The comorbidities and risk factors in children with congenital airway anomalies: A nationwide population-based study in Taiwan

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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 \(aO.R\), 7.88; 95% confidence interval [CI], 6.49–9.59), chromosome (\(aO.R\), 6.85; 95% CI, 5.03–9.34), and congenital neurologic (\(aO.R\), 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 \(aH.R\), 4.59; 95% CI, 3.85–5.48). The need for tracheostomy \(aH.R\), 2.98; 95% CI, 2.15–4.15), comorbidity with congenital heart disease (CHD) \(aH.R\), 2.52; 95% CI, 2.05–3.10), and chromosome anomaly \(aH.R\), 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: \(aH.R\) = adjusted hazard ratio, \(aO.R\) = adjusted odds ratio, CAA = congenital airway anomaly, CHD = congenital heart disease, CI = confidence interval, \(H.R\) = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, 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. Different types of CAA may have different impact on the clinical course and CAA children have an increased risk of respiratory illness and morbidity. Most of the previous clinical studies regarding CAA have focused on the clinical presentation, diagnostic strategy, and management. The prior studies have also emphasized all categories of congenital anomalies and have included CAA as a subgroup. 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, 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.
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 outpatient, 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 were 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), genetic 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 code 770.7).22-30 Children who received a tracheostomy were identified by the procedure code as 31.1 or 31.2.25,31 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: 2014-08-003AC). 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%).
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).

### 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).

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**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)                  | .595  |
| Age (n, %)                 |                     |                          |       |
| 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, %)              |                     |                          |       |
| 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)               | <.001 |
| 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 (0.2)                  | <.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.

**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 (3.16–5.04) | <.001 |
| Congenital gastrointestinal anomaly | 1.62 (1.39–2.37) | <.001 |
| Congenital genitourinary anomaly | 1.43 (1.16–1.73) | <.001 |
| Prematurity                      | 0.03 (0.83–1.05) | .224 |

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

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**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.
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 CAA patients 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 (32/6196, 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).

### Table 3
Comparison pertaining to the mortality rate in CAA patients.

| Variables                        | Total n=6341 | Mortality n=399 | Rate, % | P  |
|----------------------------------|-------------|-----------------|---------|----|
| Age                              |             |                 |         |    |
| Neonates                         | 1146        | 179             | 15.6    | <.001 |
| Infants                          | 4607        | 181             | 3.9     |    |
| Toddlers and preschoolers        | 558         | 39              | 6.6     |    |
| Gender                           |             |                 |         |    |
| Female                           | 2231        | 175             | 7.5     | .002 |
| 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     | .044 |
| 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.

• 1. P-value for the comparison of mortality rate in CAA patients with and without comorbidity.

• 2. P-value for the comparison of mortality rate in CAA patients with and without tracheostomy.

### Table 4
HR for the risk factors of mortality among CAA children.

| Variables                        | Univariate 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        | 1.00          |            |      |     | 1.00       |      |
| Gender                           |               |            |      |     |            |      |
| Female                           | 1.36          | 1.12–1.66  | .002 | 1.24| 1.02–1.51  | .035 |
| Male                             | 1.00          |            |      |     | 1.00       |      |
| 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.

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
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. [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, 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. [14] 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; [14] 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. [2,8,35] 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. [15–17] 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. [1,16,39] 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, 6.83; 95% CI, 5.03–9.34), and congenital neurologic (aOR, 5.52; 95% CI, 4.43–6.87) 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; [17,21,36–41] 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. [13,33,35,36] 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 children 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 anomalies 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.

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