Acta Cardiol Sin 2021;37:296–304
Original Article
doi: 10.6515/ACS.202105_37(3).20201019C

Pediatric Cardiology

The Postnatal Risk, Resuscitation Success Rate and Outcomes of Pediatric Sudden Death in Taiwan

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Background: The epidemiology of pediatric potentially sudden death (SD) events and the rescue rate remain unclear.

Methods: We established a birth cohort (2000-2014) from a national database 2000-2015.

Results: Of 3,097,277 live births, we identified 3126 children (56.1% male) with potentially SD events, including 887 who were rescued. The cumulative risk of potentially SD events for each neonate was 0.30, 0.62, 0.91, 1.05, and 1.13 per 1000 by 2 months, 0, 5, 11 and 14 years of age, respectively. Overall, 28.3% of the children were rescued from SD events, with a higher rate in neonates (69.6%) but lower rate in postneonatal infants. A cardiac diagnosis was noted in 596 (19.1%) patients, including congenital heart disease (CHD) (388), cardiac arrest (151), cardiomyopathy (23), myocarditis (12), Kawasaki disease (7) and arrhythmia (36). Coexisting severe CHD and events in postneonatal infancy were associated with a lower chance of resuscitation, whereas events within 1 week of age had a higher chance of resuscitation. Anoxic brain damage was noted in 174 (19.7%) patients and late death occurred in 348 (39.3%) patients after being rescued from SD. Late death was more common in males, those with anoxic brain damage, those with coexisting severe CHD, and postneonatal infants.

Conclusions: In this birth cohort study, the postnatal cumulative risk of potentially SD events was 1 in 885 newborns by 14 years of age. Postneonatal infants and those with coexisting severe CHD had the highest risk and worst outcomes.

Key Words: Adolescent • Children • Infant • Potentially sudden death event • Rescued sudden death

INTRODUCTION

Sudden death (SD) in children, although uncommon, is always devastating for the patients, family, care providers and school members. The incidence of SD in children beyond infancy ranges from 1.3 to 6.4/100 000 person-years.[1-10] Sudden death in infants may represent another disease entity, in whom the incidence is higher than in other pediatric age groups, and ranges from 0.10 to 0.80/1000.[11-15] With advances in cardiac pulmonary resuscitation, rescue from unexpected SD events is possible, i.e., rescued SD or aborted cardiac arrest.[16,17] The epidemiological data of potentially SD events, including rescued and non-rescued SD events, and the outcomes of pediatric populations have yet to be defined.

In Taiwan, since the implementation of the National Health Insurance program in 1995, which currently covers over 99% of the population (23 million adults and a pediatric population of approximately 5 million), nearly every child receives full medical services. The child health indices in Taiwan are similar to

Received: April 2, 2020 Accepted: October 19, 2020
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those in the United States.[10] A nationwide birth cohort from Taiwan that contains complete postnatal data would be appropriate for investigating the postnatal cumulative risk of potentially SD events and the outcomes for each neonate.

METHODS

The study design was approved by our institutional research board.

National Health Insurance Database and patient identification

We retrieved the complete healthcare records of children born between January 1st, 2000 and December 31st, 2014 from the National Health Insurance Database for the period from January 1st, 2000, to December 31st, 2015. These children constituted the 2000-2014 birth cohort. The period of postnatal follow-up was 1 to 14 years. We recognized that the definition of potentially SD events was controversial because the time to the onset of the events was not documented in the database. According to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), we defined potentially SD events as patients coded with SD (ICD-9-CM 798). Patients who did not survive to discharge were defined as patients with non-rescued SD events. Patients who had been resuscitated and survived to discharge were defined as patients with rescued SD events.[16,17] Patients who survived to discharge but died during follow-up were defined as late death. The patients with coexisting injury or poisoning were excluded. Each health record had a scrambled identification number and consisted of information including the date of birth, date of visit, sex, type of admission or outpatient clinic visit, diagnosis and treatment codes, reimbursement fees, and survival status at discharge. The identified patients were followed up for coexisting cardiac diseases until December 31, 2015. Their survival status was further confirmed by examining their status in the National Health Insurance Database in December 2015. Coexisting cardiac and non-cardiac diagnoses were also identified from data on coexisting main diagnoses. The coexisting cardiac diagnosis categories selected for the current study were as follows: ischemic heart disease, cardiomyopathy, myocarditis, arrhythmia disorders, congenital cardiac diseases (CHD), and other less common cardiac causes (ie, coronary artery aneurysms).[18] Severe CHD was further identified as in our previous study.[19]

Statistics

The Statistical Package for Social Sciences (SPSS, version 15.0, SPSS Inc., Chicago, IL, USA) was used for analysis. We obtained birth statistical data from the Taiwan National Statistic Yearbook of the Interior (http://sowf.moi.gov.tw/stat/year/list.htm). We classified the patients according to their age at diagnosis, and calculated the age-specific incidence of potentially SD events. We used the chi-squared test and two-sided p values to analyze the associations between variables. Statistical significance was defined as a p value less than 0.05.

RESULTS

Potentially sudden death events

Of 3,097,277 live births during 2000-2014, we identified 3126 patients who had potentially SD events. Over half (61.6%) of the potentially SD events occurred during infancy. Figure 1 presents the annual incidence of potentially SD events by age group. The annual incidence of potentially SD events was particularly high (62.2/100,000) during infancy. The annual incidence rates of potentially SD events in preschool (aged 1-5 years), elementary school (aged 6-11 years) and junior

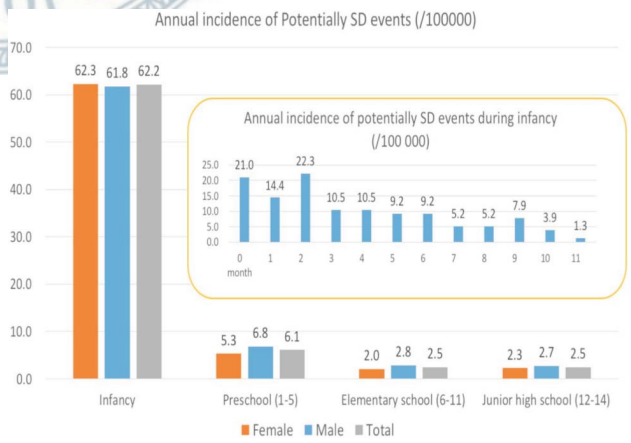


Figure 1. *The annual incidence of potentially SD event was particularly high (62.2/100 000) during infancy. During the infancy, the annual risk of potentially SD events increased to a peak at age 2 months and then decreased gradually. SD, sudden death.*

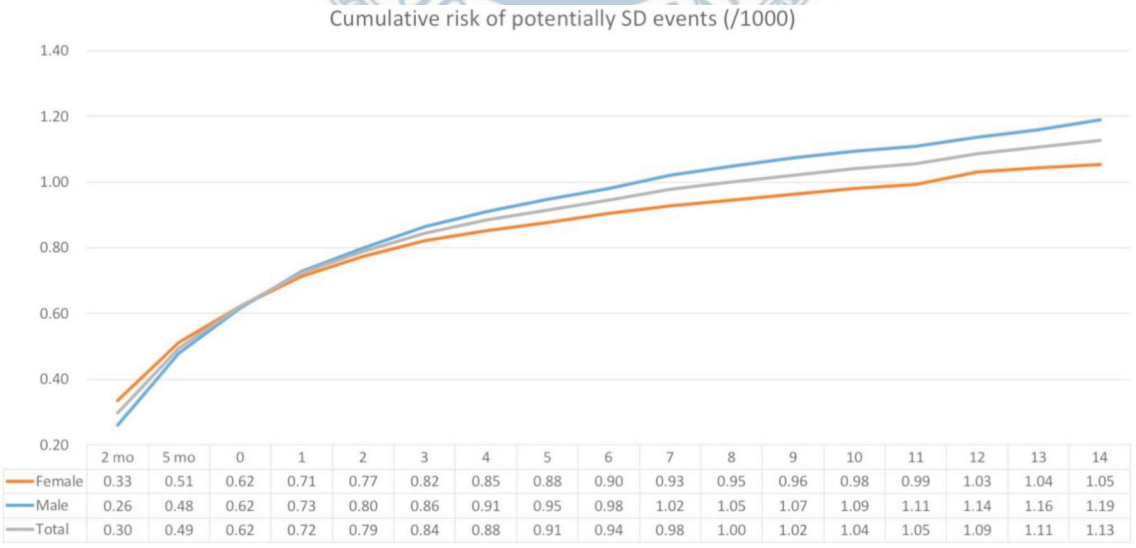
high school (aged 12-14 years) aged children were 6.1, 2.5 and 2.5/100,000 person-years, respectively. The male/female ratios of the annual incidence were 0.99, 1.29, 1.40 and 1.20, respectively. During infancy, the annual risk of potentially SD events increased to a peak at 2 months of age, and then decreased gradually. As shown in Figure 2, the cumulative risk of potentially SD events for each neonate was 0.30, 0.62, 0.91, 1.05, and 1.13 per 1000 newborns by 2 months, 0, 5, 11 and 14 years of age, respectively. Males were associated with a higher risk of potentially SD events [incidence rate ratio: 1.18, 95% confidence interval (CI): 1.08-1.28].

Rescued SD events accounted for 28.3% of all the potentially SD events. Two patients received ICD after the rescued SD events at 13.5 and 1.5 years of age, respectively, and were alive at the latest follow-up. The proportions of rescued SD events to potentially SD events were similar across the four age groups (Figure 3A). However, during infancy, neonates (aged < 1 month) had a higher chance of resuscitation (69.6%, Figure 3B), whereas postneonatal infants had a lower chance of resuscitation (range 15.2-37.2%, median 20.5%). In addition, the neonates in whom potentially SD events occurred within the age of 1 week had the highest chance (80.9%) of being resuscitated (Figure 3C).

Coexisting cardiac diagnosis

Coexisting cardiac diagnoses were present in 596 (19.1%) patients, including CHD in 388 (12.4%), cardiac arrest in 151 (4.8%), cardiomyopathy in 23 (0.7%), myocarditis in 12 (0.3%), arrhythmias in 36 (1.1%), and Kawasaki disease in 7 (0.2%). Multiple (more than one) cardiac diagnoses were present in 28 (0.9%) patients. Severe forms of CHD were noted in 80 patients, including tetralogy of Fallot in 34 patients, complex CHD (with ≥ 3 CHD lesions and 2 severe CHD lesions) in 28, transposition of great arteries in 6, hypoplastic left heart syn-

Figure 3. *(A) The overall rescued/potentially SD events from birth till 14 year-old was 28.3%. (B) During the whole infancy, the chance of successful rescues was highest in the first month of life. (C) During the newborn stage, the chance of successful rescues was highest in first week of life. SD, sudden death.*



	2 mo	5 mo	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Female	0.33	0.51	0.62	0.71	0.77	0.82	0.85	0.88	0.90	0.93	0.95	0.96	0.98	0.99	1.03	1.04	1.05
Male	0.26	0.48	0.62	0.73	0.80	0.86	0.91	0.95	0.98	1.02	1.05	1.07	1.09	1.11	1.14	1.16	1.19
Total	0.30	0.49	0.62	0.72	0.79	0.84	0.88	0.91	0.94	0.98	1.00	1.02	1.04	1.05	1.09	1.11	1.13

Figure 2. *The cumulative risk of potentially SD events for each neonate was 0.30, 0.62, 0.91, 1.05, and 1.13 per 1000 newborns by age 2 months, 0, 5, 11 and 14 years of age, respectively. Male gender was associated with higher risk of potentially SD events. SD, sudden death.*

drome in 6, tricuspid atresia in 4, double outlet right ventricle in 3, total anomalous pulmonary venous return in 3, and truncus arteriosus in 1. Other forms of CHD were secundum atrial septal defect in 116, patent ductus arteriosus in 82, ventricular septal defect in 57, endocardial cushion defect in 15, pulmonary stenosis/atresia in 20, coarctation of aorta in 8, aortic stenosis in 4, and others in 40 patients. The arrhythmia diagnoses included ventricular tachycardia/fibrillation in 14, Wolff-Parkinson-White syndrome in 9, atrial fibrillation in 1 and supraventricular tachycardia in 1, as well as bradycardia in 4 (2 sick sinus syndrome and 2 complete atrioventricular block).

Coexisting non-cardiac diseases

Coexisting non-cardiac diagnoses were present in 545 (17.4%) patients, including epilepsy in 387 (12.4%), cerebral palsy in 159 (5.1%), other central nervous system diseases in 22 (0.7%), asthma in 54 (1.7%), prematurity and perinatal disease in 39 (1.2%) and congenital non-cardiac anomaly in 22 (0.7%) patients. Multiple causes were present in 136 patients (4.4%).

Risk analysis for the outcomes of potentially SD events

As shown in Table 1, the factors associated with non-rescued SD events were coexisting cardiac disease [odds ratio (OR) = 1.48, 95% CI: 1.18-1.85, p = 0.001] and the age at a potentially SD event. The risk was particularly low in those in whom the events occurred within the age of 1 week (OR = 0.13, 95% CI: 0.07-0.24, p < 0.001), but high in whom the events occurred during postneonatal infancy (age 1-11 months) (OR = 2.41, 95% CI: 1.42-4.08, p = 0.001).

After the successful resuscitation, anoxic brain damage was noted in 174 (19.7%) patients. Male gender (OR = 1.61, 95% CI: 1.08-2.39, p = 0.020) and coexisting non-cardiac disease (OR = 7.15, 95% CI: 4.67-10.94, p < 0.001) were associated with a higher risk of anoxic brain injury. Among the patients with rescued SD events, late death still occurred in 348 (39.3%) at a median of 7 (184 ± 612) days after the rescued SD event. Late death was more likely in males (OR = 1.77, 95% CI: 1.29-2.42, p < 0.001), those with anoxic brain injury (OR = 3.09, 95% CI: 2.10-4.54, p < 0.001), and in postneonatal infants (OR = 2.87, 95% CI: 1.12-7.35, p = 0.029).

Risk analysis of potentially SD events in the subgroup with cardiac diagnoses

As shown in Table 2, risk analysis in the subgroup with coexisting cardiac disease revealed that coexisting severe CHD (OR = 2.52, 95% CI: 1.21-5.21, p = 0.013) and preexisting myocardial disease (myocarditis and cardiomyopathy) (OR = 10.98, 95% CI: 1.48-81.58, p = 0.019) increased the risk of non-rescued SD events. In contrast, coexisting tachyarrhythmias (OR = 0.25, 95% CI: 0.11-0.57, p = 0.001) was associated with a higher chance of successful resuscitation. Among those with rescued SD events in this subgroup, coexisting severe CHD (OR = 11.4, 95% CI: 1.35-91.84, p = 0.025) was associated with the highest risk of late death.

DISCUSSION

The epidemiological profile of potentially SD events and the rescue rate in pediatric populations remain unclear. This study is the first to be conducted on the basis of a birth cohort derived from a national database with complete postnatal data. We estimated the cumulative incidence of potentially SD events for each neonate, and the novel findings were as follows. First, the postnatal cumulative incidence of potentially SD events was 1.13 per 1000 newborns by the age of 14 years. Second, rescued SD events accounted for 28.3% of the patients with potentially SD events. However, late death still occurred in 39.3% of those with rescued SD events. Third, potentially SD events during postneonatal infancy and coexisting cardiac diseases, particularly the severe forms of CHD and myocardial disease, increased the risk of not being rescued.

The incidence of SD events and the outcomes in pediatric populations are still unknown. All previous studies have investigated the incidence of SD in different age groups using cross-sectional cohorts, and the postnatal cumulative risk of SD or potentially SD events (including rescued and non-rescued SD) has never been described.[2,4-10,20] Some surveillance studies have reported the epidemiology of apparently life-threatening events during infancy, however apparently life-threatening events and SD events are different disease entities, even though they may share some similarities.[21,22] In the Netherlands, a country with a very low incidence of SD

Table 1. Risk analysis of the outcomes for the patients with potentially sudden death events from a birth cohort 2000-2014

Variables	Non-rescued					
	Yes (n = 2242)	No (n = 884)	X^2 test	Multivariate analysis of non-resuscitated		
			p value	Odd ratio	95% CI	p value
Male	1258 (56.1%)	445 (50.3%)	0.005	0.96	0.81-1.14	0.630
Coexisting cardiac disease	465 (20.7%)	122 (13.8%)	< 0.001	1.56	1.24-1.96	< 0.001
Coexisting non-cardiac disease	400 (17.8%)	145 (16.4%)	0.340			
Age at potentially SD events: months*	0.52 (1.86 ± 2.79)	0.53 (2.10 ± 3.20)	0.044			
Age range						
0-1 week	45 (2.0%)	190 (21.5%)	< 0.001	0.129	0.07-0.24	< 0.001
1 week-0 month	52 (2.3%)	33 (3.7%)	0.029	0.92	0.47-1.81	0.801
1-11 months	1297 (57.9%)	310 (35.1%)	< 0.001	2.40	1.41-4.08	0.001
1-5 years	631 (28.1%)	243 (27.5%)	0.713	1.45	0.85-2.48	0.174
6-11 years	176 (7.9%)	85 (9.6%)	0.108	1.09	0.61-1.94	0.771
12-14 years	41 (1.8%)	23 (2.6%)	0.169		reference	
Variables	Anoxic brain injury					
	Yes (n = 174)	No (n = 710)	X^2 test	Multivariate analysis		
			p value	Odd ratio	95% CI	p value
Male	117 (67.2%)	328 (46.2%)	< 0.001	1.61	1.08-2.39	0.020
Coexisting cardiac disease	23 (13.2%)	99 (13.9%)	0.804			
Coexisting non-cardiac disease	79 (45.4%)	66 (9.3%)	< 0.001	7.15	4.67-10.94	< 0.001
Age at potentially SD events: months*	0.72 (1.93 ± 2.83)	0.48 (2.14 ± 3.29)	0.453			
Age range						
0-1 week	5 (2.9%)	185 (26.1%)	< 0.001	0.30	0.07-1.32	0.110
1 week-0 month	1 (0.57%)	32 (4.6%)	0.014	0.32	0.03-3.38	0.346
1-11 months	95 (54.6%)	215 (30.3%)	< 0.001	2.99	0.90-9.94	0.074
1-5 years	57 (32.8%)	186 (26.2%)	0.082	2.16	0.64-7.28	0.216
6-11 years	12 (6.9%)	73 (10.3%)	0.175	1.14	0.30-4.37	0.845
12-14 years	4 (2.3%)	19 (2.7%)	0.779		reference	
Variables	Late Death					
	Yes (n = 348)	No (n = 536)	X^2 test	Multivariate analysis		
			p value	Odd ratio	95% CI	p value
Male	218 (40.9%)	324 (65.2%)	< 0.001	1.74	1.27-2.39	0.001
Coexisting cardiac disease	59 (17.0%)	63 (11.8%)	0.029	1.44	0.94-2.22	0.095
Coexisting non-cardiac disease	61 (17.5%)	84 (15.7%)	0.466			
Anoxic brain injury	119 (34.2%)	55 (10.3%)	< 0.001	3.13	2.13-4.60	< 0.001
Age at potentially SD events: months*	0.64 (2.10 ± 3.11)	0.42 (2.10 ± 3.27)	0.999			
Age range						
0-1 week	19 (5.5%)	171 (31.9%)	0.122	0.37	0.13-1.07	0.065
1 week-0 month	12 (3.4%)	21 (3.9%)	0.719	1.65	0.51-5.38	0.407
1-11 months	181 (52.0%)	212 (24.1%)	< 0.001	2.94	1.13-7.62	0.026
1-5 years	96 (27.6%)	147 (27.4%)	0.958	1.41	0.54-3.69	0.483
6-11 years	32 (9.2%)	53 (9.9%)	0.733	1.42	0.51-3.99	0.502
12-14 years	8 (2.8%)	15 (2.3%)	0.648		reference	

CI, confidence interval; SD, sudden death. * Median (mean ± SD).

during infancy, the incidence rates of apparently life-threatening and SD events during infancy have been reported to be 0.58/1000 and 0.09/1000, respectively.[21] None of the infants with apparently life-threatening events died from SD during follow-up.[22]

As shown in the current study, based on a study cohort with complete postnatal medical data, the cumulative incidence rates of potentially SD events were 0.62 and 1.13 per 1000 newborns at 0 and 14 years of age, respectively. Over half (61.6%) of the potentially SD

Table 2. Risk analysis of the outcomes for the patients with potentially sudden death events from a birth cohort 2000-2014 who had coexisting cardiac diagnoses

Variables	Non-rescued					
	Yes (n = 465)	No (n = 131)	X^2 test	Multivariate analysis of non-resuscitated		
			p value	Odd ratio	95% CI	p value
Male	251 (55.2%)	74 (56.9%)	0.536			
Congenital heart disease	299 (64.3%)	89 (67.9%)	0.440			
Severe CHD*	71 (15.3%)	9 (6.9%)	0.013	3.25	1.61-6.56	0.001
Arrhythmias	22 (4.7%)	14 (10.7%)	0.011			
Tachyarrhythmias	12 (2.6%)	13 (9.9%)	< 0.001	0.32	0.14-0.71	0.001
WPW	5 (10.8%)	4 (3.1%)	0.101			
Brayarrhythmias	8 (1.7%)	1 (0.8%)	0.428			
Myocardial disease	34 (7.3%)	1 (0.8%)	0.005	14.01	1.91-103.0	0.010
Cardiac arrest	126 (27.1%)	25 (19.1%)	0.063			
Kawasaki disease	5 (1.1%)	2 (1.5%)	0.672			
Age at SD events: median (mean ± SD) months	8.00 (24.87 ± 35.02)	6.00 (27.78 ± 44.72)	0.432			

Variables	Anoxic brain injury					
	Yes (n = 23)	No (n = 108)	X^2 test	Multivariate analysis		
			p value	Odd ratio	95% CI	p value
Male	56 (52.3%)	328 (81.8%)	0.066			
Congenital heart disease	15 (65.2%)	74 (68.5%)	0.758			
Severe CHD*	1 (4.3%)	8 (7.4%)	0.598			
Arrhythmias	4 (17.4%)	10 (9.3%)	0.252			
Tachyarrhythmias	4 (17.4%)	9 (8.3%)	0.187			
WPW	1 (4.3%)	3 (2.8%)	0.691			
Brayarrhythmias	0	1 (0.9%)	0.643			
Myocardial disease	0	1 (0.9%)	0.643			
Cardiac arrest	3 (13.0%)	22 (20.4%)	0.417			
Kawasaki disease	0	2 (1.9%)	0.511			
Age at SD events: median (mean ± SD) months	7.00 (28.43 ± 44.72)	5.50 (27.64 ± 44.41)	0.939			

Variables	Late death					
	Yes (n = 59)	No (n = 72)	X^2 test	Multivariate analysis		
			p value	Odd ratio	95% CI	p value
Male	38 (65.5%)	36 (50.7%)	0.192			
Congenital heart disease	45 (76.3%)	44 (61.1%)	0.064			
Severe CHD*	8 (13.6%)	1 (1.4%)	0.006	11.14	1.35-91.84	0.025
Arrhythmias	3 (5.1%)	11 (15.3%)	0.060			
Tachyarrhythmias	3 (5.1%)	10 (13.9%)	0.094			
WPW	2 (3.4%)	2 (2.8%)	0.839			
Brayarrhythmias	0	1 (1.4%)	0.364			
Myocardial disease	1 (1.4%)	0	0.364			
Cardiac arrest	11 (18.6%)	14 (19.4%)	0.908			
Kawasaki disease	0	2 (2.8%)	0.197			
Anoxic brain injury	11 (18.6%)	12 (16.7%)	0.767			
Age at SD events: median (mean ± SD) months	6.00 (26.61 ± 42.54)	5.00 (28.74 ± 46.70)	0.788			

* Severe CHD: Tetralogy of Fallot, Transposition of great arteries, Double outlet of right ventricle, Truncus arteriosus, complex CHD, Hypoplastic left heart syndrome, tricuspid atresia.[19]

CHD, congenital heart disease; CI, confidence interval; SD, sudden death; WPW, Wolff-Parkinson-White syndrome.

events occurred during infancy. The annual incidence of potentially SD events during infancy (62.2 per 100,000) was 10 times or more than any other age groups. Previous studies have reported that the incidence of SD was much higher during infancy than in any other age group of children and adolescents.[1-15] Our study indicated that the risk of potentially SD events during infancy was even higher. Nevertheless, the chance of successful resuscitation from potentially SD events was relatively high in the neonates (69.6%), particularly in the neonates aged within 1 week (80.9%). Because newborns usually stay in the hospital for 3-5 days after birth, they have a higher chance of being successfully rescued during a potentially SD event. However, the chance of successful resuscitation decreased to only a median of 20.5% (range 15.2-37.2%) in the postneonatal infants (aged 1-11 months). Due to the high incidence of potentially SD events and lowest chance of successful resuscitation, the postneonatal infants were the most vulnerable group in our pediatric population. This age-related difference may be due to differences in maturation and organ reserve, disease spectrum, and presenting rhythm, etc., however it remains mostly undefined. Although gender is a known predictor of survival in adults, data for children are inconsistent.[23-25] In the current study, male gender was associated with a higher risk of potentially SD events and worse outcomes (anoxic brain injury and late death) if resuscitated.

The neurological outcomes of pediatric SD events are ill-defined. In a previous study of out-of-hospital cardiac arrest, which also enrolled children and young adults with SD events, 91% of those who survived to 30 days had a cerebral performance category score of 1 or 2 (good cerebral performance or moderate cerebral disability) at hospital discharge.[24] Long-term neurological deficits were noted in 13% of the survivors.[26] In the current study, anoxic brain damage was noted in 19.7% of those who were rescued from potentially SD events, and was associated with late death after the rescued SD event. This suggests that the presence of neurological deficits may reflect the severity of sequelae from potentially SD events.

Coexisting cardiac diseases carry a significant risk of SD in pediatric populations.[7,8,27] In this study, 19.1% of the patients had a coexisting cardiac diagnosis as an independent risk factor for non-rescued SD. Subgroup analysis revealed significant risks from severe CHD and myocardial diseases. In contrast, coexisting tachyarrhythmias were associated with a higher chance of being rescued from potentially SD events. An initial shockable rhythm has been identified as an independent factor associated with survival to discharge among children with out-of-hospital cardiac arrest.[28]

Coexisting non-cardiac diagnoses, as an independent risk factor of anoxic brain damage, were presented in 17.4% of the patients. Nevertheless, the majority of our children who suffered from potentially SD events did not have underlying diseases identified prior to the events. Modern techniques such as molecular autopsy may help to reveal the etiology of unexplained SD, such as long QT syndromes.[29-31] Comprehensive molecular screening plays an important role in secondary prevention among survivors and affected families.[1]

Limitations

Our findings were robust, however there are still some limitations to this study. First, we were not able to assess the medical charts of the patients directly because the birth cohort was derived from the National Health Insurance Database. The coexisting diseases may have been underdiagnosed and the severity of organ damage after the potentially SD events could not be assessed. Second, some patients died suddenly before reaching the hospital. They might not have had an accurate diagnosis, and hence the incidence of potentially SD events may have been underestimated. Third, with the age distribution of the cohort, we may have underestimated the number of children who had potentially SD events after 10 years of age. Finally, children older than 15 years, considered to be a vulnerable age group for SD, could not be examined in this study.

CONCLUSIONS

This birth cohort study provides data of the postnatal cumulative risk of potentially SD events (1 in 885) by 14 years of age. Over half of the events occurred during infancy. Postneonatal infants and those with coexisting severe CHD were at the highest risk of such events and had the worst outcomes.

CONFLICTS OF INTEREST

The authors have indicated they have no potential conflicts of interest to disclose.

FUNDING SOURCE

This study was supported by grants from Taiwan Ministry of Science and Technology (106-2314-B-002-208-MY1).

FINANCIAL DISCLOSURE

The authors have no financial relationships relevant to this article to disclose.

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