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Original Article

Laryngotracheobronchial anomalies in infants and the related risk factors of in-hospital mortality

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Abstract

Background: Laryngotracheobronchial anomalies (LTBAs) may cause respiratory problems during early childhood, and increase the risk of hospitalization or mortality in diseased children. This study investigated the initial hospitalization age and risk factors for in-hospital mortality in infants diagnosed with LTBAs during their first 5 years of life.
Methods: Hospitalized infants diagnosed with LTBAs were retrieved from Taiwan's National Health Insurance Research Database from 2003 to 2005. Their medical claim data were traced up to 59 months of age. The age distribution of all LTBA cases was analyzed, and then the enrolled infants were grouped into two age groups. Hospitalization-related comorbidities and risk factors for in-hospital mortality were also analyzed.
Results: A total of 1272 LTBA cases were retrieved. Most of them (976, 76.7%) were initially hospitalized at an age of 0–3 months, and 47 infants (3.7%) died. These enrolled cases were grouped into early and late LTBA groups, with ages of 0–3 months and 4–11 months, respectively. Patients in the late LTBA group had significantly more acute airway infections/asthma and neurological diseases, more frequent hospitalizations, longer hospitalization stay, and higher in-hospital mortality than did the early LTBA group ($p < 0.001$). The adjusted odds ratios (aORs) for in-hospital mortality were significantly higher in the children aged 4–11 months [aOR = 2.50, 95% confidence intervals (CI): 1.36–4.60], or having perinatal disease (aOR = 2.00, 95% CI: 1.07–3.73), cardiovascular disease (aOR = 2.45, 95% CI: 1.30–4.60), other congenital anomalies (aOR = 2.42, 95% CI: 1.28–4.60), and neurological diseases (aOR = 2.32, 95% CI: 1.18–4.53).
Conclusion: Most infants with LTBAs were initially diagnosed and hospitalized when they were aged 3 months or younger. The risk factors for in-hospital mortality of the children with LTBAs included being diagnosed and treated at an age of 4 months and older, and the presence of perinatal disease, cardiovascular anomalies, other congenital anomalies, neurological diseases, and an age of 4 months and older.

Keywords: airway anomaly; airway malacia; hospitalization; infant; in-hospital mortality

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Laryngotracheobronchial anomalies (LTBAs) may cause different degrees of respiratory problems which are usually more severe when patients are younger, due to their narrower sizes of airways. These patients may suffer from respiratory distress and airway infections, and require frequent hospitalizations, especially in severe cases. The life quality and growth of the diseased children can be influenced, and the family's burden can be increased. Sometimes, it is a challenge for pediatricians to take care of infants with severe LTBAs. Since LTBAs are not rare among children with pulmonary diseases, an investigation of their hospitalization features and risk factors of mortality during early childhood is important for future care.

LTBAs are heterogeneous diseases including absence, atresia, stenosis and diverticulum of the airway, cartilage anomalies, congenital cleft thyroid and cartilage, laryngocele, and congenital laryngeal stridor.[1−3] Vocal cord paralysis, congenital anomalies of large vessels and abnormalities of the central nervous system may present similar symptoms, and should be taken into differential diagnosis. In mild forms of LTBAs, the symptoms are usually mild and self-limiting by the age of 2 years. Hospitalization is required for patients with comorbidities and other medical conditions including airway infections, other congenital anomalies, gastroesophageal or laryngopharyngeal reflux, and central nervous system diseases.[4−11] Although most patients are diagnosed during early months of life, some are diagnosed during later infancy or childhood.[6,12,13] Different clinical presentations and disease courses between those diagnosed at early or late infancy periods have been investigated.[11] Most reported studies on children's LTBAs have focused on airway malacia, the most common type of LTBAs, and most of them were conducted at a single hospital and only followed up the patients for a short period of time.[2,4,5,8,11,12,14] Thus, an investigation of the clinical outcomes of hospitalized children with LTBAs for multicenter cases and observation for a longer period may provide more information for pediatricians caring for these patients in the future.

The single-payer National Health Insurance (NHI) program in Taiwan was launched in 1995 and covered > 99.5% of the nation's inhabitants.[15] The claims data from Taiwan's National Health Insurance Research Database (NHIRD) have provided trustworthy information for population-based research in children and adults for > 10 years.[16−21] Therefore, it is worthwhile evaluating the clinical outcomes of children with LTBAs using Taiwan's NHIRD for a nationwide, multicentered investigation.

We hypothesized that the diagnosed ages and the presence of comorbidities in infants with LTBAs may influence their clinical outcomes. Therefore, the purpose of this study was to investigate the diagnostic ages and risk factors for in-hospital mortality in hospitalized infants diagnosed with LTBAs during their first 5 years of life.

2. Methods

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan (VGH IRB No.2012-06-006A). There was no patient consent required because the data were analyzed anonymously and no personal information could be connected to the data in this study.

2.1. Study population

Hospitalization claims data of Taiwan's NHIRD were used for analysis. The hospitalization claims data contain scrambled and encrypted personal identification numbers, dates of birth, gender, diagnostic codes using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM),[22] procedural codes, and admission and discharge dates.

Infants born between 2003 and 2005 and admitted at an age of 0−11 months with a discharge diagnosis of LTBAs (ICD-9-CM code: 748.3) were retrieved for analysis. The hospitalization records of all patients were traced until they were 59 months of age. The enrolled infants were grouped into two age groups according to the findings of age distribution and compared.

Data on hospitalization frequency, total hospital stay, age at receiving the earliest bronchoscopy examinations (ICD-9-CM codes: 31.72, 33.22, 33.23, 33.24, 33.26, 33.27, and 31.72) and tracheostomy (ICD-9-CM codes: 31.1, 31.21, and 31.29), and the discharge diagnoses and status were retrieved and analyzed. Clinical Classification Software (CCS) 2010 version was used to classify the diagnoses into clinically meaningful categories.[23] Acute airway infections included the diagnoses of pneumonia, bronchitis, and other upper and lower airway infections (CCS codes: 122, 125, 133, 134).[23]Special attention was also paid to the categories of cardiovascular anomalies (CCS code: 213), other congenital anomalies (CCS code: 217), perinatal diseases (CCS code: 224), esophageal diseases (CCS code: 138), and neurological diseases (including epilepsy and other central nervous system disease (CCS code: 83) for which the discharge diagnoses were further classified and analyzed by the first three digits of the ICD-9-CM codes.[22,23]

2.2. Data analysis

The database management software PostgreSQL (version 9.34, The PostgreSQL Global Development Group, Los Angeles, CA, USA) was used for data processing,[24] and SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Mann-Whitney *U* test was used for comparisons between two groups with continuous variables, and the Chi-square test was used to compare categorical variables. Logistic regression modeling was used to analyze the odds ratio (ORs) for associated factors with the in-hospital mortality rate among the patients with LTBAs. The decision threshold for eligibility was $p < 0.10$ for the univariate model and to remain in the multivariate model. A p value < 0.05 was used to determine statistical significance.

3. Results

From the nationwide claims of 11,642,140 hospitalizations, there were 173,785 (1.5%) infants aged 0−11 months who

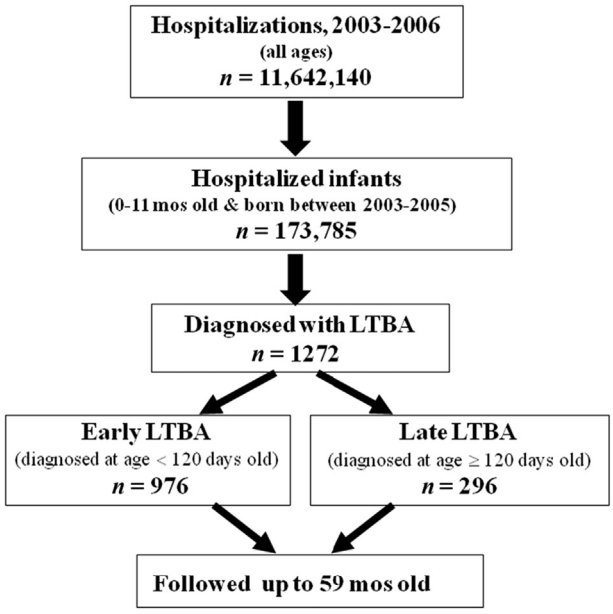

Fig. 1. Flow chart of the recruitment process. LTBA = laryngotracheobronchial anomaly.

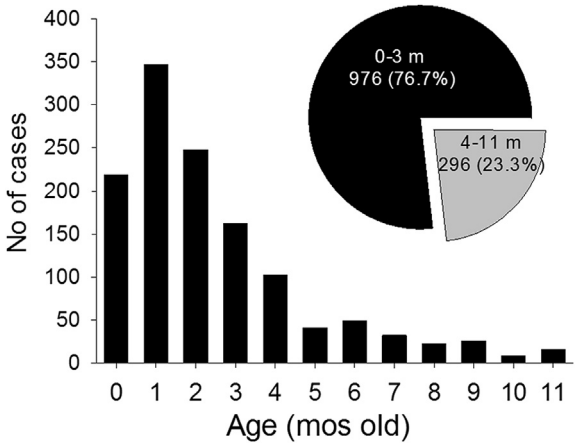

Fig. 2. Age distribution of the enrolled infants when first diagnosed with laryngotracheobronchial anomalies. m = months old.

required treatment in hospital. Among these hospitalized infants, 1272 (0.7%) were hospitalized with a diagnosis of LTBA (Fig. 1).Since a total number of 649,343 infants were born in Taiwan from 2003 to 2005, the incidence of hospitalized LTBA was 0.2%.

Among these hospitalized LTBA infants, the median age at the initial diagnosis of LTBA was 66 days old (approximately 2 months old) (Table 1).Among enrolled infants, there were 976 (76.7%) infants hospitalized and diagnosed at an age of 0–3 months, and 296 (23.3%) infants diagnosed at an age of 4–11 months (Fig. 2). These enrolled infants were grouped to early (0–3 months old) and late LTBA (4–11 months old) groups. There were more boys (63.9%) than girls (36.1%), especially in the late LTBA group ($p < 0.01$). Compared to the early LTBA group, infants of the late LTBA group had a significantly higher frequency of hospitalization ($p < 0.001$) and longer hospital stay ($p < 0.001$) (Table 1).

With regard to the specific diagnostic procedure, only 418 (32.9%) of the infants received bronchoscopic examinations (Table 1). The median ages at first bronchoscopy were 72 days old (approximately 2.5 months old) and 188 days old (approximately 6 months old) in the early and late LTBA groups, respectively. During the first 5 years of life, only six (0.5%) of the infants received a tracheostomy, and 47 infants (3.7%) died in hospital. The late LTBA group had a significantly higher mortality rate (7.1%) than the early LTBA group (2.7%) ($p < 0.001$) (Table 1).

According to the first 5 years of hospitalization records of the enrolled infants, the most common diagnosis during admission was acute airway infection or asthma (81.4%), including asthma, pneumonia, bronchitis, and other upper and

Table 1
Characteristics of the infants diagnosed with laryngotracheobronchial anomalies and their clinical outcomes during the first 5 years of life.

	Total (n = 1272)	Early LTBA[a] (n = 976)	Late LTBA[b] (n = 296)	p[c]
Gender				0.009
Male, n (%)	813 (63.9)	605 (62.0)	208 (70.3)	
Female, n (%)	459 (36.1)	371 (38.0)	88 (29.7)	
Male-to-female ratio	1.8	1.6	2.4	
Age at diagnosis (days old)[d]	66 (38–115)	53 (32–78)	182 (141–238)	<0.001
Hospitalization frequency[d]	3 (2–6)	3 (2–6)	4 (2–9)	<0.001
Total hospitalization days[d]	22 (9–49)	22 (10–56)	3 4 (11–95)	<0.001
Bronchoscopy, n (%)	418 (32.9)	322 (33.0)	96 (32.4)	0.858
Age at first bronchoscopy (days old)[d]	59 (34–90)	72 (40–131)	188 (139–242)	<0.001
Tracheostomy, n (%)	6 (0.5)	4 (0.4)	2 (0.7)	0.559
Age at tracheotomy (days old)[d]	281 (106–666)	263 (103–530)	553 (144–962)	0.533
In-hospital mortality, n (%)	47 (3.7)	26 (2.7)	21 (7.1)	<0.001
Age at death (days old)[d]	278 (134–534)	171 (98–339)	359 (252–604)	0.006

LTBA = laryngotracheobronchial anomalies.
[a] Diagnosed at < 120 days of age.
[b] Diagnosed at age ≥120 days of age.
[c] Comparing the early and late LTBA groups.
[d] median (interquartile range).

lower airway infections. The late LTBA group had a significantly higher percentage of hospitalization-related acute airway infections/asthma than the early LTBA group (87.2% vs. 79.6%, $p = 0.003$) (Table 2). Additionally, there were 248 (19.5%) patients who had previously been hospitalized before their enrolled hospitalizations, and significantly more patients in the late LTBA group (36.8%) than in the early LTBA group (14.2%) ($p < 0.001$).

Perinatal diseases ($n = 305$, 24.0%), cardiovascular anomalies ($n = 295$, 23.2%), other congenital anomalies ($n = 206$, 16.2%), esophageal diseases (n=180, 14.2%), and central nervous system diseases including epilepsy ($n = 160$, 12.6%) were also not uncommon in the infants with LTBAs. Respiratory problems and perinatal infections were the most common perinatal diseases, and there were no significant differences between the two groups. Most of the cardiovascular anomalies were congenital septal defects (69.8% of all cardiovascular anomalies). Only 100 (33.9%) of the infants with cardiovascular anomalies required surgical intervention, and there was also no significant difference between the two groups. With regard to congenital anomalies other than cardiovascular anomalies, musculoskeletal anomalies were most common, and they tended to be more common in the late than the early group ($p = 0.079$). Although there was no significant difference in comorbid chromosome anomalies between the two groups, the percentage of infants with Down syndrome was significantly higher in the late (3.0%) than the early (1.1%) LTBA group ($p = 0.020$).

One hundred and eighty (14.2%) of the enrolled infants had comorbid esophageal disease, and it tended to be more common in the late (17.2%) than the early (13.2%) LTBA group ($p = 0.083$) (Table 2). Furthermore, 160 (12.6%) of the enrolled infants had diseases of the central nervous system or epilepsy, with significantly more patients in the late (18.2%) than the early (10.9%) group ($p < 0.001$). The top five most common comorbidities at death were cardiac anomalies ($n = 17$, 36.2%), respiratory failure ($n = 17$, 36.2%), septicemia ($n = 16$, 34.0%), other congenital anomalies ($n = 12$, 25.5%), and pneumonia ($n = 10$, 21.3%).

The univariate logistic regression analysis for potential risk factors associated with in-hospital mortality among the patients with LTBAs revealed that age at diagnosis of LTBAs, perinatal diseases, cardiovascular anomalies, other congenital anomalies, and central nervous system diseases including epilepsy were significant factors ($p < 0.01$). Gender, acute airway infections or asthma, and esophageal disease were all not significant ($p > 0.10$), so they were excluded from multivariate analysis. In multiple logistic regression analysis, the risk-adjusted ORs (aORs) for in-hospital mortality remained significantly higher in the late group than in the early group (aOR = 2.50, 95% CI = 1.36−4.60). The presence of perinatal diseases (aOR = 2.00, 95% CI = 1.07−3.73), cardiovascular anomalies (aOR = 2.45, 95% CI = 1.30−4.61), other congenital anomalies (aOR = 2.42, 95% CI = 1.28−4.60), or neurological disease (epilepsy or other central nervous system diseases) (aOR = 2.50, 95% CI = 1.36−4.60) also had significantly higher aORs than in the children without those diseases (Table 3).

4. Discussion

In this study, we demonstrated that most of the children with LTBAs were initially hospitalized and diagnosed at an age of 0−3 months. However, a significantly higher frequency of hospitalization, longer hospital stay, and higher mortality rate were found during the first 5 years of life of the infants diagnosed with LTBAs at an age of 4−11 months. The risk factors for in-hospital mortality were age at diagnosis of

Table 2
Hospitalization-related comorbidities in the infants with laryngotracheobronchial anomalies during the first 5 years of life.

	Total ($n = 1272$)	Early LTBA[a] ($n = 976$)	Late LTBA[b] ($n = 296$)	p[c]
Acute airway infections/asthma, *n* (%)	1035 (81.4)	777 (79.6)	258 (87.2)	0.003
Hospitalized earlier than LTBA diagnosis, *n* (%)	248 (19.5)	139 (14.2)	109 (36.8)	<0.001
Perinatal disease, *n* (%)	305 (24.0)	233 (23.9)	72 (24.3)	0.873
Respiratory problem, *n* (%)	173 (13.6)	141 (14.4)	32 (10.8)	0.110
Perinatal infection, *n* (%)	105 (8.3)	73 (7.5)	32 (10.8)	0.068
Cardiovascular anomaly, *n* (%)	295 (23.2)	222 (22.7)	73 (24.7)	0.494
Septal defect, *n* (%)	206 (16.2)	150 (15.4)	56 (18.9)	0.140
Receiving cardiac surgery, *n* (%)	100 (7.9)	71 (7.3)	29 (9.8)	0.225
Other congenital anomaly, *n* (%)	206 (16.2)	149 (15.3)	57 (19.3)	0.103
Musculoskeletal anomaly, *n* (%)	91 (7.2)	63 (6.5)	28 (9.5)	0.079
Chromosomal anomaly, *n* (%)	48 (3.8)	40 (4.1)	17 (5.7)	0.230
Down syndrome, *n* (%)	20 (1.6)	11 (1.1)	9 (3.0)	0.020
Esophageal disease, *n* (%)	180 (14.2)	129 (13.2)	51 (17.2)	0.083
Reflux esophageal disease[d]	176 (13.8)	127 (13.0)	49 (16.6)	0.122
Neurological disease, *n* (%)	160 (12.6)	106 (10.9)	54(18.2)	<0.001

CNS = central nervous system; LTBA = laryngotracheobronchial anomalies.
[a] Diagnosed at < 120 days of age.
[b] Diagnosed at ≥ 120 days of age.
[c] Comparing the early and late LTBA groups.
[d] International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code: 530.81 or 530.11 or 530.1 or 530.8 or 530.10 or 530.2.

Table 3
Odds ratios for in-hospital mortality of the infants with laryngotracheobronchial anomalies during the first 5 years of life.

	Discharge status			OR (95% CI)	*p*	aOR (95% CI)[a]	*p*
	Total *n*	Alive, *n* (%)	Dead, *n* (%)				
Age at the diagnosis of LTBAs							
0–3 mo old	976	950 (97.3)	26 (2.7)	1	—	1	—
4–11 mo old	296	275 (92.9)	21 (7.1)	2.79 (1.55–5.04)	0.001	2.50 (1.36–4.60)	0.003
Perinatal disease							
No	967	942 (97.4)	25 (2.6)	1	—	1	—
Yes	305	283 (92.8)	22 (7.2)	2.93 (1.63–5.27)	<0.001	2.00 (1.07–3.73)	0.030
Cardiovascular anomaly							
No	977	954 (97.6)	23 (2.4)	1	—	1	—
Yes	295	271 (91.9)	24 (8.1)	3.67 (2.04–6.61)	<0.001	2.45 (1.30–4.61)	0.005
Other congenital anomaly							
No	1066	1038 (97.4)	28 (2.6)	1	—	1	—
Yes	206	187 (90.8)	19 (9.2)	3.77 (2.06–6.88)	<0.001	2.42 (1.28–4.60)	0.007
Neurological disease							
No	1112	1080 (97.1)	32 (2.9)	1	—	1	—
Yes	160	145 (90.6)	15 (9.4)	3.49 (1.85–6.60)	<0.001	2.32 (1.18–4.53)	0.014

CNS = central nervous system; LTBA = laryngotracheobronchial anomalies; OR = odds ratio; aOR = adjusted odds ratio.
[a] Adjusted for all factors other than itself.

LTBAs, perinatal diseases, cardiovascular anomalies, other congenital anomalies, and neurological diseases.

In the present study, LTBAs occurred more in male infants, which is consistent with the results of other studies.[1] After further dividing the patients by age, we found that the male predominance was more evident in the late group. Male infants are usually more vulnerable than female infants and may thus be more liable to LTBAs.[25] Nevertheless, the univariate analysis in the present study did not find a significant influence of gender on in-hospital mortality.

Whether airway anomalies increase the risk of airway infections is controversial. While Friedman et al[26] reported no increased risk of upper airway infections in patients with any airway anomaly, Yalcin et al[9] reported opposite findings. In our study, airway infections including pneumonia, bronchitis, and other upper and lower airway infections were the main comorbidities, accounting for 81.4% of the enrolled infants. The reason may be related to abnormal anatomical and histological structures leading to aspiration and high susceptibility to infections.[6,9] Physicians should be aware of airway infections in patients with LTBAs, because we also found that pneumonia and respiratory failure were important comorbidities at death. Although more cases of the late LTAB group had acute airway infections, our result did not find it a significant risk factor for the in-hospital mortality.

Neurological diseases including seizures, developmental delay, mental retardation, cerebral palsy, microcephaly, and hypotonia had been reported in 8–48% of infants with airway malacia,[6–10]and our findings (12.6%) are consistent with those previous reports. It had been hypothesized that airway malacia is a consequence of an underdeveloped or abnormally integrated central nervous system.[6] On the one hand, impaired vagal nerve function may lead to decreased laryngeal tone, and on the other hand, neuromuscular hypotonia may cause collapsed supporting muscles in the pharynx. Both defects are probably related to laryngotracheal anomalies.[6] Most patients with mild neurological diseases become symptom free with age, however some patients, and especially hypotonic infants, may have problems with breathing and feeding, and even require surgical interventions including tracheostomy.[6–10] In the present study, cases that underwent tracheostomy were <1%, so we could not find any role of tracheostomy in cases with neurological disease for in-hospital mortality.

Comorbid congenital heart diseases had been reported in 10–58% of patients with airway malacia, and up to one third of these patients required surgical intervention.[4,6–10] In addition, the incidence of airway malacia with comorbid genetic disorders and congenital anomalies including Down syndrome, VACTERL association, and 22q11.2 microdeletion syndrome have been reported in infants with an incidence ranging from 8% to 52%, which is consistent with our results.[6–10] For patients with impaired cardiac function resulting from congenital heart diseases, airway anomalies may further affect oxygenation.[6] In our analysis, congenital heart diseases and congenital anomalies were two of the five most commonly diagnosed comorbidities at death. The additive effect of congenital heart diseases and other congenital anomalies may therefore worsen the symptoms of LTBAs and cause death.

A significantly higher in-hospital mortality rate in the late LTBA group compared with the early LTBA group was demonstrated in the present study. The causalities between early and late LTBA groups may be different. Different from the early LTBA group, infants of the late LTBA group may have had delayed diagnosis due to indistinct symptoms or later onset of the disease. It is possible that some late LTBAs were secondary to respiratory complications during their hospitalizations. In this study, we have demonstrated that infants in the late LTBA group more commonly had neurological diseases and a tendency to have more common perinatal infections, musculoskeletal anomalies, and esophageal diseases which are frequently complicated with respiratory problems (Table 2).The multiple logistic regression analysis also showed that perinatal disease, cardiovascular anomaly, other congenital

anomaly, and neurological disease were all significant risk factors in addition to age for in-hospital mortality (Table 3). These findings support that underlying diseases play important roles in late LTBAs and in-hospital mortality. Later diagnosis usually results in later treatment. Hence, underlying complex diseases and later-diagnosed LTBAs are all related risk factors for in-hospital mortality in diseased infants.

The problems of the early LTBA group may more commonly be congenital, so that their symptoms onset earlier, and correct diagnosis and treatment are earlier. Furthermore, these infants had fewer underlying diseases compared to the late LTBA group, so their airway problems were more easily controlled and the in-hospital mortality rate was lower.

To our best knowledge, the influence of age difference in diseased young patients' mortality has not been reported in infants with airway anomalies. However, a similar finding that older young children (12−23 months old) had a higher mortality risk than younger children (0−11 months old) with abusive head trauma was reported in the US recently.[27] Therefore, age may play an important role in the outcome of young children's diseases. We suggest taking the patient's age into consideration in predicting outcome in young infants with LTBAs, and for future studies of other young children's diseases.

There are some limitations in this study. Firstly, we only analyzed the hospitalization datasets, and LTBAs and comorbidities could have been underdiagnosed because the mild forms may have been treated only in an ambulatory setting. Secondly, the ICD-9-CM code 748.3 includes different types of anomalies, including malacia, dysgenesis, and stenosis, from the larynx, trachea, and bronchial airways. We did not have enough information to identify the types of LTBAs. Thirdly, the insurance claim data did not include the patients' history or laboratory results, so the disease severity could not be taken into consideration in the analysis. Fourthly, our study datasets could not provide detailed information about patients' managements which might also play a role in the patients' outcome. Lastly, the mortality case number ($n = 47$) is rather low compared to surviving cases ($n = 1225$), and we should be very careful in interpreting the ORs for in-hospital mortality. Therefore, further studies will be necessary to elucidate the points limited by the claims data of Taiwan's NHIRD.

In conclusion, most infants with LTBAs were initially diagnosed and hospitalized when they were aged 3 months and younger. The risk factors for in-hospital mortality of the young children with LTBAs during their first 5 years of life included being diagnosed and treated at an age of 4 months and older, and having perinatal disease, cardiovascular anomalies, other congenital anomalies, and neurological diseases. Therefore, clinical physicians should pay attention to small infants with upper airway symptoms and treat them aggressively, especially in those with underlying complex diseases.

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