

## Respiratory health status is associated with treatment outcomes in pulmonary tuberculosis

A. N. Gupte,\* S. Selvaraju,<sup>†</sup> M. Paradkar,<sup>‡</sup> K. Danasekaran,<sup>†</sup> S. V. B. Y. Shivakumar,<sup>§</sup> K. Thiruvengadam,<sup>†</sup> C. Dolla,<sup>†</sup> G. Shivaramakrishnan,<sup>†</sup> N. Pradhan,<sup>‡</sup> R. Kohli,<sup>‡</sup> S. John,<sup>†</sup> S. Raskar,<sup>‡</sup> D. Jain,<sup>‡</sup> A. Momin,<sup>‡</sup> B. Subramanian,<sup>†</sup> A. Gaikwad,<sup>‡</sup> R. Lokhande,<sup>¶</sup> N. Suryavanshi,<sup>‡</sup> N. Gupte,\* S. Salvi,<sup>#</sup> L. Murali,<sup>†</sup> W. Checkley,\* J. E. Golub,\* R. Bollinger,\* P. Chandrasekaran,<sup>†</sup> V. Mave,\* A. Gupta\*

\*Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; <sup>†</sup>National Institute for Research in Tuberculosis, Chennai, <sup>‡</sup>Byramjee Jeejeebhoy Government Medical College-Johns Hopkins University Clinical Research Site, Pune, <sup>§</sup>Johns Hopkins University India Office, Pune, <sup>¶</sup>Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Pune, <sup>#</sup>Chest Research Foundation, Pune, India

### SUMMARY

**BACKGROUND:** The association between respiratory impairment and tuberculosis (TB) treatment outcomes is not clear.

**METHODS:** We prospectively evaluated respiratory health status, measured using the Saint George's Respiratory Questionnaire (SGRQ), in a cohort of new adult pulmonary TB cases during and up to 18 months following treatment in India. Associations between total SGRQ scores and poor treatment outcomes of failure, recurrence and all-cause death were measured using multivariable Poisson regression.

**RESULTS:** We enrolled 455 participants contributing 619 person-years at risk; 39 failed treatment, 23 had recurrence and 16 died. The median age was 38 years (interquartile range 26–49); 147 (32%) ever smoked. SGRQ scores at treatment initiation were predictive of

death during treatment (14% higher risk per 4-point increase in baseline SGRQ scores, 95%CI 2–28,  $P = 0.01$ ). Improvement in SGRQ scores during treatment was associated with a lower risk of failure (1% lower risk for every per cent improvement during treatment, 95%CI 1–2,  $P = 0.05$ ). Clinically relevant worsening in SGRQ scores following successful treatment was associated with a higher risk of recurrence (15% higher risk per 4-point increase scores, 95%CI 4–27,  $P = 0.004$ ).

**CONCLUSION:** Impaired respiratory health status was associated with poor TB treatment outcomes. The SGRQ may be used to monitor treatment response and predict the risk of death in pulmonary TB.

**KEY WORDS:** TB; Saint George's Respiratory Questionnaire; respiratory health status; treatment outcomes

TUBERCULOSIS (TB) DISEASE IS THE leading infectious killer worldwide, with over 10.4 million incident cases and 1.7 million deaths in 2016.<sup>1</sup> Pulmonary TB (PTB), the most common form of the disease, is characterized by granuloma formation, necrosis and cavitation in lung tissue.<sup>2</sup> Lung impairment in TB may persist despite microbiological cure, and studies have found an association between previous TB and chronic lung sequelae.<sup>3</sup> Lung impairment in TB may also affect treatment efficacy. Granulomatous lesions, fibrosis and cavitation have been shown to impair drug penetration in affected lung tissue, and may lead to drug resistance.<sup>4,5</sup> Furthermore, greater severity of pulmonary disease has been shown to be associated with delayed time to culture conversion and may also be associated with a higher risk of relapse.<sup>6</sup> Prospective assessments of lung impairment may therefore help identify TB

patients at risk of poor treatment outcomes who may benefit from targeted monitoring and adjunctive therapies to limit lung injury and improve treatment efficacy.

Chest radiography (CR) is used widely to measure the severity and extent of PTB disease. However, CR evaluations fail to reliably predict poor treatment outcomes, and their use is further limited by within- and between-reader variability.<sup>7–9</sup>

Positron emission tomography/computed tomography (PET/CT) has recently been used to measure the extent and severity of lung involvement in TB.<sup>10–12</sup> PET/CT may also correlate with response to anti-tuberculosis treatment and, possibly, long-term clinical outcomes.<sup>13,14</sup> However, PET/CT is technically challenging, expensive to perform and is an invasive procedure with inherent safety considerations, which limits its use in routine clinical care of

drug-susceptible TB patients. Simple tools to evaluate lung impairment and their role in monitoring TB patients during clinical care are needed.

Standardized questionnaires are widely used to measure respiratory health and response to treatment in patients with chronic lung diseases.<sup>15,16</sup> Respiratory questionnaires are simple to administer, easy to implement and address patient-centered outcomes. Respiratory questionnaires are gaining importance in 'personalized medicine', are sensitive to changes in health status, and capture the impact of disease, which is often missed by chest imaging modalities.<sup>17</sup> While studies have evaluated respiratory health status during anti-tuberculosis treatment,<sup>18,19</sup> its association with treatment outcomes in TB and the role of respiratory questionnaires for monitoring response to anti-tuberculosis treatment have not been studied.

The objective of our study was to measure the association between respiratory health status, assessed using the Saint George's Respiratory Questionnaire (SGRQ), and poor treatment outcomes in drug-susceptible PTB patients in India.

## MATERIALS AND METHODS

We enrolled a cohort of new adult (age  $\geq 18$  years) PTB cases through the Cohort for Tuberculosis Research by the Indo-US Medical Partnership (CTRIUMPH) study at Byramjee Jeejeebhoy Government Medical College-Sassoon General Hospitals (BJGMC-SGH) in Pune and the National Institute for Research in Tuberculosis (NIRT) in Chennai, India, between August 2014 and December 2017.<sup>20</sup>

PTB cases were diagnosed by the presence of acid-fast bacilli (AFB) on smear microscopy, *Mycobacterium tuberculosis* DNA on Xpert<sup>®</sup> MTB/RIF (Cepheid, Sunnyvale, CA, USA), *M. tuberculosis* growth on Mycobacterial Growth Indicator Tube (MGIT) liquid culture or Löwenstein-Jensen (LJ) solid culture media, or based on clinical judgement in the absence of microbiological confirmation of TB.

Individuals with drug-resistant disease, pregnant women and those with previous TB were excluded. We also excluded individuals with a self-reported history of chronic lung disease. Participants were enrolled within 7 days of TB treatment initiation and prospectively evaluated at 2 months, treatment completion (6 months), 12 months, 18 months and 24 months thereafter.

Sociodemographic, clinical and laboratory data were collected using standardized questionnaires and operating procedures. Consistent with previous surveys, 'never smokers' were classified as individuals who self-reported smoking  $< 100$  tobacco products during their lifetime.<sup>21</sup> 'Current smokers' were classified at enrollment as individuals who smoked  $\geq 100$  tobacco products during their lifetime and continued to smoke on a regular basis during the

preceding 30 days. Glycated hemoglobin (HbA<sub>1c</sub>) levels were tested at enrollment (BioRad Laboratories, Hercules, CA, USA). 'Diabetes mellitus' (DM) was defined as HbA<sub>1c</sub>  $\geq 6.5\%$  or prior diagnosis by a physician. Cavitory disease was identified on CR evaluation at enrollment.

Respiratory health status was assessed using the SGRQ, a respiratory disease-specific health-related quality of life instrument validated for use in PTB.<sup>22</sup> The SGRQ measures patient-perceived respiratory health status in the domains of respiratory symptoms, disturbance in routine activities and the psychosocial impact of the disease.<sup>23</sup> Translated versions of the SGRQ in Hindi, Marathi and Tamil were administered to study participants in their native language by trained study staff at enrollment and all follow-up visits. The total SGRQ score, a weighted average calculated from the three domain scores, measures an individual's respiratory health status and correlates with lung functional impairment, exercise capacity and the partial pressure of oxygen in arterial blood (PaO<sub>2</sub>).<sup>15,23</sup> Total SGRQ scores range from 0 to 100, whereby a score of 0 indicates optimal respiratory health status, and higher scores indicate worse respiratory health status. The SGRQ can be used as a sensitive tool to compare respiratory health status between populations and within individuals over time. The minimum clinically important difference in total SGRQ scores has been found to be 4 points.<sup>15,23,24</sup>

'Treatment failure' was defined as *M. tuberculosis* growth on MGIT or LJ culture, or symptoms suggestive of TB disease and AFB detected on smear microscopy in participants with unavailable culture results during the last 2 months of treatment. 'Recurrent TB' was defined as *M. tuberculosis* growth on MGIT or LJ culture, or symptoms suggestive of TB disease and AFB detected on smear microscopy in participants with unavailable culture results among TB cases who successfully completed treatment. 'Successful completion of treatment' was defined as the absence of symptoms suggestive of TB disease and microbiological evidence of *M. tuberculosis*. 'Death' was defined as all-cause mortality.

The median (interquartile range [IQR]) of total SGRQ scores during anti-tuberculosis treatment, and up to 18 months following treatment completion, were summarized and compared by participant characteristics at enrollment using the Wilcoxon sign-rank, Wilcoxon rank-sum or Kruskal-Wallis tests, as appropriate. Single-variable and multivariable random-effects Poisson regression with person-time as offset were used to measure the association between total SGRQ scores and poor TB treatment outcomes of failure, recurrence and all-cause death. Total SGRQ scores were analyzed as fixed (enrollment and 6-month scores) and time-varying (time-updated scores during follow-up) continuous expo-

sure in separate regression analysis. Random effects were modelled as within-individual correlations of total SGRQ scores for time-updated analysis. Single- and multivariable Poisson regression with person-time as offset were used to measure the association between absolute and per cent decline in total SGRQ scores during treatment with treatment failure. Person-time at risk of failure and all-cause mortality were calculated from enrollment to the time of the first incident outcome or right-censoring. Person-time at risk for recurrence was calculated from treatment completion to the time of the first incident outcome or right-censoring among participants who did not fail treatment. Multivariable analysis adjusted for potential confounders was identified using review of the literature and exploratory data analysis. Statistical significance was determined at  $P < 0.05$ . Data were analysed using Stata v 15.0 (StataCorp, College Station, TX, USA).

All study participants provided written informed consent in their native language. The study protocol was approved by the Institutional Review Boards of Johns Hopkins School of Medicine, Baltimore, MD, USA; BJGMC-SGH, Pune; and NIRT, Chennai, India.

## RESULTS

We enrolled 455 adult PTB cases contributing 619 person-years (py) at risk. The median follow-up time in our cohort was 18 months. Overall, 39 (184.8 events/1000 py) participants failed treatment, 23 had recurrent TB (55.6 events/1000 py) and 16 died (27.8 events/1000 py). The median age and body mass index (BMI) at enrollment was respectively 38 years (IQR 26–49) and 17.7 kg/m<sup>2</sup> (IQR 15.8–20.4); 256 (56%) were underweight (BMI < 18.5 kg/m<sup>2</sup>). Overall, 297 (65%) were male, 16 (4%) had human immunodeficiency virus (HIV) coinfection and 115 (25%) had DM. Ever smoking was reported by 147 TB cases (32%), with a median pack-year exposure of 8 (IQR 3–26) (Table 1).

The median SGRQ score at enrollment was 40 (IQR 25–57), declining significantly to 20 (IQR 9–33;  $P < 0.001$ ) by 2 months and 9 (IQR 3–19;  $P < 0.001$ ) by 6 months of treatment. The median SGRQ scores did not change significantly beyond treatment completion and were respectively 8 (IQR 2–20;  $P = 0.42$ ), 5 (IQR 2–17;  $P = 0.07$ ) and 5 (IQR 2–17;  $P = 0.76$ ) at 12, 18 and 24 months (Figure 1). Compared with younger participants, those aged >50 years had lower improvement in SGRQ scores during 6 months of treatment (Table 1).

SGRQ scores at enrollment did not differ significantly between participants who failed treatment, had recurrent TB or were cured. However, participants who died had a 15-point higher median SGRQ score at enrollment than those who were cured ( $P = 0.01$ ) (Figure 2). After adjusting for age, sex, ever

smoking, BMI, HIV coinfection and DM, every clinically relevant (4-point) increase in SGRQ scores at enrollment was associated with a 14% (95% confidence interval [CI] 2–28,  $P = 0.01$ ) higher risk of death during and following treatment (Table 2).

Although we did not detect significant differences in SGRQ scores at enrollment between TB patients who failed treatment compared with those who were cured, every 1% and 4-point reduction in SGRQ scores between enrollment and 6 months was associated with respectively a 1% (95%CI 2–1,  $P = 0.05$ ) and 9% (95%CI 17–1,  $P = 0.04$ ) lower risk of treatment failure after adjusting for potential confounders. However, we did not find similar associations with per cent and absolute change in SGRQ scores during the first 2 months of treatment (Table 3). As expected, participants who failed treatment had significantly higher SGRQ scores at 6 months than those who were cured (Figure 2).

Finally, every 4-point increase in time-updated SGRQ scores following successful treatment was associated with a 15% (95%CI 4 to 27%,  $P = 0.004$ ) higher risk of recurrent TB after adjusting for potential confounders. However, enrollment and 6-month SGRQ scores were not predictive of recurrent TB in our study population (Table 2).

## DISCUSSION

We observed that respiratory health status improved significantly during anti-tuberculosis treatment and stabilized at treatment completion. However, worse respiratory health status was associated with poor treatment outcomes, specifically, recurrence and death. We also found that a greater improvement in respiratory health status during treatment was associated with a lower risk of treatment failure. Finally, we found a higher risk of death among TB patients with higher SGRQ scores at treatment initiation, and propose additional studies to validate the use of the SGRQ as a triage test for identifying TB patients at the greatest risk of death during treatment.

SGRQ scores declined significantly during anti-tuberculosis treatment, indicating considerable improvement in respiratory health status with standard multidrug treatment. While this phenomenon has been described in studies from Indonesia and South Africa, scholars have not evaluated trends in SGRQ scores beyond treatment completion.<sup>18,19</sup> Our data suggested that respiratory health status tended to stabilize by treatment completion, with no clinically or statistically significant change during the subsequent 18 months. We also found that TB patients aged >50 years had poor improvement in SGRQ scores during treatment. Increasing age has long been identified as an important risk factor for chronic lung diseases and functional impairment.<sup>25,26</sup> Whether our findings are suggestive of pre-existing lung disease or

**Table 1** Total SGRQ scores by pulmonary TB case characteristics at enrollment\*

Enrollment characteristics	n (%)	Total SGRQ scores				Change in total SGRQ scores from entry to 6 months, %	
		Entry median [IQR]	P value <sup>†</sup>	6 months median [IQR]	P value <sup>†</sup>	β (95%CI)	P value <sup>†</sup>
Age, years			0.81		0.61		0.05
18–29	153 (34)	39 [23–58]		8 [4–17]		–67 (–76 to –59)	
30–39	96 (21)	41 [29–51]		6 [2–20]		–71 (–85 to –56)	
40–49	98 (22)	37 [23–56]		10 [3–19]		–60 (–71 to –49)	
≥50	107 (24)	42 [24–61]		11 [3–24]		–57 (–67 to –46)	
Sex			0.01		0.15		0.41
Female	158 (35)	44 [32–59]		9 [3–23]		–68 (–74 to –61)	
Male	297 (65)	37 [22–56]		8 [3–18]		–61 (–68 to –54)	
BMI, kg/m <sup>2</sup>			0.14		0.04		0.29
<18.5	256 (57)	41 [28–59]		10 [4–22]		–62 (–70 to –54)	
18.5–25	159 (36)	36 [23–55]		6 [2–17]		–68 (–76 to –61)	
≥25	32 (7)	43 [20–58]		10 [4–22]		–51 (–73 to –28)	
Smoking			0.84		0.70		0.22
Never	308 (68)	40 [23–57]		9 [3–20]		–64 (–71 to –58)	
Former	85 (19)	40 [27–57]		10 [4–20]		–57 (–69 to –44)	
Current	62 (14)	40 [24–53]		7 [2–19]		–68 (–80 to –57)	
HIV			0.50		0.75		0.59
Not infected	437 (96)	40 [26–57]		9 [3–19]		–63 (–68 to –58)	
Co-infected	16 (4)	38 [13–52]		7 [2–23]		–69 (–119 to –20)	
Diabetes mellitus			0.54		0.49		0.46
No	312 (73)	40 [28–56]		8 [3–20]		–65 (–72 to –58)	
Yes	115 (27)	40 [22–59]		10 [2–19]		–60 (–69 to –51)	
Duration of illness, months			<0.001		0.68		0.06
<1	100 (22)	28 [14–49]		6 [3–18]		–48 (–63 to –32)	
1–3	231 (51)	42 [27–60]		10 [3–20]		–70 (–75 to –65)	
≥3	116 (26)	41 [28–56]		9 [2–20]		–63 (–74 to –52)	
Cavitation			0.03		0.20		0.68
No	201 (54)	38 [21–56]		6 [2–20]		–63 (–71 to 54)	
Yes	170 (46)	42 [28–58]		9 [4–19]		–64 (–72 to 56)	
AFB smear			0.05		0.62		0.83
Negative	189 (45)	37 [25–51]		9 [3–20]		–62 (–71 to –52)	
1+	133 (32)	41 [26–57]		8 [2–20]		–63 (–72 to –53)	
2+	73 (18)	51 [23–67]		10 [2–20]		–64 (–75 to –54)	
3+	21 (5)	34 [23–59]		15 [2–20]		–63 (–87 to –39)	

\* Total number of participants by clinical characteristic strata at enrollment may not add up to 455 due to some participants with unknown data.

<sup>†</sup> P values measure the difference in total SGRQ scores and per cent change in SGRQ scores using the Kruskal-Wallis and Student's *t*-test, respectively.

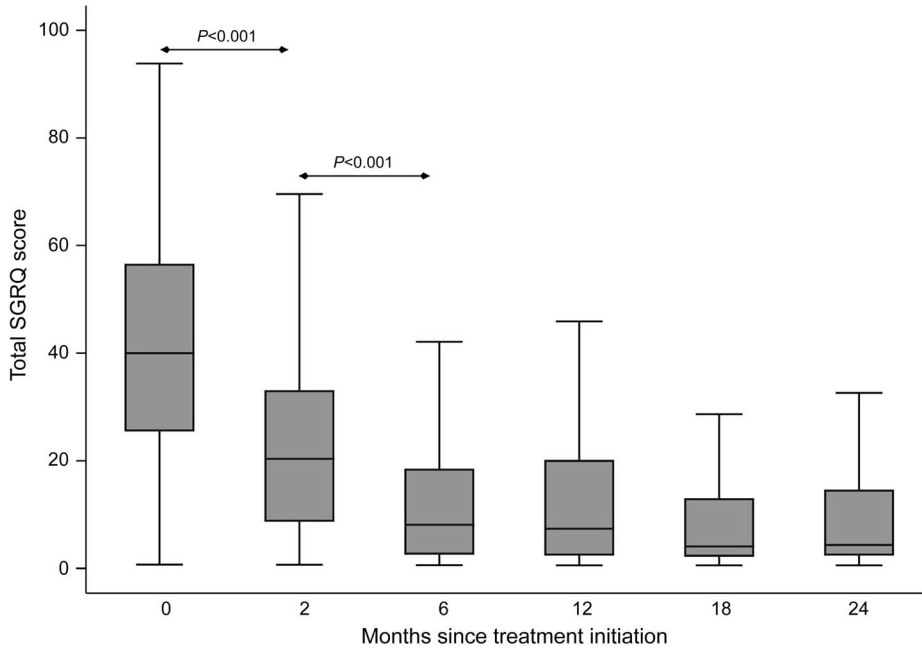
SGRQ = Saint George's Respiratory Questionnaire; TB = tuberculosis; IQR = interquartile range; CI = confidence interval; BMI = body mass index; HIV = human immunodeficiency virus; AFB = acid-fast bacilli.

that immune senescence in old age hampers lung healing and repair mechanisms in TB needs further study.<sup>27,28</sup> Regardless, future studies should evaluate the role of routine monitoring for chronic lung impairment among TB patients aged >50 years.

A novel finding from our study was the association of SGRQ scores with poor treatment outcomes in TB. We found that TB cases with worse respiratory health status carried a higher risk of death and recurrent TB, whereas those with poor improvement in respiratory health status during treatment had a higher risk of failure. Poor lung function has long been associated with a higher risk of all-cause mortality in apparently healthy individuals.<sup>29</sup> Subsequent studies have confirmed this association in various disease states, particularly chronic lung diseases.<sup>30–32</sup> We extended those findings to a cohort of PTB patients by identifying an association between worse respiratory health status at treatment initiation and higher risk of subsequent mortality. While the SGRQ does not

directly measure vital capacity, SGRQ scores inversely correlate with key lung function indices, exercise capacity and PaO<sub>2</sub>.<sup>15,23,24</sup> The SGRQ could serve as a simple and inexpensive patient-centered triage test for the early identification of TB patients at the greatest risk of death.

We found that improvements in respiratory health status were associated with a lower risk of treatment failure. While this may simply reflect subjective improvements in health status following treatment initiation independent of treatment efficacy, changes in respiratory health status may also be indicative of the underlying microbiological response to treatment. TB patients with lower improvements in their respiratory health status were more likely to fail treatment in our study, which suggests the role respiratory health status monitoring plays in identifying TB patients at a risk of failure. Furthermore, there is growing interest in the utility of host-directed therapies (HDTs), i.e., adjunctive therapies that

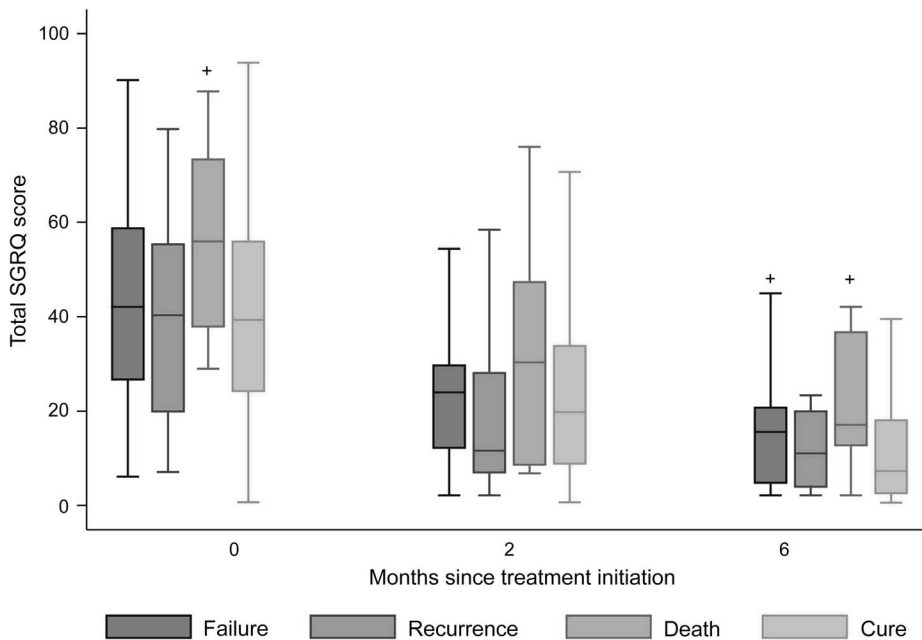


**Figure 1** Boxplots of total SGRQ scores by study visit among all pulmonary tuberculosis cases. The y-axis depicts total SGRQ scores and the x-axis depicts months since treatment initiation. *P* values were calculated using the Wilcoxon sign-rank test comparing the difference in total SGRQ scores between study visits. Only statistically significant *P* values are reported. SGRQ = Saint George’s Respiratory Questionnaire.

modulate immune mechanisms in the host to improve treatment efficacy in TB and prevent lung injury.<sup>33,34</sup> By demonstrating an association of respiratory health status with treatment failure, we provide a rationale

for early intervention with HDTs to improve clinical outcomes in TB.

While we did not find a predictive association between worse respiratory health status at treatment



**Figure 2** Boxplots of total SGRQ scores by study visit, stratified by treatment outcomes. Analysis set was restricted to participants who completed at least 18 months of follow-up or experienced a poor treatment outcome before 18 months. + = statistically significant difference in total SGRQ scores compared to participants who were cured calculated using the Wilcoxon rank-sum test. SGRQ = Saint George’s Respiratory Questionnaire.

**Table 2** Risk of poor TB treatment outcomes for each 4-point increment in total SGRQ scores, analyzed separately as time-updated, enrollment and 6-month exposures

Outcomes	Time-updated SGRQ scores*		Enrollment SGRQ scores		6-month SGRQ scores	
	IRR (95%CI)	P value	IRR (95%CI)	P value	IRR (95%CI)	P value
Unadjusted						
Composite <sup>†</sup>	1.11 (1.04–1.18)	0.001	1.01 (0.96–1.06)	0.60	—	—
Failure	0.93 (0.85–1.02)	0.11	1.01 (0.94–1.08)	0.84	—	—
Recurrence	1.17 (1.06–1.29)	0.002	0.98 (0.89–1.08)	0.81	1.03 (0.88–1.21)	0.66
Death	1.12 (0.99–1.27)	0.07	1.12 (1.01–1.24)	0.03	—	—
Adjusted <sup>‡</sup>						
Composite <sup>†</sup>	1.11 (1.03–1.19)	0.002	1.01 (0.96–1.07)	0.56	—	—
Failure	1.02 (0.92–1.12)	0.70	0.99 (0.92–1.07)	0.90	—	—
Recurrence	1.15 (1.04–1.27)	0.004	1.02 (0.92–1.13)	0.63	1.02 (0.88–1.19)	0.73
Death	1.18 (1.04–1.33)	0.008	1.14 (1.02–1.28)	0.01	—	—

\* Random-effects analysis for within-individual correlations of total SGRQ scores.

<sup>†</sup> Included failure, recurrence and death.

<sup>‡</sup> Adjusted for age, sex, ever-smoking, BMI, HIV coinfection and diabetes mellitus.

TB = tuberculosis; SGRQ = Saint George's Respiratory Questionnaire; IRR = incidence rate ratio; CI = confidence interval; BMI = body mass index; HIV = human immunodeficiency virus.

completion and recurrent TB, clinically relevant increments in time-updated SGRQ scores following successful treatment were associated with a 15% higher risk of recurrence. Recent PET/CT studies in treated TB patients have found subclinical 'hotspots' of active inflammation in the lungs, suggesting the presence of persistent *M. tuberculosis* foci despite successful treatment.<sup>35</sup> While we could not differentiate between TB relapse and re-infection in our study, the majority (20/23, 87%) of recurrent TB cases occurred within 12 months of treatment completion, suggesting a higher likelihood of TB relapse. Sequential SGRQ scores may correlate with bacterial replication, progression of underlying lung inflammation and disease in treated TB patients, and partly explain the association of time-updated SGRQ scores and recurrent TB in our cohort. Further studies measuring the association between lung inflammation and SGRQ scores in individuals who develop TB relapse identified using *M. tuberculosis* strain typing are needed.

Our study had two main limitations. First, pre-existing chronic lung disease, particularly among older smokers, could have confounded the association between SGRQ scores and death. However,

given that our study population predominantly comprised young never smokers after excluding those with a history of chronic lung disease, and our objective was to measure the association between respiratory health status and treatment outcomes, undiagnosed chronic lung diseases are unlikely to diminish the importance of our study findings. Second, we included all causes of death irrespective of their causal relationship with TB, which limited the use of SGRQ scores as a predictive tool for deaths causally associated with TB.

Despite these limitations, our study is the first to demonstrate an association between clinically meaningful changes in respiratory health status and treatment outcomes in PTB patients in a high-burden setting. We provide novel evidence to support the role of respiratory health status assessments using the SGRQ as a patient-centered approach in monitoring TB patients for response to treatment and poor clinical outcomes, specifically death, in resource-limited settings.

#### Acknowledgements

Data in this manuscript were collected as part of the Regional Prospective Observational Research for Tuberculosis (RePORT) India Consortium. This project has been funded in whole or in part

**Table 3** Risk of treatment failure per 4-point absolute or 1% decline in total SGRQ scores during anti-tuberculosis treatment\*

Change in total SGRQ score	Unadjusted		Adjusted <sup>†</sup>	
	IRR (95%CI)	P value	IRR (95%CI)	P value
0–2 months				
Per 1% decline	1.00 (0.96–1.05)	0.81	1.00 (0.97–1.06)	0.68
Per 4-point decline	1.06 (0.76–1.47)	0.70	1.17 (0.75–1.82)	0.46
0–6 months				
Per 1% decline	0.99 (0.98–1.00)	0.06	0.99 (0.98–0.99)	0.05
Per 4-point decline	0.92 (0.83–1.00)	0.07	0.91 (0.83–0.99)	0.04

\* Absolute and per cent declines in total SGRQ scores were included in separate models.

<sup>†</sup> Adjusted for age, sex, ever-smoking, body mass index, HIV coinfection and diabetes.

SGRQ = Saint George's Respiratory Questionnaire; IRR = incidence rate ratio; CI = confidence interval.

with Federal funds from the Government of India's (GOI) Department of Biotechnology (DBT; New Delhi), the Indian Council of Medical Research (ICMR; New Delhi, India), the United States National Institutes of Health (NIH; Bethesda, MD, USA), National Institute of Allergy and Infectious Diseases (NIAID; Bethesda, MD), and Office of AIDS Research (OAR; Bethesda, MD), and distributed in part by CRDF Global (Arlington, VA, USA). Research reported in this publication was also supported by NIAID, NIH under award number R01AI097494 and UM1AI069465, the Wyncote Foundation, Philadelphia, PA, USA, and the Ujala Foundation, Newton Square PA, USA.

ANG was supported by NIH Research Training Grant # D43 TW009340 funded by the NIH Fogarty International Center, National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, National Heart, Lung, and Blood Institute and National Institute of Environmental Health Sciences (all Bethesda, MD, USA).

Disclaimer: The contents of this publication are solely the responsibility of the authors and do not represent the official views of the DBT, ICMR, NIH, or CRDF Global. Any mention of trade names, commercial projects, or organizations does not imply endorsement by any of the sponsoring organizations. The authors also acknowledge support from Persistent Systems (Pune, India) in kind.

Conflicts of interest: none declared.

## References

- World Health Organization. Global tuberculosis report, 2017. WHO/HTM/TB/2017.23. Geneva, Switzerland: WHO, 2017.
- Dheda K, Booth H, Huggett J F, Johnson M A, Zumla A, Rook G A. Lung remodeling in pulmonary tuberculosis. *J Infect Dis* 2005; 192: 1201–1209.
- Byrne A L, Marais B J, Mitnick C D, Lecca L, Marks G B. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015; 32: 138–146.
- Kempker R R, Rabin A S, Nikolaishvili K, et al. Additional drug resistance in *Mycobacterium tuberculosis* isolates from resected cavities among patients with multidrug-resistant or extensively drug-resistant pulmonary tuberculosis. *Clin Infect Dis* 2012; 54: e51–54.
- Ong C W, Elkington P T, Friedland J S. Tuberculosis, pulmonary cavitation, and matrix metalloproteinases. *Am J Respir Crit Care Med* 2014; 190: 9–18.
- Panjabi R, Comstock G W, Golub J E. Recurrent tuberculosis and its risk factors: adequately treated patients are still at high risk. *Int J Tuberc Lung Dis* 2007; 11: 828–837.
- Ralph A P, Ardian M, Wiguna A, et al. A simple, valid, numerical score for grading chest x-ray severity in adult smear-positive pulmonary tuberculosis. *Thorax* 2010; 65: 863–869.
- Kriel M, Lotz J W, Kidd M, Walzl G. Evaluation of a radiological severity score to predict treatment outcome in adults with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2015; 19: 1354–1360.
- Murthy S E, Chatterjee F, Crook A, et al. Pretreatment chest x-ray severity and its relation to bacterial burden in smear positive pulmonary tuberculosis. *BMC Med* 2018; 16: 73.
- Heysell S K, Thomas T A, Sifri C D, Rehm P K, Houghton E R. 18-fluorodeoxyglucose positron emission tomography for tuberculosis diagnosis and management: a case series. *BMC Pulm Med* 2013; 13: 14.
- Hofmeyr A, Lau W F, Slavina M A. *Mycobacterium tuberculosis* infection in patients with cancer, the role of 18-fluorodeoxyglucose positron emission tomography for diagnosis and monitoring treatment response. *Tuberculosis (Edinb)* 2007; 87: 459–463.
- Demura Y, Tsuchida T, Uesaka D, et al. Usefulness of 18F-fluorodeoxyglucose positron emission tomography for diagnosing disease activity and monitoring therapeutic response in patients with pulmonary mycobacteriosis. *Eur J Nucl Med Mol Imaging* 2009; 36: 632–639.
- Martinez V, Castilla-Lievre M A, Guillet-Caruba C, et al. (18)F-FDG PET/CT in tuberculosis: an early non-invasive marker of therapeutic response. *Int J Tuberc Lung Dis* 2012; 16: 1180–1185.
- Chen R Y, Dodd L E, Lee M, et al. PET/CT imaging correlates with treatment outcome in patients with multidrug-resistant tuberculosis. *Sci Transl Med* 2014; 6: 265ra166.
- Jones P W. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001; 56: 880–887.
- Curtis J R, Patrick D L. The assessment of health status among patients with COPD. *Eur Respir J Suppl* 2003; 41: 36S–45S.
- Curtis J R, Martin D P, Martin T R. Patient-assessed health outcomes in chronic lung disease: what are they, how do they help us, and where do we go from here? *Am J Respir Crit Care Med* 1997; 156: 1032–1039.
- Maguire G P, Anstey N M, Ardian M, et al. Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. *Int J Tuberc Lung Dis* 2009; 13: 1500–1506.
- Kastien-Hilka T, Rosenkranz B, Sinanovic E, Bennett B, Schwenkglens M. Health-related quality of life in South African patients with pulmonary tuberculosis. *PLOS ONE* 2017; 12: e0174605.
- Gupte A, Padmapriyadarsini C, Mave V, et al. Cohort for Tuberculosis Research by the Indo-US Medical Partnership (CTRIUMPH): protocol for a multicentric prospective observational study. *BMJ Open* 2016; 6: e010542.
- Centers for Disease Control and Prevention. National Health Interview Survey. Atlanta, GA, USA: CDC, 2018. <https://www.cdc.gov/nchs/nhis/index.htm>. Accessed December 2017.
- Pasipanodya J G, Miller T L, Vecino M, et al. Using the St. George respiratory questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis. *Chest* 2007; 132: 1591–1598.
- Jones P W, Quirk F H, Baveystock C M. The St George's Respiratory Questionnaire. *Resp Med* 1991; 85 (Suppl B): 25–31; discussion 3–7.
- Jones P W. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; 19: 398–404.
- Rennard S I, Vestbo J. Natural histories of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 878–883.
- Buist A S, McBurnie M A, Vollmer W M, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370: 741–750.
- Fukuchi Y. The aging lung and chronic obstructive pulmonary disease: similarity and difference. *Proc Am Thorac Soc* 2009; 6: 570–572.
- Janssens J P, Pache J C, Nicod L P. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999; 13: 197–205.
- Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. *Med Chir Trans* 1846; 29: 137–252.
- Young R P, Hopkins R, Eaton T E. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007; 30: 616–622.
- Burney P G, Hooper R. Forced vital capacity, airway obstruction and survival in a general population sample from the USA. *Thorax* 2011; 66: 49–54.

- 
- 32 Godfrey M S, Jankowich M D. The vital capacity is vital: epidemiology and clinical significance of the restrictive spirometry pattern. *Chest* 2016; 149: 238–251.
  - 33 Wallis R S, Hafner R. Advancing host-directed therapy for tuberculosis. *Nat Rev Immunol* 2015; 15: 255–263.
  - 34 Wallis R S, Maeurer M, Mwaba P, et al. Tuberculosis—advances in development of new drugs, treatment regimens, host-directed therapies, and biomarkers. *Lancet Infect Dis* 2016; 16: e34–46.
  - 35 Malherbe S T, Shenai S, Ronacher K, et al. Persisting positron emission tomography lesion activity and *Mycobacterium tuberculosis* mRNA after tuberculosis cure. *Nat Med* 2016; 22: 1094–1100.



## R É S U M É

**CONTEXTE :** L'association entre une détérioration de la fonction respiratoire et les résultats du traitement de la tuberculose (TB) n'est pas claire.

**MÉTHODE :** Nous avons prospectivement évalué le statut de la fonction respiratoire, mesurée par le questionnaire respiratoire de St George (SGRQ), dans une cohorte de nouveaux cas de TB pulmonaire adulte pendant le traitement et jusqu'à 18 mois suivant le traitement en Inde. Les associations entre les scores totaux du SGRQ et des résultats défavorables du traitement comme un échec, une rechute et un décès de toutes causes ont été mesurées par la régression multivariable de Poisson.

**RÉSULTATS :** Nous avons enrôlés 455 participants aboutissant à 619 personnes années à risque ; 39 ont eu un échec, 23 ont eu une rechute et 16 sont décédés. L'âge médian a été de 38 ans (intervalle interquartile [IQR] 26–49) et 147 (32%) avaient fumé à un moment.

Les scores SGRQ lors de la mise en route du traitement ont été prédictifs de décès pendant le traitement (risque plus élevé de 14% par augmentation du score SGRQ initial de 4 points, IC95% 2–28,  $P = 0,01$ ). L'amélioration des scores SGRQ pendant le traitement a été associée à un risque plus faible d'échec (risque plus faible de 1% pour chaque pourcentage d'amélioration pendant le traitement, IC95% 1–2%,  $P = 0,05$ ). Une détérioration cliniquement significative des scores SGRQ suivant un traitement réussi a été associée à un risque plus élevé de rechute (risque plus élevé de 15% par augmentation de 4 points des scores, IC95% 4–27%,  $P = 0,004$ ).

**CONCLUSION :** Une détérioration de la fonction respiratoire a été associée à des résultats défavorables du traitement de la TB. Le SGRQ peut être utilisé pour suivre la réponse au traitement et prédire le risque de décès dans la TB pulmonaire.

## R E S U M E N

**MARCO DE REFERENCIA:** No se ha dilucidado la asociación entre el deterioro de la función respiratoria y los desenlaces del tratamiento antituberculoso.

**MÉTODOS:** Se estudió de manera prospectiva la función respiratoria, medida con el cuestionario respiratorio St George (SGRQ), de una cohorte de casos nuevos de tuberculosis (TB) pulmonar en adultos hasta 18 meses después de haber finalizado el tratamiento, en la India. Se aplicó un modelo de regresión multivariante de Poisson con el fin de analizar las asociaciones entre la puntuación total del SGRQ y los desenlaces desfavorables del tratamiento, la recurrencia de la TB y las muertes por todas las causas.

**RESULTADOS:** Se incluyeron en el estudio 455 participantes que contribuyeron con un seguimiento de 619 años-persona; se presentaron 39 fracasos, 23 recurrencias y 16 defunciones. La mediana de la edad fue 38 años (amplitud intercuartil [IQR] 26–49) y 147 habían fumado en algún momento de la vida (32%). Las

puntuaciones del SGRQ al comienzo del tratamiento fueron pronósticas de la muerte durante el tratamiento (un aumento del 14% del riesgo por cada cuatro puntos de aumento en la puntuación inicial del SGRQ, IC95% 2–28;  $P = 0,01$ ). La mejoría en la puntuación del SGRQ durante el tratamiento se asoció con un menor riesgo de fracaso terapéutico (una disminución de 1% del riesgo por cada porcentaje de mejoría durante el tratamiento, IC95% 1–2;  $P = 0,05$ ). La agravación de la puntuación del SGRQ con repercusión clínica tras un tratamiento eficaz se asoció con un mayor riesgo de recurrencia de la TB (aumento del 15% del riesgo por cada cuatro puntos de aumento de la puntuación, IC95% 4–27;  $P = 0,004$ ).

**CONCLUSIÓN:** El deterioro de la salud respiratoria se asoció con desenlaces desfavorables del tratamiento de la TB. El cuestionario SGRQ se puede utilizar en la supervisión de la respuesta al tratamiento y para pronosticar el riesgo de muerte en los casos de TB pulmonar.