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Factors influencing outcome of inpatient pediatric resuscitation

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The aims of this study were: 1) To define the rate of long-term survivors (LTS) after cardiopulmonary resuscitation (CPR) in children; 2) To identify the predictors of survival in pediatric resuscitation; and 3) To assess the outcome six months after discharge. Three groups of patients were identified based on outcome: 1. Long-term survivors (LTS), who were discharged, 2. Short-term survivors (STS), who survived longer than 24 hours after CPR but not until discharge, and 3. Nonsurvivors (NS), who died within 24 hours after their arrest.

Of the 67 patients, 10 (14.9%) children were STS, while 46 (68.7%) were NS. Only eleven (16.4%) were LTS who were eventually discharged from the hospital and six were alive six months after discharge. Four patients had neurological sequelae.

Less than 5 minutes' duration of CPR and reactive pupils at the onset of cardiopulmonary arrest (CPA) were the most important factors that predicted long term survival.

We suggest that a positive pupillary light reflex at the onset of CPA and the duration of CPR should be considered as important predictors of survival in children with CPA.

Key words: pediatric life support, cardiopulmonary resuscitation, outcome, cardiopulmonary arrest.

Pediatric cardiopulmonary arrest (CPA) as a sudden event is not common during childhood[1]. In a retrospective survey of arrests, Eisenberg et al.[2] found an incidence of 12.7/100,000 in children under 18 years of age.

Cardiopulmonary arrest is often the end result of a progressive deterioration in respiratory and circulatory functions[3]. The outlook for survival after life support is very good for pediatric patients. For patients in the emergency department, the outcome is not as good, and reported outcomes of cardiopulmonary resuscitation (CPR) in infancy and childhood are variable[2,4-8]. Some of the variability arises from the lack of clear distinction in many published reports between a respiratory arrest, which can often have a good outcome[2,6,9], and a cardiac arrest, which has a much worse outcome[2,5,10].

In general, the outcome of cardiac arrest in children is worse than the outcome of cardiac arrest in adults[11]. This difference is attributed to the difference in the pathogenesis of cardiac arrest between adults and children. The most common cause of cardiac arrest in adults is cardiac diseases, whereas it is respiratory failure in children. Within the pediatric age group, there are different underlying causes of cardiac arrest at different ages. Asphyxia is the commonest cause of cardiac arrest at birth. In infancy and later childhood, the most common causes are respiratory illnesses followed by sepsis and trauma[12]. Accidents are the most frequent cause of mortality among children older than one year. CPR in trauma life support should be adapted to the special features of trauma[13].

Studies that have been published on this subject use different terminology and methodology in data collection, which makes comparisons, evaluation of efficacy, and the performance of meta-analyses etc. difficult[14]. The reported survival rates of inpatient pediatric CPR range from 15 to 65%[4,6,7,10,15-18].

The aims of this study were: 1) To define the rate of long-term survivors (LTS) after CPR in children, 2) To identify the predictors of survival in pediatric resuscitation, and 3) To assess the outcome six months after discharge.

Material and Methods

Sixty-seven consecutive series of patients presenting with CPA at the Department of Pediatrics of Istanbul University over a 10-month period were evaluated prospectively. Three groups of patients were identified based on outcome: 1. Long-term survivors (LTS), who were discharged, 2. Short-term survivors (STS), who survived longer than 24 hours after CPR but not until discharge, and 3. Nonsurvivors (NS), who died within 24 hours after their arrest. LTS were followed for six months.

Advanced life support, which included ventilation, chest compressions, and drug administration in all patients, was performed according to the standards established by the American Heart Association, the American Academy of Pediatrics and the European Resuscitation Council[3,12,19-21]. All doctors and nurses who practiced CPR had attended either the Pediatric Advanced Life Support (PALS) Education Programs at the Emergency Department (ED) or a PALS course for two days at the Department of Pediatrics.

The following definitions from the American Heart Association and European Resuscitation Council were used: respiratory arrest = no spontaneous ventilation; cardiac arrest = no cardiac output by palpation or auscultation; and cardiorespiratory arrest = absence of both spontaneous ventilation and cardiac output[22]. The first one recognizing a patient with CPA was either a doctor or a nurse and the CPR was given by one or more physicians and two nurses. A medical technician also attended the procedure at the ED during the daytime.

Data pertaining to the prearrest, arrest, and postarrest periods were obtained and evaluated. The prearrest data included: age, sex, diagnosis and Glasgow coma scale. The arrest data included: location and type of arrest, electrocardiographic rhythm at onset of CPR, pupillary light and cornea reflex at the onset of CPR, resuscitation drugs given, duration of CPR (CPR start-stop interval), blood pH and bicarbonate level during CPR, and number of rescuers. The postarrest data recorded included: return of spontaneous circulation (ROSC) time and return of spontaneous respiration (ROSR) time.

Subjects were assigned a diagnostic category based on their primary diagnosis (underlying primary diseases such as perinatal asphyxia, chronic renal failure, etc.) and secondary diagnoses (complications of underlying primary diseases such as acute gastroenteritis, convulsion, etc.). Sepsis syndrome was diagnosed in patients with: a) clinical evidence of infection, b) fever (temperature >38.3°C), c) tachycardia, d) tachypnea, and e) white blood cell count abnormalities[23]. The duration of CPR was defined from initiation of life support measures until restoration of spontaneous circulation such as acceptable cardiac output, blood pressure, and normal sinus rhythm[24].

The number of LTS was compared with the total number of STS and NS by the chi-square test and the values of $p<0.05$ were considered as statistically significant. Variables found to be significant were then tested in a stepwise multiple logistic-regression analysis and independent predictors of outcome were identified. Beta coefficients from significant independent predictors were converted to adjusted odds ratios with 95 percent confidence intervals.

Results

Of the 67 patients, 10 (14.9%) children were STS, while 46 (68.7%) children were NS. Only 11 children (16.4%) were LTS who were eventually discharged from the hospital and six of them were alive at six months after discharge. Five (45.4%) of the 11 LTS died in an average of 2.2 months (2 weeks-5 months) after discharge from the hospital. Of the six patients alive at six months after discharge, two (33.3%) children were without neurological sequela, while four (66.7%) children were with moderate-to-severe neurological sequelae (Fig. 1). Of four patients with neurological sequelae, two died eight and nine months after discharge, respectively. The other two patients without neurological sequelae were still alive one year after discharge.

Most CPAs (73.2%) occurred in patients under the age of one year. The median age of the 67 patients was 28.5±55.3 months (range: 1 month-18 years). The difference between age and LTS was not statistically significant (p: 0.71).

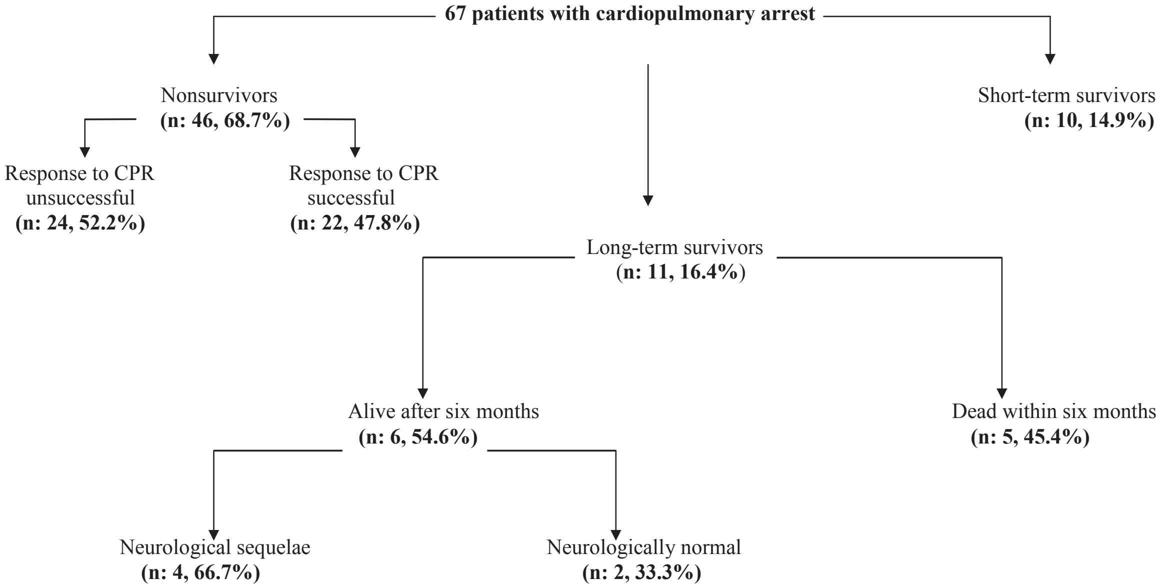

Fig. 1. Outcome of pediatric cardiopulmonary resuscitation.

Of the 67 patients studied, 39 were male (58.2%) and 28 were female (41.8%). The male/female ratio was 1.4. The difference between sex and the rate of LTS was not statistically significant (p: 0.077).

Sixty-seven patients had a total of 118 diagnoses according to primary diagnosis and secondary diagnoses. Table I shows the underlying disease categories for the 67 arrest victims. The most common diagnosis involved was sepsis syndrome (21.2%). The remainder of the subjects were classified into the following categories: central nervous system diseases (20.3%), cardiovascular (17%), respiratory (15.3%), gastrointestinal (8.5%) and others (17.7%). Of 40 patients with underlying congenital or chronic disease, only three were LTS, while 8 of 27 patients with no underlying congenital or chronic disease survived for the long-term. The difference was statistically significant (p: 0.020). Of 25 patients with sepsis syndrome, only two were LTS. Table II shows the diagnosis categories according to the underlying congenital or chronic disease.

Of 24 patients with Glasgow coma scale (GCS) equal or above eight, 10 were LTS, versus only one of 43 patients with GCS below eight. The difference was statistically significant (p: 00007).

Locations of CPR were emergency observation room (n: 12), emergency department (n: 4), pediatric intensive care unit (PICU) (n: 29) and other pediatric units (n: 22). Statistical analysis revealed no significant correlation between LTS and location of CPR during arrest (p: 0.29).

Among the patients, 10 had respiratory arrest only (i.e., they had a palpable pulse and no spontaneous ventilation throughout resuscitation) and did not require chest compression; five of these (50%) survived to hospital discharge. Of the 57 patients who had a cardiac-respiratory arrest, only six patients (10.5%) survived to hospital discharge. A statistically significant relationship between outcome and type of arrest was found ($p<0.007$).

ECG rhythm strips documenting cardiac rhythm were available for 28 patients. The most prevalent cardiac rhythms during arrest were asystole and terminal bradycardia. Asystole was the most common rhythm, accounting for 22 cardiac arrests (78.6%). In this study, only one patient presented with ventricular fibrillation and did not survive. Of the 22 patients with asystole, only two (9%) were LTS, while four of five (80%) patients with bradycardia or normal rhythm survived for the long-term.

Table I. Diagnoses of Hospitalized Pediatric Patients Requiring CPR (N: 67)

Diagnoses	Number of patients (%)
Sepsis syndrome	25 (21.2)
Central nervous system	24 (20.3)
Perinatal asphyxia	4
Meningitis*	6
Convulsion*	4
Acute encephalopathy*	2
Intracranial hemorrhage	2
Hydrocephalus	2
Corpus callosum agenesis	1
Brain tumors	1
Guillain-Barré syndrome	1
Microcephaly	1
Cardiovascular	20 (17)
Congenital heart disease	12
Myocarditis*	3
Cardiac tamponade*	4
Rheumatic heart disease	1
Respiratory	18 (15.3)
Pneumonia*	10
Bronchiolitis	3
Respiratory distress syndrome*	2
Pneumothorax*	2
Foreign body aspiration	1
Gastrointestinal	10 (8.5)
Acute gastroenteritis*	3
Severe malnutrition	3
Extrahepatic biliary atresia	2
Necrotizing enterocolitis*	1
Intestinal volvulus	1
Others	21 (17.7)
Prematurity	8
Multiple malformation syndrome	3
Chronic renal failure	4
Immunodeficiency	2
Malignant tumors (extracranial)	1
Unknown	3
Total Number	118

• Sixty-seven patients had a total of 118 diagnoses. Eighty-one were primary diagnosis, thirty-seven were secondary diagnosis (10 patients had more than 1 primary diagnosis).

* Secondary diagnosis.

Relation between ECG rhythm at the onset of CPA (asystole and other rhythm) and LTS was found to be significant (p: 0.0095).

The pupillary light and cornea reflexes at the onset of CPR were evaluated in 64 and 43 patients, respectively. Of 34 patients with reactive pupils, 10 were LTS, while only one of 30 patients with nonreactive pupils survived for the long-term. The difference was statistically significant (p: 0.0057). Of 26 patients with a positive cornea reflex, nine were LTS, while only one of 17 patients without a cornea reflex was LTS. The difference was statistically significant (p: 0.03).

Adrenaline administration was not required in 12 patients. In this group, six patients (45%) were LTS. Eight patients received one dose (0.01 mg/kg/dose), and forty-seven patients received more than one dose of adrenaline; of these, three (37.5%) and two (4.2%) were

Table II. Underlying Congenital or Chronic Diseases in 67 Patients

Categories of diseases	Number of patients
Congenital diseases	19
Corpus callosum agenesis	1
Microcephaly	1
Congenital heart disease	12
Multiple malformation syndrome	3
Immunodeficiency	2
Chronic diseases	21
Perinatal asphyxia	4
Intracranial hemorrhage	2
Hydrocephalus	2
Brain tumors	1
Guillain-Barré syndrome	1
Rheumatic heart disease	1
Protein-calorie malnutrition	3
Extrahepatic biliary atresia	2
Chronic renal failure	4
Malignant tumors (extracranial)	1
Other diseases	78
Sepsis syndrome	25
Meningitis	6
Convulsion	4
Acute encephalopathy	2
Myocarditis	3
Cardiac tamponade	4
Pneumonia	10
Bronchiolitis	3
Respiratory distress syndrome	2
Pneumothorax	2
Foreign body aspiration	1
Acute gastroenteritis	3
Necrotizing enterocolitis	1
Intestinal volvulus	1
Prematurity	8
Unknown	3
Total Number	118

LTS, respectively. The difference between patients who received one or more than one dose of adrenaline was statistically significant (p: 0.002).

Cardiopulmonary resuscitation duration correlated inversely with LTS. Three of the four patients (75%) resuscitated for 5 minutes or less survived to be discharged from the hospital, compared with eight of the 63 patients (12.7%) in whom CPR lasted longer than 5 minutes. Differences between survival rates according to the duration of CPR were significant (p: 0.012).

The blood pH and bicarbonate levels were evaluated in 42 patients. The blood pH during CPR was equal or below 7.0 in 27 of 42 children, and the initial pH was above 7.0 in 15 of 42 children (p: 0.0048). The blood bicarbonate level during CPR was equal or below 10 in 16 of 42 children, and the initial bicarbonate level was above 10 in 26 of 42 children (p: 0.10).

At least one doctor and two nurses gave CPR. In 40 patients, three to five professionals were involved, while more than five professionals were involved in 27 patients. In these groups, LTS rate was 22.5% (9 patients) and 7.4% (2 patients), respectively. We did not find any correlation between the number of rescuers and the outcome (p: 0.094).

The ROSC and the ROSR times were determined in 42 and 45 patients, respectively. The ROSC time was equal to or less than 5 minutes in 7 survivors, although it was longer than 5 minutes in 4 survivors. This finding was determined to be significant (p: 0.010). The ROSR time was equal to or less than 5 minutes in 4 survivors, although it was longer than 5 minutes in 2 survivors. This finding was also determined to be significant (p: 0.042).

The results of our study related to the factors associated and not associated with LTS are shown in Table III.

Variables found to be significant were subsequently tested in a stepwise multiple logistic-regression analysis, and independent predictors

Table III. Predictors Associated and Not Associated With LTS After a Cardiac or Respiratory Arrest

Variable	Survival to hospital discharge (N: 11)	STS and NS (N: 56)	P Value
Prearrest			
Age			0.71
<1 years old (n: 49)	9	40	
≥1 years old (n: 18)	2	16	
Sex			
Female (n: 28)	2	26	0.077
Male (n: 39)	9	30	
Underlying congenital or chronic disease*			
Yes (40)	3	37	0.020
No (27)	8	19	
Glasgow Coma Scale (GCS)*			
< 8 (43)	1	42	
≥ 8 (24)	10	14	0.00007
During arrest			
Location of CPR			
Emergency observation room (12)	3	9	
Emergency department (4)	–	4	
Pediatric intensive care (29)	5	24	
Other pediatric units (22)	3	19	0.29
Type of Arrest*			
Respiratory without cardiac (10)	5	5	0.007
Respiratory and cardiac (57)	6	51	
Electrocardiographic rhythm onset CPR*			
Asystole (22)	2	20	0.0095
Other (6) (1 VF, 5 bradycardia or normal rhythm)	4	2	
Reactive pupils*			
No (30)	1	29	0.0057
Yes (34)	10	24	
Cornea reflex at the onset of CPR*			
No (17)	1	16	0.03
Yes (26)	9	17	
Number of epinephrine doses given*			
1 dose (8)	3	5	
> 1 doses (47)	2	45	0.002
CPR duration*			
≤ 5 min (4)	3	1	0.012
> 5 min (63)	8	55	
Blood pH level during CPR*			
≤ 7 (27)	3	24	0.0048
>7 (15)	8	7	
Blood bicarbonate level during CPR			
≤ 10 (16)	2	14	
> 10 (26)	9	17	0.10
Number of rescuers			
≤ 5 persons (40)	9	31	
> 5 persons (27)	2	2	0.094
Postarrest			
Return of spontaneous circulation (ROSC)*			
≤ 5 min (13)	7	6	0.010
> 5 min (29)	4	25	
Return of spontaneous respiration (ROSR)*			
≤ 5 min (10)	4	6	
> 5 min (25)	2	23	0.042

*Statistically significant. STS: Short-term survivors. NS: Nonsurvivors. VF: Ventricular fibrillation.

of outcome were found to be less than 5 minutes' duration of CPR and reactive pupils at the onset of CPR.

Discussion

Little is known about prognostic factors that determine the outcome after in-hospital CPR. Out-of-hospital pediatric arrests have survival rates ranging from 2% to 25%[10,25-31]. On the other hand, inpatient pediatric arrests have better results, ranging from 15% to 65%[4,6,7,10,15-18,31-33]. In our study, of the 67 patients, 10 (14.9%) were STS, while 46 (68.7%) children were NS. Only 11 children (16.4%) were LTS and eventually discharged from the hospital and six of them were alive for six months after discharge (Fig. 1). In this report, LTS rate was similar to the rates of previous studies of inpatient pediatric arrests, which range from 15% to 65%[4,6,7,10,15-18].

In our study, most CPA (73.2%) occurred in patients under the age of one year. This was also similar to the rates in other studies of CPR in children[5,7,9,10,17,26,34,35]. The difference between age and the rate of LTS was not statistically significant (p: 0.71), and it was similar to the results of other studies on CPR in children[10,18,35-37].

Sex did not correlate with LTS (p: 0.077) and this finding was similar to the results of previous studies[10,27,37,38].

In-hospital assessment is critical to establish the underlying diagnosis and subsequently guide therapy[39]. Poor neurological outcome is related to the patient's underlying illness[15]. The primary diagnosis of pediatric patients most often involves the respiratory system[7]. In our series, a sepsis syndrome was found in 21.2% of arrest victims, central nervous system diseases in 20.3%, cardiovascular causes in 17%, and respiratory causes in 15.3%. LTS of inpatient CPR is poor in patients with sepsis syndrome[40]. Torres et al.[40] reported that most of the CPA patients were diagnosed as sepsis syndrome, which is similar with our study. In a retrospective study of pediatric inpatient and outpatient CPR, Friesen et al.[5] reported that none of nine patients with sepsis syndrome survived to hospital discharge. The high mortality might reflect the critical state of the underlying illness[15]. In a prospective study of adult inpatient CPR, Bedell et al.[41] reported that none of 42 patients with sepsis syndrome survived. Ludwig et al.[7] reported that respiratory etiology was found in 43% of hospitalized patients, cardiac etiology in 21%, and central nervous system in 19%. Suominen et al.[18] reported that cardiac etiology was found in 71.2% of hospitalized patients and respiratory etiology in 8.5%. Calkins et al.[42] reported that CPR after blunt injury in children rarely results in survival.

Mullie et al.[43] reported that GCS could be helpful in predicting outcome in patients resuscitated after out-of-hospital cardiac arrest. We found significantly improved LTS rate after in-hospital CPA if the GCS at prearrest phase was equal or above eight.

Outcomes from CPR are expected to vary, depending on the location of the arrest[16,37,44,45], because there is variability in the underlying conditions, the experience of the personnel performing CPR, and the time that elapses between actual arrest and start of CPR. Pediatric CPR effectiveness data are often difficult to interpret because the outcomes of the arrests are not segregated by location. Thus, different locations with differences in monitoring capabilities result in differences in response times and personnel experience[37]. The poorer prognosis for patients in the emergency department may be attributed to delayed recognition of the arrest and to limited prehospital care. Von Seggern et al.[36] and Suominen et al.[18] reported that LTS rates for intensive care arrest victims were 31% and 18.4%, respectively. On the contrary, Barzilay et al.[34] reported that LTS rate in patients who arrested in the PICU was lower (8.1%), despite continuous monitoring, immediate recognition, and treatment compared with those arrested during invasive procedures (50%). None of our patients arrested in the catheterization laboratory or operating room. After CPR in the pediatric cardiac intensive care unit, the rate of survival was found to be 42% by Parra et al.[33]. In our study, we found the LTS rate in patients who arrested in the PICU as 17.2%. LTS rates were not significantly different among different units in the hospitalized patients. Similarly, Suominen et al.[18] reported that the location of CPR did not affect LTS rate.

The outcome of cardiac arrest in children is worse than the outcome in adults[11]. The most common underlying cause of cardiac arrest in children is respiratory failure. The poor long-term outcome of many cardiac arrests in childhood can be understood by an appreciation of the severity of cellular anoxia, which has to occur before the child's previously healthy heart succumbs. Prevention of injury and earlier recognition of illness is clearly a more effective approach in these children[12]. In earlier studies, children with a respiratory arrest who still had palpable pulse had a better outcome than those with a cardiac arrest[16,17,35,46]. LTS rate in children with a respiratory arrest was 24.3-84%[6,16,17,27,47,48,49], while in those with a CPA this was 3.4-37%[6,9,15,16,35,40,49] in previous reports. Our series confirmed that pure respiratory arrests had a significantly better outcome than cardiac arrest.

The most common arrhythmias associated with cardiopulmonary collapse in infants and children were found to be asystole[2,16,25,28,50] or asystole/bradycardia[5,9,10]. In our study, in 28 children in whom a cardiac rhythm was noted, asystole was found in 78%. The findings of previous studies were similar[2,16,28]. Ventricular fibrillation was an uncommon rhythm disturbance in pediatric CPR[2,9,34,50], and was found in 9% of pediatric CPAs[2]. Of 28 CPA victims, we detected ventricular fibrillation in only one patient.

Nichols et al.[10] reported that pupillary reaction and motor response at the onset of advanced life support did not correlate with long-term survival. Quan et al.[51] noted that reactive pupils at the scene predicted good outcomes in pediatric submersion victims. In contrast to Nichols et al.'s study[10], we found that the presence of the pupillary light reflex and cornea reflex at the onset of CPR were related with a good prognosis. In addition, pupillary light reflex was found to be one of the two most important prognostic factors affecting outcome of CPA by stepwise logistic regression analysis.

Patients who needed comparatively fewer doses of resuscitation drugs also had improved survival[10,34,35]. Nichols et al.[10] showed that the necessity for an increasing number of doses of adrenaline was a reliable predictor of a poor outcome. Gillis et al.[16] reported that the predictors of nonsurvival were an administration of more than one IV bolus of adrenaline or more than two doses of adrenaline and bicarbonate given combined. In our study, patients who did not require a dose of adrenaline had a high rate of long-term survival (50%). The outcome was also significantly poor in the group which received more than one dose of adrenaline.

A review of the literature identified six previous studies in which the duration of resuscitation after a pediatric CPA had been assessed. Zaritsky et al.[35] noted that all survivors of CPA, inside or outside the hospital, underwent CPR for less than 10 minutes. Gillis et al.[16] found no survivors if CPR after an in-hospital cardiac arrest lasted more than 15 minutes. Barzilay et al.[34] found significantly improved survival after both in-hospital and out-of-hospital arrests if the duration of CPR was less than 5 minutes, and in the study by Nichols et al.[10], the threshold was 15 minutes. Innes et al.[17] found that no patients survived if CPR after an in-hospital or out-of-hospital CPA lasted more than 30 minutes. Schindler et al.[27] found no survivors if CPR after an out-of-hospital CPA lasted more than 20 minutes. As in the above-mentioned studies, we found that duration of resuscitation was a strong predictor of survival. CPR lasting $\leq$5 minutes was found to be one of the most important prognostic factors affecting outcome of CPA (Table III).

In our study, initial pH was a predictor of poor outcome, but other researchers found that metabolic and acid-base variables during resuscitation did not significantly affect long-term outcome[34,35]. Initial blood bicarbonate values did not significantly affect survival to hospital discharge. Initial pH and $PaCO_2$ values indicate severe derangement in homeostasis, both in survivors and non-survivors, and reflect poor prognosis[34].

Life support is not expected to be successful with only one rescuer. In most instances, more than one rescuer is required. Considering the ABCs of life support, generally five persons are needed to perform all the procedures of CPR. We could not find any correlation between the outcomes of CPR performed by three to five or more rescuers.

We suggest that a positive pupillary light reflex at the onset of CPA and CPR duration should be considered as important predictors of survival in children with CPA.

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