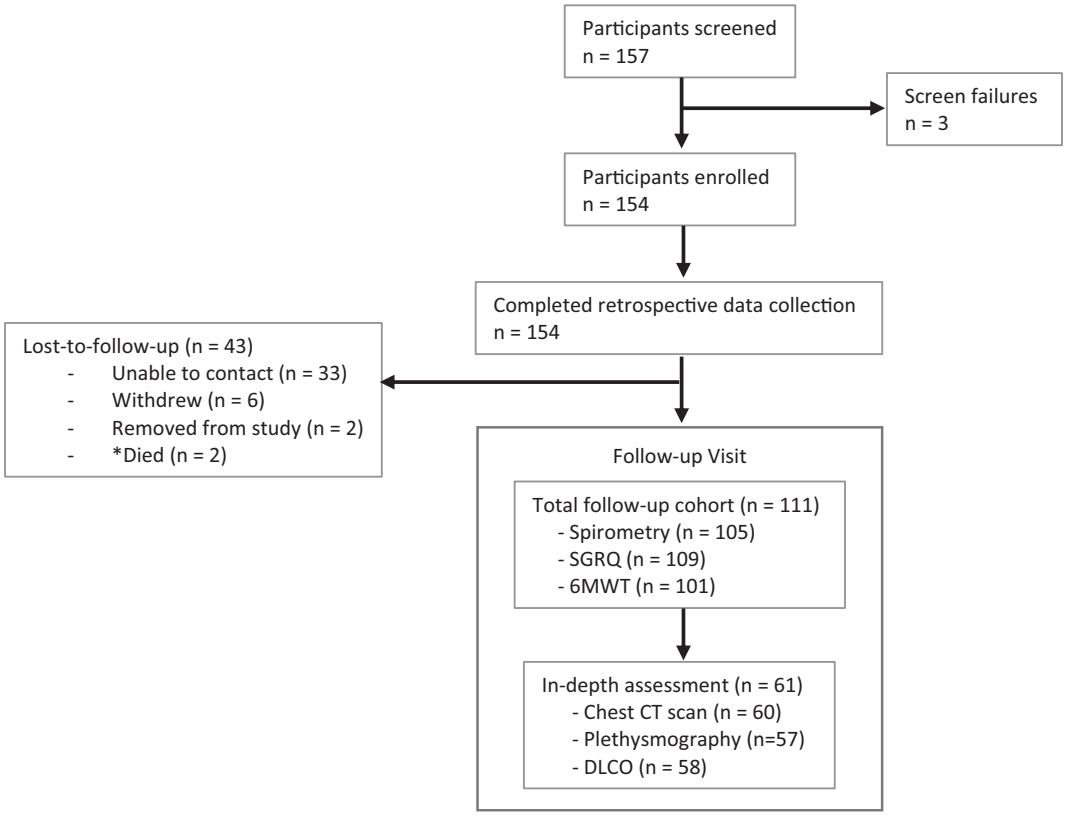


Fig. 1: Participant flow diagram demonstrating the participants screened, enrolled, screen failures, lost-to-follow-up, and both groups at follow-up (total cohort and in-depth cohort) with specified numbers per investigation, where n is the total number of participants in the specified group. Participants completed one follow-up visit within 40-days post-discharge, whereby those completing the in-depth assessment completed their visit over more than one day in order to carry out all the procedures. *Causes of death: 1–post-partum cardiomyopathy and pulmonary embolism, 1–advanced HIV with pneumocystis jirovecii pneumonia. Abbreviations: 6MWT, six-minute walking-test; CT, computed tomography; DLCO, diffusing capacity testing for the lung for carbon monoxide; SGRQ, St George's Respiratory Questionnaire.

	Participants n = 111, n (%), or median (IQR)	
Age, years	50.5 (36.4–58.7)	
Sex		
Female	73 (65.8%)	
Racial profile		
Black African	103 (92.8%)	
Mixed ancestry	7 (6.3%)	
Asian	1 (0.9%)	
Education level		
Primary school	15 (13.5%)	
Secondary school	49 (44.1%)	
High school (or equivalent)	37 (33.3%)	
Vocational training	4 (3.6%)	
University	4 (3.6%)	
Higher than University	2 (1.8%)	
Employment status, n = 109		
Employed (formally or informally)	23 (21.1%)	
Not employed (includes student and retired)	84 (77.1%)	
Not specified	2 (1.8%)	
Country of birth		
South Africa	107 (96.4%)	
Country other than South Africa	4 (3.6%)	
TB infection		
Latent TB infection (positive IGRA)	47 (43.5%)	
TB disease history	21 (18.9%)	
<6 months prior (including active cases)	4 (3.6%)	
>2 years prior	16 (14.4%)	
Unknown date	1 (0.9%)	
HIV infection		
HIV negative	71 (64.0%)	
HIV positive	40 (36.0%)	
HIV positive on ART (n = 40)	33 (82.5%)[d]	
CD4 cell count, n = 33		
Median (IQR)	131 (46–328)	
<200	20 (60.6%)	
200–500	10 (30.3%)	
>500	3 (9.1%)	
BMI, kg/m^2	Male (n = 38)	Female (n = 73)
Overall median (IQR)	24.0 (20.4–28.6)	31.4 (24.3–34.6)
<18.5	5 (13.2%)	5 (6.8%)
18.5–<25	16 (42.1%)	15 (20.5%)
25–<30	10 (26.3%)	11 (15.1%)
30–<35	4 (10.5%)	23 (31.5%)
>35	3 (7.9%)	19 (26.0%)
Smoking		
No smoking history	87 (79.8%)	
Current smoking[a]	18 (16.5%)	
Past smoking	4 (3.7%)	

(Table 1 continued in next column)

	Participants n = 111, n (%), or median (IQR)
(Continued from previous column)	
COVID-19 vaccination status	
Received COVID-19 vaccine prior to admission	6 (5.4%)
Did not receive COVID-19 vaccine	105 (94.6%)
Other Comorbidities	
Pre-existing hypertension	40 (36.0%)
Newly diagnosed hypertension	5 (4.5%)
Pre-existing diabetes mellitus	20 (18.0%)
Newly diagnosed Diabetes mellitus	14 (12.6%)
Neurological condition[b]	12 (10.8%)
Psychiatric condition[c]	11 (9.9%)
Heart failure	6 (5.4%)
Pre-existing lung diseases other than previous TB (asthma, COPD)	8 (7.2%)
Other (rheumatic, STIs, renal failure, cancer)	12 (10.8%)
Length of hospital stay, days	10 (7–15)
Highest Covid-19 WHO severity score during hospital stay	
Score 3 (hospitalisation, no oxygen)	36 (32.4%)
Score 4 (nasal cannula or face mask oxygen)	66 (59.5%)
Score 5 (NIV or HFNC)	6 (5.4%)
Score 6 (IMV)	2 (1.8%)
Score 7 (IMV + vasopressors or ECMO)	1 (0.9%)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CD4, cluster of differentiation 4, COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; HIV, human immunodeficiency virus; IMV, invasive mechanical ventilation; IGRA, interferon-gamma release assay; IQR, interquartile range; NIV, non-invasive ventilation; STI, sexually transmitted infection; TB, tuberculosis; WHO, World Health Organization. Missing data: IGRA–2 indeterminate, 1 missing. ART–Unknown for 4 PLWHIV. CD4 count–unknown for 7 participants. Smoking status–Unknown for 2 participants. [a]Current smoking defined as any smoking within two weeks prior to hospitalisation for Covid-19. [b]Neurological condition includes prior history of cerebrovascular accident or epilepsy. [c]Psychiatric condition includes bipolar mood disorder, major depressive disorder, minor neurocognitive disorder, substance use disorder, and prior attempted suicide with no confirmed psychiatric diagnosis. [d]Of PLWHIV, 6 newly diagnosed and one unwilling to commit to ART initiation.

Table 1: **Participant baseline characteristics.**

all three in-depth investigations. Median follow-up was 13 days- (IQR 8–14 days) and 27.5 days post-discharge (IQR 23–33 days) for the initial and in-depth visits, respectively.

Characteristics of the 111 participants we followed up (see Table 1), 65.8% were female and the median age was 50.5 years (IQR 36.4–58.7 years), with a racial profile of black African (92.8%), mixed (6.3%), and Asian

(0.9%). Positive IGRA was detected in 43.5% (47/108) and a history of previous TB disease in 18.9% (21/111). HIV status was known in all 111 participants, with 40 (36%) being HIV positive, with a median CD4 count of 131 cells/m^3 and 82.5% (33/40) of these on antiretroviral therapy (ART). Other common comorbidities included hypertension (40.5%), diabetes mellitus (30.6%) and obesity (43.2%), with females having a higher BMI than males. Participants predominantly had moderate COVID-19 disease (WHO score 3 and 4, 91.8%), and a small proportion had severe disease (WHO score 5–7, 8.1%). COVID-19 diagnosis was confirmed in all participants, 98.2% by RT-PCR and two by rapid-antigen test. Six of the 111 participants (5.4%) had received the COVID-19 vaccine prior to admission. From the six who received the COVID-19 vaccine, the median age was higher than the total cohort (61.6-years, IQR 57–62.9), four had hypertension, two had diabetes mellitus, five had BMI >30 kg/m^2, five had WHO COVID-19 severity stage four, and one had WHO COVID-19 severity stage five. The characteristics of the in-depth cohort (n = 61) were similar to those of the total cohort (see Annex 3). Among the enrolled participants who did not complete follow-up (n = 43), median age (54.2 years), sex (53.5% female), TB disease history (16.3%, n = 7) and HIV infection (30.2%, n = 13) were similar to the overall cohort, however, the racial profile differed (black African 76.7%, mixed race 11.6%, Asian 7.0%, Caucasian 4.7%).

At follow-up, common reported symptoms were tiredness (47.7%), cough (45.9%), breathlessness with exercise (45.0%), headache (38.7%), and shortness of breath (37.8%). We found elevated SGRQ scores in all three domains (median symptoms score—38.3, activity score—27.7, impact score—13.9), and 78.9% had an elevated total score, with females scoring higher than males in all domains. Additionally, those with TB disease history and HIV-uninfected also showed higher total scores. Median 6MWT distance (6MWD) 6MWD was 300 m (IQR 210–400 m), where 66.3% walked a distance less than 350 m. Females and those with TB disease history showed markedly reduced 6MWD compared to comparator groups, with median distances of 280 m and 245 m, respectively. Median oxygen saturation changes pre- and post- 6MWT were negligible. Table 2 demonstrates these SGRQ total scores and 6MWD by participant characteristic subgroups.

We conducted spirometry on 105/111 participants, where results can be seen in Table 2 according to participant characteristic subgroups (absolute values are found in Annex 4). Normal spirometry was recorded in 50.5%, while 42.9% (45/105) had restriction, 1.0% (1/105) had obstruction, 3.8% (4/105) had a mixed impairment and 1.9% (2/105) had FEV1 below LLN only. While the predominant impairment type was restriction, the majority of these participants had mild to moderate impairment (46.7%, 21/45 and 48.9%, 22/45 respectively), and only 4.4% (2/45) had severe impairment. The participant with obstruction had moderate impairment, with any smoking history and no TB disease prior. The four participants with mixed pattern had severe impairment, where three had a TB history and two had any smoking history.

In the in-depth lung function test (LFT) in 58/111 participants (Table 3) we found overall lung volume parameters were normal, apart from residual volume (RV), however there was a considerable proportion of participants with their individual parameters being below 80% of predicted. This was found in 29.3% with FVC below 80% pred, 31.6% with a TLC below 80% pred, and 64.9% with RV below 80% pred. Median DLCO was reduced at 78% predicted (IQR 64%–91%), where 53.4% had DLCO <80% pred. We found an abnormal chest-CT in 86.7% (52/60) of participants with ground glass opacities (GGO) (65.0%) as the most common finding, followed by linear opacity (55.0%), septal thickening/reticulation (43.3%), bronchiectasis (40.0%), bronchial wall thickening (34.5%) and pleural thickening (20.0%). Overall, COVID-19-related changes were reported in 71.7% (43/60). Further chest-CT findings can be found in Annex 5.

Fig. 2 (Fig. 2a–d) shows the relationship between different combinations of outcome assessments. Fig. 2a demonstrates abnormalities for DLCO, TLC and chest-CT results, where the overlap between all three outcomes was 23.2% (13/56). Chest-CT with COVID-19-related changes contained the highest number of participants, with 73.2% (41/56), with the overlap between chest-CT and DLCO consisting of 48.2% (27/56). Only four participants had abnormal DLCO and/or TLC but no COVID-19 findings on chest-CT. Outcome overlap between TLC, chest-CT results and FVC can be seen in Fig. 2b, where only 14.3% (8/56) had evidence of all three abnormal outcomes, and again chest-CT demonstrated the highest proportion of abnormal results with 73.2% (41/56), with 42.9% (24/56) of participants having an abnormal chest-CT but no other abnormality. All participants with abnormal FVC also had abnormal chest CT or abnormal TLC and only three participants with abnormal TLC had no CT-abnormalities. Further relationships between SGRQ, 6MWT and total cohort FVC can be seen in Fig. 2c. Abnormal outcomes in all three assessments were found in 31.3% (30/96). Few participants had only one abnormal outcome 13.5% (13/96) in SGRQ, 9.4% (9/96) in 6MWT, and 1.0% (1/96) in FVC. Where two outcomes were reported abnormal, SGRQ contained the highest number of participants (61/64), followed by 6MWT (53/64) and FVC (44/64), with the greatest overlap of 52.1% (50/96) seen between 6MWT and SGRQ. A great majority of participants with abnormal FVC also had abnormal SGRQ (42.7%, 41/96). Fig. 2d shows the overlap between chest-CT, SGRQ total scores and 6MWT for the in-depth subgroup. A high proportion of participants had all three outcomes at

Patient group	Spirometry (n, %) (n = 105)				6MWD (median in meters, IQR) (n = 101)	SGRQ Total Scores (median, IQR) (n = 109)
	Normal	Restriction	Obstruction	Mixed		
All patients	53/105 (50.5%)	45/105 (42.9%)	1/105 (1.0%)	4/105 (3.8%)	300 (210–400)	21.6 (9.2–48.3)
Male	13/36 (36.1%)	20/36 (55.6%)	1/36 (2.8%)	1/36 (2.8%)	390 (290–460)	18.1 (5.2–47.0)
Female	40/69 (58.0%)	25/69 (36.2%)	0/69 (0%)	3/69 (4.3%)	280 (180–340)	22.5 (10.3–50.3)
TB disease[a]	6/20 (30.0%)	9/20 (45.0%)	0/20 (0%)	3/20 (15.0%)	245 (160–430)	26.5 (14.2–68.8)
No TB disease	47/85 (55.3%)	36/85 (42.4%)	1/85 (1.2%)	1/85 (1.2%)	300 (230–400)	20.7 (7.2–46.6)
HIV infection	16/39 (41.0%)	18/39 (46.2%)	0/39 (0%)	3/39 (7.7%)	295 (200–410)	17.3 (10.2–39.3)
No HIV infection	37/66 (56.1%)	27/66 (40.9%)	1/66 (1.5%)	1/66 (1.5%)	300 (220–400)	23.6 (9.0–50.3)
Smoking history	10/21 (47.6%)	8/21 (38.1%)	1/21 (4.8%)	2/21 (9.5%)	320 (210–460)	15.2 (3.6–38.8)
No smoking history	42/82 (51.2%)	36/82 (43.9%)	0/82 (0%)	2/82 (2.4%)	290 (210–390)	21.7 (10.1–50.3)
Smoking unknown	1/2 (50.0%)	1/2 (50.0%)	0/2 (0%)	0/2 (0%)	265 (190–340)	36.8 (36.8–36.8)

Explanation: All values given n (%) or median (IQR) where specified. GLI reference ranges used where z-score −1.64 was considered LLN for FVC and FEV1 (16, 17). Restriction considered FVC < LLN with preserved FEV1/FVC-ratio. Obstruction considered FEV1/FVC ratio < LLN. Mixed pattern considered FEV1/FVC-ratio < LLN combined with FVC < LLN. FEV1/FVC ratio > LLN considered normal. 6MWD ≤350 m considered abnormal (14, 15). Normal SGRQ total score ≤7 (12, 13). Abbreviations: 6MWD, 6-min walking distance; 6MWT, 6-min walking-test; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HIV, human immunodeficiency virus; IQR, interquartile range; LLN, lower limit of normal; SGRQ, St George's Respiratory Questionnaire; TB, tuberculosis. Missing data: Spirometry (6 excluded due to medical contra-indications: 2—positive Covid-19 rapid antigen test at visit, 2—unstable cardiac condition, 2—unstable respiratory condition and 1 with haemoptysis), 6MWT (n = 10 excluded on clinical judgement), SGRQ (n = 2 missed window for the questionnaire). [a]TB disease defined as previous reported TB disease, which was treated, or active TB disease (does not include latent TB infection).

Table 2: **Spirometry, 6MWT and SGRQ outcomes in different clinical subgroups.**

44.6% (25/56), with SGRQ and chest-CT containing majority of the abnormal outcomes at 92.9% (52/56) between both investigations (78.6% [44/56] with elevated SGRQ scores, 71.4% [40/56] with chest-CT COVID-19 changes).

We conducted risk factor analysis to predict the following outcomes: FVC <LLN, chest-CT COVID-19-related changes, TLC below 80% pred, and DLCO below 80% pred (Table 4 and Annex 6 showing numbers per strata). TB disease (history/active), PLWHIV with CD4 <200 cells/mm^3, and low and high BMI (<18.5 kg/m^2 and >35 kg/m^2) demonstrated significant associations with abnormal outcomes in FVC, TLC and DLCO. Initial COVID-19 severity showed increased risk in abnormal FVC and DLCO, however these were not statistically significant. Further risk factor analysis for 6MWT and SGRQ outcomes for the same variables can be seen in Annex 7, where low BMI, initial COVID-19 severity, and multiple comorbidities showed increased risk for elevated SGRQ total scores. Multi-variable regression analysis, which was partially hampered by low numbers in individual strata, indicated generally robust estimates with minimal confounding between factors (see Annex 8).

Discussion

This is the first study, to our knowledge, describing detailed lung and related functional outcomes post-COVID-19 in Africa. Our findings reveal the burden of respiratory morbidity across multiple assessments within six-weeks post-COVID-19. Features on Chest-CT and DLCO demonstrated potential in detecting COVID-19-related pathology, with LFT characterising a predominant restrictive impairment, suggesting a fibrotic lung phenotype post-COVID-19. Pre-existing

Parameter	Absolute value, median (IQR) (L)	%pred., median (IQR)	<80% pred[a] % (n)
FVC[d]	2.88 (2.40–3.28)	89 (78–97)	29.3% (17/58)
FEV1[d]	2.29 (1.96–2.75)	92 (78–101)	27.6% (16/58)
FEV1/FVC-ratio[d] (%)	82.0 (79.0–86.0)	103 (100–109)	5.2% (3/58)[b]
Inspiratory capacity (IC)	2.05 (1.64–2.51)	112 (88–130)	21.1% (12/57)[c]
Total lung capacity (TLC)	3.87 (3.42–4.29)	84 (77–97)	31.6% (18/57)[c]
Residual volume (RV)	1.20 (1.03–1.32)	74 (65–86)	64.9% (37/57)[c]
RV/TLC ratio	31.0 (24.0–35.0)	85 (76–96)	33.3% (19/57)[c]
DLCO	6.32 (5.25–7.54)	78 (64–91)	53.4% (31/58)

Abbreviations: %pred, percentage of predicted; DLCO, diffusing capacity for the lung; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; IC, inspiratory capacity; IQR, interquartile range; LLN, lower limit of normal; RV, residual volume; TLC, total lung capacity. [a]<80% predicted for FVC, FEV1, IC, TLC, RV, RV/TLC ratio and DLCO according to GLI reference ranges (17); and. [b]FEV1/FVC ratio < LLN considered abnormal/obstruction. [c]Missing data: One participant unable to perform plethysmography-specific procedures. [d]Spirometry data is from the in-depth assessment, which was done at a median of 29 days (IQR 26–33 days) after discharge, and was conducted at a study-partner site.

Table 3: **In-depth lung function outcomes: spirometry, plethysmography and diffusion capacity testing for the lung (n = 58).**

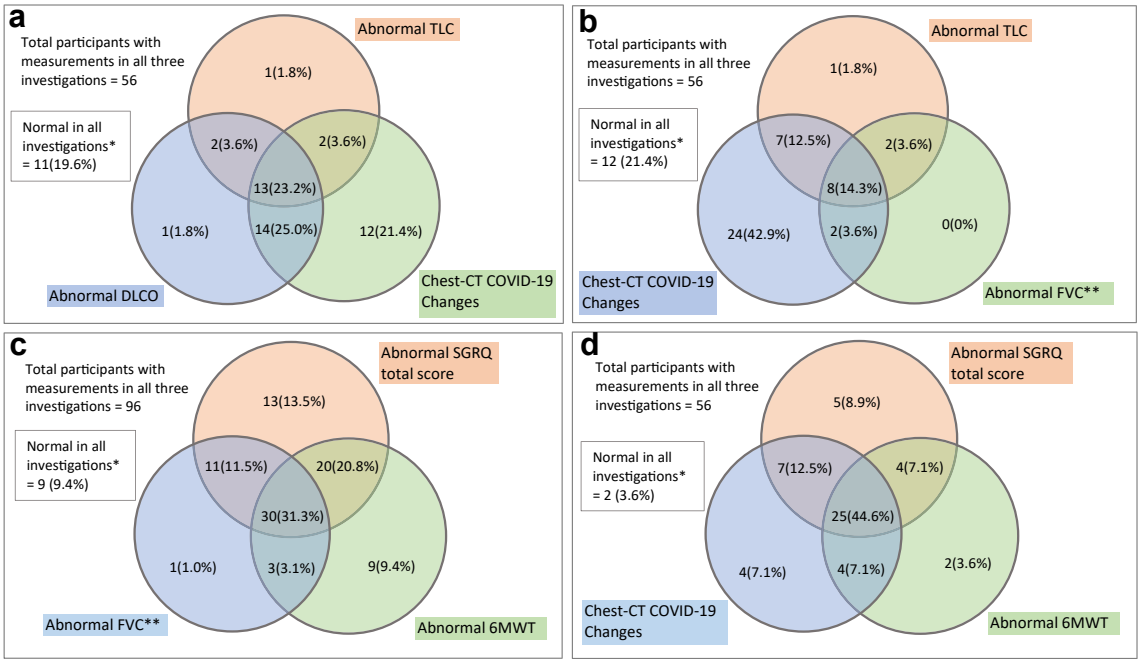


Fig. 2: Venn diagrams demonstrating the overlap between Abnormal Outcomes **(a)** Abnormal TLC, COVID-19 Changes on Chest-CT, and Abnormal DLCO. **(b)** COVID-19 Changes on Chest-CT, Abnormal FVC assessed at In-Depth Investigation, and Abnormal TLC. **(c)** Abnormal SGRQ Total Scores, Abnormal 6MWT Distance and Abnormal FVC for the Total Cohort at Initial Follow-Up Visit. **(d)** Abnormal SGRQ Total Scores, Abnormal 6MWT Distance and COVID-19 Changes on Chest-CT for the In-Depth Cohort. Each colour represents an individual investigation in each image (a, b, c and d). The colours in each image do not necessarily correlate to the same investigation. *Normal defined as no Covid-19 changes on chest-CT, DLCO ≥80% predicted, TLC ≥80% predicted, FVC ≥−1.64 z-score, SGRQ total score ≤7, and/or 6MWT distance ≥350 m. **FVC reported in **(b)** is from the in-depth assessment, which was done median of 29 days (IQR 26–33 days) after discharge and was conducted at a study-partner site, and **(c)** FVC reported is from total follow up cohort, which was done at the study site at the initial follow up visit median 13 days (IQR 8–14 days) after discharge. Abnormal defined as: TLC <80% predicted, Chest-CT demonstrates Covid-19 changes as per Annex 2, DLCO <80% predicted, FVC <−1.64 z-score, SGRQ total score >7, and/or 6MWT distance <350 m. Referenced according to GLI and ERS/ATS references for lung function test (16, 17), SGRQ total score (12, 13), and 6MWT distance (14, 15). Abbreviations: 6MWT, six-minute walking-test; ERS/ATS, European Respiratory Society/American Thoracic Society; CT, computed tomography; DLCO, diffusing capacity for the lung for carbon monoxide; FVC, forced vital capacity; GLI, Global Lung Initiative; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

comorbidities showed a strong impact in worse lung outcomes, with specific focus on TB disease, abnormal BMI and HIV-infection with CD4 <200 cells/mm^3.

These lung and functional outcomes demonstrate a high morbidity post-COVID-19, showing symptom burden, anatomical lung pathology, functional impairment, and impact on quality of life. We found 86.7% with abnormal chest-CT, with 71.7% of those having COVID-19-specific changes (GGO and fibrotic patterns) suggesting that chest-CT could be important to not only detect abnormality, but to also characterise COVID-19-specific abnormality and pre-existing pathology. We found just over half of the in-depth subgroup had impaired DLCO, which is in keeping with the literature showing persistent DLCO impairment post-COVID-19.[2,19] Notably, although half of the participants had spirometry abnormalities, there was minimal overlap with chest-CT, where chest-CT and DLCO showed predominance in detecting post-COVID-19-specific morbidity. This was highlighted in another study where chest-CT had poor correlation with LFT outcomes.[20] LFT may, however, help characterise the underlying lung pathology and explain the findings in SGRQ and 6MWT, as well as understand chest-CT findings on a physiological level.

SARS-CoV-2 infection causes diffuse alveolar epithelial injury and secondary fibroproliferation resulting in chronic alveolar and vascular remodelling and subsequent pulmonary fibrosis.[21] Our findings support this notion, reflecting a fibrotic lung phenotype through restrictive lung impairment (31.6% with TLC <80% pred, 42.9% with FVC <LLN), reduced DLCO, and signs of early fibrosis on chest-CT.[2,19,21] A comparative study by Huang and colleagues,[22] reported 75.4% with abnormal LFT one-month post-hospitalisation, compared to our 49.5% but a similar DLCO impairment at 53.4% and a predominant restriction on LFT. Our high burden of chest-CT abnormalities mirrors Wang et al.'s,[23] findings at one-month, where GGO, pleural thickening, interlobular septal thickening, bronchiectasis, and linear opacities were reported, further

Risk factor	FVC < LLN		TLC <80% predicted		DLCO <80% predicted		Chest-CT COVID-19 changes	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
Age (per 10 years)	1.01 (0.86–1.17)	0.943	1.24 (0.92–1.69)	0.162	1.23 (1.01–1.49)	0.035	1.31 (1.12–1.54)	0.001
Sex–Male	1.44 (0.96–2.14)	0.076	2.01 (0.96–4.21)	0.066	1.29 (0.82–2.01)	0.271	1.00 (0.74–1.34)	0.977
TB disease[a] vs no TB disease	1.32 (0.85–2.05)	0.211	2.35 (1.11–5.01)	0.026	2.65 (1.69–4.16)	<0.0001	0.98 (0.51–1.90)	0.958
HIV infection and CD4 count (cells/mm^3)								
HIV negative	1.00	–	1.00	–	1.00	–	1.00	–
HIV positive, CD4 ≥200	1.01 (0.53–1.93)	0.967	0.88 (0.32–2.41)	0.798	0.95 (0.41–2.19)	0.911	1.31 (0.82–2.10)	0.258
HIV positive, CD4 <200	1.56 (1.01–2.41)	0.047	0.62 (0.11–3.49)	0.586	1.93 (1.14–3.26)	0.014	1.47 (1.16–1.86)	0.001
BMI (kg/m^2)								
<18.5	2.01 (1.20–3.38)	0.008	2.12 (0.66–6.87)	0.209	1.93 (0.92–4.06)	0.083	1.40 (0.49–4.01)	0.530
18.5–<25	1.00	–	1.00	–	1.00	–	1.00	–
25–<30	0.89 (0.43–1.86)	0.759	0.47 (0.12–1.78)	0.265	0.81 (0.36–1.84)	0.619	1.12 (0.67–1.88)	0.659
30–<35	0.83 (0.37–1.84)	0.647	1.00 (0.30–3.35)	0.994	1.00 (0.44–2.30)	0.992	1.19 (0.68–2.07)	0.539
≥35	2.09 (1.22–3.57)	0.007	1.27 (0.39–4.14)	0.691	1.27 (0.58–2.80)	0.554	1.50 (0.89–2.54)	0.129
COVID-19 Severity								
WHO score 3	1.00	–	1.00	–	1.00	–	1.00	–
WHO score 4	1.42 (0.84–2.40)	0.188	0.87 (0.37–2.03)	0.740	1.80 (0.75–4.37)	0.191	0.85 (0.58–1.25)	0.412
WHO score 5–7	1.91 (0.89–4.14)	0.098	0.93 (0.32–2.68)	0.894	2.39 (0.86–6.62)	0.094	1.02 (0.66–1.56)	0.934
Smoking history vs no smoking history[b]	0.91 (0.53–1.58)	0.746	0.61 (0.17–2.16)	0.446	0.66 (0.25–1.71)	0.388	1.04 (0.64–1.67)	0.881
Diabetes mellitus vs no diabetes mellitus[c]	1.37 (0.87–2.14)	0.170	1.57 (0.72–3.42)	0.259	0.85 (0.52–1.39)	0.524	0.86 (0.64–1.17)	0.344
Hypertension vs no hypertension[d]	1.91 (1.18–3.09)	0.009	1.37 (0.62–3.00)	0.434	1.14 (0.67–1.92)	0.633	0.92 (0.67–1.25)	0.591
Number of comorbidities (per unit)	1.15 (0.99–1.34)	0.075	1.07 (0.80–1.42)	0.654	0.97 (0.81–1.16)	0.756	0.97 (0.88–1.06)	0.479

Explanation: Results of separate poisson regression models for each risk factor, only adjusted for age and sex. Sample sizes and event numbers for each stratum and investigation can be seen in Annex 6 and 7 and Annex 8. Abbreviations: BMI, body mass index; CD4, cluster of differentiation 4; CI, confidence interval; CT, computed tomography; DLCO, diffusing capacity for the lung; FVC, forced expiratory capacity; HIV, human immunodeficiency virus; LLN, lower limit of normal; RR, relative risk; TB, tuberculosis; TLC, total lung capacity; WHO, World Health Organization. [a]TB disease included past and current TB disease, excludes latent TB infection. [b]Smoking history includes current and/or past smoking. [c]Diabetes mellitus includes chronic diabetes mellitus and newly diagnosed diabetes mellitus. [d]Hypertension includes chronic hypertension and newly diagnoses hypertension.

Table 4: **Association of potential risk factors with abnormal lung outcomes.**

indicating early pulmonary fibrosis.[23] Similar post-viral sequelae are reported post-SARS and post-Middle East Respiratory Syndrome (MERS) infections, with sequelae up to two years post-infection.[24] Although arguments for ventilator-induced lung injury or acute-respiratory distress syndrome are plausible,[25,26] our cohort's limited severe COVID-19 cases (9 of 111) with only one who received invasive mechanical ventilation, imply that the findings are rather consequences of SARS-CoV-2 infection. Longitudinal follow-up of lung function and chest-CT to track the sequelae progression are important to determine the impact of underlying comorbidities and the potential for recovery.

Pre-existing comorbidities such as TB, low BMI, and HIV with CD4 <200 cells/mm^3 are shown to almost double the risk of abnormal lung and related outcomes in our study, which are known to impact lung health in African settings.[27,28] It is unclear whether participants with these pre-existing comorbidities had pre-existent lung damage. However, only few participants had obstruction or mixed LFT impairment, which were normally described for post-TB lung disease and PLWHIV.[10,29] In addition, acute COVID-19 studies demonstrate a high BMI (>30 kg/m^2) having a worse prognosis[30]; whereas our study found that both low and very high BMI had a strong association with impaired lung function. Sex did not appear to be related significantly to worse outcomes in any of the assessments. Our cohort's markedly reduced median 6MWD of 300 m (IQR 210–400 m) is substantially lower than Huang et al.'s[22] 6MWD of 561.97 m at one-month post-hospitalisation.[22] Furthermore, our high SGRQ scores reveal high symptom burden and impact on quality of life, comparable to other studies.[19,21] While chest-CT and LFT describe prevalent pathologies and resulting functional impairment, 6MWT and SGRQ help to understand the resulting morbidity burden. However, due the multifactorial nature of these assessments, the attributable risk of COVID-19 and comorbidities cannot be disentangled. Longitudinal studies post-COVID-19 have shown improvement in lung function, chest-CT and DLCO, suggesting that COVID-19-related morbidity may have better potential for improvement compared to those with pre-existing lung pathology.[2,21]

The limitations of our study include the small and single-centre cohort with only post-hospitalisation data and primarily moderate COVID-19 disease. Evidence suggests that post-COVID-19 sequelae are more prevalent in hospitalised and severe cases, although it does occur after mild disease as well.[2] Our results are,

therefore, confined to the relevant post-hospitalisation group and may produce some bias toward overestimating the disease burden due to the participant characteristics and the sampling methods. The small cohort also prevented risk assessment in larger multivariable models, particularly for smaller groups such as those who received the COVID-19 vaccine. Our short follow-up period speculates the impact on outcomes from SARS-CoV 2-related unresolved acute inflammation and infection, as well as morbidity related to hospital interventions including ventilation, which is complicated to disentangle. This may lead to bias in overestimating the disease burden, and further long-term data is needed. Lack of baseline pre-COVID-19 data, especially with a focus on lung outcomes, is another limitation, considering the impact of pre-existing pathology. Furthermore, the literature lacks meaningful thresholds for clinical tests in post-COVID-19 patients resulting in variability in interpretations of results. The possibility of response and follow-up bias and the subjective rating of symptoms might affect reporting of outcomes. Due to these factors, the generalizability of our findings may be limited. Despite these, our data remains relevant to clinicians and healthcare providers as it shows the prevalent pathologies, the associated morbidity burden, and that those with pre-existing comorbidities have a higher risk for abnormal findings and should therefore be screened for these.

Our study's strengths lie in uniquely detailing the pulmonary post-COVID-19 components in an African cohort, accounting for TB, HIV, and non-communicable diseases. The follow-up also links pre-existing morbidity and acute COVID-19 disease to recovery and the potential sequelae. We conducted sophisticated objective and subjective assessments to determine not only the prevalence of pathology but the impact on quality of life and function. This insight could guide the development of context-specific standardised diagnostic and management algorithms and the allocation of healthcare services.

There is scarce data on post-COVID-19 sequelae in African populations with pre-existing comorbidities. Our study reveals respiratory morbidity post-COVID-19 with high symptom burden, lung- and functional impairment with impact on quality of life, where pre-existing comorbidities show a strong association with worse outcomes. Chest-CT features, DLCO abnormalities and restrictive lung function impairment support that COVID-19 causes a fibrotic lung phenotype. This knowledge is crucial to guide post-COVID-19 management and health resource allocation in resource-limited settings. Longitudinal follow-up data are needed to understand what long-term morbidity burden remains prevalent in patients who were hospitalised with COVID-19 disease.

Contributors

NG and AR contributed to the literature search. OI, FS, AM, CM, SV, MH, SC, and AR contributed to the study funding acquisition, conceptualisation, methodology and project administration. FR, RS, ES, LZ contributed to software and resources. NG, OI, ES and AR contributed to the data analysis and creation of tables and figures. NG, OI, IK, SC, and AR contributed to data interpretation. NG and AR drafted the manuscript, and all authors reviewed the manuscript critically for intellectual content. NG, ES and AR verified the underlying data. All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication and approve the final draft of the manuscript.

Data sharing statement

Data can be made available through the Data Governance committee at the Aurum Institute that reviews all applications and ensures necessary approvals are in place and the data will be stored securely before data is released.

Declaration of interests

Andrea Rachow declares a grant obtained from Bundesministerium für Bildung und Forschung (BMBF) for post-TB research. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102588.

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