

Efficiency of the Lung Flute for sputum induction in patients with presumed pulmonary tuberculosis

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Abstract

Introduction: High quality sputum helps increase the sensitivity of the diagnosis of pulmonary tuberculosis.

Objectives: To evaluate the efficiency of the acoustic device (Lung Flute; LF) in sputum induction compared with the conventional method, hypertonic saline inhalation (HSI).

Methods: In this crossover study, patients with presumed pulmonary tuberculosis submitted 3 consecutive sputa: the first sputum without induction and the second and third ones using LF and HSI. We compared the efficiency of the 2 induction methods.

Results: Sixty-four participants were eligible. Thirty-five (54.6%) patients had negative smears on the first sputum without induction. Among those patients, 25.7% and 22.9% patients were smear-positive after using LF and HSI, respectively ($P = .001$). The positive conversion rate was not significantly different between the methods. The first samples without induction yielded 65.7% positive cultures, whereas 71.4% and 77.1% of the samples from LF and HSI were positive, respectively ($P = .284$). Similar results were observed in the nucleic acid amplification test [no induction (60.0%), LF (72.0%) and HSI (60.0%); $P = .341$]. In 29 smear-positive patients on the first sputum without induction, we observed no significant increase in smear grade, culture yield and nucleic acid amplification test positivity with either method. LF tended to induce fewer adverse events; desaturation (3.1% vs 11.1%; $P = .082$) and throat pain (1.5% vs 9.5%; $P = .057$). LF showed significantly fewer total adverse events (15.8% vs 34.9%; $P = .023$).

Conclusions: Our study showed LF had similar sputum induction efficiency to HSI with relatively fewer complications.

KEYWORDS

cough, pulmonary infection, symptom, tuberculosis

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1 | INTRODUCTION

Early diagnosis of pulmonary TB is essential for the effective treatment of TB and infection control. Sputum smear microscopy is still the only method in many settings for the diagnosis of active TB. This method requires high-quality sputum samples for high-sensitivity detection of acid-fast bacilli (AFB). One study regarding sputum sample quality among pulmonary TB patients suggested that purulent or blood-tinged sputum showed significant positive correlation with AFB smear positivity compared to mucoid or saliva specimens.¹ However, some patients, including small children, elderly people and people living with human immunodeficiency virus (HIV) generally expectorate paucibacillary or no sputum. In such cases, hypertonic saline inhalation (HSI) is currently recommended to induce sputum. This method requires the use of an ultrasonic nebuliser and aseptic hypertonic saline solution, which are not readily available in resource-limited settings. Thus, there is need for a simple sputum induction method that requires no electricity or complicated device.

The Lung Flute (LF; Medical Acoustics, Buffalo, New York) is an acoustic device invented in 2002 for promoting sputum expectoration. It is small, light and consists only of a mouthpiece with an internal reed attached to a 36.8-cm-long rectangular hardened plastic tube (Figure 1). LF requires no other device or external power source for operation. When the patient exhales gently through the mouthpiece, LF generates 18–22 Hz of acoustic waves and 110–115 dB output with a pressure of 2.5 cm H₂O. These waves travel downward along the tracheobronchial tree and vibrate the secretions and sputum. As a result, LF can increase sputum clearance and ease expectoration. In 2012, the World Health Organization recognised LF as an innovative medical device for diagnosing pulmonary TB, particularly in resource-limited settings.² The US Food and Drug Administration approved LF as a sputum induction device for diagnostic purposes in 2006.³

Fujita et al. showed that LF is able to induce sputum expectoration efficiently in patients with suspected pulmonary TB who are unable to expectorate sputum immediately.⁴ However, thus far, no controlled study has compared the sputum induction efficiency between LF and HSI. The objective of this study was to evaluate the sputum induction efficiency of LF in comparison with HSI for the bacteriological diagnosis of the patients with presumed pulmonary TB.

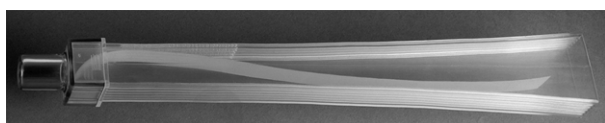


FIGURE 1 Image of the Lung Flute

2 | PARTICIPANTS AND METHODS

2.1 | Participants

This was a multicentre randomised non-blinded crossover study conducted at 6 TB hospitals in Japan. The patients who were highly suspected of harbouring active pulmonary TB, and who could not easily expectorate sputum, were screened between 1 December 2010 and 31 November 2013. Patients were asked to expectorate sputum forcefully. If the first sample obtained was less than 2+ positive in smear microscopy, they were eligible for the study. If the first sputum smear microscopy of the participants was positive, patients began anti-TB treatment immediately. The exclusion criteria were as follows: a 3+ sputum AFB smear microscopy result at enrolment, asthma, haemoptysis, chronic hypoxemia (SpO₂ < 90% in ambient air), easy expectoration of spontaneous sputum and no understanding of sputum induction procedures. Additionally, patients who were treated with anti-TB drugs for more than 5 days were excluded to avoid the TB treatment effect on laboratory examination results.

2.2 | Sputum induction procedures

The enrolled participants were randomly assigned to 2 groups, A and B, after expectorating their first sputum sample without induction. Participants in group A submitted their second sputum sample using LF and on the following day submitted their third sample using HSI; the order was reversed for the participants in group B. To avoid any residual effect of the previous sputum induction, we collected the 2 sputum samples at least 24 hours apart. LF was used according to the manufacturer's instructions, and the procedure was performed in the morning. Briefly, after a deep inhalation, patients exhaled twice into the mouthpiece of the LF. Then, they rested for 2 or more normal breaths and repeated the process 20 times under the care and observation of the medical staff. The HSI with 3% hypertonic saline was performed using an ultrasonic humidifier for 10 minutes. Within 3 hours of performing either sputum induction, the participants expectorated sputum into a sterile cup.

2.3 | Laboratory procedures

Sputum samples were digested and decontaminated using the standard N-acetyl-L-cysteine-2% NaOH decontamination method. After neutralisation with phosphate buffer (PB, pH 6.8), samples were centrifuged at 3000 g for 15 minutes at 4°C. After centrifugation, the supernatant was discarded, and the sediment was re-suspended in 1 ml of PB. The AFB smear examination was performed using auramine O fluorescence microscopy using 50 µl of the suspension. We utilised

500 µl out of each suspension for the culture using the mycobacteria growth indicator tube (MGIT; Becton Dickinson, Franklin Lakes, New Jersey). In the positive culture, *Mycobacterium tuberculosis* (MTB) bacilli were identified by lateral flow immunoprecipitation (Capilia TB; TAUNS, Izunokuni-shi Japan). Mycobacterial DNA was extracted from 200 µl of the suspension using an automatic system (Magstration System 12GC PLUS, Precision Science System, Chiba, Tokyo) according to the manufacturer's instructions. The extracted DNA samples were stored at -80°C until nucleic acid amplification. Quantitative nucleic acid amplification was performed by real-time polymerase chain reaction (PCR) using the QuantStudio 12K Flex Real-Time PCR system (Applied Biosystems, Foster City, California), according to the method previously reported.⁵

2.4 | Clinical data and adverse events

Using a standardised questionnaire, data about the basic characteristics of the participants, including their age, sex, body mass index and chest radiograph findings (the presence of lung cavitation and the extent of the disease) were collected. We monitored the SpO₂ of the participants during the sputum induction. Any adverse events of sputum induction, including throat discomfort, throat pain, dyspnoea, wheezing, severe cough, numbness, tremor and nausea, as well as the number of participants whose SpO₂ decreased more than 3% during or after the sputum induction, were recorded.

2.5 | Statistical analysis

Fisher's exact test was used to compare the categorical data between groups and methods. Cochran's *Q* test was used to compare the results of binary data among more than 3 paired groups. McNemar's test was used to compare the results of binary data among 2 paired groups. The Kruskal–Wallis test was used to compare the sputum AFB smear positivity grade and time to positivity (in days) of the samples without induction with those using LF and HSI. We used the unpaired Student's *t*-test to compare 2 consecutive variables that followed a normal distribution. To compare 2 consecutive variables that followed a non-normal distribution, we used the Mann-Whitney *U* test. A difference was regarded as statistically significant when $P < .05$. STATA version 12.1 (StanCorp, College Station, Texas) was used for statistical analysis.

2.6 | Ethical consideration

The institutional review boards of all 6 participating hospitals approved this study. All eligible participants provided written informed consent before enrolment.

3 | RESULTS

3.1 | Participants

Although 67 participants were enrolled in total, 1 withdrew consent during the early phase of TB treatment. One participant in each group was excluded from the analysis because their culture results records were incomplete. Then, a total of 64 subjects with presumed to be suffering from TB, 32 in group A and 32 in group B, were finally included in the analysis (Figure 2).

The mean \pm standard deviation (SD) age of participants was 58 ± 17 years. Of the 64 participants, 22 (34.3%) were female. The mean body mass index was 20 ± 3 kg/m². On chest radiograph, 28 (43.7%) participants presented lung cavitation (s); of these, 7 (10.9%) presented extensive involvement of over 50% of the lung field. There was no significant difference in the basic characteristics or chest radiograph findings between the 2 groups [A ($n = 32$) and B ($n = 32$); Table 1]; nor was there any significant difference in the smear positivity distribution between the groups on the first sample (Figure 3A,B) ($P = .883$). All of 64 patients successfully expectorated the sputa within 3 hours after using LF and HSI. Among the 64 patients, 35 had AFB-negative smears while 29 had AFB-positive smears in their first samples (Figure 3C).

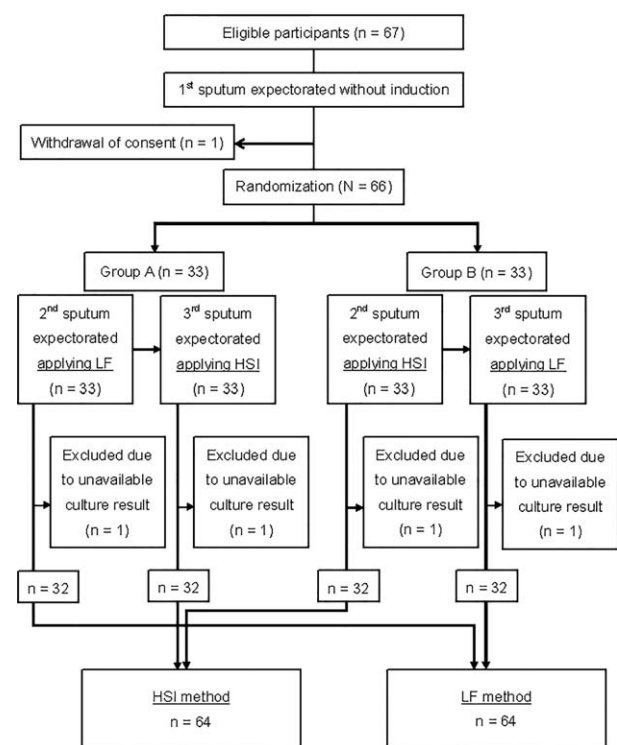


FIGURE 2 A crossover study profile and process of enrolment, randomisation and final inclusion. Abbreviations: HSI, hypertonic saline inhalation; LF, Lung Flute

TABLE 1 Comparison of basic characteristics and chest radiograph findings in Groups A and B

	Group A (n = 32)	Group B (n = 32)	P value
Age (mean ± SD) ^a	61 ± 18	56 ± 17	.323
Female (%) ^b	12 (37.5)	10 (31.2)	.793
BMI (kg/m ²) ^a	20 ± 3	20 ± 2	.743
Chest X-ray findings			
Cavity formation (%) ^b	13 (40.6)	15 (46.8)	.801
Extensive lesions (%) ^b	3 (9.3)	4 (12.5)	1.00
No description (%) ^b	1 (3.1)	0 (0.0)	1.00

Abbreviation: BMI, body mass index; SD, standard deviation.

^aAn unpaired *t*-test was used to compare parametric data.

^bFisher's exact test was used to compare categorical data. Data are shown as mean ± SD or the number with its corresponding percentage.

3.2 | Diagnostic efficiency of LF and HSI

Among the 64 participants, no significant difference was observed in liquid culture positivity {79.6% [95% confidence interval (95% CI): 67.7–88.7] in the first sputum sample, 82.8% [95% CI: 71.3–91.0] in the sputum sample with LF and 85.9% [95% CI: 74.9–93.3] in sputum sample with HSI; $P = .440$ }, median time to detection [11.0 days (95% CI: 10.0–14.7)] of the first sputum sample [13.0 days (95% CI: 12.0–14.0)] in the sputa with LF and 12.5 days (95% CI: 10.5–14.0) in those with HSI; $P = .437$) and PCR positivity between the first sputum samples without induction [77.7% (95% CI: 64.4–87.9)] and those obtained using LF [79.6% (95% CI: 66.4–89.3)] and HSI [74.0% (95% CI: 60.3–85.0); $P = .600$].

In total, the first sputum sample of 35 patients was smear-negative for AFB. Among these, statistically significant AFB smear conversions (from negative to positive) were determined in both LF and HSI ($P = .003$, Cochran's *Q* test). The number of patients with smear conversion was 9 [25.7% (95% CI: 12.4–43.2), $P = .001$] for LF and 8 [22.8% (95% CI: 10.4–40.1), $P = .001$] for HSI (Figure 4). No significant difference was observed in the smear positive conversion rate between LF and HSI ($P = .738$, McNemer's test). The liquid culture positivity tended to be higher in the sputa induced by LF [71.4% (95% CI: 53.6–85.3)] and HSI [77.1% (95% CI: 59.8–89.5)] than in the sputa of the first samples [65.7% (95% CI: 47.7–80.8)] ($P = .284$) (Table 2). The median time to detection also tended to be shorter with LF [14.0 days (95% CI: 13.0–18.7)] and HSI [14.0 days (95% CI: 11.0–19.6)] compared with the first samples in this subgroup [17.0 days (95% CI: 12.0–20.5)] ($P = .798$) (Table 2). The sputum samples of 10 patients among 35 patients with smear-negative results were not prepared for nucleic acid amplification because their storage condition was inappropriate. Therefore, PCR was performed on 25 patients

among those with smear-negative results. PCR positivity tended to be higher in the samples obtained with LF [72.0% (95% CI: 50.0–87.9)], compared with those obtained with HSI [60.0% (95% CI: 38.6–78.8)] and those without sputum induction [60.0% (95% CI: 38.6–78.8)] ($P = .341$) (Table 2).

In the remaining 29 first sputum smear-positive patients out of 64 participants, no significant increase of smear positivity was observed by either LF or HSI ($P = .418$, Cochran's *Q* test). No significant difference was observed in

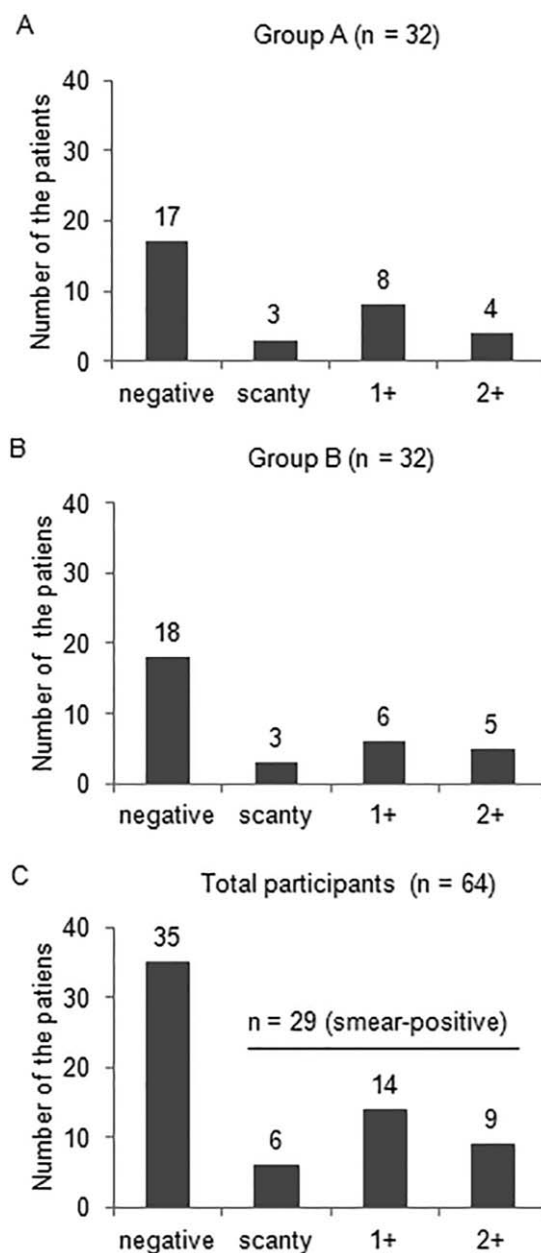


FIGURE 3 Acid-fast bacilli (AFB) smear positivity in spontaneously expectorated sputum. A, AFB smear positivity in group A (n = 32). B, AFB smear positivity in group B (n = 32). *The Mann-Whitney *U* test was used to compare the distribution of sputum smear positivity between groups A and B. C, Overall sputum acid-fast bacilli smear positivity (n = 64). Abbreviations: AFB, acid-fast bacilli

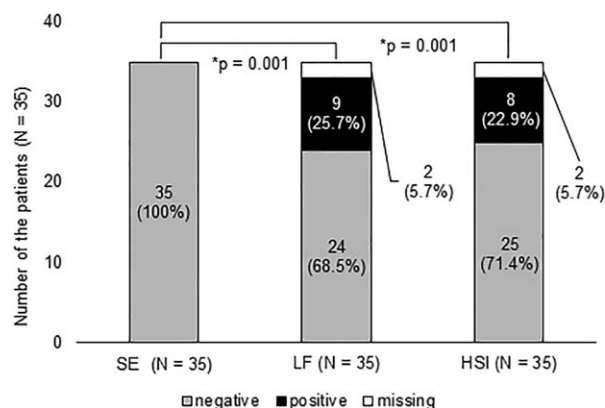


FIGURE 4 Changes in AFB smear results after sputum induction by Lung Flute and hypertonic saline inhalation compared with sputum without induction (in initial sputum AFB negative cases). *The McNemer's test was used to compare smear positivity between spontaneous expectoration and Lung Flute or hypertonic saline inhalation. Abbreviations: AFB, Acid-fast bacilli; HSI, hypertonic saline inhalation; LF, Lung Flute; SE, spontaneous expectoration

culture positivity, time to detection, or PCR positivity between the sputa with and without induction (Table 2).

3.3 | Adverse events with LF and HSI

We were able to obtain the information of adverse events from 63 out of the 64 total patients because the adverse event data of 1 patient were not recorded for an unknown reason. Thirty-two adverse events were recorded. LF tended to result in less throat discomfort and throat pain ($P = .248$ and $P = .057$, respectively) (Table 3). The proportion of cases in which SpO₂ decreased over 3% after the induction tended to be lower with LF (3.17% vs 11.1%, $P = .082$). The total number of adverse events was significantly lower in LF (10 events) than in HSI (22 events) ($P = .023$, Table 3).

4 | DISCUSSION

This study compared the performance of 2 sputum induction methods, LF and HSI. Our findings indicated that LF and

TABLE 2 Liquid culture yield, time to detection and PCR positive yield of the first sputum (no induction) of smear-negative and smear-positive patients

Spontaneously expectorated sputum smear-negative cases (n = 35)				
Culture positivity N (%)	SE (n = 35)	LF (n = 35)	HSI (n = 35)	*P value
	23 (65.7)	25 (71.4)	27 (77.1)	.284
Median time to detection days (95% CI)	SE (n = 21) ^a	LF (n = 23) ^a	HSI (n = 24) ^a	**P value
	17.0 (12.0–20.5)	14.0 (13.0–18.7)	14.0 (11.0–19.6)	.798
PCR positivity N (%)	SE (n = 25) ^b	LF (n = 25) ^b	HSI (n = 25) ^b	*P value
	15 (60.0)	18 (72.0)	15 (60.0)	.341
Spontaneously expectorated sputum smear-positive cases (n = 29)				
Culture positivity N (%)	SE (n = 29)	LF (n = 29)	HSI (n = 29)	*P value
	29 (100.0)	27 (93.1)	28 (96.5)	.418
Median time to detection days (95% CI)	SE (n = 26) ^a	LF (n = 25) ^a	HSI (n = 26) ^a	**P value
	8.5 (6.0–11.0)	12.0 (8.0–13.8)	10.5 (8.45–13.5)	.124
PCR positivity N (%)	SE (n = 29) ^b	LF (n = 29) ^b	HSI (n = 29) ^b	*P value
	27 (93.1)	25 (86.2)	19 (65.5)	.548

Abbreviations: HSI, hypertonic saline inhalation; LF, Lung Flute; PCR, polymerase chain reaction; SE, spontaneous expectoration; 95% CI, 95% confidence interval. Data are presented as number with the corresponding percentage and median (95% CI).

^aCochran's Q test.

^bKruskal–Wallis test were used for statistical analysis.

^aNumber of available cases for time to detection.

^bNumber of available polymerase chain reaction (PCR) samples.

TABLE 3 Frequency of adverse events by sputum induction method

Adverse events	LF (n = 63) ^a	HSI (n = 63) ^a	*P value
>3% decrease in SpO ₂	2 (3.1)	7 (11.1)	.082
Throat discomfort	0 (0.0)	2 (3.1)	.248
Throat pain	1 (1.5)	6 (9.5)	.057
Dyspnoea	2 (3.1)	2 (3.1)	.691
Wheezing	2 (3.1)	2 (3.1)	.691
Severe cough	2 (3.1)	3 (4.7)	.500
Numbness	1 (1.5)	0 (0.0)	.500
Total events	10 (15.8)	22 (34.9)	.023

Abbreviations: HSI, hypertonic saline inhalation; LF, Lung Flute.

^aNumber of available final data on adverse events.

*Fisher's exact test was used. All data are presented as a number with the corresponding percentage.

HSI contributed to the conversion of smear results from patients presumed of harbouring active pulmonary TB and whose first sample was AFB smear negative. We observed no statistically significant difference with regard to liquid culture positivity, time to detection, or positive PCR rate between LF and HSI. Therefore, our results demonstrated that both LF and HSI are similarly capable of inducing high-quality sputum samples. Hensler et al. first reported the feasibility and utility of HSI for obtaining sputum samples of adequate quality from patients with suspected pulmonary TB who were unable to expectorate sputum.⁶ Since that report was published, several studies have shown the benefits and tolerability of sputum induction with various concentrations of hypertonic saline.^{7,8} Therefore, HSI is currently regarded as a feasible method for promoting sputum expectoration. Because it is less invasive than gastric aspiration or bronchoscopy, HSI is also recommended for inducing high-quality sputum in young children.^{9,10} Additionally, several studies have shown the efficacy of HSI for diagnosing pulmonary TB, particularly in patients infected with HIV who are known to have paucibacillary sputum.^{11,12} Although HSI is simple, it requires sterile hypertonic saline and an electric ultrasonic humidifier, so it is difficult to perform in resource-limited settings.

In this study, the use of LF was simple and had a similar capability of inducing sputum compared with HSI. Several studies showed that LF can be an efficient method for obtaining appropriate sputum samples for the cytological and molecular analyses of early lung cancer detection.^{13,14} Furthermore, using LF helps ease the expectoration of sputum and ameliorates the symptoms of patients with chronic obstructive pulmonary disease.¹⁵ Our study demonstrated

that LF method tended to result in fewer cases of SpO₂ reduction and fewer throat-related adverse events than HSI. These findings suggest that the LF, like HSI, can be used to promote sputum expectoration in patients with presumed TB that may aid the diagnosis.

A limitation of our study is the small sample size, which precluded any conclusions about the statistical non-inferiority of LF compared with HSI in terms of sputum induction capacity. Another limitation was that the determination of the eligibility of participants who felt no immediate urge to expectorate sputum depended on their subjective statements. However, the induction process was normally introduced when the patient reported no immediate urge to expectorate sputum. Thus, the criterion was reasonably reliable in our estimation.

The findings in this study indicated that the LF method might generally be user-friendly and preferable above HSI. Usually, a disposable mouthpiece is used with HSI to prevent cross-contamination, and more attention should be paid to the possibility of contamination via other non-disposable parts of the ultrasonic nebuliser. In contrast, LF was designed for individual use and can, therefore, be kept free of cross-contamination. Moreover, because LF requires no external power source and is easily portable, it could serve as a practical method even for the patients living in remote areas with a limited power supply. Thus, we consider that LF could be a potential replacement of HSI.

5 | CONCLUSIONS

LF was useful for the induction of high-quality sputum to diagnose active pulmonary TB, had a similar efficacy to HSI and generally resulted in less adverse events. Although further studies will be required for a full performance evaluation of the LF, this device could be used as a sputum induction tool.

ACKNOWLEDGMENT

The authors thank Ms Fukuyo Ishido for her support in recording patient data. LF was kindly donated by Acoustic Innovations Co., Ltd.

CONFLICT OF INTEREST

The authors have explicitly stated that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study and performed data collection. All authors read and approved the final manuscript.

Performed the statistical analysis: Sakashita

Wrote the manuscript: Sakashita

Interpretation of results: Sakashita, Fujita, Mitarai

Drafted the final manuscript: Sakashita, Fujita, Mitarai

ETHICS

The institutional review boards of all 6 participating hospitals approved this study. This study was registered with University hospital Medical Information Network (UMIN) Clinical Trials Registry (CTR) on December 8, 2010, at Tokyo, Japan. The clinical trial registration number is UMIN000004676.

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How to cite this article: Sakashita K, Fujita A, Takamori M, et al. Efficiency of the Lung Flute for sputum induction in patients with presumed pulmonary tuberculosis. *Clin Respir J.* 2017;00:1–7. <https://doi.org/10.1111/crj.12697>