



Clinical paper

Patterns of multiorgan dysfunction after pediatric drowning[☆]

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ABSTRACT

Aims: To evaluate patterns of multiorgan dysfunction and neurologic outcome in children with respiratory and cardiac arrest after drowning.

Methods: Single center retrospective chart review of children aged 0–21 years admitted between January 2001 and January 2012 to the pediatric intensive care unit at Children's Hospital of Pittsburgh with a diagnosis of drowning/submersion/immersion. Organ dysfunction scores were calculated for first 24 h of admission as defined by the Pediatric Logistic Organ Dysfunction Score-1 (PELOD-1) and Pediatric Multiple Organ Dysfunction Score (P-MODS). Neurologic outcome at hospital discharge was assigned Pediatric Cerebral and Overall Performance Category Scale scores.

Results: We identified 60 cases of pediatric drowning in which 21 children experienced cardiorespiratory arrest (CA) and 39 had respiratory arrest (RA). All children with CA had multiorgan failure and 81% had a poor neurologic outcome at hospital discharge while 49% of children with RA had multiorgan failure and none had an unfavorable neurological outcome ($p < 0.001$). The most common organ failures in both CA and RA groups within the first 24 h of admission were respiratory, followed by neurologic, cardiovascular, gastrointestinal, hematological, and least commonly, renal.

Conclusion: Patterns of organ failure differ in children with CA and RA due to drowning. The contribution of multiorgan failure to poor outcome and evaluation of the impact of augmenting cerebral resuscitation with MOF-targeting therapies after drowning deserves to be explored.

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1. Introduction

Drowning is the leading cause of unintentional injury-related death and disability worldwide between the ages of 1 and 4 years and the third leading cause in the United States between the ages of 1 and 21 years.¹ Drowning occurs from primary respiratory impairment due to submersion in a liquid medium,^{2–4} and is followed by breath-holding and involuntary laryngospasm that leads to hypercapnia, hypoxemia, and if prolonged, respiratory (RA) and or cardiorespiratory arrest (CA).^{2,5,6} Systemic hypoxemia and/or ischemia during RA or CA, respectively, increase the risk of hepatic,

renal, and neurologic organ injury and reversible or irreversible impairment of function.^{2,5,7}

Duration of submersion under water and need for cardiopulmonary resuscitation (CPR) after extraction are associated with outcome in pediatric drowning. Children who progress to CA and have generalized edema present on early brain computed tomography uniformly have poor outcomes.⁸ Children with RA are still at increased risk of disability and death.⁹ Reports on neurologic outcome and mortality after drowning-related RA are lacking but mortality in all-cause acute respiratory failure is 22–40% in children.^{10,11}

Typpo and colleagues¹² have reported on multiple organ dysfunction syndrome (MODS) on Day 1 of pediatric intensive care unit (PICU) admission and found an incidence of 18%, with 30–35% of those having an unfavorable neurologic outcome. Post-resuscitation MODS is not well described after pediatric drowning specifically. Our primary objective was to explore the severity and patterns of MODS in the first 24 h in children with CA and RA after drowning.

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Table 1
Patient, drowning, and outcome characteristics.

	Overall	RA (n = 39)	CA (n = 21)
Age, years	2.4 (0.1–16.6)	2.9 (0.4–16.6)	1.9 (0.1–15.1)
Gender, male	36 (60)	23 (59)	13 (62)
Ethnicity			
Caucasian	50 (85)	33 (85)	17 (81)
Black	8 (14)	4 (10)	4 (19)
Other/missing	2 (1)	2 (5)	0 (0)
Location			
Home swimming pool	30 (50)	21 (54)	9 (43)
Bath tub	12 (20)	6 (15)	6 (28)
Public pool	9 (15)	7 (18)	2 (10)
Other	9 (15)	5 (13)	4 (19)
PICU LOS, days	4 (1–60)	2 (1–11)	12 (1–60)
Hospital LOS, days	5 (1–103)	3 (1–15)	21 (1–103)
Duration of resuscitation, min	N/A	N/A	30 (2–90)
Disposition of survivors			
Home	41 (68)	39 (100)	2 (10)
Rehabilitation facility	11 (18)	0 (0)	11 (52)
Unfavorable neurologic outcome	17 (28)	0 (0)	17 (81)
Mortality at hospital discharge	8 (14)	0 (0)	8 (38)

Data is expressed in median (range) or n (%). RA: Respiratory arrest, CA: Cardiac arrest, PICU: Pediatric Intensive Care Unit, LOS: Length of Stay, min: minutes.

2. Methods

This is a single center retrospective chart review of children aged 0–21 years admitted between January 2001 and January 2012 to the PICU at Children's Hospital of Pittsburgh with a diagnosis of drowning, submersion, or immersion per International Classification of Diseases, volume 9 (ICD-9) codes (994.1, E830, E830.1–830.9, E832, E910, E910.1–910.4, E910.8, E910.9, E954, E965, E984, E979.8). The Institutional Review Board of University of Pittsburgh approved the study and informed consent was waived.

Data collected included patient and incident characteristics and resuscitation, post-resuscitation details during the Emergency Medical Services, Emergency Department, and PICU care periods for the first 24 h after admission. Pediatric Logistic Organ Dysfunction Score-1 (PELOD-1) and Pediatric Multiple Organ Dysfunction Score (P-MODS) were calculated for the first 24 h of hospitalization.^{13,14} In addition, we used the first 24-h scores since the largest data set reporting on organ dysfunction in PICU patients by Typpo and colleagues¹² utilized scores on day 1. Both scoring systems assign a score based on the severity of organ dysfunction. Normal function for each organ system as defined by the PELOD-1 score is as follows: *Neurologic system* – Glasgow Coma Scale (GCS) score of 12–15 and reactive pupils; *Cardiovascular system* – age-dependent values for heart rate and systolic blood pressure; *Renal system* – age appropriate creatinine values; *Respiratory system* – $P_aO_2/F_iO_2 > 69.8$ mmHg and $P_aCO_2 \leq 87.8$ mmHg and no need for mechanical ventilation; *Hematological system* – white blood cell (WBC) count $\geq 4.5 \times 10^9/L$ and a platelet (PLT) count $\geq 35 \times 10^9/L$; and *Hepatic system* – aspartate transaminase (AST) < 950 iU/L and an international randomized ration (INR) < 1.4 . In the event of missing data, normal function was assumed as described by Graciano and colleagues.¹³ Normal function for each organ system as defined by the P-MODS system is as follows: *Cardiovascular system* – Lactic acid < 1 mmol/L; *Respiratory system* – $P_aO_2/F_iO_2 > 150$ mmHg; *Hepatic system* – Bilirubin < 0.5 mg/dL; *Hematological system* – Fibrinogen > 150 mg/dL; and *Renal system* – Blood Urea Nitrogen < 20 mg/dL. MODS was defined as two or more organ dysfunctions.¹⁵

Neurologic outcome at hospital discharge was assigned Pediatric Cerebral and Overall Performance Category Scale scores (PCPC/POPC) using clinical notes. Favorable neurologic outcome was defined as a PCPC/POPC less than or equal to 3 or no change in the baseline score. Unfavorable neurologic outcome represented patients with severe neurologic impairment with PCPC/POPC > 3 . To compare organ dysfunction in both neurologic outcome groups,

we used P-MODS as the MODS score since it lacks a neurologic component.

Drowning victims were categorized into two groups: CA and RA. CA was defined as need for CPR by healthcare personnel (Emergency Medical Services or Emergency Department) whereas RA was defined as apnea or cyanosis with palpable pulse and therefore lack of need for CPR.

Non-parametric numeric data are presented as median [interquartile range] or total number of patients (percentages), while parametric data are presented as mean \pm standard error of the mean (SEM). Fisher exact tests for categorical variables were performed for outcome groups. The Wilcoxon rank sum test was used to compare organ dysfunction scores and neurologic outcome. Spearman's rank correlation was used to test the relationship between duration of CPR and organ dysfunction in children with CA after drowning. All *p*-values were two-tailed and values less than 0.05 were considered significant. Data analysis was performed using SigmaStat 3.5 (Systat Software, Inc.).

3. Results

3.1. Patients and drowning characteristics

We identified 60 children who met study criteria over the study period with a median age of 2.4 years and 60% were males (Table 1). Fifty-seven events occurred in the summer months (May–October). Forty-one (68%) of the events were unwitnessed and the median reported submersion time was 2 min (range 0–30 min). Median CPR duration in children with CA was 2 min and ranged from 1 to 90 min. Thirty-nine (65%) children were in RA and 21 (35%) were in CA at the drowning location. Most 41 (68%) children were intubated and the initial recorded temperature on hospital arrival was 35.7 °C [24–39.3 °C]. All but 2 children were transferred by Emergency Medical Services to a referring hospital emergency department; the remaining 2 children presented to a referring hospital with family members. Children were subsequently transferred to Children's Hospital of Pittsburgh emergency department prior to PICU admission or were directly admitted to the PICU where 15/21 of children in CA group remained pulseless. Six of those 15 pulseless children died, 7 were discharged to a rehabilitation facility and 2 discharged home. Overall, 17/60 patients had severe neurological impairment and 8/60 children died. All of the children who had

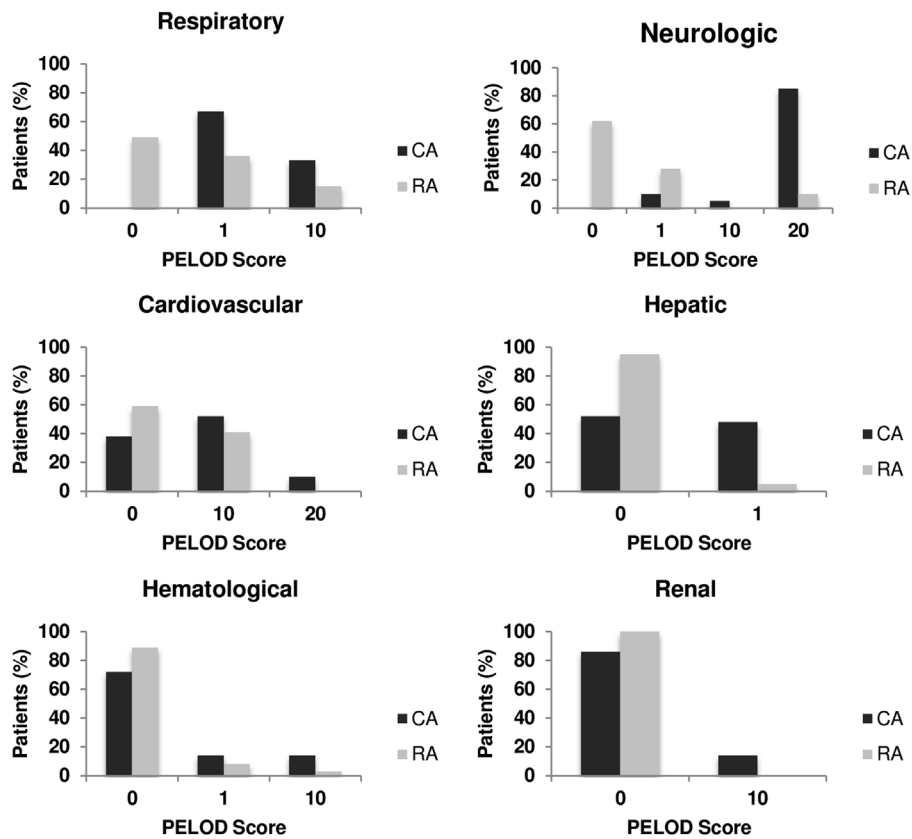


Fig. 1. Organ dysfunction by arrest group. Overall, most common organ failure within first 24 h of PICU admission was respiratory, followed by neurologic, cardiovascular, hepatic and renal systems in both the CA and RA groups.

severe neurological impairment and those who died had suffered a CA (Table 1).

3.2. Frequency, patterns, and clinical impact of organ failure

Forty (66%) children had MODS, 7 (12%) had a single organ dysfunction, and 13 (22%) had no organ failure. Of the children with MODS, 21/40 (52%) had CA and 19/40 (48%) had RA. 100% of children in CA group vs. 49% of children in RA group had MODS. Children with CA had higher PELOD-1 and P-MODS scores than children with RA (CA vs. RA; PELOD-1: 32 ± 3.2 vs. 9 ± 1.5; P-MODS: 6 ± 3 vs. 1 ± 2, p < 0.01) (Table 2). In addition, children with CA had more severe organ dysfunction in each organ system affected (Fig. 1).

In both CA and RA patients, the respiratory system was most frequently affected, followed by neurologic, cardiovascular, hepatic, hematologic, and lastly the renal system. The only exception to this pattern was noted in patients with RA and single organ dysfunction, where the most commonly affected system was cardiovascular followed by respiratory then neurologic. More children with CA had

neurologic, respiratory, hepatic, and renal system dysfunction (all p < 0.05); whereas there were no differences between groups in occurrence of cardiovascular and hematologic system dysfunction (Fig. 2).

The duration of mechanical ventilation was longer in the CA vs. RA group (21.4 ± 5.3 days vs. 3.8 ± 0.6 days, p < 0.05). Nineteen of the 39 RA patients had an arterial blood gas performed in the first 24 h of ICU admission while all of the CA children had an arterial blood gas done. Of the children with an arterial blood gas, the worst PaO₂/F_iO₂ was not different by group (151 ± 69 vs. 179 ± 58, CA vs. RA group respectively, p = 0.35). Three children received inhaled nitric oxide for poor oxygenation, all in the CA group. Initial non-sedated GCS score was lower in the CA vs. RA group (4 ± 1 vs. 12 ± 1, p < 0.001). Nearly all (35/40) children with MODS had neurologic failure (non-sedated GCS < 12) compared to 2/20 in the non-MODS group (p < 0.01). Eighteen of 21 children in the CA vs. 7/39 in the RA group required inotropic or vasopressor support. One child required veno-arterial extracorporeal membrane oxygenation in the CA group. In children with CA, longer CPR durations showed a trend for increased number of organ dysfunction (p = 0.09) (Table 3).

Table 2

Organ dysfunction scores by arrest type. Patients who suffered a cardiorespiratory arrest had more organ dysfunction and more severe multiorgan failure in the first 24 h after admission.

	CA N = 21	RA N = 39	p-value
Number of organ dysfunctions	3.5 ± 0.2	1.5 ± 0.2	<0.001
PELOD	32 ± 3	9 ± 1.5	<0.001
P-MODS	6 ± 3	1 ± 2	<0.01

Data expressed as mean ± standard error of the mean. CA: cardiorespiratory arrest, RA: respiratory arrest.

Table 3

CPR duration and number of organ dysfunctions. This table depicts the percentage of patients with a certain number of organ dysfunctions according to CPR duration. Total number of patients = 21.

CPR duration (minutes)	Number of organ dysfunctions			
	2	3	4	5
≤10	1 (16.7)	3 (50)	2 (33.3)	0 (0)
11–30	3 (37.5)	0 (0)	3 (37.5)	2 (25)
>30	0 (0)	2 (28.6)	5 (71.4)	0 (0)

N (%); p = 0.093; CPR: cardiopulmonary resuscitation.

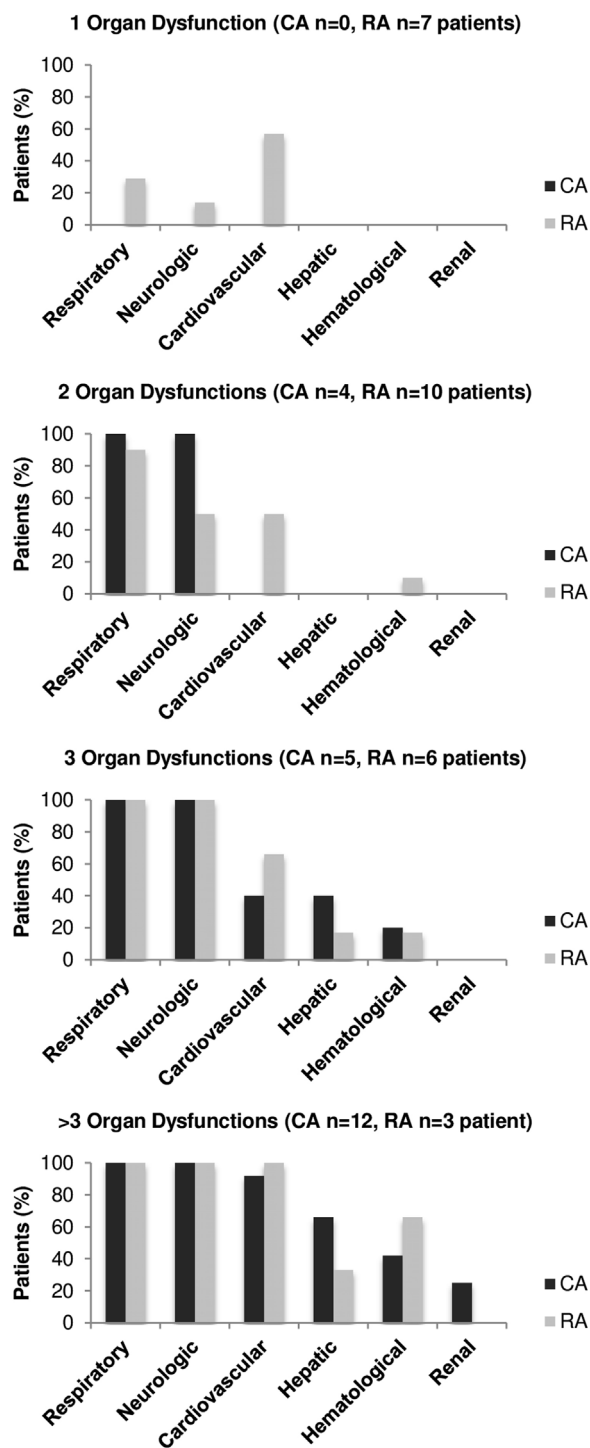


Fig. 2. Patterns of organ dysfunction. Figures below show patterns of organ dysfunction in patients with 1, 2, 3 and >3 organ failures as defined by PELOD-1 score >0 for each organ. No CA patient had less than 2 organ dysfunctions and the cardiovascular system was the most common organ failure in patients with RA. CA: cardiac arrest, RA: respiratory arrest, PELOD: pediatric logistic organ dysfunction score.

Highest blood AST levels in the first 24 h of admission for the CA group averaged 456 ± 210 iU/L vs. 83 ± 22 iU/L for the RA group ($p < 0.001$); whereas INR for the CA group was 1.4 ± 0.2 vs. 1.1 ± 0.05 for the RA group ($p < 0.001$). There were no differences in lowest white blood cell or platelet counts or creatinine values between CA or RA groups. Lastly, one child in the CA group required continuous renal replacement therapy and subsequently intermittent hemodialysis.

3.3. Neurologic outcome

Twenty-eight percent of all children had an unfavorable neurologic outcome or severe neurologic impairment. Eighty percent of children with CA had an unfavorable neurologic outcome in comparison to none of the RA children. CPR duration for CA children with unfavorable neurologic outcome was 37.9 ± 6.3 min vs. 6 ± 2 min in the favorable outcome group ($p < 0.01$). In addition, children with unfavorable neurologic outcome had a higher number of organ failures than the favorable outcome group (3.6 ± 0.2 vs. 1.6 ± 0.2 , $p < 0.001$), the latter was also reflected in the P-MODS scores where the unfavorable outcome group P-MODS score was 6 ± 0.8 vs. 2 ± 0.3 for the favorable outcome group.

4. Discussion

To our knowledge, this is the first study to describe and compare early (first 24 h of PICU admission) patterns of organ dysfunction in children with CA or RA due to drowning. Multiorgan dysfunction and unfavorable neurologic outcome were more common and more severe after CA in comparison to children with RA. The most common organ system failures in both groups were the respiratory, neurologic and cardiovascular systems. Although having RA did not preclude development of early MODS, favorable neurologic outcomes were frequently attained.

The hallmark of MODS is the development of progressive physiologic dysfunction in 2 or more organ systems after alterations in systemic homeostasis.^{16,17} Risk factors are diverse and include infection, non-infectious inflammatory conditions, traumatic or burn injury, ischemia, toxin exposure, and immune system activation.¹⁷ Whether these divergent stimuli produce phenotypic organ injury by a single common pathway is unknown. In the pediatric literature, MODS is reported to occur in approximately 10–56% of all PICU admissions and has an associated mortality of 10–54%.^{15,18–23} Typpo and colleagues explored MODS incidence in a general pediatric population that included children with traumatic and non-traumatic diagnoses using the International Pediatric Sepsis Consensus Conference criteria on day 1 of PICU admission. They reported an 18% rate of MODS with a corresponding mortality rate of 10%. The incidence of MODS in our study was significantly higher at 56%, with a similar mortality rate of 14% and all patients who died had at least 3 organ failures. Similar to our findings in pediatric drowning, respiratory dysfunction was the most frequently reported organ dysfunction. Different from our findings, cardiovascular dysfunction was the next most common organ dysfunction followed by neurologic dysfunction.¹² Interestingly, 30–35% of the patients in the Typpo study with MODS had an unfavorable neurologic outcome in contrast to our specific drowning population in which 50% of children with MODS had unfavorable neurologic outcome.¹² This difference may be partly attributable to differences in pathophysiology that lead to organ dysfunction unique to drowning vs. MODS of all causes including the large number of children suffering asphyxial CA in our study. Thus drowning represents a unique physiological phenotype in contrast to other causes of MODS, suggesting that resuscitation and post-resuscitation therapeutic strategies should be targeted to phenotype.^{24,25}

As stated previously, pediatric drowning literature has focused on individual organ dysfunctions.^{3,7,24,26,27} Lung injury, frequently reported in the drowning literature, is characterized by abnormal surfactant function and increased capillary endothelial permeability.⁷ This injury leads to increased intrapulmonary shunting, ventilation/perfusion mismatch, atelectasis, and poor lung compliance, which cause further hypoxemia and hypercarbia. When severe enough, this process may lead to ARDS. Next,

the most significant consequence of drowning and the most frequent cause of death is hypoxic-ischemic brain injury. The degree of neurologic injury is related to the duration of cardiac arrest and CPR, the effectiveness of initial CPR, and secondary cerebral injuries after resuscitation.^{7,28,29} Drowning patients frequently have ventilation and oxygenation derangements for hours to days post-resuscitation. Recent studies that may impact treatment for some drowning patients have shown that hyperoxia and hypoxia are associated with increased mortality in CA patients,²⁹ and hypocapnia and hypercapnia post-CA are independently associated with poor neurologic outcome.³⁰ In addition, arterial hypotension, seen in up to 40% of patients in this study, after return of spontaneous circulation is also a predictor of in-hospital death and poor outcome after CA.³¹ These studies suggest that treating and preventing secondary organ insults in the post-resuscitation period may affect neurological outcome. Problematically, there are no prospective studies demonstrating the best physiologic targets and management approach for oxygenation, ventilation, and blood pressure in pediatric patients who drown with or without CA, but an approach similar to post-CA resuscitation should be considered until more data are available.³²

Lastly, in our patient population, renal dysfunction occurred in only 3/60 (5%) children, all with CA. Renal dysfunction incidence has been reported to be between 2 and 40% in the pediatric population including those without MODS. There are differences in the frequency of kidney dysfunction by disease presentation. A study by Akcan-Arikan and colleagues³³ found that the frequency of acute kidney injury was lower in children with CA (66%) than in children with sepsis or septic shock (87%); the frequency of other organ dysfunctions was not reported.¹² This difference may be related to inherent differences in vulnerability of the kidney to hypoxia/ischemia in CA vs. inflammation and coagulation dysregulation with or without hypoxia/ischemia in sepsis and septic shock.³⁴

Our data show that despite the occurrence of MODS after RA, children with drowning often have favorable outcomes with supportive ICU care. Research on the outcomes of RA is scarce, but Schindler and colleagues compared outcomes after all-cause out-of-hospital pediatric RA and CA.⁹ Forty-three percent (9/21) of RA patients survived to discharge and while a considerable 30% (3/9) of survivors had an unfavorable neurologic outcome. None of the 8% (6/80) of CA survivors in their series had a favorable outcome and only 9/80 children in the CA group had drowned, and none survived.⁹ However, the majority of RA patients in the Schindler study had a traumatic etiology, making our results less comparable as children with traumatic CA generally have poor outcomes.³⁵

The limitations of our study include the retrospective nature of the review and collection of organ dysfunction data was limited to the first day after PICU admission. In addition, P-MODS and PELOD-1 scores were not reported as part of the patient's chart and were calculated based on available laboratory data and health care professional notes. Pre-drowning and hospital discharge PCPC and POPC scores were assigned retrospectively after review of medical records. Assessment of outcomes was limited to hospital discharge although full recovery and rehabilitation after drowning may take years. Detailed neuropsychological outcome testing was not performed which would be particularly important to assess in the RA patients where favorable outcome was achieved. Recent literature by Suominen and colleagues³⁶ suggests that discharge examination is not a reliable indicator of the pediatric drowning victim neurologic outcome and there is a need for proper neurological and neurophysiological assessments to determine the severity of the neurologic insult. In addition, the study of MODS in the pediatric population is the lack of use of a uniform scoring system in all published studies, thus

making data interpretation and comparisons challenging. Finally, our study did not investigate the effects of different therapeutic approaches on outcomes in children with MODS after pediatric drowning.

5. Conclusions

Drowning with CA conferred the greatest risk for early MODS and resulted in a worse neurologic outcome than children with RA, but MODS in children with RA did not result in unfavorable outcome. Prospective research is needed to discern whether or not specific therapies targeting extra-cerebral facets of MODS, particularly, respiratory, and cardiovascular targets in the resuscitation and post-resuscitation periods may confer added benefit to current brain-oriented therapy to improve outcomes after pediatric drowning, especially in the setting of CA.

Conflict of interest statement

None declared.

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