Observational Study

Medicine®

OPEN

The comorbidities and risk factors in children with congenital airway anomalies

A nationwide population-based study in Taiwan

Yu-Sheng Lee, MD, PhD[a,b], Pei-Chen Tsao, MD, MSc[a,b], Mei-Jy Jeng, MD, PhD[a,b,c], Wen-Jue Soong, MD[a,b,*]

Abstract

The comorbidities and risk factors associated with congenital airway anomalies (CAAs) in children are undecided. This study aimed to investigate the comorbidities commonly associated with CAA and to explore the prognosis and risk factors in CAA children.

This nationwide, population-based cohort study was conducted between 2000 and 2011 with children aged 0 to 5 years assigned to either a CAA group (6341 patients) that diagnosed with CAA or an age- and gender-matched control group (25,159 patients) without CAA, using the Taiwan National Health Insurance Research Database (NHIRD). Descriptive, logistic regression, Kaplan–Meier, and Cox regression analyses were used for the investigation.

Cleft lip/palate (adjusted odds ratio [aOR], 7.88; 95% confidence interval [CI], 6.49–9.59), chromosome (aOR, 6.85; 95% CI, 5.03–9.34), and congenital neurologic (aOR, 5.52; 95% CI, 4.45–6.87) anomalies were the comorbidities most highly associated with CAA. Of the 31,500 eligible study patients, 636 (399 in the CAA group and 237 in the control group) died during the follow-up period (6.3% vs 0.9%, $P < .001$). The mortality risk after adjusting for age, gender, and comorbidities elevated significantly among CAA patients (adjusted hazard ratio [aHR], 4.59; 95% CI, 3.85–5.48). The need for tracheostomy (aHR, 2.98; 95% CI, 2.15–4.15), comorbidity with congenital heart disease (CHD) (aHR, 2.52; 95% CI, 2.05–3.10), and chromosome anomaly (aHR, 2.34; 95% CI, 1.70–3.23) were the independent risk factors most greatly related to CAA mortality.

This study demonstrated that CAA was most highly associated with the comorbidities as cleft lip/palate, chromosome, and congenital neurologic anomalies. The CAA children had a significantly elevated mortality risk; the need for tracheostomy, CHD, and chromosome anomaly were the most related risk factors of mortality for CAA. Further studies are warranted to clarify the involved mechanisms.

Abbreviations: aHR = adjusted hazard ratio, aOR = adjusted odds ratio, CAA = congenital airway anomaly, CHD = congenital heart disease, CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, NI = neuromuscular impairment.

Keywords: congenital airway anomaly, National Health Insurance, National Health Insurance Research Database

1. Introduction

Congenital airway anomaly (CAA) is a heterogeneous congenital respiratory disorder extending from the nose, pharynx, larynx, trachea, and bronchus to the lung, such as choanal atresia, laryngomalacia, tracheomalacia, bronchomalacia, and congenital stenosis of larynx, trachea, and bronchus. CAA has been reported with an incidence of 0.1% to 2% in population.[1] Different types of CAA may have different impact on the clinical course and CAA children have an increased risk of respiratory illness and morbidity.[2]

Most of the previous clinical studies regarding CAA have focused on the clinical presentation, diagnostic strategy, and management.[2–14] The prior studies have also emphasized all categories of congenital anomalies and have included CAA as a subgroup.[15–17] CAA and other congenital anomalies may have some shared embryogenesis or pathogenesis pathways, however, with respect to the associations between CAA and other congenital anomalies, the available epidemiologic information is scant. Furthermore, there has been no relevant large-scale, population-based, longitudinal cohort study to explore the relationship between age at CAA diagnosis, gender, and comorbidities in CAA patients, and mortality risk.

An exacerbation of symptoms with compromised respiratory status would become apparent in CAA patients with comorbid medical conditions,[2,18] which may cause life-threatening events and even death. Early diagnosis and optimal management are crucial for these CAA patients. Exploring the prognosis and risk factors for CAA patients could help parents and physicians to pay particular attention to this clinical condition and improve the health care quality.

Editor: Oana Marginean.

Funding/support: This work was supported by a grant from Taipei Veterans General Hospital (V102B-047).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Division of Neonatology, Department of Pediatrics, Taipei Veterans General Hospital, [b] Department of Pediatrics, [c] Institute of Emergency and Critical Care Medicine, National Yang-Ming University, School of Medicine, Taipei, Taiwan.

[*] Correspondence: Wen-Jue Soong, Division of Neonatology, Department of Pediatrics, Taipei Veterans General Hospital, #201, Section 2 Shih-Pai Road, Taipei 112, Taiwan (e-mail: wjsoong@vghtpe.gov.tw).

Medicine (2018) 97:18(e0561)

Received: 14 March 2016 / Accepted: 4 April 2018

http://dx.doi.org/10.1097/MD.0000000000010561

The National Health Insurance Research Database (NHIRD) in Taiwan offers a nationwide, population-based, multiinstitutional database for research purposes. The aim of this study was to use the NHIRD to examine the association between CAA and comorbidities, and to explore the prognosis and risk factors in CAA children.

2. Methods

2.1. Data source

This study was based on data from the NHIRD released by the National Health Research Institute (NHRI). Taiwan began the National Health Insurance (NHI) program in 1995 to provide comprehensive health care. Enrollment in the NHI program is mandatory and there are presently more than 23 million enrollees representing approximately 99% of population.[19] The NHI program offers integrated medical care, including out-patient, in-patient, emergency, dental, and traditional Chinese medicine services, as well as medication prescriptions.

The NHIRD includes the registry and reimbursement claims data from the NHI system, ranging from demographic data to detailed orders from ambulatory and in-patient care. The NHIRD is managed and publicly released by the NHRI, and contains registration files and original reimbursement claims data for all enrollees in Taiwan. These features make the NHIRD one of the largest and most complete nationwide health care service datasets in the world.[20] The diagnostic codes of the patients in the NHIRD are in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and are established by board-certified physicians in their corresponding specialties. The diagnostic accuracy for the major diseases in the NHIRD has been well validated.[21–23] Information about the enrollment and medical utilization for all NHI beneficiaries were included in the NHIRD. All information that may potentially identify any individual patient has been encrypted before the database was released. The confidentiality of the database was in accordance with the data regulations of the Bureau of NHI and the NHRI, Taiwan. The NHRI has guarded the privacy and provided data to researchers who obtained ethical approval.

2.2. The identification of patients with CAA (CAA group)

A retrospective cohort study was conducted from 1 January 2000 to 31 December 2011. All inpatient data were collected for analysis during the 12-year period. Using the CAA diagnostic codes (ICD-9-CM 748) (see Supplement, http://links.lww.com/MD/C237) as in earlier epidemiologic studies of CAA,[8,24] 6341 CAA children aged 0 to 5 years who were born since 1 January 2000 were identified. Patients who was born before 1 January 2000 or aged more than 5 years at CAA diagnosis were excluded.

The first date for each patient's CAA diagnosis recorded in the NHIRD was defined as the index date. Information regarding the gender, age at CAA diagnosis, follow-up period, comorbidities, and in-hospital mortality was collected for analysis. The age at CAA diagnosis was classified into neonates (newborn up to 28 days), infants (aged more than 4 weeks but less than 12 months), and toddlers and preschoolers (aged between 1 and 5 years).

The comorbidities evaluated for each child were congenital neurologic anomalies (ICD-9-CM 740–742), congenital heart diseases (CHDs) (ICD-9-CM 745, 746, 747.0–4), cleft lip/palate (ICD-9-CM 749), congenital gastrointestinal anomalies (ICD-9-CM 750.3, 751), congenital genitourinary anomalies (ICD-9-CM 752, 753), congenital musculoskeletal anomalies (ICD-9-CM 754–756), chromosome anomaly (ICD-9-CM 758), prematurity (ICD-9-CM 765), neuromuscular impairment (NI) (ICD-9-CM 318, 330, 334, 335, 343, 359), and chronic lung disease (ICD-9-CM code770.7).[25–30] Children who received a tracheostomy were identified by the procedure code as 31.1 or 31.2.[28,31] Mortality was defined according to the discharge status recorded in the NHIRD.

2.3. The identification of patients without CAA (control group)

Patients without CAA were classified into the control group and were randomly selected from the same NHIRD database. Each CAA patient was matched with 4 patients without CAA by age and gender on the index date within the same observational period. A total of 25,159 children served as the control group; the same recorded variables as for the CAA group were used for analysis.

Provider and hospital characteristics, including patient volume, hospital level, and geographic variation may influence the outcome measurement. The covariate data available may be different between the 2 groups.

All the enrolled patients were followed until their death or 31 December 2011, whichever was earlier.

The Institutional Review Board of Taipei Veterans General Hospital, Taiwan approved the study (IRB approval number: 2014-08-005AC). Because all personal identifying information had been encrypted before the database was released, the review board requirement for written informed consent was waived.

2.4. Statistical analysis

All data were linked by the SQL server 2008 (Microsoft Corporation, Redmond, WA) and analyzed by the SPSS statistical software version 19.0 for Windows (SPSS Inc., Chicago, IL). Continuous variables were described as mean (standard deviation [SD]) and compared using the independent *t* test. Categorical variables were described as percentages and compared with the Chi-square or Fisher exact test as appropriate. Multivariate logistic regression analysis with adjusted odds ratio (aOR) among CAA and control groups was used to assess the association between CAA and other congenital anomalies to clarify the possible risk factors for CAA. The Cox proportional-hazards model and Kaplan–Meier analysis with log-rank test were applied to estimate the difference in the cumulative incidences of mortality between the CAA and control groups. The Cox regression analysis with hazard ratio (HR) among CAA group was performed to evaluate the independent risk factors of mortality for CAA. A two-tailed $P < .05$ was considered to be statistically significant.

3. Results

3.1. The demographic and clinical characteristics of the CAA and control groups

A total of 31,500 children aged 0 to 5 years were enrolled with 6341 in the CAA group. There were 2,624,968 children born between 2000 and 2011 in Taiwan; the birth prevalence of CAA was estimated as 241.6 cases per 100,000 neonates. The median diagnostic age of CAA was 2 months with the inter-quartile range of 1 to 5 months. Most of the 6341 CAA patients were diagnosed at the infant stage (72.7%) and a male gender (4020, 63.4%)

Table 1

The demographic and clinical characteristics of the CAA and control groups.

Variables	CAA group n = 6341		Control group n = 25,159		P
Median age (IQR), mo	2 (1–5)		2 (1–5)		
Age (n, %)					.595
Neonates	1146	18.1	4454	17.7	
Infants	4607	72.7	18,284	72.7	
Toddlers and preschoolers	588	9.3	588	9.6	
Gender (n, %)					.860
Female	2321	36.6	9239	36.7	
Male	4020	63.4	15,920	63.3	
Comorbidity (n, %)					
CHD	1158	18.3	968	3.8	<.001
Congenital musculoskeletal anomaly	508	8.0	278	1.1	<.001
Prematurity	474	7.5	1730	6.9	.095
NI	456	7.2	100	0.4	<.001
Cleft lip/palate	385	6.1	167	0.7	<.001
Congenital neurologic anomaly	303	4.8	150	0.6	<.001
Congenital genitourinary anomaly	232	3.7	428	1.7	<.001
Chromosome anomaly	228	3.6	61	0.2	<.001
Congenital gastrointestinal anomaly	129	2.0	168	0.7	<.001
Chronic lung disease	134	2.1	54	0.2	<.001
Tracheostomy, with (n, %)	145	2.3	5	0.02	<.001
F/U, y, mean (SD)	5.9 (3.4)		6.2 (3.2)		<.001
Mortality	399	6.3	237	0.9	<.001

CAA = congenital airway anomaly, CHD = congenital heart disease, IQR = inter-quartile range, NI = neuromuscular impairment, SD = standard deviation.

predominance was found. The male to female gender ratio for in the CAA group was 1.7.

The most common comorbidity in the CAA group was CHD (18.3%). Children in the CAA group had a significantly higher prevalence of comorbidities excepting prematurity than the control group. The rate for tracheostomy was significantly greater in the CAA group (2.3% vs 0.02%, $P < .001$). The mean follow-up period was shorter (5.9 [3.4] vs 6.2 [3.2] years, $P < .001$) and the mortality rate was higher (6.3% vs 0.9%, $P < .001$) in the CAA group (Table 1).

3.2. Association of CAA and other congenital anomalies

After adjusting for the comorbidities as other congenital anomalies and prematurity, patients with cleft lip/palate (aOR, 7.88; 95% confidence interval [CI], 6.49–9.59) had the highest probability to associate with CAA followed by chromosome (aOR, 6.85; 95% CI, 5.03–9.34) and congenital neurologic (aOR, 5.52; 95% CI, 4.45–6.87) anomalies (Table 2).

Table 2

The association of CAA and comorbidities by multivariate logistic regression.

Variables	aOR	(95% CI)	P
Cleft lip/palate	7.88	(6.49–9.59)	<.001
Chromosome anomaly	6.85	(5.03–9.34)	<.001
Congenital neurologic anomaly	5.52	(4.45–6.87)	<.001
Congenital musculoskeletal anomaly	5.35	(4.55–6.30)	<.001
CHD	4.58	(4.16–5.04)	<.001
Congenital gastrointestinal anomaly	1.82	(1.39–2.37)	<.001
Congenital genitourinary anomaly	1.43	(1.18–1.73)	<.001
Prematurity	0.93	(0.83–1.05)	.224

Adjusted for CHD, congenital neurologic, musculoskeletal, chromosome, gastrointestinal, genitourinary anomalies, cleft lip/palate, and prematurity. aOR = adjusted odds ratio, CAA = congenital airway anomaly, CHD = congenital heart disease, CI = confidence interval.

3.3. Prognosis and mortality risk factors in CAA patients

Children in the CAA group had a higher mortality risk than the control group (crude HR, 6.76; 95% CI, 5.75–7.93), and it remained significant even after adjusting for covariates (adjusted HR [aHR], 4.59; 95% CI, 3.85–5.48). The cumulative incidence of mortality in the CAA group was significantly higher than that in the control group (log-rank $P < .001$). The significant difference increased rapidly during the 0 to 3 years after the case enrollment (Fig. 1).

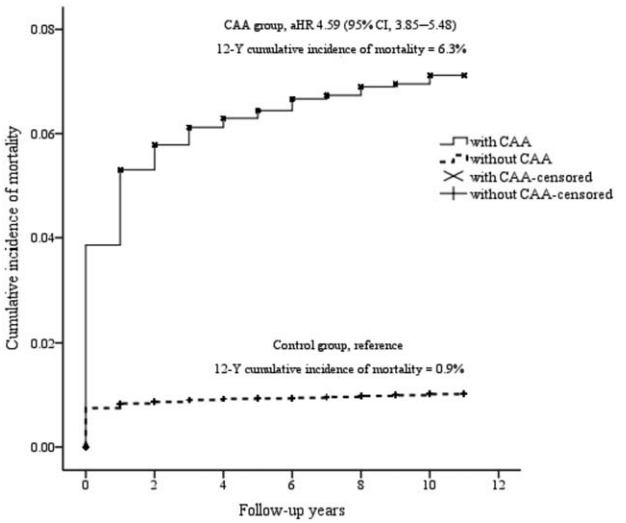

Figure 1. Differences pertaining to the cumulative incidence of mortality and aHR for CAA and control groups, *P*-value for log-rank test <.001. Adjusted for CHD, congenital neurologic anomaly, congenital musculoskeletal anomaly, chromosome anomaly, congenital gastrointestinal anomaly, congenital genitourinary anomaly, cleft lip/palate, prematurity, NI, chronic lung disease, and tracheostomy. aHR = adjusted hazard ratio, CAA = congenital airway anomaly, CHD = congenital heart disease, NI = neuromuscular impairment.

Table 3

Comparison pertaining to the mortality rate in CAA patients.

Variables	Total n = 6341	Mortality n = 399		
	n	n	Rate, %	*P*
Age				<.001
Neonates	1146	179	15.6	
Infants	4607	181	3.9	
Toddlers and preschoolers	588	39	6.6	
Gender				.002
Female	2321	175	7.5	
Male	4020	224	5.6	
Comorbidity				
Chromosome anomaly	228	45	19.7	<.001*
Congenital neurologic anomaly	303	55	18.2	<.001*
Congenital gastrointestinal anomaly	129	18	14.0	<.001*
CHD	1158	160	13.8	<.001*
Congenital musculoskeletal anomaly	508	69	13.6	<.001*
Congenital genitourinary anomaly	232	20	8.6	.137*
Cleft lip/palate	385	11	2.9	.004*
Prematurity	474	93	19.6	<.001*
NI	456	69	15.1	<.001*
Chronic lung disease	134	18	13.4	.001*
Tracheostomy, with	145	47	32.4	<.001†

CAA = congenital airway anomaly, CHD = congenital heart disease, NI = neuromuscular impairment.
* *P*-value for the comparison of mortality rate in CAA patients with and without comorbidity.
† *P*-value for the comparison of mortality rate in CAA patients with and without tracheostomy.

Among CAA patients, neonates had the highest mortality rate (neonates, 15.6%; infants, 3.9%; toddlers and preschoolers, 6.6%; $P < .001$) during the 12-year follow-up period. Female patients with CAA also had a higher mortality rate than male patients (7.5% vs 5.6%, $P = .002$). The CAA patients with chromosome, neurologic, gastrointestinal, cardiovascular and musculoskeletal congenital anomalies, cleft lip/palate, prematurity, NI, and chronic lung disease had higher mortality rates than those without. The mortality rate for CAA patients who underwent tracheostomy was 32.4% (47/145), which was significantly higher than that in patients without tracheostomy (352/6196, 5.7%) (Table 3).

By Cox univariate proportional hazards analysis, there was an increased mortality risk in the CAA patients with one of the following features: neonates; female gender; chromosomal, neurologic, gastrointestinal, cardiovascular, and musculoskeletal anomalies; and prematurity, NI, chronic lung disease, and the need for tracheostomy. With the Cox multivariate proportional hazards analysis, the mortality risk was increased significantly in CAA children diagnosed at neonates (aHR, 1.96; 95% CI, 1.33–2.87) and female gender (aHR, 1.24; 95% CI, 1.02–1.51). The need for tracheostomy (aHR, 2.98; 95% CI, 2.15–4.15), CHD (aHR, 2.52; 95% CI, 2.05–3.10), and chromosome anomaly (aHR, 2.34; 95% CI, 1.70–3.23) were the independent risk factors most significantly related to mortality among CAA patients. The CAA patients who also had cleft lip/palate exhibited a lower mortality risk (aHR, 0.33; 95% CI, 0.18–0.61) (Table 4).

CAA children combined with congenital cardiovascular, neurologic, musculoskeletal, chromosome anomalies, NI, prematurity, and the need for tracheostomy had a significantly higher cumulative incidence of mortality than those without, and CAA patients with cleft lip/palate had a significantly lower cumulative incidence of mortality than those without (Fig. 2).

4. Discussion

This is the first large-scale nationwide population-based analysis with the largest sample size to investigate the comorbidities and risk factors in CAA children aged 0 to 5 years. In this large observational study, we demonstrated that cleft lip/palate and chromosome and congenital neurologic anomalies were the comorbidities most highly associated with CAA. There was an evidence of an elevated mortality risk with CAA with an aHR of 4.59 after a median 6-year follow-up period. The need for tracheostomy, comorbidity with CHD, and chromosome anomaly were the independent risk factors most significantly

Table 4

HR for the risk factors of mortality among CAA children.

Variables	Univariate			Multivariate*		
	HR	95% CI	*P*	aHR	95% CI	*P*
Age						
Neonates	2.33	1.65–3.30	<.001	1.96	1.33–2.87	.001
Infants	0.57	0.41–0.81	.002	0.72	0.51–1.03	.074
Toddlers and preschoolers	1			1		
Gender						
Female	1.36	1.12–1.66	.002	1.24	1.02–1.51	.035
Male	1			1		
Comorbidity						
CHD	3.07	2.52–3.75	<.001	2.52	2.05–3.10	<.001
Congenital neurologic anomaly	3.28	2.47–4.36	<.001	1.80	1.34–2.43	<.001
Congenital musculoskeletal anomaly	2.44	1.88–3.16	<.001	1.57	1.20–2.05	.001
Chromosome anomaly	3.52	2.58–4.79	<.001	2.34	1.70–3.23	<.001
Congenital gastrointestinal anomaly	2.33	1.45–3.74	<.001	0.85	0.52–1.39	.504
Congenital genitourinary anomaly	1.40	0.89–2.19	.143			
Cleft lip/palate	0.43	0.24–0.79	.006	0.33	0.18–0.61	<.001
Prematurity	3.95	3.14–4.99	<.001	2.02	1.52–2.69	<.001
NI	2.69	2.07–3.48	<.001	2.08	1.56–2.78	<.001
Chronic lung disease	2.24	1.40–3.60	.001	0.84	0.50–1.39	.491
Tracheostomy, with	5.93	4.38–8.05	<.001	2.98	2.15–4.15	<.001

aHR = adjusted HR, CAA = congenital airway anomaly, CHD = congenital heart disease, CI = confidence interval, HR = hazard ratio, NI = neuromuscular impairment.
* All of the variables with $P < .1$ in univariate analyses were included in the Cox multivariate analysis.

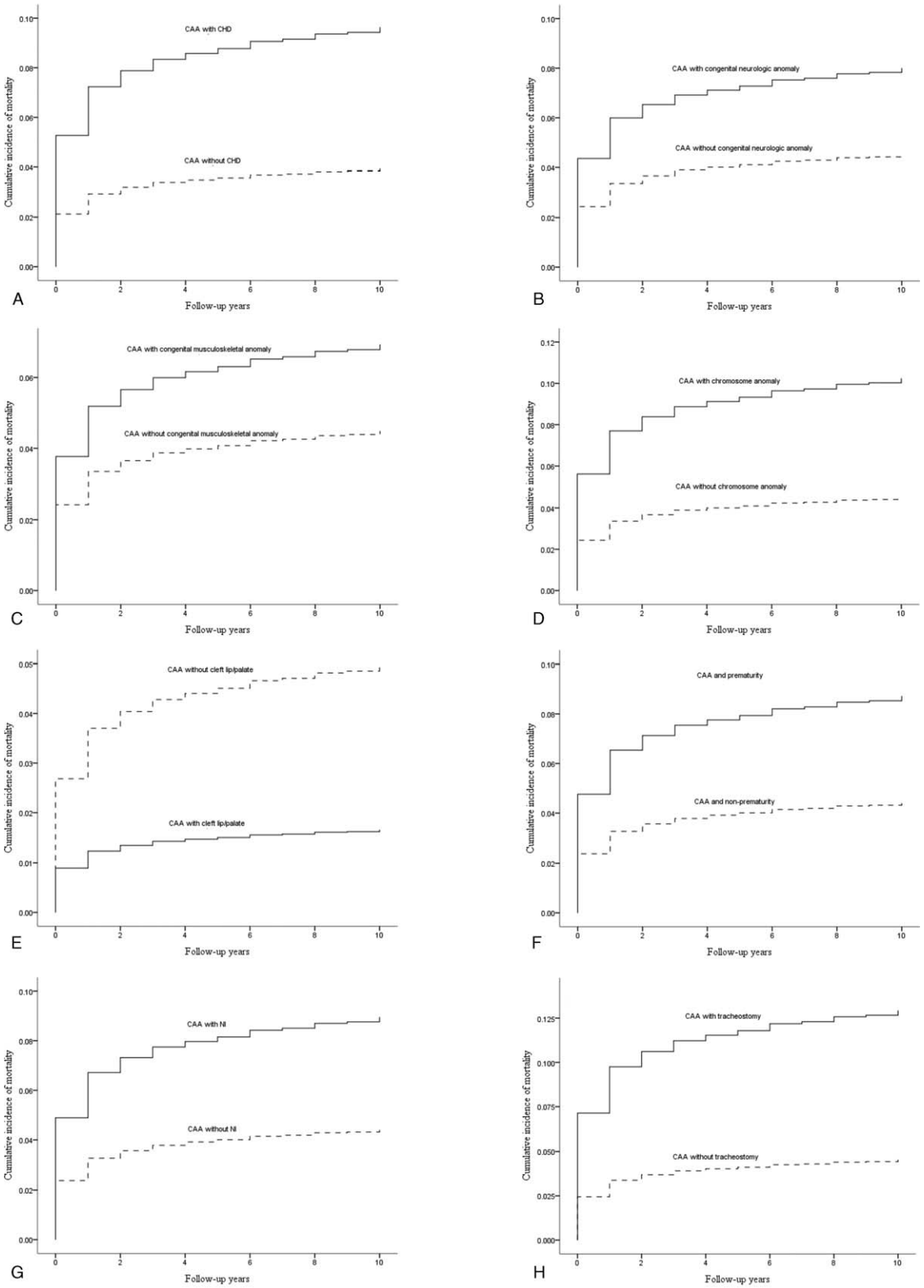

Figure 2. Hazard curve of mortality for CAA patients combined with comorbidities or not (A) CHD; (B) congenital neurologic anomaly; (C) congenital musculoskeletal anomaly; (D) chromosome anomaly; (E) cleft lip/palate; (F) prematurity; (G) NI; and (H) tracheostomy. Adjusted for age, gender, CHD, congenital neurologic anomaly, congenital musculoskeletal anomaly, chromosome anomaly, cleft lip/palate, prematurity, NI, and tracheostomy. CAA = congenital airway anomaly, CHD = congenital heart disease, NI = neuromuscular impairment.

related to CAA mortality. The validity of the results may have been reinforced by the use of nationwide, population-based across institutional data and longitudinal follow-up over time.

The birth prevalence of CAA was 241.6 cases per 100,000 neonates, which was comparable with the previous studies.[1,13,15,16] The wide range of the reported prevalence about congenital anomalies reflected the complex interactions of genetic and/or environmental factors, which may influence embryogenesis and/or fetal growth and may possibly vary with time or geography.[17] Because CAA is often an underdiagnosed disease,[32,33] the different detection rates may be a cause for the discrepancy as well.

The suspicion for CAA is usually suggested based on clinical history and physical examination.[34] Apart from lethal CAA conditions such as tracheal agenesis or atresia, most of the CAA patients post the time of birth exhibit mild respiratory symptoms. We demonstrated that the median age for the diagnosis of CAA was 2 months. The evaluation regarding the possibility of CAA may be arranged until the patients develop progressive symptoms of respiratory distress, cyanotic spells, recurrent respiratory infections, feeding difficulties, or failure to thrive[34]; this may be the reason that in most cases CAA are diagnosed after the neonatal stage. However, the present results showed that the CAA patients diagnosed at the neonatal stage have the highest mortality rate and the greatest mortality risk. CAA diagnosis at an early age may be due to respiratory deterioration, and exacerbations may be due to the severity of CAA lesions. Further study on the severity and spectrum of CAA at different age strata may provide more information.

We found a predominance in male gender pertaining to CAA, which was consistent with the prior studies.[2,18,35] However, the mortality risk in female CAA patients was higher than that in male patients. There may be no ideal explanation for the difference in prevalence and mortality risks between the genders.

CAA may be isolated or occur in association with congenital anomalies that do not affect the airway.[35–37] We illustrated that patients with congenital anomalies had a higher probability of having CAA and that cleft lip/palate and chromosome (such as Down syndrome, Patau syndrome, and Edward syndrome, etc) and congenital neurologic anomalies (such as Encephalocele, Microcephalus, and Spina bifida, etc) were the anomalies most highly associated with CAA. Etiology about CAA includes the anatomic, cartilaginous, neurologic, reduction, migration, and selection theories.[1,38,39] CAA and other congenital anomalies may occur concurrently in the same individual, perhaps through possible common pathways. The abnormal embryogenesis and underdeveloped or abnormally integrated nervous system might be the reason for the association between CAA and other congenital anomalies. A close monitoring of the probability of CAA may be necessary for patients with congenital anomalies, especially patients with cleft lip/palate (aOR, 7.88; 95% CI, 6.49–9.59), chromosome (aOR, 6.85; 95% CI, 5.03–9.34), and congenital neurologic (aOR, 5.52; 95% CI, 4.45–6.87) anomalies. To reduce the morbidity and mortality caused by CAA, these results should be used to guide early clinical identification before respiratory compromise can develop.

The prognosis and life-threatening time interval for the CAA children may be an issue of clinical significance. We showed that children in CAA group are 4.59 times more at the risk of mortality than those in control group. A significantly rapid increase in the difference in the cumulative incidence of mortality was also noted during the 0 to 3 years after the CAA diagnosis. Therefore, physicians who care for the CAA children should be aware of the elevated mortality risk, and the 0 to 3 years after CAA diagnosis may be the critical period for the potential adverse events.

The increased prevalence of CAA in patients with genetic or syndromic diseases has been recognized, such as Trisomy 21, DiGeorge, VACTERL, and Klippel-Feil[5,7,36,40,41]; however, the mortality risk has not been well evaluated. This demonstrated that CAA patients with chromosome anomaly have a higher mortality risk. Disease complexity and multiple organ system involvement may be the reason for increased mortality risk.

CAA is believed to be significantly associated with CHD.[10,33,35,36,42] The temporal and spatial proximity between the development of the cardiovascular and respiratory systems can provide simultaneous exposure risks to intrauterine insults or abnormal developments.[42] It has been postulated that the mortality risk is significantly increased among CHD children and comorbid CAA.[10] The significantly increased mortality risk among CAA patients who also had CHD may be due to the long-term mutual interaction of the respiratory and cardiovascular pathologies. Because of the higher mortality risk, CAA children may deserve more investigation about the possibility of concomitant CHD.

Potential life-threatening respiratory compromise may develop among CAA children, and tracheostomy may be needed for survival. It has been proposed that pediatric patients with tracheostomy may be at risk of death,[28] and that the mortality rate of all children with tracheostomy was around 5% to 8%.[25,43,44] This study demonstrated that the mortality rate of CAA children with tracheostomy was 32.4%, which was higher than the reported mortality rate of all children with tracheostomy in the prior studies. We showed that the need for tracheostomy was also an independent risk factor for mortality in the CAA patients. Tracheostomy may be considered as the proxy of severity and the clinically severe CAA patients may have a significantly elevated mortality risk.

We showed that cleft lip/palate was significantly associated with CAA, and CAA patients with a cleft lip/palate had a lower mortality risk. Because the follow-up examinations for patients with cleft lip/palate may be regularly scheduled, the heightened surveillance may increase the likelihood of early detection and prompt management for CAA that may decrease the mortality risk. Additional study regarding the extent of potential detection bias on the mortality risk among CAA with cleft lip/palate is required before any conclusions can be drawn.

The major strengths of the study were the population-based design and the complete coverage of CAA cases, wherein the possibility of loss to follow-up was essentially eliminated.

Nevertheless, this study had some limitations worth considering. First, because this study was epidemiologic in nature, it could not establish a causative link between CAA, comorbidities, and mortality. Second, personal information, including CAA phenotype and severity and environmental factors, was not documented in the NHIRD. An analysis of the possible relationships between these personal characteristics and the mortality risk was not possible. Third, some unmeasured factors, such as CAA children who received flexible endoscopic evaluation or rigid ventilation bronchoscopy before tracheostomy, may influence the risk factors and mortality. Finally, because this study was conducted in Taiwan, the extent to which the findings can be generalized to other populations warrants discussion.

5. Conclusion

CAA was diagnosed mostly at infants with the median diagnostic age of 2 months, and male gender predominance was found. Cleft lip/palate, chromosome, and neurologic anomalies were the congenital anomalies most highly associated with CAA. Although CAA is a rare disease, the CAA children had a significantly elevated mortality risk. The mortality risk was increased in CAA children who were diagnosed at neonates and female gender. The need for tracheostomy, comorbidity with CHD, and chromosome anomaly were the independent risk factors most greatly related to CAA mortality. Further studies are warranted to clarify the potential mechanism for the association and mortality risk in CAA patients.

Acknowledgments

The authors thank the NHIRD for the data provided by the NHI Administration, Ministry of Health and Welfare and managed by NHRI. The authors also thank Enago (www.enago.tw) for the English language review.

Author contributions

Designed the study, analyzed the data, and wrote the manuscript: Yu-Sheng Lee.

Involved in the study design and helped to draft the manuscript: Mei-Jy Jeng, Pei-Chen Tsao, Wen-Jue Soong.

All of the authors read and roved the final manuscript.

Conceptualization: Yu-Sheng Lee, Pei-Chen Tsao, Mei-Jy Jeng.
Data curation: Yu-Sheng Lee.
Formal analysis: Yu-Sheng Lee.
Funding acquisition: Yu-Sheng Lee.
Investigation: Yu-Sheng Lee, Pei-Chen Tsao, Mei-Jy Jeng.
Methodology: Yu-Sheng Lee, Pei-Chen Tsao.
Resources: Mei-Jy Jeng.
Supervision: Mei-Jy Jeng, Wen-Jue Soong.
Writing – original draft: Yu-Sheng Lee.
Writing – review & editing: Mei-Jy Jeng, Wen-Jue Soong.

References

[1] Ghaye B, Szapiro D, Fanchamps JM, et al. Congenital bronchial abnormalities revisited. Radiographics 2001;21:105–19.
[2] Masters IB, Zimmerman PV, Pandeya N, et al. Quantified tracheobronchomalacia disorders and their clinical profiles in children. Chest 2008;133:461–7.
[3] Kussman BD, Geva T, McGowan FX. Cardiovascular causes of airway compression. Paediatr Anaesth 2004;14:60–74.
[4] Noel CV, Kovalchin JP, Adler B, et al. Incidence of tracheobronchial anomalies found with hypoplastic left heart syndrome. Congenit Heart Dis 2014;9:294–9.
[5] Alli A, Gupta S, Elloy MD, et al. Laryngotracheal anomalies in children with syndromic craniosynostosis undergoing tracheostomy. J Craniofac Surg 2013;24:1423–7.
[6] Khariwala SS, Lee WT, Koltai PJ. Laryngotracheal consequences of pediatric cardiac surgery. Arch Otolaryngol Head Neck Surg 2005;131:336–9.
[7] Wang CC, Chen SJ, Wu ET, et al. Lower airway anomalies in children with CATCH 22 syndrome and congenital heart disease. Pediatr Pulmonol 2013;48:587–91.
[8] Mehta RP, Chesnulovitch K, Jones DT, et al. Pediatric deaths due to otolaryngologic causes: a population-based study in Massachusetts, 1990–2002. Laryngoscope 2005;115:1923–9.
[9] Pfammatter JP, Casaulta C, Pavlovic M, et al. Important excess morbidity due to upper airway anomalies in the perioperative course in infant cardiac surgery. Ann Thorac Surg 2006;81:1008–12.
[10] Lee YS, Jeng MJ, Tsao PC, et al. Prognosis and Risk factors for congenital airway anomalies in children with congenital heart disease: A Nationwide Population-Based Study in Taiwan. PLoS One 2015;10: e0137437.
[11] Peng YY, Soong WJ, Lee YS, et al. Flexible bronchoscopy as a valuable diagnostic and therapeutic tool in pediatric intensive care patients: a report on 5 years of experience. Pediatr Pulmonol 2011;46:1031–7.
[12] Yalcin E, Dogru D, Ozcelik U, et al. Tracheomalacia and bronchomalacia in 34 children: clinical and radiologic profiles and associations with other diseases. Clin Pediatr (Phila) 2005;44:777–81.
[13] Jiao H, Xu Z, Wu L, et al. Detection of airway anomalies in pediatric patients with cardiovascular anomalies with low dose prospective ECG-gated dual-source CT. PLoS One 2013;8:e82826.
[14] Elliott M, Roebuck D, Noctor C, et al. The management of congenital tracheal stenosis. Int J Pediatr Otorhinolaryngol 2003;67(Suppl 1):S183–192.
[15] Rankin J, Pattenden S, Abramsky L, et al. Prevalence of congenital anomalies in five British regions, 1991-99. Arch Dis Child Fetal Neonatal Ed 2005;90:F374–E379.
[16] Dastgiri S, Stone DH, Le-Ha C, et al. Prevalence and secular trend of congenital anomalies in Glasgow, UK. Arch Dis Child 2002;86:257–63.
[17] Sarkar S, Patra C, Dasgupta MK, et al. Prevalence of congenital anomalies in neonates and associated risk factors in a tertiary care hospital in eastern India. J Clin Neonatol 2013;2:131–4.
[18] Altman KW, Wetmore RF, Marsh RR. Congenital airway abnormalities in patients requiring hospitalization. Arch Otolaryngol Head Neck Surg 1999;125:525–8.
[19] Chen YJ, Wu CY, Shen JL, et al. Cancer risk in patients with chronic urticaria: a population-based cohort study. Arch Dermatol 2012;148: 103–8.
[20] Lee YS, Chen YT, Jeng MJ, et al. The risk of cancer in patients with congenital heart disease: a nationwide population-based cohort study in Taiwan. PLoS One 2015;10:e0116844.
[21] Lin CC, Lai MS, Syu CY, et al. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. J Formos Med Assoc 2005;104:157–63.
[22] Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20:236–42.
[23] Cheng CL, Lee CH, Chen PS, et al. Validation of acute myocardial infarction cases in the national health insurance research database in taiwan. J Epidemiol 2014;24:500–7.
[24] Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980–1997. Pediatrics 2000;106:205–9.
[25] Berry JG, Graham RJ, Roberson DW, et al. Patient characteristics associated with in-hospital mortality in children following tracheotomy. Arch Dis Child 2010;95:703–10.
[26] Srivastava R, Downey EC, Feola P, et al. Quality of life of children with neurological impairment who receive a fundoplication for gastroesophageal reflux disease. J Hosp Med 2007;2:165–73.
[27] Connor JA, Gauvreau K, Jenkins KJ. Factors associated with increased resource utilization for congenital heart disease. Pediatrics 2005;116: 689–95.
[28] Berry JG, Graham DA, Graham RJ, et al. Predictors of clinical outcomes and hospital resource use of children after tracheotomy. Pediatrics 2009;124:563–72.
[29] Gianicolo EA, Bruni A, Rosati E, et al. Congenital anomalies among live births in a polluted area. A ten-year retrospective study. BMC Pregnancy Childbirth 2012;12:165.
[30] Fisher PG, Reynolds P, Von Behren J, et al. Cancer in children with nonchromosomal birth defects. J Pediatr 2012;160:978–83.
[31] Altman KW, Wetmore RF, Marsh RR. Congenital airway abnormalities requiring tracheotomy: a profile of 56 patients and their diagnoses over a 9 year period. Int J Pediatr Otorhinolaryngol 1997;41:199–206.
[32] Healy F, Hanna BD, Zinman R. Pulmonary complications of congenital heart disease. Paediatr Respir Rev 2012;13:10–5.
[33] Lee SL, Cheung YF, Leung MP, et al. Airway obstruction in children with congenital heart disease: assessment by flexible bronchoscopy. Pediatr Pulmonol 2002;34:304–11.
[34] Richter GT, Thompson DM. The surgical management of laryngomalacia. Otolaryngol Clin North Am 2008;41:837–64. vii.
[35] van Veenendaal MB, Liem KD, Marres HA. Congenital absence of the trachea. Eur J Pediatr 2000;159:8–13.
[36] Olney DR, Greinwald JHJr, Smith RJ, et al. Laryngomalacia and its treatment. Laryngoscope 1999;109:1770–5.

[37] Benjamin B, Pitkin J, Cohen D. Congenital tracheal stenosis. Ann Otol Rhinol Laryngol 1981;90:364–71.
[38] Landry AM, Thompson DM. Laryngomalacia: disease presentation, spectrum, and management. Int J Pediatr 2012;2012:753526.
[39] Thompson DM. Abnormal sensorimotor integrative function of the larynx in congenital laryngomalacia: a new theory of etiology. Laryngoscope 2007;117:1–33.
[40] Bertrand P, Navarro H, Caussade S, et al. Airway anomalies in children with Down syndrome: endoscopic findings. Pediatr Pulmonol 2003;36:137–41.
[41] Huang RY, Shapiro NL. Structural airway anomalies in patients with DiGeorge syndrome: a current review. Am J Otolaryngol 2000;21:326–30.
[42] Guillemaud JP, El-Hakim H, Richards S, et al. Airway pathologic abnormalities in symptomatic children with congenital cardiac and vascular disease. Arch Otolaryngol Head Neck Surg 2007;133:672–6.
[43] Wood D, McShane P, Davis P. Tracheostomy in children admitted to paediatric intensive care. Arch Dis Child 2012;97:866–9.
[44] Lewis CW, Carron JD, Perkins JA, et al. Tracheotomy in pediatric patients: a national perspective. Arch Otolaryngol Head Neck Surg 2003;129:523–9.