Pulmonary function of children with tracheomalacia and associated clinical factors

Wicharn Boonjindasup MD1,2,3 | Julie M. Marchant PhD3,4 | Margaret S. McElrea PhD3,4 | Stephanie T. Yerkovich PhD1,3 | Rahul J. Thomas MD3,4 | Ian B. Masters PhD3,4 | Anne B. Chang PhD1,3,4

1Menzies School of Health Research, Child Health Division, NHMRC Centre for Research Excellence in Paediatric Bronchiectasis (AusBREATHE), Charles Darwin University, Casuarina, Northern Territory, Australia
2Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
3Australian Centre for Health Services Innovation @ Centre for Healthcare Transformation, Queensland University of Technology, Brisbane, Queensland, Australia
4Department of Respiratory & Sleep Medicine, Queensland Children's Hospital, Brisbane, Queensland, Australia

Correspondence
Wicharn Boonjindasup, Australian Centre for Health Services Innovation @ Centre for Healthcare Transformation, Queensland University of Technology, 62 Graham St, South Brisbane, Brisbane, QLD 4101, Australia.
Email: elm.boonjindasup@menzies.edu.au

Abstract

Objective: Spirometry is easily accessible yet there is limited data in children with tracheomalacia. Availability of such data may inform clinical practice. We aimed to describe spirometry indices of children with tracheomalacia, including Empey index and flow-volume curve pattern, and determine whether these indices relate with bronchoscopic features.

Methods: From the database of children with tracheomalacia diagnosed during 2016–2019, we reviewed their flexible bronchoscopy and spirometry data in a blinded manner. We specially evaluated several spirometry indices and tracheomalacia features (cross-sectional lumen reduction, malacic length, and presence of bronchomalacia) and determined their association using multivariable regression.

Results: Of 53 children with tracheomalacia, the mean (SD) peak expiratory flow (PEF) was below the normal range [68.9 percent of predicted value (23.08)]. However, all other spirometry parameters were within normal range [Z-score forced expired volume in 1 s (FEV₁) = −1.18 (1.39), forced vital capacity (FVC) = −0.61 (1.46), forced expiratory flow between 25% and 75% of vital capacity (FEF25%–75%) = −1.43 (1.10), FEV₁/FVC = −1.04 (1.08)], Empey Index = 8.21 (1.59). The most common flow-volume curve pattern was the “knee” pattern (n = 39, 73.6%). Multivariable linear regression identified the presence of bronchomalacia was significantly associated with lower flows: FEV₁ [coefficient (95% CI) = −0.78 (−1.54, −0.02)], FEF25%–75% [−0.61 (−1.22, 0)], and PEF [−12.69 (−21.13, −4.25)], all p ≤ 0.05. Other bronchoscopic-defined tracheomalacia features examined (cross-sectional lumen reduction, malacic length) were not significantly associated with spirometry indices.

Conclusion: The “knee” pattern in spirometry flow-volume curve is common in children with tracheomalacia but other indices, including Empey index, cannot be used to characterize tracheomalacia. Spirometry indices were not significantly associated with bronchoscopic tracheomalacia features but children with tracheobronchomalacia have significantly lower flow than those with tracheomalacia alone.

Pediatric Pulmonology 2022;57:2437–2444. wileyonlinelibrary.com/journal/ppul

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. Pediatric Pulmonology published by Wiley Periodicals LLC.
1 | INTRODUCTION

Children with tracheomalacia (TM) have common respiratory symptoms (e.g., wheeze and cough)\(^1\) and are not uncommonly seen in pediatric pulmonology practice.\(^2\) TM in children is predominantly diagnosed on direct inspection using flexible bronchoscopy (FB). Although, the universal definition of TM in children remains controversial, TM is commonly defined as deformity in the shape of the trachea at end-expiration\(^3,4\) or a reduction of >50% in the tracheal cross-sectional lumen\(^2\) during spontaneous respiration.

There is limited data on the utility of pulmonary function tests (PFTs) in TM diagnosis and assessment. Previous pediatric TM studies revealed that abnormal spirometry parameters and flow-volume curve, that is, expiratory flow limitation and the “knee” pattern, may or may not be present.\(^5–10\) Another possible spirometry-derived indicator of TM may include the Empey Index \(\text{EI} = \text{ratio of forced expired volume in 1 s (FEV} _{1})\) to peak expiratory flow (PEF)\(^11\) which reflects upper airway obstruction.\(^11\) Other PFT abnormalities reported in children with TM included variations in tidal end-expiratory flow,\(^12\) maximum expiratory flow at functional residual capacity,\(^13–15\) ratio of forced to tidal flows at mid-tidal volume,\(^13\) thoracic gas volume,\(^14,16\) and pulmonary resistance.\(^14,16\) All the studies of complex PFTs were small and used a vague definition of TM; and some were undertaken in infants using chest squeeze. In addition, none of the studies evaluated whether PFTs indices related to bronchoscopic TM characteristics (e.g., severity). Due to this paucity of evidence, spirometry and other PFTs have not been considered an important diagnostic tool for TM\(^2\) despite their wide availability and the simplicity of testing.

Data on these spirometry indices may be useful in clinical practice as such data may help in both clinical assessment and our understanding of the condition. Thus, we examined various aspects of spirometry in children with TM and related their spirometry data to TM findings on FB. In children with TM, we aimed to (i) describe spirometry indices, including parameters and flow-volume curve pattern and the EI, and (ii) evaluate if any of these indices related to bronchoscopic TM features, including cross-sectional lumen reduction, malacic length, and bronchomalacia (BM) involvement. We hypothesized that (i) children with TM have identifiable spirometry including parameters lower than normal population range and the “knee” pattern flow-volume curve and (ii) there is an association between these spirometry parameters and bronchoscopic TM features. We also described the bronchoalveolar lavage (BAL) findings.

2 | METHODS

2.1 | Study population

Our retrospective cohort study was based on the databases of children who underwent FB and spirometry at Queensland Children’s Hospital during 2016–2019. We included all children diagnosed with TM by FB and had spirometry performed within 2 years. Exclusion criteria were (i) spirometry was unacceptable according to standard guidelines\(^17,18\); (ii) incomplete FB examination, that is, trachea and main bronchi not clearly and fully visualized; or (iii) the interval between FB and spirometry was >2 years. The Children’s Health Queensland Human Research Ethics Committee (EX/21/QCHQ/75855) approved the study and granted exemption.

2.2 | Data collection

Demographics and medical history were reviewed and extracted from electronic medical records including FB and spirometry data. The spirometry and FB data were reviewed by respiratory pediatricians who were blinded to all other data. At our center, FBs are performed during spontaneous breathing under general anesthesia, inserted through nasal cavity and digitally recorded using an Olympus video bronchoscope.\(^19\) TM is usually assessed while positive pressure ventilation is withheld. In addition, BAL is carried out for some patients as per international guidelines\(^20\) as is usual practice at our centre for cytology and microbiology.\(^21,22\)

The archived FB videos were examined by an experienced pediatric respiratory bronchoscopist (Ian B. Masters) to assess TM blinded to the child’s clinical details. TM characteristics, when present, were specifically examined for three features at quiet end-expiration by direct visual inspection. These were (i) cross-sectional lumen reduction severity (shape alteration with <50% reduction), mild (50%–75%), moderate (75%–90%), or severe (>90%) (Figure 1), (ii) extent (malacic length as one-third trachea or more than one-third by examining upper one-third, middle one-third, and/or lower one-third of the trachea), and (iii) presence of left and/or right mainstem BM, that is, tracheobronchomalacia (TBM). Due to lack of standard definition, we identified any reduction of cross-sectional bronchial lumen as presence of BM.

Our PFT laboratory undertakes spirometry according to standard guidelines,\(^17,18\) using a Jaeger Vantwort Pneumo spirometer. The spirometry records extracted were FEV\(_1\), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity (FEF\(_{25–75}\)), ratio of FEV\(_1\) to FVC (FEV\(_1\)/FVC), PEF, EI, bronchodilator reversibility, and flow-volume curve pattern. FEV\(_1\), FVC, FEF\(_{25–75}\) and FEV\(_1\)/FVC percent of predicted value and z-score were calculated using Global Lung Function Initiative reference data.\(^23\) PEF was calculated for percent of predicted value using an Australian-based reference equation.\(^24\) The flow volume curves were examined independently by two respiratory pediatricians (W. B. and A. B. C.) to identify the pattern as the “knee” or others. The “knee” pattern was characterized by an expiratory plateau or gradually decreasing slope followed by a convex inflection\(^25,26\) (Figure 2). Any disagreement was discussed and resolved by consensus.
Baseline data were presented as means and standard deviation (SD) or medians and interquartile range (IQR), depending on normality of the data distribution. Univariable and multivariable linear regression were performed to assess whether TM clinical factors were associated with any of the spirometry parameters. The clinical factors were age, cross-sectional lumen reduction (any-to-mild TM vs. moderate-to-severe TM), malacic length (one-third trachea vs. longer than one-third) and BM involvement (TM vs. TBM). Stata/SE 15.1 (StatCorp) was used for statistical analysis. A two-tailed \( p < 0.05 \) was considered statistically significant.

### RESULTS

Of the 2169 children in the FB database during 2016–2019, 505 children were diagnosed with TM. Of these, only 76 children had acceptable spirometry (primarily due to age as most children were too young to undertake spirometry). We further excluded nine children whose FB video recordings were incomplete and 14 children who had spirometry >2 years of their FB. Thus, 53 children with both TM and spirometry values were included in the final analysis.

The characteristics of the 53 children with TM are presented in Table 1. The median interval between FB and spirometry was 61 days (IQR 31–317); approximately two-thirds of the children had spirometry and FB performed within 6 months and 80% of the...
Children had both within the same year. Brassy cough was the most characteristic cough quality. The most common respiratory comorbidity was chronic suppurative lung disease (CSLD), including protracted bacterial bronchitis and bronchiectasis. There were 8 (15.1%) children who had no other respiratory problems than TM or TBM. There were 23 (43.4%) child who had more than one respiratory comorbidity: 8 (15.1%) children with asthma and CSLD, 1 (1.9%) child with asthma and congenital cardiovascular anomaly, 3 (5.7%) child with CSLD and trachea–esophageal fistula, 3 (5.7%) children with CSLD and congenital cardiovascular anomaly, 1 (1.9%) child with CSLD and laryngomalacia, 2 (3.8%) children with CSLF and chronic rhinosinusitis, 4 (15.1%) children with asthma, CSLD, and trachea–esophageal fistula, and 1 (1.9%) child with CSLD, congenital cardiovascular anomaly, laryngomalacia, and vocal cord palsy. FB assessment (Table 1) found, 12 (22.6%) children had moderate-to-severe TM, 15 (28.3%) had more than one-third malacic tracheal segments, while 21 (39.6%) had TBM.

### TABLE 1 Characteristics of children with TM

| Demographics | N = 53 |
|--------------|--------|
| **Sex, n (%)** |        |
| Male         | 30 (56.6%) |
| Female       | 23 (43.4%) |
| **Age in years, median (IQR)** | 7.58 (5.78–10.17) |
| **Anthropometry, median (IQR)** |        |
| Weight (kg)  | 26 (21.2–38.2) |
| Height (cm)  | 124.2 (113–143.9) |
| **Cough quality, n (%)** |        |
| Brassy       | 36 (67.9%) |
| Wet          | 8 (15.1%)  |
| Dry          | 5 (9.4%)   |
| Variable     | 4 (7.6%)   |
| **Respiratory comorbidities, n (%)** |        |
| Protracted bacterial bronchitis | 16 (30.2%) |
| Bronchiectasis unrelated to cystic fibrosis | 14 (26.4%) |
| Asthma       | 14 (26.4%) |
| Tracheoesophageal fistula | 12 (22.6%) |
| CF bronchiectasis | 6 (11.3%) |
| Congenital cardiac/vascular anomalies | 6 (11.3%) |
| Chronic rhinosinusitis | 2 (3.8%) |
| Laryngomalacia | 2 (3.8%) |
| Subglottic or tracheal stenosis | 1 (1.9%) |
| Vocal cord palsy | 1 (1.9%) |

| Flexible bronchoscopy |        |
| Tracheomalacia severity, n (%) |        |
| Up to 50% narrowing | 5 (9.4%) |
| 50%–75% narrowing | 36 (67.9%) |
| 75%–90% narrowing | 11 (20.8%) |
| More than 90% narrowing | 1 (1.9%) |
| Tracheomalacia segments, n (%) |        |
| Upper 1/3 | 2 (3.8%) |
| Middle 1/3 | 13 (24.5%) |
| Lower 1/3 | 22 (41.5%) |
| Upper + middle | 2 (3.8%) |
| Middle + lower | 11 (20.8%) |
| All | 3 (5.7%) |
| Bronchomalacia segments, n (%) |        |
| Right mainstem | 1 (1.9%) |
| Left mainstem | 16 (30.2%) |
| Both | 4 (7.5%) |

| Spirometry |        |
| Parameters, mean (SD) |        |
| FEV₁ Z-score | −1.18 (1.39) |
| FEV₁ percent of predicted value | 85.26 (17.34) |
| FVC Z-score | −0.61 (1.46) |
| FVC percent of predicted value | 92.85 (17.61) |
| FEF₂₅₋₇₅ Z-score | −1.43 (1.10) |
| FEF₂₅₋₇₅ percent of predicted value | 68.78 (23.08) |
| FEV₁/FVC | 0.82 (0.08) |
| FEV₁/FVC Z-score | −1.04 (1.08) |
| PEF percent of predicted value | 62.95 (16.23) |
| Empey Index | 8.21 (1.59) |
| Flow-volume curve pattern, n (%) |        |
| Knee | 39 (73.6%) |
| Others (normal, scooping, restrictive, mixed) | 14 (26.4%) |
| Bronchodilator reversibility, n (%) |        |
| Not done | 43 (81.1%) |
| Significant response | 4 (7.6%) |
| No significant response | 6 (11.3%) |

Note: Forced expiratory volume in first second (FEV₁), forced vital capacity (FVC) and forced expiratory flow between 25% and 75% of vital capacity (FEF₂₅₋₇₅%) percent of predicted value and Z-score were calculated using Global Lung Function Initiative reference data.²³
Abbreviations: CF, cystic fibrosis; IQR, interquartile range; PEF, peak expiratory flow; TM, tracheomalacia.

²Increase of FEV₁ or FVC more than 12% and/or 0.2 L.¹⁷,¹⁸
Spirometry indices of children with TM in this study are also presented in Table 1. The majority of the children with TM in this study (73.6%) had flow-volume curves showing the “knee” pattern (Figure 2). Mean values for all key spirometry parameters were within normal population range, except for low PEF percent of predicted value (<80%). Despite normal mean values, 17 (32.1%) children had abnormally low FEV₁ of z-score < −1.64, 13 (24.5%) had FVC z-score < −1.64, 22 (41.5%) had FEF₂₅%–₇₅% z-score < −1.64, and 18 (34%) had FEV₁/FVC z-score < −1.64. Only 28 (52.8%) had EI > 8 and 6 (11.3%) had EI > 10.

The associations between spirometry parameters and TM features are presented in Table 2. Using univariable linear regression, only the presence of BM was associated with FEV₁, FEF, and PEF. Neither age, lumen reduction nor malacic length were associated with any of the spirometry parameters investigated. When TBM was corrected for these factors, the presence of TBM was significantly associated with lower FEV₁, FEF, and PEF, but not EI or FEV₁/FVC.

There was no significant association between any of the spirometry parameters with BAL airway neutrophilia (r range −0.00–0.02; all p > 0.05) or the presence of bacteria (r range −0.14 to 0.05; all p > 0.05). Other BAL data of the children with TM are presented and discussed in the Supporting Information.

4 | DISCUSSION

We evaluated several common and rarely reported spirometry-derived indices of 53 children with TM identified over a 4-year period. We found that the “knee” pattern was the most common pattern of spirometry flow-volume curve. We also found that PEF percent of predicted value was below population norms but other spirometry parameters including EI were within the population range. Among the TM features assessed, the presence of mainstem BM was significantly associated with lower FEV₁, FEF₂₅%–₇₅%, and PEF compared to TM alone. There were no significant associations between other TM features and the spirometry parameters.

Although spirometry is widely available, there is a relative paucity of data on spirometry characteristics in children with TM. Hence our findings significantly add to the currently sparse data, including rarely reported spirometry-derived indices like EI and flow-volume curve pattern. Further, this is the first study to evaluate the association of bronchoscopically-defined TM features with spirometry indices. We included any(TM) (shape alteration with ≤50% reduction in cross-sectional lumen), as opposed to using the ERS definition (>50% reduction)2 to improve generalizability. Another strength of our small study is the blinded nature of the data reviewed.

The “knee” pattern of flow-volume curve was the most common pattern in our cohort of children with TM. The pattern is presumed to be airflow limitation due to excessive airway collapse and then sudden airflow decrease, resulting in the flatter slope and then convexity shown on the expiratory limb of flow-volume curve.27,28 Unfortunately, the “knee” pattern has been infrequently studied in pediatric TM.6,10 While we found approximately three quarters of children with TM showed the “knee” pattern, it was reported in only 4 of 19 children (22%) in a previous study.6 The prevalence of the “knee” pattern in children with TM suggests that the presence of the “knee” provides supportive diagnosis of TM, although its sensitivity and specificity need to be evaluated before it can be confidently utilized in clinical practice.

Our findings of normal FEV₁, FVC, and FEV₁/FVC in children with TM were consistent with most previous studies. The largest pediatric TM study of 115 children but only 45 children had spirometry undertaken,9 and the study reported normal FEV₁, FVC, and FEV₁/FVC but a slight reduction in PEF (mean 74.7% SD 19.4). In another study of pulmonary function on long-term follow up, FEV₁ and FVC were within normal population range, while FEF₂₅%–₇₅% (mean 54% SD 15) and PEF (mean 60% SD 14) were low.6 Only small case series of children with TM reported low values and showed an improvement of FEV₁ and FEF₂₅%–₇₅% following aortopexy.

Our cohort did not have an increased EI suggesting it is unlikely to be useful in clinical practice for diagnosing TM. We examined EI as it is a simple parameter to calculate from spirometry and an elevated EI (ratio >10) may indicate an upper airway obstruction.11 The cut-off of 10 was observed in children with various upper airway obstructions, including tracheal stenosis, vocal cord dysfunction, subglottic stenosis, TM/TBM and persisting laryngomalacia, and revealed sensitivity 93% and specificity 41%.29 However, a small study found that children born with esophageal atresia and TM had EI > 8.7 and the ratio > 8 significantly correlated with respiratory symptoms but the ratio > 10 did not.7 This may explain why using the traditional cut-off of >10 we did not find a significant relationship between EI and TM in our cohort.

Our multivariable model was used to assess whether certain features of TM are associated with altered spirometric values, and included age (as it is believed that TM improves spontaneously with growth),30 cross-sectional lumen reduction, malacic length and BM involvement (as these could contribute to increased airway resistance). We found that the presence of any mainstem BM was significantly associated with lower airflow values (FEV₁, FEF₂₅%–₇₅%, and EI). This could be simply explained by the addition of choke point during forced expiration, with BM acting as another choke point and effectively resulting in a series of airway resistors. As the magnitude of airflow is inversely relates to resistance, we speculate an increase in total resistance in TBM to be the mechanism for greater decreasing airflow.

Theoretically, increased cross-sectional lumen reduction and longer malacic length should result in higher resistance and lower airflows but we did not find any significant association between these features of TM severity with spirometry parameters. Reasons for this can only be speculated. Possible reason includes spirometry being performed by forced expiratory maneuver which generally generates turbulent airflow, while bronchoscopic TM characteristics were assessed during quiet respiration under anesthesia. With the increase of flow velocity and turbulent airflow, increased airway resistance, as well as expiratory flow limitation, is difficult to predict and could be
| Table 2 | The association between TM clinical factors and spirometry parameters |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                          | FEV₁ z-score             | FVC z-score              | FEF₂₅%–₇₅% z-score        | FEV₁/FVC z-score         | PEF percent of predicted value | Empey Index |
|                          | Coefficient (95% CI)     | Coefficient (95% CI)     | Coefficient (95% CI)      | Coefficient (95% CI)     | Coefficient (95% CI)          | Coefficient (95% CI)     | Coefficient (95% CI)     | Coefficient (95% CI)     |
| Univariable regression analysis |                        |                          |                          |                          |                                      |                          |                          |                          |
| Age                      | -0.06 (-0.19, 0.07)      | 0.33                     | -0.10 (-0.23, 0.04)      | 0.15                     | 0.01 (-0.09, 0.12)               | 0.77                     | 0.04 (-0.06, 0.14)      | 0.41                     | 1.38 (-0.09, 2.85)      | 0.07                     | 0.06 (-0.09, 0.21)      | 0.41                     |
| Lumen reductiona          | -0.72 (-1.62, 0.18)      | 0.11                     | -0.73 (-1.68, 0.21)      | 0.13                     | -0.54 (-1.26, 0.18)             | 0.14                     | -0.17 (-0.89, 0.55)    | 0.64                     | -3.73 (-14.47, 7.01)   | 0.49                     | -0.37 (-1.42, 0.69)    | 0.49                     |
| TM lengthb               | -0.36 (-1.19, 0.48)      | 0.39                     | -0.29 (-1.17, 0.59)      | 0.51                     | -0.22 (-0.88, 0.45)            | 0.52                     | -0.13 (-0.79, 0.53)    | 0.69                     | -2.57 (-12.39, 7.25)   | 0.6                      | 0.28 (-0.69, 1.24)     | 0.57                     |
| BM present               | -0.72 (-1.49, 0.04)      | 0.06                     | -0.58 (-1.39, 0.24)      | 0.16                     | -0.58 (-1.18, 0.03)            | 0.06                     | -0.25 (-0.86, 0.37)    | 0.42                     | -12.87 (-21.37, -4.37) | <0.01                    | 0.49 (-0.40, 1.39)     | 0.28                     |
| Multivariable regression analysis |                        |                          |                          |                          |                                      |                          |                          |                          |
| Age                      | -0.07 (-0.20, 0.05)      | 0.26                     | -0.11 (-0.24, 0.03)      | 0.11                     | 0.01 (-0.09, 0.11)              | 0.86                     | 0.04 (-0.06, 0.15)     | 0.43                     | 1.30 (-0.09, 2.70)     | 0.07                     | 0.06 (-0.09, 0.21)      | 0.45                     |
| Lumen reductiona          | -0.78 (-1.69, 0.13)      | 0.09                     | -0.81 (-1.77, 0.15)      | 0.1                      | -0.57 (-1.30, 0.16)             | 0.13                     | -0.15 (-0.91, 0.61)    | 0.69                     | -3.95 (-14.09, 6.19)   | 0.44                     | -0.39 (-1.49, 0.71)    | 0.48                     |
| TM lengthb               | -0.10 (-0.93, 0.74)      | 0.82                     | 0.00 (-0.88, 0.88)       | 1                       | -0.07 (-0.74, 0.61)             | 0.85                     | -0.11 (-0.81, 0.58)    | 0.74                     | -1.90 (-11.18, 7.39)   | 0.68                     | 0.29 (-0.72, 1.30)     | 0.56                     |
| BM present               | -0.78 (-1.54, -0.02)     | 0.04                     | -0.65 (-1.45, 0.15)      | 0.11                     | -0.61 (-1.22, 0.00)            | 0.05                     | -0.22 (-0.87, 0.39)    | 0.48                     | -12.69 (-21.13, -4.25) | <0.01                    | 0.47 (-0.45, 1.39)     | 0.31                     |

Note: Bold = significant association between the spirometry parameter and the TM feature.
Abbreviations: BM, bronchomalacia; FEF₂₅%–₇₅%, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; TM, tracheomalacia.

aLumen reduction was categorized by cross-sectional area change as any-to-mild (up to 75% reduction) and moderate to severe (more than 75%).
bTM length was categorized by the extent of malacic tracheal segment as one-third trachea or more than one-third.
found irrespective of TM findings on FB. Another possible reason is the impact of sedation on glottic motion. Children with TM are able to generate auto-positive end expiratory pressure PEEP (with glottic closure to presumably raise lung volume and increase expiratory flow.\textsuperscript{15,31} During sedation, there is clearly decrease in muscle tone of the upper airway, so the ability to generate auto-PEEP is lost which could result in different magnitude of tracheal alteration compared to fully awake state. The absence of the relationship may also relate to our small sample size but it may also partially explain the lack of relationship between clinical features and TM severity.\textsuperscript{2,32} Nevertheless, a clinical study which found no association between malacia type and severity of lesions (objectively measured) with respiratory illness profile\textsuperscript{32} somewhat supports our finding.

Despite our several novel findings, our study has several limitations. As noted above, our sample size was small. Although TBM in this study was assessed by a single expert's visual inspection, the assessment is still relatively subjective as it was not measured. A recent study reported that there was poor inter-rater agreement among respiratory pediatricians on the presence and severity of TBM assessed by FB.\textsuperscript{33} Also, the spirometry and FB were not undertaken concurrently and this may have influenced our findings as TM characteristics change with age and concurrent illness, that is, tracheobronchial infection or inflammation.\textsuperscript{3} However, in the sole prospective FB-defined TM study in children where the cross-sectional lumen was objectively measured twice, in 60% of children the malacic area increased while the remainder decreased or were unchanged.\textsuperscript{3} Hence, while TM characteristics change with age, the severity does not always improve and our findings would remain valid despite the timing of spirometry and FB.

5 | CONCLUSION

In children with TM, PEF was slightly low, while other spirometry parameters including EI were either normal or equivocal. The “knee” pattern in spirometry flow-volume curves was found in the majority of, but not all, children. The presence of BM along with TM was significantly associated with lower FEV1, FEF\textsubscript{25-75} and PEF. These spirometry characteristics may aid clinicians in recognizing TM in children but more evidence is needed to confirm our findings. A prospective study of children with TM to precisely determine their pulmonary function at the time of FB, as well as its changes over time, is required.

AUTHOR CONTRIBUTIONS
Anne B. Chang and Wicharn Boonjindasup contributed to the study conception and design. Ian B. Masters, Anne B. Chang, Wicharn Boonjindasup and Rahul J. Thomas undertook investigation. Material preparation, data curation, and formal analysis were performed by Wicharn Boonjindasup under Anne B. Chang, Julie M. Marchant, Margaret S. McElrea and Stephanie T. Yerkovich supervision. Wicharn Boonjindasup wrote the first draft of the manuscript. All the authors were involved in preparation of manuscript, reviewed and approved the final manuscript.

ACKNOWLEDGMENTS
We sincerely thank the respiratory scientists of Queensland Children's Hospital and the staff of Cough & Airway Research Group of Australian Centre for Health Services Innovation for supporting this study. W. B. is supported by a Charles Darwin University PhD scholarship. A. B. C. is supported by an Australian National Health and Medical Research Council (NHMRC) Practitioner Fellowship (APP1058213) and a top-up fellowship from the Children's Hospital Foundation (Grant 50286). J. M. M. is supported by an Early Career Fellowship Grant from Queensland Children's Hospital Foundation (RPC0772019) and the Australian NHMRC Centre for Research Excellence in Paediatric Bronchiectasis. This study was not funded. Open access publishing facilitated by Charles Darwin University, as part of the Wiley - Charles Darwin University agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Wicharn Boonjindasup https://orcid.org/0000-0003-2942-9380

REFERENCES
1. Masters IB, Chang AB, Patterson L, et al. Series of laryngomalacia, tracheomalacia, and bronchomalacia disorders and their associations with other conditions in children. Pediatr Pulmonol. 2002;34:189-195.
2. Wallis C, Alexopoulou E, Antón-Pacheco JL, et al. ERS statement on tracheomalacia and bronchomalacia in children. Eur Respir J. 2019;54:1900382.
3. Masters IB, Zimmerman PV, Chang AB. Longitudinal quantification of growth and changes in primary tracheobronchomalacia sites in children. Pediatr Pulmonol. 2007;42:906-913.
4. Su SC, Masters IB, Buntain H, et al. A comparison of virtual bronchoscopy versus flexible bronchoscopy in the diagnosis of tracheobronchomalacia in children. Pediatr Pulmonol. 2017;52:480-486.
5. Boogaard R, Huijmsans SH, Pijnenburg MWH, Tiddens HAWM, de Jongste JC, Merkus PJFM. Tracheomalacia and bronchomalacia in children: incidence and patient characteristics. Chest. 2005;128:3391-3397.
6. Moore P, Smith H, Greer RM, McElrea M, Masters IB. Pulmonary function and long-term follow-up of children with tracheobronchomalacia. Pediatr Pulmonol. 2012;47:700-705.
7. Olbers J, Gatzinsky V, Jönsson L, et al. Physiological studies at 7 years of age in children born with esophageal atresia. Eur J Pediatr Surg. 2015;25:397-404.
8. Shell R, Allen E, Mutabagani K, et al. Compression of the trachea by the innominate artery in a 2-month-old child. Pediatr Pulmonol. 2001;31:80-85.
9. Weber TR, Keller MS, Fiore A. Aortic suspension (aortopexy) for severe tracheomalacia in infants and children. Am J Surg. 2002;184:573-577.
10. Uchida DA. Late presentation of double aortic arch in school-age children presumed to have asthma: the benefits of spirometry and examination of the flow-volume curve. *Respir Care*. 2009;54:1402-1404.

11. Empey DW. Assessment of upper airways obstruction. *Br Med J*. 1972;3:503-505.

12. Abdel-Rahman U, Simon A, Ahrens P, Heller K, Moritz A, Fieguth HG. Aortopexy in infants and children—long-term follow-up in twenty patients. *World J Surg*. 2007;31:2255-2259.

13. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schidlow DV. *Dx* of secondary tracheomalacia in children presumed to have asthma: the benefits of spirometry and examination of the flow-volume curve. *Respir Care*. 2009;54:1402-1404.

14. Beardsmore CS, MacFadyen UM, Johnstone MS, Williams A, Simpson H. Clinical findings and respiratory function in infants with tracheomalacia. *Ann Thorac Surg*. 1990;9:170-176.

15. Davis S, Jones M, Kisling J, Angelicchio C, Tepper RS. Effect of continuous positive airway pressure on forced expiratory flows in infants with tracheomalacia. *Am J Respir Crit Care Med*. 1998;158:148-152.

16. Johnston MR, Loeber N, Hillyer P, Stephenson LW, Edmunds LH, Jr. External stent for repair of secondary tracheomalacia. *Ann Thorac Surg*. 1980;30:291-296.

17. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.

18. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med*. 2019;200:e70-e88.

19. Masters IB, Chang AB. Tracheobronchomalacia in children. *Expert Rev Respir Med*. 2009;3:425-439.

20. de Blieck J, Midulla F, Barbato A, et al. Bronchoalveolar lavage in children. ERS Task Force on bronchoalveolar lavage in children. *European Respiratory Society*. *Eur Respir J*. 2000;15:217-231.

21. Chang AB, Faoagali J, Cox NC, et al. A bronchoscopic scoring system for airway secretions—airway cellularity and microbiological validation. *Pediatr Pulmonol*. 2006;41:887-892.

22. Wurzel DF, Marchant JM, Clark JE, et al. Wet cough in children: infective and inflammatory characteristics in broncho-alveolar lavage fluid. *Pediatr Pulmonol*. 2014;49:561-568.

23. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324-1343.

24. Hibbert ME, Lannigan A, Landau LI, Phelan PD. Lung function values from a longitudinal study of healthy children and adolescents. *Pediatr Pulmonol*. 1989;7:101-109.

25. Shin HH, Sears MR, Hancox RJ. Prevalence and correlates of a ‘knee’ pattern on the maximal expiratory flow-volume loop in young adults. *Respirology*. 2014;19:1052-1058.

26. Altalag A, Road J, Wilcox P, Aboulhosn K. Spirometry. In: Altalag A, Road J, Wilcox P, Aboulhosn K, eds. *Pulmonary Function Tests in Clinical Practice*. 2nd ed. Springer International Publishing; 2019:1-38.

27. Mead J. Expiratory flow limitation: a physiologist’s point of view. *Fed Proc*. 1980;39:2771-2775.

28. Lunn WW, Sheller JR. Flow volume loops in the evaluation of upper airway obstruction. *Otolaryngol Clin North Am*. 1995;28:721-729.

29. Coates A, Gauld L. The empey index predicts upper airway obstruction in children [abstract]. *Respirology*. 2019;24:4-12.

30. McNamara VM, Crabbe DC. Tracheomalacia. *Paediatr Respir Rev*. 2004;5:147-154.

31. Gunatilaka CC, Hysinger EB, Schuh A, et al. Neonates with tracheomalacia generate auto-positive end-expiratory pressure via glottis closure. *Chest*. 2021;160:2168-2177.

32. Masters IB, Zimmerman PV, Pandeya N, Petsky HL, Wilson SB, Chang AB. Quantified tracheobronchomalacia disorders and their clinical profiles in children. *Chest*. 2008;133:461-467.

33. Burg G, Hossain MM, Wood R, Hysinger EB. Evaluation of agreement on presence and severity of tracheobronchomalacia by dynamic flexible bronchoscopy. *Ann Am Thorac Soc*. 2021;18:1749-1752.

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Boonjindasup W, Marchant JM, McElrea MS, et al. Pulmonary function of children with tracheomalacia and associated clinical factors. *Pediatric Pulmonology*. 2022;57:2437-2444. doi:10.1002/ppul.26054