

Original Article

Clinical utility of Leicester Cough Score as a correlate of sputum conversion and inflammatory resolution in pulmonary Tuberculosis during Intensive phase therapy

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ABSTRACT

Objectives: The objectives of the study are to primarily assess changes in LCS during the intensive phase of anti-TB therapy and secondarily to examine associations between LCS and microbiological and inflammatory indicators and high-sensitivity C-reactive protein [hsCRP] and to explore whether baseline LCS predicts sputum culture conversion at 2 months.

Materials and Methods: This was a prospective observational cohort study conducted at a single tertiary-care. Fifty-six treatment-naïve adults (≥ 18 years) with microbiologically confirmed pulmonary TB were enrolled at treatment initiation. LCS (range 3-21) was assessed at baseline and after the 2-month intensive phase. Sputum smear microscopy and Löwenstein-Jensen culture were used to assess bacteriological status, and baseline hsCRP was measured.

Statistical Analysis: Continuous variables were summarized as mean \pm standard deviation or median (interquartile range [IQR]). Paired comparisons used the paired t-test or Wilcoxon signed-rank test, and between-group comparisons used non-parametric tests as appropriate. Associations were assessed using Spearman's correlation. Receiver operating characteristic (ROC) analysis was performed to evaluate baseline LCS for predicting 2-month sputum culture conversion.

Results: Median LCS improved from 9.75 (IQR 7.60–10.90) at baseline to 17.0 (IQR 15.72–17.77) at 2 months ($Z = -6.151, p < 0.001$). Median hsCRP declined from 42.56 mg/L to 8.64 mg/L ($p < 0.001$). Sputum culture conversion occurred in 47 of 56 patients (83.9%). Baseline LCS did not differ significantly between converters and non-converters ($p = 0.101$) and correlated poorly with baseline hsCRP ($\rho = -0.14, p = 0.303$). In contrast, follow-up LCS and improvement in LCS were significantly greater among patients who achieved sputum conversion.

Conclusions: LCS is a highly responsive and feasible patient-reported outcome measure that captures clinically meaningful symptomatic improvement during the intensive phase of anti-TB therapy. However, baseline LCS shows limited association with microbiological burden or systemic inflammation and should not be used as a stand-alone predictor of early sputum culture conversion.

Keywords: Leicester cough score, Patient-reported outcomes, Pulmonary tuberculosis, Sputum conversion, Treatment response

INTRODUCTION

Tuberculosis (TB) remains a leading infectious cause of mortality globally, with an estimated 10 million new cases and 1.4 million deaths.^[1] Effective treatment is available for drug-susceptible pulmonary TB, yet monitoring a patient's response to therapy remains challenging. Standard practice relies on bacteriological indicators, such as sputum smear microscopy and culture, to evaluate the early treatment response. However, these tools have significant limitations. Sputum smears have low sensitivity and cannot differentiate between viable and non-viable bacilli, while culture, although more sensitive, is time-consuming and resource-intensive.^[2-4] Moreover, even culture conversion at 2 months is not an absolute predictor of final treatment success, especially in subsets like drug-resistant TB.^[5,6] There is thus an urgent need for alternative or adjunct biomarkers that are rapid, safe, and reflective of disease activity to guide clinical decisions during TB therapy.^[7]

Clinical symptoms, particularly cough, present a potential complementary indicator of treatment response. Cough is the most common symptom of pulmonary TB and is routinely assessed during therapy. Active pulmonary TB typically presents with a persistent cough, among other constitutional symptoms.^[8] Moreover, cough frequency and severity tend to diminish with effective anti-TB treatment, with objective studies showing significant reductions in cough episodes within the 1st weeks of therapy.^[9] However, until recently, symptom monitoring in TB has been largely qualitative and subjective, relying on patient recall and basic checklists. This subjective approach can be unreliable due to variability in patient perception and recall bias.^[10] Furthermore, symptomatic improvement may not always parallel bacteriological clearance, highlighting the need to better understand the relationship between patient-reported symptoms and objective disease markers (evidence shows cough and other clinical symptoms often improve independently of culture or smear results).^[11] To systematically quantify symptom changes, validated patient-reported outcome measures are needed (studies using standardized quality of life (QoL) instruments demonstrate measurable symptomatic change).^[12]

The Leicester cough questionnaire (LCQ) was originally developed to measure the impact of chronic cough on QoL in a standardized manner.^[13] It consists of 19 items across physical, psychological, and social domains, each scored on a 7-point Likert scale, yielding a total score ranging from 3 (worst cough-related QoL) to 21 (best).^[12] The LCQ is a valid, internally consistent, and responsive instrument in chronic cough populations.^[13] Importantly, the LCQ has also been applied in TB contexts. Turner *et al.*^[14] validated the LCQ in patients with pulmonary TB and found it to be a reliable measure of cough-specific QoL in this

population, responsive to early treatment effects. Their study demonstrated substantial improvement in LCQ scores within the first few weeks of therapy, supporting its potential utility as an outcome measure in TB. Another study reported that cough- and sputum-related QoL (measured by LCQ and a related questionnaire) was significantly impaired in active TB and improved after 2 months of treatment.^[12] These findings suggest that a Leicester cough score (LCS), derived from the total LCQ score, could serve as a practical tool to monitor symptomatic response during TB therapy.

Despite these indications, the role of LCS as a quantitative monitoring tool and its relationship with bacteriological and inflammatory markers in TB has not been fully elucidated. In particular, it remains unclear whether improvements in LCS correlate with conventional microbiological indicators such as sputum smear grade, time to culture positivity (TTP), or sputum culture conversion, and whether baseline LCS has any prognostic relevance for early bacteriological response. Given the subjective nature of cough and the biological heterogeneity of pulmonary TB, the ability of baseline cough-related QoL measures to predict microbiological outcomes warrants careful evaluation.

In this study, we aimed to investigate the utility of the LCS in adult patients with pulmonary TB during the intensive phase of treatment. Specifically, our objectives were (1) to assess changes in LCS over the intensive phase of therapy, (2) to examine the relationship between LCS and microbiological and inflammatory indicators of disease (including sputum smear grading, TTP, and serum C-reactive protein [CRP] levels), and (3) to evaluate whether baseline LCS is associated with sputum culture conversion at 2 months. We hypothesized that LCS would show significant improvement with effective therapy and explored whether baseline LCS demonstrated any association with early bacteriological response, recognizing that this association might be limited. By evaluating LCS in this context, we seek to clarify its role as a patient-reported outcome measure for symptom monitoring rather than as a surrogate marker of microbiological treatment response in TB care.

MATERIALS AND METHODS

Study design and setting

This study represents a prospective observational cohort with a pre-planned secondary analysis of existing data. Adult patients with pulmonary TB were recruited between May 2023 and November 2024 from the directly observed treatment (DOT) center of a single tertiary-care teaching hospital (UCMS, India). The primary cohort was designed to evaluate sputum conversion and hematological biomarkers; the present analysis specifically evaluated the role of cough-related QoL using the LCQ.

Participants

Treatment-naïve adults (≥ 18 years) with microbiologically confirmed pulmonary TB were enrolled at the time of diagnosis and treatment initiation. Diagnosis was established using sputum smear microscopy, cartridge-based nucleic acid amplification test (CBNAAT), and Löwenstein-Jensen (LJ) culture.

Exclusion criteria were extrapulmonary TB without pulmonary involvement, known hematological disorders, HIV infection, rifampicin-resistant TB on CBNAAT, inability to produce sputum for follow-up testing, and any condition precluding completion of the cough questionnaire (e.g., cognitive impairment or severe concurrent respiratory illness).

Diabetes mellitus, smoking status, and chronic airway diseases were not systematically recorded and are acknowledged as potential confounders.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee for Human Research (IEC-HR, UCMS; approval no. IECHR-2023-59-85-R1). Written informed consent was obtained from all participants before enrollment. Participation was voluntary, and confidentiality was ensured through anonymization of study data.

LCQ and score derivation

Cough-related QoL was assessed using the LCQ, a validated 19-item instrument comprising physical, psychological, and social domains. Each item is scored on a 7-point Likert scale, yielding a total score ranging from 3 (worst) to 21 (best).^[13]

The LCQ was administered in person at the DOT center, primarily as a self-administered questionnaire; assistance was provided by trained study personnel when required.

Validated local-language versions were used where available; otherwise, the questionnaire was translated and back-translated following standard procedures.

The LCS refers to the total LCQ score. LCS was assessed at two time points:

1. Baseline, at initiation of anti-TB therapy
2. Follow-up at completion of the 2-month intensive phase.

All 56 participants completed both baseline and follow-up LCQ assessments; there were no missing LCS data.

Microbiological assessment

At baseline and follow-up, sputum samples were examined using Ziehl-Neelsen smear microscopy and culture on LJ solid medium. Smear results were graded semi-quantitatively

(negative, scanty, 1+, 2+, or 3+) according to national guidelines.

TTP was recorded manually in weeks based on visible growth on LJ medium, as liquid culture systems were not used. Sputum culture conversion was defined as a change from culture-positive at baseline to culture-negative at 2 months.

Inflammatory marker assessment

Baseline serum high-sensitivity CRP (hsCRP) was measured using an immunoturbidimetric assay (manufacturer details added in revised manuscript), with results reported in mg/L. The assay reference range was applied as per manufacturer specifications.

Statistical analysis

Data were analyzed using IBM Statistical Package for the Social Sciences Statistics. Continuous variables were summarized as mean \pm standard deviation (SD) or median with interquartile range (IQR), depending on distribution. Categorical variables were expressed as frequencies and percentages.

Normality was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots.

- Paired comparisons between baseline and follow-up LCS were performed using the paired t-test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data.
- Between-group comparisons (e.g., converters vs. non-converters) were conducted using the Mann-Whitney U test.
- Comparisons across more than two groups were performed using the Kruskal-Wallis test.
- Associations between continuous variables were assessed using Spearman's rank correlation coefficient (ρ).

To evaluate the predictive ability of baseline LCS for sputum culture conversion at 2 months, receiver operating characteristic (ROC) curve analysis was performed. The optimal cut-off value was identified using the Youden Index. Area under the curve (AUC) with 95% confidence intervals (CI) and p values against the null hypothesis (AUC = 0.5) were calculated.

Given multiple correlation analyses, results were interpreted cautiously, and the exploratory nature of the study is acknowledged. A $p < 0.05$ was considered statistically significant.

Sample size considerations

No formal a priori sample size calculation was performed specifically for analyses involving the LCS, as this investigation represents a pre-planned secondary analysis of an existing prospective cohort. The cohort size ($n = 56$)

was determined by the parent study, which was designed to evaluate sputum culture conversion and hematological biomarkers during anti-TB therapy. The available sample size was sufficient to robustly assess within-patient change in LCS over the intensive phase, the primary outcome of this analysis, as evidenced by a large observed effect size and statistically significant paired comparisons. However, the study was not designed or powered to detect modest associations between baseline LCS and microbiological outcomes or to provide definitive prognostic discrimination in ROC analyses. Accordingly, all analyses examining associations with microbiological and inflammatory markers, as well as prediction of sputum culture conversion, were conducted on an exploratory basis and interpreted with appropriate caution.

RESULTS

Baseline patient characteristics

Fifty-six treatment-naïve adults with microbiologically confirmed pulmonary TB were enrolled from May 2023 to November 2024 [Table 1]. The mean age was 30.86 ± 11.84 years, and 29 (51.8%) participants were male. All participants were sputum-positive at diagnosis by smear microscopy and culture. Sputum culture conversion occurred in 47 of 56 patients (83.9%) at the end of the intensive phase. Median cough duration before treatment initiation was 8 weeks (IQR 4-12). Seventy percent of patients reported weight loss, and ~50% had intermittent fever or night sweats. Baseline systemic inflammation was moderate, with a median hsCRP of 42.56 mg/L (IQR 33.51-61.86). Patient-reported cough burden was substantial at baseline, with a median LCS of 9.75 (IQR 7.60-10.90). At follow-up, the median LCS improved to 17.0 (IQR 15.72-17.77).

Change in LCS over the intensive phase

There was a marked improvement in LCS from baseline to the end of the intensive phase. Median LCS increased from 9.75 to 17.0, with a median change (Δ LCS) of 7.1 points. This improvement was statistically significant (Wilcoxon signed-rank test, $Z = -6.151$, $p < 0.001$). More than 90% of patients exceeded the minimal clinically important difference (MCID) of 1.3 points, indicating clinically meaningful symptomatic improvement.

Association between LCS and microbiological parameters

Baseline LCS did not differ significantly across baseline sputum smear grading categories (Kruskal-Wallis $\chi^2 = 1.908$, $p = 0.385$). Similarly, baseline LCS showed no significant

Table 1: Baseline and follow-up characteristics of the study population ($n=56$).

Characteristic	Value
Age (years)	30.86±11.84 (mean±SD)
Sex (%)	
Male	29 (51.8)
Female	27 (48.2)
Pulmonary tuberculosis status (%)	
Sputum-positive at diagnosis	56 (100)
Sputum-positive at follow-up	9 (16.1)
Sputum culture conversion at 2 months	47 (83.9)
Leicester Cough Score (total LCQ score, range 3–21)	
Baseline	9.75 (7.60–10.90), median (IQR)
Follow-up (2 months)	17.0 (15.72–17.77), median (IQR)
Baseline hsCRP (mg/L)	42.56 (33.51–61.86), median (IQR)

LCQ: Leicester Cough questionnaire, LCS: Leicester Cough score, hsCRP: High-sensitivity C-reactive protein. SD: Standard deviation

association with sputum smear grading at follow-up ($\chi^2 = 2.739$, $p = 0.254$) or with the change in LCS over time ($\chi^2 = 1.306$, $p = 0.520$) [Table 2].

In contrast, follow-up sputum smear status was significantly associated with both follow-up LCS and change in LCS. Patients who became smear-negative at follow-up demonstrated significantly higher follow-up LCS values ($\chi^2 = 20.464$, $p < 0.001$) and greater improvement in LCS ($\chi^2 = 6.456$, $p = 0.040$) compared to those who remained smear-positive.

There was no correlation between baseline LCS and baseline TTP (Spearman's $\rho = 0.00$, $p = 1.000$). However, follow-up TTP showed a moderate positive correlation with follow-up LCS ($\rho = 0.73$, 95% CI 0.03–0.90, $p = 0.027$), indicating better cough-related QoL among patients with lower bacillary burden at follow-up. The correlation between follow-up TTP and change in LCS showed a positive trend but did not reach statistical significance ($\rho = 0.63$, $p = 0.067$) [Table 3].

Association between LCS and systemic inflammation

Baseline hsCRP showed no statistically significant correlation with baseline LCS ($\rho = -0.20$, $p = 0.146$), follow-up LCS ($\rho = -0.23$, $p = 0.094$), or change in LCS ($\rho = -0.01$, $p = 0.945$) [Table 4].

LCS and sputum culture conversion

Baseline LCS did not differ significantly between patients who achieved sputum culture conversion and those who

Table 2: Association between LCS and sputum smear grading ($n=56$).

A. Association with baseline sputum smear grading			
Baseline smear grade	LCS at baseline Median (IQR)	LCS at follow-up Median (IQR)	Change in LCS Median (IQR)
Negative	NA	10.1 (7.8–10.9)	NA
1+	12.05 (8.75–14.07)	7.55 (6.47–9.84)	5.85 (3.72–7.80)
2+	9.1 (7.6–10.7)	9.01 (9.01–9.01)	7.3 (5.11–9.90)
3+	9.8 (7.5–10.6)	NA	7.3 (5.65–8.45)
Kruskal-Wallis χ^2	1.908	2.739	1.306
P-value	0.385	0.254	0.520
B. Association with follow-up sputum smear grading			
Follow-up smear grade	LCS at baseline Median (IQR)	LCS at follow-up Median (IQR)	Change in LCS Median (IQR)
Negative	10.1 (7.8–10.9)	17.3 (16.45–17.85)	7.6 (6.05–9.65)
1+	7.55 (6.47–9.84)	12.65 (10.47–14.20)	4.4 (2.36–5.73)
2+	9.01 (9.01–9.01)	10.8 (10.8–10.8)	1.79 (1.79–1.79)
3+	NA	NA	NA
Kruskal-Wallis χ^2	2.739	20.464	6.456
P-value	0.254	<0.001	0.040

LCS: Leicester Cough score, IQR: Interquartile range, NA: Not available (no observations in that category)

did not (median 10.1 vs. 7.9; $p = 0.101$). In contrast, follow-up LCS was significantly higher in patients who achieved sputum conversion ($p < 0.001$), and the improvement in LCS over time was also significantly greater in converters ($p = 0.013$) [Table 5].

Patients who achieved sputum conversion had significantly lower baseline hsCRP levels compared to non-converters (median 38.9 vs. 72.65 mg/L; Wilcoxon-Mann-Whitney U test, $W = 27.000$, $p < 0.001$).

ROC analysis of baseline LCS

ROC analysis demonstrated that baseline LCS had poor discriminatory ability for predicting sputum culture conversion at 2 months (AUC = 0.563, 95% CI 0.40–0.72; $p = 0.43$ against AUC = 0.5). The optimal cut-off value (≥ 7.55) yielded low specificity, limiting clinical utility [Table 6 and Figure 1]. These findings indicate that baseline LCS is not a reliable predictor of early bacteriological response.

Summary of findings

In summary, intensive-phase anti-TB therapy resulted in substantial symptomatic and inflammatory improvement across the cohort. While LCS was highly responsive to treatment and reflected symptomatic recovery, baseline LCS showed limited association with microbiological burden or systemic inflammation and demonstrated poor predictive value for sputum culture conversion.

Table 3: Correlation between LCS and time to culture positivity ($n=56$).

LCS variable	Spearman's ρ	95% Confidence Interval	p-value
Baseline LCS	0.00	–0.92–0.67	1.000
Follow-up LCS	0.73	0.03–0.90	0.027
Change in LCS (Δ LCS)	0.63	–0.10–0.90	0.067

LCS: Leicester Cough score

Table 4: Correlation between LCS and high-sensitivity C-reactive protein ($n=56$).

LCS variable	Spearman's ρ	95% Confidence Interval	p-value
Baseline LCS	–0.20	–0.48 to 0.11	0.146
Follow-up LCS	–0.23	–0.49 to 0.06	0.094
Change in LCS (Δ LCS)	–0.01	–0.32 to 0.28	0.945

LCS: Leicester Cough score

DISCUSSION

Our study demonstrates that cough-related QoL improves markedly during TB therapy, even when traditional microbiological or inflammatory markers do not change in parallel. We observed a significant rise in LCQ scores following treatment initiation, consistent with prior reports. For example, Suzuki *et al.*^[12] showed that mean LCQ scores increased by ~2.28 points after 2 months of therapy, regardless of smear grade or lung cavitation. Likewise, Turner *et al.*^[14]

Table 5: Association of sputum culture conversion with LCS and baseline hsCRP ($n=56$).

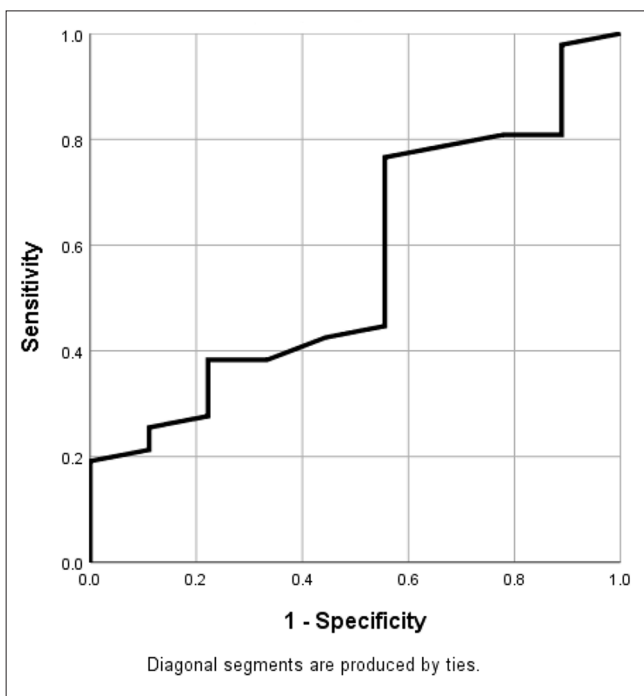
Variable	Sputum converters ($n=47$)	Non-converters ($n=9$)	p -value
LCS (median, IQR)			
Baseline LCS	10.1 (7.8–10.9)	7.9 (6.5–9.01)	0.101
Follow-up LCS	17.3 (16.45–17.85)	12.4 (10.7–13.8)	<0.001
Change in LCS (Δ LCS)	7.6 (6.05–9.65)	3.8 (1.79–5.20)	0.013
Baseline hsCRP (mg/L)			
Mean \pm SD	40.76 \pm 16.64	69.82 \pm 11.80	<0.001
Median (IQR)	38.9 (31.17–54.34)	72.65 (70.93–78.45)	<0.001
Range (min–max)	11.88–72.34	43.45–78.89	—

Statistical notes: (1) LCS comparisons were performed using the Man-Whitney U test, (2) hsCRP comparisons were performed using the Wilcoxon-Mann-Whitney U test, (3) Two-sided $P<0.05$ was considered statistically significant. LCS: Leicester Cough score, hsCRP: High-sensitivity C-reactive protein, IQR: Interquartile range, SD: Standard deviation

Table 6: Diagnostic performance of baseline LCS for predicting sputum culture conversion ($n=56$).

Baseline LCS cut-off	Sensitivity (%)	Specificity (%)	Youden's J
≥ 7.55	78.7	33.3	0.453
≥ 7.70	76.6	44.4	0.444
≥ 7.85	72.3	44.4	0.417
≥ 10.25	42.6	55.6	0.382

LCS: Leicester Cough score

**Figure 1:** ROC curve for baseline LCS predicting 2-month sputum conversion (AUC 0.563), illustrating poor discrimination.

validated the LCQ in pulmonary TB and reported a median 5.1-point increase in LCQ after just 2 weeks of treatment ($p = 0.003$). Together, these findings and our results confirm that the LCQ is a responsive instrument for capturing symptomatic improvement during TB therapy, supporting its use as a patient-reported treatment-monitoring tool.

Our findings align with international literature on cough and TB care. Prospective and retrospective studies have consistently shown that TB patients experience substantial relief of cough and sputum symptoms soon after effective therapy begins. Suzuki *et al.*^[12] observed improved cough-related QoL post-treatment in all patients, independent of initial disease severity. Similarly, Turner *et al.*^[14] demonstrated high reliability (Cronbach's $\alpha = 0.93$) and validity of the LCQ in TB, with early and substantial score improvements. These parallels suggest that the LCQ behaves in TB much as it does in other chronic cough conditions, capturing real changes in symptom burden over time. In non-TB populations, the LCQ has been validated in chronic respiratory diseases such as bronchiectasis, nontuberculous mycobacterial lung disease, and COPD as a sensitive measure of cough impact.^[10,15] Takao *et al.*,^[15] for example, found the LCQ to be a useful health-related QoL tool in nontuberculous mycobacterial lung disease.

Beyond cough-specific instruments, symptom-based clinical scores have long been used to monitor TB patients. The WHO-endorsed Bandim TB score is a well-known example. Wejse *et al.*^[16] developed a composite symptom-and-sign score that declined steadily with successful treatment; in their cohort of 698 patients, 96% of survivors had lower scores at treatment completion than at baseline, and higher baseline scores predicted mortality. Rudolf *et al.*^[17] subsequently refined this tool (TBscore II) and demonstrated significant score reductions at 2 and 6 months of therapy (Cohen's $d \sim 0.5$ – 0.7), with failure to improve by $\geq 25\%$ at

2 months predicting treatment failure. These symptom-based tools reinforce the concept that patient-reported or clinician-assessed symptoms often improve with therapy and can provide meaningful information on the clinical course. Our findings are consistent with this paradigm in showing substantial symptomatic improvement measured by LCQ. However, unlike composite symptom scores designed with prognostic intent, the LCQ appears less suited for predicting microbiological endpoints.

Importantly, we observed no significant correlation between baseline LCQ scores and measures of bacterial burden or systemic inflammation. This finding is consistent with prior evidence. Miranda *et al.*,^[18] for example, reported that baseline CRP levels did not reliably distinguish patients with higher sputum *Mycobacterium tuberculosis* (MTB) loads or predict early culture positivity at treatment initiation.

The lack of correlation between cough-related QoL and microbiological markers likely reflects biological heterogeneity. Cough arises from airway irritation, inflammation, and structural lung involvement, processes that do not scale linearly with bacillary load. The “Making cough count” report highlighted that cough frequency is a poor proxy for bacterial shedding: some patients with infrequent cough released large quantities of MTB, whereas others with frequent cough did not.^[10] By extension, patient-reported cough impact, as measured by the LCQ, may diverge substantially from objective microbiological measures. Thus, the absence of association between LCQ and smear grade, TTP, or CRP in our study is consistent with the view that cough-related QoL scores capture a different dimension of disease, namely symptom experience, than laboratory-based markers.

We also observed that LCQ scores improved even among patients who remained culture-positive at the end of the intensive phase. In other words, cough-related QoL improved regardless of whether sputum conversion occurred within 2 months. This mirrors the findings of Suzuki *et al.*^[12] who reported that cough and sputum-related QoL improved “regardless of clinical characteristics.” In clinical practice, many patients experience symptomatic relief soon after starting therapy, as bacterial replication is suppressed and inflammation begins to subside. Such early symptomatic improvement may precede, or occur independently of, bacteriological clearance. Turner *et al.*^[14] similarly demonstrated substantial subjective improvement within the first 2 weeks of therapy. These observations emphasize that LCQ primarily reflects treatment-related symptomatic benefit rather than sterilizing activity. Clinically, this implies that patient-perceived improvement does not guarantee rapid culture conversion, and conversely, the absence of a prominent cough does not necessarily indicate microbiological cure.

Consistent with this dissociation, the predictive performance of baseline LCQ for early sputum culture conversion was poor in our cohort (AUC ~0.5-0.6). Baseline cough severity did not meaningfully distinguish converters from non-converters. This likely reflects the multifactorial nature of cough, which is influenced by airway hyperreactivity, smoking status, coexisting lung pathology, and individual perception, in addition to infection-related factors. In contrast, sputum conversion is driven primarily by bacillary burden, drug susceptibility, host immune response, and treatment adherence. As a result, a patient with severe cough-related impairment may convert as rapidly as one with milder symptoms. Our findings are consistent with reports cautioning against the use of cough metrics as surrogate markers of microbiological activity. Williams *et al.*^[19] demonstrated that objective cough counts were poorly associated with MTB output in exhaled air samples, suggesting that neither subjective nor objective cough measures reliably reflect bacillary load or transmission risk. The low AUC observed in our study reinforces that baseline LCQ should not be considered a stand-alone predictor of microbiological outcome.

The strengths of this study include its prospective design and systematic use of a validated patient-reported outcome measure from treatment initiation. The use of a culturally adapted LCQ and standardized microbiological assessments adds to the reliability of the findings. However, several limitations should be acknowledged. The sample size was modest, limiting statistical power and precision, particularly for predictive analyses. LCQ assessments were limited to baseline and the end of the intensive phase, precluding evaluation of longer-term symptom trajectories. The questionnaire was not formally revalidated in the study population, and objective cough monitoring was not performed. Potential confounders such as smoking status, diabetes, or chronic airway disease were not systematically captured, and selection bias may have occurred if severely ill patients were less able to complete questionnaires. These limitations constrain interpretation and underscore that our findings should be viewed as exploratory.

Overall, the LCQ appears useful for documenting patient-perceived symptomatic improvement during TB therapy but should not replace microbiological markers in guiding clinical decision-making. Improvement in cough-related QoL may provide reassurance to patients and clinicians that therapy is producing symptomatic benefit, even when cultures remain positive. However, reliance on LCQ to predict early sputum conversion would be inappropriate. Our study adds to emerging evidence that comprehensive TB monitoring should integrate patient-reported outcomes with established laboratory measures. Future research may explore combining subjective cough assessments with

objective cough monitoring and biomarker panels to develop more holistic approaches to treatment monitoring in TB.

CONCLUSION

The LCS proved to be a highly responsive, feasible, and patient-centered tool for monitoring symptomatic improvement during the intensive phase of anti-TB therapy in routine DOT settings. The majority of patients experienced clinically meaningful improvement in cough-related QoL, with >90% exceeding the MCID. Follow-up LCS and the magnitude of improvement were significantly greater among patients who achieved sputum culture conversion, indicating that symptomatic recovery parallels effective treatment response.

However, baseline LCS demonstrated limited association with microbiological burden, systemic inflammation, or early bacteriological response and showed poor discriminatory ability for predicting 2-month sputum culture conversion. Baseline LCS should therefore not be used as a stand-alone predictor of early sputum conversion or treatment success. These findings highlight the biological dissociation between patient-reported cough severity and bacillary clearance during TB therapy.

Overall, LCS is best positioned as a complementary patient-reported outcome measure for symptom monitoring, patient counseling, and assessment of treatment-related QoL improvement, rather than as a surrogate marker of microbiological response. Future studies with larger, multicenter cohorts, longer follow-up, and integration of objective cough monitoring or biomarker panels may help clarify the role of cough assessment within comprehensive TB treatment-monitoring frameworks.

Author's contributions: HY: Methodology, laboratory work, data collection, data analysis, interpretation of result and preparation of the original manuscript draft; BK: Conceptualization, Supervision, study design, critical revision of the manuscript; PH: Data curation, validation of results, and assistance in interpretation of findings.

Ethical approval: The research/study was approved by the Institutional Review Board at IEC-HR UCMS, approval number IECHR-2023-59-85-R1, dated 30th April 2023.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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