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Pulmonary function of children with tracheomalacia and associated clinical factors

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Abstract

Objectives: 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 (FEV_1) = −1.18 (1.39), forced vital capacity (FVC) = −0.61 (1.46), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25\%-75\%}$) = −1.43 (1.10), FEV_1/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: FEV_1 [coefficient (95% CI) −0.78 (−1.54, −0.02)], $FEF_{25\%-75\%}$ [−0.61 (−1.22, 0)], and PEF [−12.69 (−21.13, −4.25)], all $p \le 0.05$. 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.

KEYWORDS
child, lung function test, respiratory, spirometry, tracheomalacia

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 [EI = ratio of forced expired volume in 1 s (FEV_1) to peak expiratory flow (PEF)] 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] 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) evaluated 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 Vyntus 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.

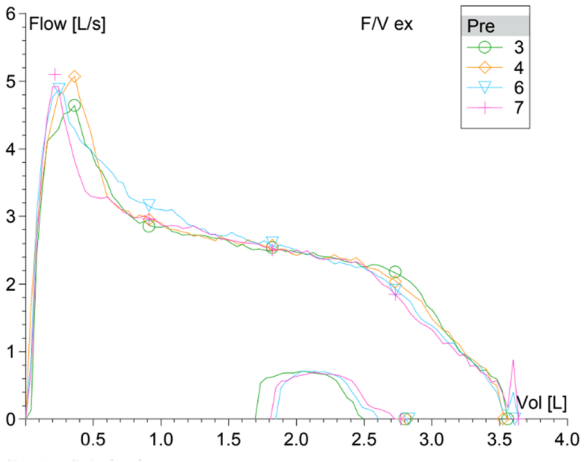

FIGURE 1 The "knee" pattern on expiratory limb of spirometry flow-volume curve

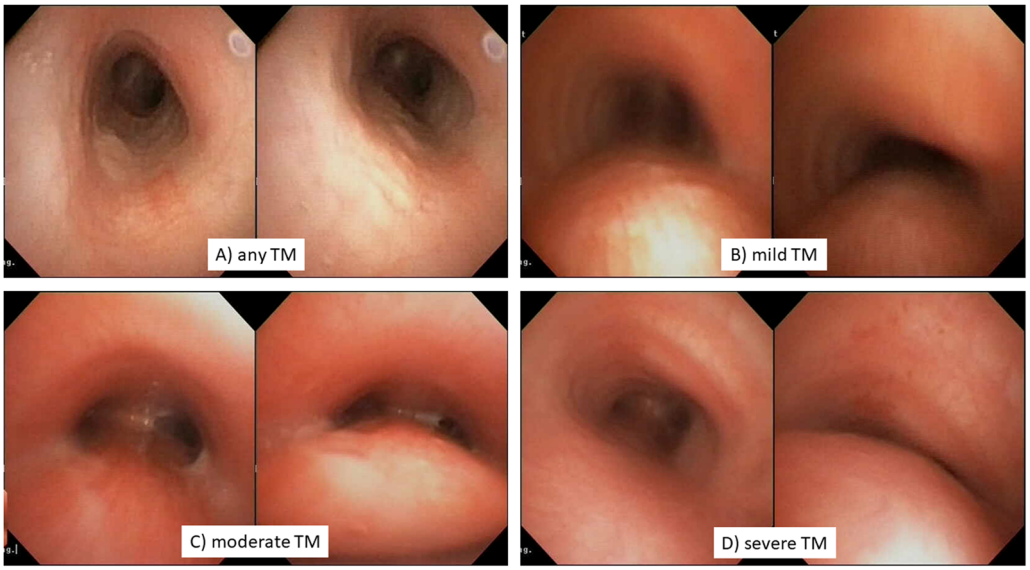

FIGURE 2 Cross-sectional tracheal lumen reduction severity in this study: (A) any tracheomalacia (TM) = shape alteration with <50% reduction, (B) mild TM = 50%–75%, (C) moderate TM = 75%–90%, and (D) severe TM ≥ 90%.

2.3 | Statistical analysis

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.

3 | 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

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)	
FEV_1 *Z*-score	−1.18 (1.39)
FEV_1 percent of predicted value	85.26 (17.34)
FVC *Z*-score	−0.61 (1.46)
FVC percent of predicted value	92.85 (17.61)
$FEF_{25\%-75\%}$ *Z*-score	−1.43 (1.10)
$FEF_{25\%-75\%}$ percent of predicted value	68.78 (23.08)
FEV_1/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[a]	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 ($FEF_{25\%-75\%}$) 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.

[a]Increase of FEV_1 or FVC more than 12% and/or 0.2 L.[17,18]

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.

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%).[24] Despite normal mean values, 17 (32.1%) children had abnormally low FEV_1 of *z*-score < −1.64, 13 (24.5%) had FVC z-score < −1.64, 22 (41.5%) had $FEF_{25\%-75\%}$ *z*-score < −1.64, and 18 (34%) had FEV_1/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 FEV_1, 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 FEV_1, FEF, and PEF, but not EI or FEV_1/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 FEV_1, $FEF_{25\%-75\%}$, 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 FEV_1, FVC, and FEV_1/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,[5] and the study reported normal FEV_1, FVC, and FEV_1/FVC but a slight reduction in PEF (mean 74.7% SD 19.4). In another study of pulmonary function on long-term follow up, FEV_1 and FVC were within normal population range, while $FEF_{25\%-75\%}$ (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 FEV_1[9] and $FEF_{25\%-75\%}$[8] 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 (FEV_1, $FEF_{25\%-75\%}$, 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

	FEV_1 z-score		FVC z-score		$FEF_{25\%-75\%}$ z-score		FEV_1/FVC z-score		PEF percent of predicted value		Empey Index	
	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*	Coefficient (95% CI)	*p*
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 reduction[a]	−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 length[b]	−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 reduction[a]	−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 length[b]	−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; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75%; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; TM, tracheomalacia.

[a]Lumen reduction was categorized by cross-sectional area change as any-to-mild (up to 75% reduction) and moderate to severe (more than 75%).

[b]TM 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 generate auto-positive end expiratory pressure PEEP) with glottic closure to presumably raise lung volume and increase expiratory flow.[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.[2,32] Nevertheless, a clinical study which found no association between malacia type and severity of lesions (objectively measured) with respiratory illness profile[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.[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.[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.[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, $FEF_{25\%-75\%}$, 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. Changand 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.

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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.

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SUPPORTING INFORMATION

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

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