

Title: Associations between initial serum pH value and outcomes of pediatric out-of-hospital cardiac arrest

ABSTRACT

Introduction: Pediatric out-of-hospital cardiac arrest (OHCA) is one of the most critical conditions seen in the emergency department (ED). Although initial serum pH value is reported to be associated with outcome in adult OHCA patients, the association is unclear in pediatric OHCA patients. Thus, we aimed to identify the association between initial pH value and outcome among pediatric OHCA patients.

Methods: This study was a retrospective analysis of a multicenter prospective cohort registry (Japanese Association for Acute Medicine out-of-hospital cardiac arrest registry) from 87 hospitals in Japan. We included pediatric OHCA patients younger than 16 years of age who were registered in this registry between June 2014 and December 2017. Of the 34,754 patients in the database, 458 patients were ultimately included in the analysis. We equally divided the patients into four groups, based on their initial pH value, and conducted a multivariate logistic regression analysis to calculate the adjusted odds ratios of the initial pH value on hospital arrival with their 95% confidence intervals for the primary outcome.

Results: The median (interquartile range) age was 1 (0–6) year, and 77.9% (357/458) of the first monitored rhythm was asystole. The primary outcome was 1-month survival. The overall 1-month survival was 13.3% (61/458), and a 1-month favorable neurologic outcome was seen in 5.2% (24/458) of cases. The adjusted odds ratios and 95% confidence intervals for the pH 6.81–6.64, pH 6.63–6.47, pH <6.47, and pH unknown groups compared with the pH $\geq$ 6.82 group for 1-month survival were 0.39 (0.16–0.97), 0.13 (0.04–0.44), 0.03 (0.00–0.24), and 0.07 (0.02–0.21), respectively.

Conclusions: This study demonstrated the association between the initial pH value on hospital arrival and 1-month survival among pediatric OHCA patients.

Keywords: JAAM-OHCA, child, pH, OHCA, prognosis, neurologic outcome

1. INTRODUCTION

Pediatric out-of-hospital cardiac arrest (OHCA) is one of the most critical conditions seen in the emergency department (ED). It is usually caused by non-cardiac etiology such as respiratory failure, drowning, accident, and airway obstruction, and the probability of successfully resuscitating these patients is much lower than that in adults (1-4). Although some pediatric OHCA patients make dramatic recoveries, this is rare (5, 6). Therefore, it is difficult to judge whether the resuscitation should be continued or withdrawn in a real clinical setting. To support decision-making, information about the clinical factors associated with the outcome is required, but adequate evidence of pediatric OHCA patient outcomes is lacking.

However, several biomarkers have been reported as being associated with the outcome of OHCA in adults, such as lactate or pH values, so perhaps this information could be helpful for difficult decision-making during the resuscitation of pediatric OHCA patients (7-10). Of particular use is the pH value, as it is the representative value of metabolic acidosis due to unstable circulation and respiratory acidosis of respiratory failure. Furthermore, it is generally easy to access this information because a blood gas assessment is routinely performed in the ED. For these reasons, we hypothesized that the initial pH value might be associated with the outcome of pediatric OHCA patients and could potentially be useful for decision-making

in clinical settings. The aim of this study was to identify the association between initial pH value and outcome in pediatric OHCA patients.

2. METHODS

2.1 Study design and setting

This study was a retrospective analysis of the Japanese Association for Acute Medicine out-of-hospital cardiac arrest (JAAM-OHCA) registry between June 2014 and December 2017. The use of data from the registry and retrospective analysis of anonymized data were approved by the Ethics Committee of Kyoto Daini Red Cross Hospital (ID: S29-32), and each hospital also approved the JAAM-OHCA registry protocol as necessary. The ethics committee of each institution waived the need for informed consent for registration in the JAAM-OHCA and the retrospective analysis because of the anonymous nature of the data.

2.2 JAAM-OHCA registry

The JAAM-OHCA registry is a nationwide, multicenter prospective registry that includes 87 medical institutions (66 of which are university hospitals and/or tertiary critical care centers) in Japan. This registry collected both pre- and post-hospitalization data, integrated by the JAAM-OHCA registry committee. Pre-hospitalization data were obtained from the All-Japan Utstein Registry of the Fire and Disaster Management Agency. In-hospital data were collected by physicians or medical staff at each institution via an Internet-based system.

2.3 Study participants

We included OHCA patients aged younger than 16 years who were registered in the JAAM-OHCA registry between June 2014 and December 2017. We excluded patients older than 16 years of age, those whose age was unknown, and those in whom resuscitation was not attempted at the hospital. We also excluded those who had no prehospital data and those for whom the main cause of OHCA was trauma or hanging.

2.4 Data collection, variables, and potential bias

We collected and described the following clinical data from the JAAM-OHCA registry: sex, age, arrest witnessed, bystander performed cardiopulmonary resuscitation (CPR), first monitored rhythm, cause of cardiac arrest, time of transportation, and time from awareness to the first blood test. We stratified the patients by age into the following groups: <1 year, 1-5 years, 6-11 years, and 12-15 years; this was done on the basis of the statistics provided by the Japanese government (11).

We classified the cause of cardiac arrest as cardiogenic or not cardiogenic. The distinction between cardiogenic and not cardiogenic was based on the definition of the Utstein style. The standard format recommended by the International Liaison Committee on Resuscitation (ILCOR), Utstein style, listed as "cause of arrest is that an arrest is presumed to be of cardiac etiology unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination, or any other non-cardiac cause as best determined by rescuers." Therefore, cases that could not be diagnosed as noncardiogenic were judged as presumptive cardiogenic with a diagnosis of exclusion (12, 13). Moreover, we classified the first monitored rhythm as a shockable rhythm or a non-shockable rhythm.

The primary exposure of this study was the initial pH value obtained from a blood gas assessment performed upon hospital arrival. We equally divided the patients into four groups, based on their initial pH value, and clarified the trend of the relationship between initial pH value and outcome.

The primary outcome of this study was the 1-month survival, and the secondary outcome was the 1-month neurologic outcome. The neurologic outcome was assessed on the basis of the Pediatric Cerebral Performance Category (PCPC) scores (14). PCPC scores measure the degree of cognitive function, and the scores range from 1 to 6: 1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative, and 6 = brain death (14). We considered PCPC scores of 1 and 2 to indicate favorable neurologic outcomes, whereas PCPC scores of 3, 4, and 5 were considered to indicate unfavorable neurologic outcomes.

2.5 Statistical methods

We described the patients' characteristics and distribution of patients in each pH group. We set the pH group as the explanatory variable and outcome as the objective variable to identify the association between initial pH value and outcome. We conducted a logistic regression analysis to generate crude odds ratios (ORs) and 95% confidence intervals (CIs) for the pH groups. For potential confounders, we designated the covariates as sex, categorized age, the first monitored rhythm, and bystander performed CPR, and then conducted multivariable logistic regression analyses to calculate the adjusted ORs and 95% CIs for the pH groups. We performed subgroup analysis to investigate the difference in the association between initial pH value and outcome in terms of age.

100 All statistical analyses were performed using the JMP Pro® 14 software (SAA Institute Inc., Cary, NC,
101 USA).

102

103 **3. RESULTS**

104 **3.1. Patient characteristics**

105 A total of 34,754 patients were listed in the JAAM-OHCA registry, but 458 of them were ultimately
106 included in the analysis. Patient selection is depicted in the flowchart in Figure 1, and patient characteristics
107 are described in Table 1. In summary, the median (interquartile range, IQR) age of our patients was 1 (0-6)
108 year, 61.1% (280/458) were male, 77.9% (357/458) of the first monitored rhythms were asystole, and
109 cardiogenic cardiac arrest occurred in 41.3% (189/458) of cases. The pH groups were categorized as
110 follows: pH ≥ 6.82 , 6.81-6.64, 6.63-6.47, and < 6.47 . Those with missing blood gas data were categorized as
111 “unknown.”

112

113 **3.2. Outcome and primary analysis**

114 The overall 1-month survival rate was 13.3% (61/458), and the rate of favorable neurologic outcomes at 1
115 month was 5.2% (24/458). The survival rate in the group with pH ≥ 6.82 was 45.8% (33/72), pH 6.64-6.82
116 was 16.4% (12/73), pH 6.47-6.64 was 6.9% (5/72), pH < 6.47 was 1.4% (1/70), and pH unknown was 5.8%
117 (10/171). The proportions of favorable neurologic outcome in each pH category were as follows: 25.0%
118 (18/72) for pH ≥ 6.82 , 3.5% (6/171) for pH unknown, and 0% for the other groups (Table 2 and Figure 2).

119 We list the crude ORs and adjusted ORs with 95% CI in Table 3, and the forest plot of the adjusted ORs
120 with 95% CI is shown in Figure 3. The ORs of survival decrease with acidosis.

122 **3.3 Subgroup analysis**

123 The results of the subgroup analysis for survival and favorable neurologic outcome after 30 days are shown
124 in Figure 4. Analysis indicated that survival deteriorated with decreasing initial pH value, although there
125 was some variation based on the age category. In all age categories, an initial pH value below 6.82 indicated
126 an unfavorable neurologic outcome.

128 **4. DISCUSSION**

129 **4.1 Key observations**

130 Using the nationwide, multicenter prospective OHCA registry, we found that the pediatric OHCA patients
131 with a lower initial pH value had lower survival rates. Our results may be helpful when making the decision
132 on whether to continue with or cease resuscitation.

134 **4.2 Previous literature and strength of the study**

135 Compared with previous studies, our study has several strengths, some of which are as follows. This is the
136 first study to identify the association between initial pH value and prognosis in pediatric OHCA patients. As
137 regards the prognostic factors in pediatric OHCA patients, previous literature has included details on in-
138 hospital cardiac arrest (IHCA) patients(15-17). However, the physiology of IHCA may differ from that of

OHCA in the following characteristics: arrest witnessed, bystander CPR, comorbidity, and causes of cardiac arrest. For this reason, previous results may be inadequate for use with pediatric OHCA patients. In pediatric OHCA patients, previous studies mainly focused on descriptive information (2, 3, 18), and there were few studies that identified clinical factors associated with prognosis adjusted by confounders. Our findings of the association between initial pH value and outcome in pediatric OHCA may be valuable for clinicians in the ED. Another strength of our study is its applicability to the clinical settings. Some retrospective studies reported that a quantitative electroencephalogram (EEG) or computed tomography (CT) is useful for predicting the prognosis (17, 19). However, the patients in these studies were limited to those who were successfully resuscitated and were admitted to the pediatric intensive care unit after cardiac arrest. It seems clinically difficult to use observations from these examinations while attempting resuscitation in the ED, and clinicians may not consider cases in which the patient's condition was unstable after resuscitation to be particularly helpful. Moreover, the interpretation of EEG or CT requires skill and experience, and these tests could be difficult to perform during resuscitation. In contrast, the pH value is objective, easy to interpret, and can be obtained easily and repeatedly. As a result, we consider that the initial pH value may play an important role in predicting prognosis, compared with the tests featured in previous studies. Finally, the results of our study were consistent with the association demonstrated between initial pH value and outcome in adult OHCA patients or other settings; perhaps, the results may even be generalizable to include all cardiac arrest patients. In adult OHCA, the association between pH value and prognosis has been reported (8, 20, 21). In pediatric IHCA, a previous study using the Pediatric Emergency Care Applied Research Network database also reported an association between lactic acidosis and in-hospital mortality (22).

Therefore, we assume that the identified association between pH value and outcome in pediatric OHCA patients is consistent with the previous results. Additionally, this study was based on the nationwide data of pediatric OHCA in Japan; thus, we believe that this result can be generalized to pediatric OHCA patients in other countries with similar demographics or medical background as Japan.

4.3 Interpretation of results

We suggest that severe acidemia may lead to cerebral injury or multiple organ failure and an unfavorable outcome. Here, we consider some of the potential mechanisms for our findings. Cardiac arrest causes tissue oxygen deficiency and metabolic acidosis, thereby leading to a low pH value in the blood (23). The pH may be a marker for the duration and grade of severity of hypoperfusion to the vital organs (8, 21, 24). Oxygen deficiency in the brain causes brain damage and leads to an unfavorable neurologic outcome (25). In OHCA patients, cardiac output by chest compressions during resuscitation may be low (26). Regarding metabolic acidosis, some observational studies have reported that it is associated with neurologic outcome in OHCA patients (21, 27). Respiratory acidosis indicates inadequate discharge of carbon dioxide that is mostly caused by low venous return during chest compressions and insufficient alveolar ventilation during resuscitation (26). Therefore, it is possible that lower pH values may represent lower cerebral blood flow and venous return, as well as insufficient ventilation. These conditions are all associated with an unfavorable neurologic outcome.

4.4 Clinical implications

The initial pH values may be a factor for considering the resuscitation strategy. When the decision to terminate the resuscitation for a pediatric OHCA is considered, the guideline states that there are no validated clinical decision rules, and the decision may vary considerably across physicians and institutions (28). However, it also states that some factors such as CPR time, the event witnessed, number of doses of epinephrine, etiology of arrest, first and subsequent rhythm, and age may contribute to the decision making of terminate the resuscitation (28). Similar to these factors, this study suggests that the initial pH value could be used to consider the resuscitation strategy.

Importantly, the termination of resuscitation should not be decided based solely on the initial pH value. It is because previous studies reported that some patients with severe acidemia did survive with favorable neurologic outcomes (9, 29). The decision to terminate the resuscitation is final and cannot be rescinded. Therefore, it is important to comprehensively decide to terminate resuscitation, along with other medical factors. Moreover, shared decision-making adapted to various values and the concept of palliative care are also essential (30, 31).

Based on these ideas, clinicians should not make quick decisions to terminate the resuscitation based only on the initial pH value but should make shared decisions with the family by considering multidisciplinary aspects in the discussions.

4.5 Limitations

Our study is not without limitations. First, the timing of the blood gas analysis was not strictly defined, which may have introduced measurement bias. Although, the time from arrival at the hospital to the blood

test was within 20 minutes in most cases (median [IQR] was 8 [4-17] minutes), the differences in the timings of the blood tests might lead to a risk of measurement bias. Second, we classified patients with missing blood gas analysis data into the “pH unknown” group, which might have introduced a risk of bias. However, we presumed that the pH unknown group mostly included severe cases in which blood gas could either not be obtained or resuscitation was stopped at an early stage. This was because the adjusted ORs and 95% CIs for the primary outcome in the pH unknown group were almost the same as that of the low pH groups (pH 6.63-6.47 and pH <6.47). Third, the exclusion of cases where no resuscitation was attempted or where pre-hospital data were missing could be a selection bias. Fourth, (and the most important limitation) we adjusted for the cause of cardiac arrest (cardiogenic or noncardiogenic); however, the accuracy of the causal classification of cardiac arrest is unknown. The Utstein style classification has been noted to have limited fidelity for defining the causes of cardiac arrest (32). In particular, defining “presumed cardiogenic” as a cardiac arrest for which no cause has been identified may not be appropriate in pediatric patients. In a detailed classification of the causes of cardiac arrest in our results, the “presumptive cardiogenic” category constituted 34.5% of the total causes of arrest and approximately 84% of the causes of cardiogenic arrest (Supplementary Table S1). Autopsies to determine the cause of cardiac arrest are not routinely conducted in Japan (33); therefore, classifying cardiogenic cardiac arrest as being “presumptive cardiogenic” in cases of unexplained cardiac arrest may be more common than it should be. In the prospective registries of pediatric OHCA in other countries, the classification of the causes of cardiac arrest will be categorized as either reversible (e.g., the 4H's and 4T's) or nonreversible. Furthermore, the cause has been classified as medical cause, trauma, drug overdose, drowning, asphyxiation, sports-related, or suicide (34). In studies of pediatric

OHCA, it may be better to classify the causes differently than in adult studies. Nevertheless, we used this classification system because the Utstein style has received international consensus as the standard classification system. The use of uniform data collection based on the Utstein-style guidelines for reporting cardiac arrests, and the large sample size were intended to minimize these potential sources of biases. Finally, the external validity and generalizability to the other settings such as other countries or other healthcare conditions were unknown. Moreover, there might be other unadjusted confounding factors such as CRP quality and respiratory management based on local health care levels and manpower at play. These limitations might have affected the results.

5. CONCLUSIONS

This study demonstrated the association between the initial pH value on hospital arrival and the 1-month survival among pediatric OHCA patients. About half of pediatric OHCA patients with an initial pH value higher than 6.82 may survive with resuscitation efforts. Therefore, the initial pH result may be a useful indicator for clinicians who must determine the appropriateness of continuing resuscitation of pediatric OHCA patients.

ACKNOWLEDGMENTS

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Table 1. Characteristics of the study participants

	Total (n=458)	pH ≥6.82 (n=72)	pH 6.81- 6.64 (n=73)	pH 6.63- 6.47 (n=72)	pH <6.47 (n=70)	pH unknow n (n=171)
Male, n(%)	280(61.1)	49(68.1)	44(60.3)	45(62.5)	44(62.9)	98(57.3)
Age, median(IQR)	1(0-6)	10(2.3-14)	4(1-9)	1(0-4)	0(0-2)	0(0-1)
< 1 years, n(%)	228(49.8)	7(9.7)	15(20.5)	35(48.6)	44(62.9)	127(74.3)
1-5	111(24.2)	22(30.6)	27(37.0)	22(30.6)	14(20.0)	26(15.2)
6-11	55(12.0)	14(19.4)	18(24.7)	8(11.1)	5(7.1)	10(5.8)
12-15	64(14.0)	29(40.3)	13(17.8)	7(9.7)	7(10.0)	8(4.7)
Arrest witnessed, n(%)	110(24.0)	44(61.1)	21(28.8)	16(22.2)	6(8.6)	23(13.5)
Bystander performed CPR, n(%)	273(59.6)	46(63.9)	41(56.2)	36(50.0)	51(72.9)	99(57.9)
First monitored rhythm						
Asystole, n(%)	357(77.9)	35(48.6)	52(71.2)	57(79.2)	64(91.4)	149(87.1)
PEA	59(12.9)	15(20.8)	16(21.9)	12(16.7)	6(8.6)	10(5.8)
VF/pVT	17(3.7)	11(15.3)	3(4.1)	0(0.0)	0(0.0)	3(1.8)
Unknown	25(5.5)	11(15.3)	2(2.7)	3(4.2)	0(0.0)	9(5.3)
Cardiogenic cardiac arrest, n(%)	189(41.3)	33(45.8)	27(37.0)	23(31.9)	34(48.6)	72(42.1)
Cause of not cardiogenic, n(%)	269(58.7)	39(54.2)	46(63.0)	49(68.1)	36(51.4)	99(57.9)
Suffocation, n(%)	40(8.7)	6(8.3)	9(12.3)	10(13.9)	2(2.9)	13(7.6)
Drowning	32(7.0)	5(6.9)	7(9.6)	5(6.9)	5(7.1)	10(5.8)
Toxin	2(0.4)	1(1.4)	1(1.4)	0(0.0)	0(0.0)	0(0.0)
Unknown	195(42.6)	27(37.5)	29(39.7)	34(47.2)	29(41.4)	76(44.4)
Call-hospital arrival interval, min (IQR)	28(23-36)	29.5(24-3)	28(23-37)	28(23-34.5)	25(22-33.5)	30(23-39)
Time from hospital arrival to first blood test, min (IQR)	8(4-17)	8(4-18)	8(2.3-14.8)	6.5(3-13.5)	9.5(3.8-19.3)	-
pH, median (IQR)	6.64 (6.47-6.82)	6.99 (6.88-7.18)	6.72 (6.67-6.77)	6.54 (6.50-6.59)	6.39 (6.33-6.42)	-

IQR: interquartile range, CPR: cardio pulmonary resuscitation, PEA: pulseless electrical activity, pVT: pulseless ventricular tachycardia, VF: ventricular fibrillation.

Table 2. Primary outcome and secondary outcome

	total	pH ≥6.82	pH 6.81-6.64	pH 6.63-6.47	pH <6.47	pH unknown
	(n=458)	(n=72)	(n=73)	(n=72)	(n=70)	(n=171)
Primary outcome						
Survival, n (%)	61 (13.3)	33 (45.8)	12 (16.4)	5 (6.9)	1 (1.4)	10 (5.8)
Secondary outcome						
Favorable neurological outcome, n (%)	24 (5.2)	18 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.5)

Note: Favorable neurological outcome is a Pediatric Cerebral Performance Category score ≥1-2.

Table 3. Analysis of the association between pH and primary outcome

pH variables	Survival (%)	Crude ORs (95% CI)	Adjusted ORs (95% CI)
≥6.82	45.8% (33/72)	Reference	Reference
6.81-6.64	16.4% (12/73)	0.23 (0.11-0.50)	0.34 (0.16-0.97)
6.63-6.47	6.9% (5/72)	0.09 (0.03-0.25)	0.13 (0.04-0.44)
<6.47	1.4% (1/70)	0.02 (0.00-0.13)	0.03 (0.00-0.24)
Unknown	5.8% (10/171)	0.07 (0.03-0.16)	0.07 (0.02-0.21)

OR: odds ratio, CI: confidence interval.

best determined by rescuers."

The classification specified in the above table was made by the attending physician based on the clinical course and, therefore, the validity of the diagnosis is unclear.

FIGURE LEGENDS

Fig. 1. Flow chart of patient selection.

JAAM-OHCA: the Japanese Association for Acute Medicine out-of-hospital cardiac arrest,

OHCA: out-of-hospital cardiac arrest.

Fig. 2. Survival proportion and favorable neurologic outcome proportion by each pH group.

The proportion of cases that survived in the $\text{pH} \geq 6.82$ group was 45.8% (33/72) and for favorable neurologic outcome this proportion was 25% (17/72). The lower the pH, the worse the survival rate. The favorable neurologic outcome was 0 below pH 6.82.

Favorable neurologic outcome is indicated by a PCPC score ≥ 1 -2.

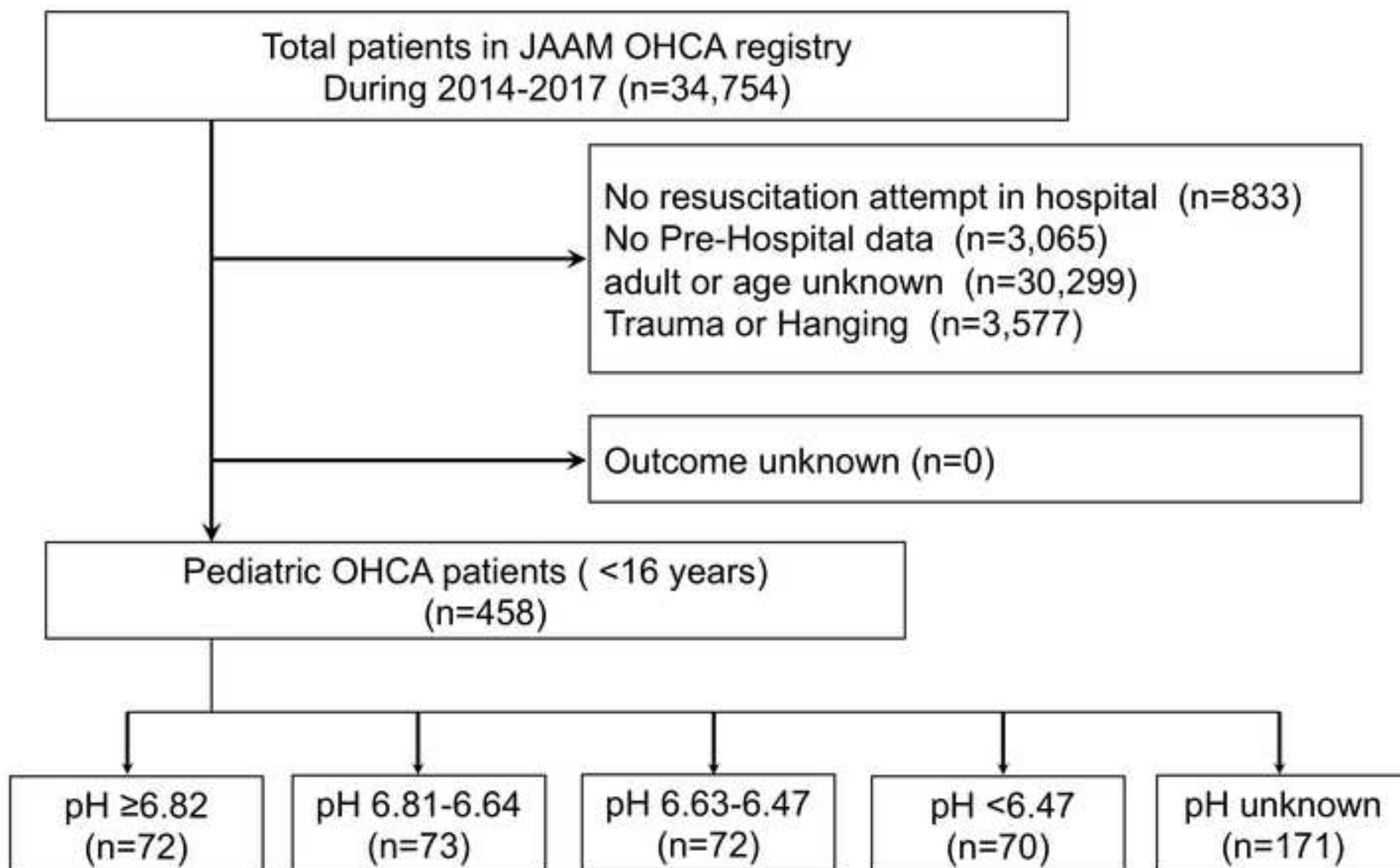
PCPC: Pediatric Cerebral Performance Category.

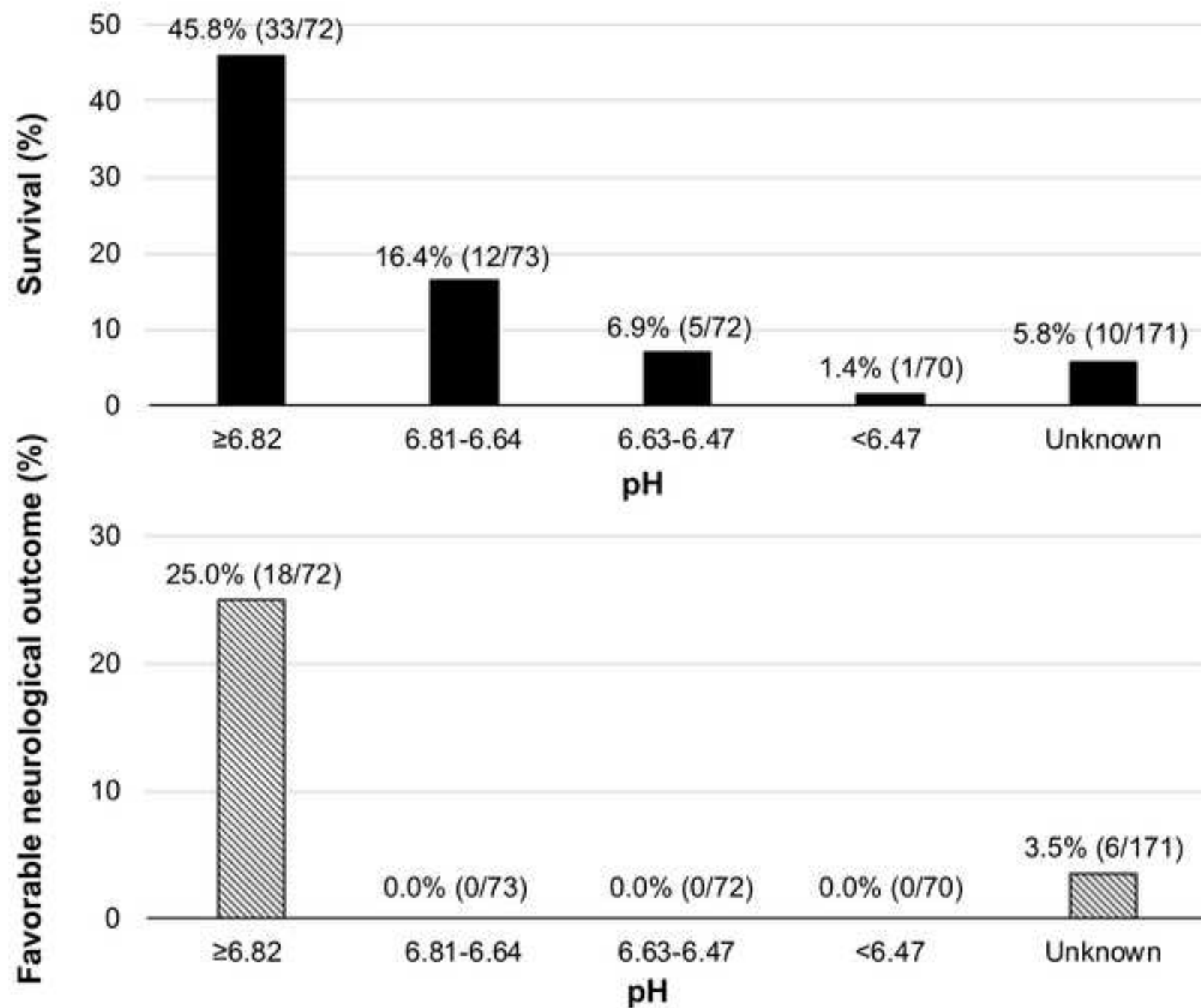
Fig. 3. Forest-plot of adjusted odds ratio for survival in each pH group.

The odds of survival decrease as the pH goes below 6.8.

The odds ratio was adjusted by sex, categorized age, the first monitored rhythm, and bystander performed CPR.

Fig. 4. Outcome proportion for each pH group, by categorized age in the subgroup analysis.





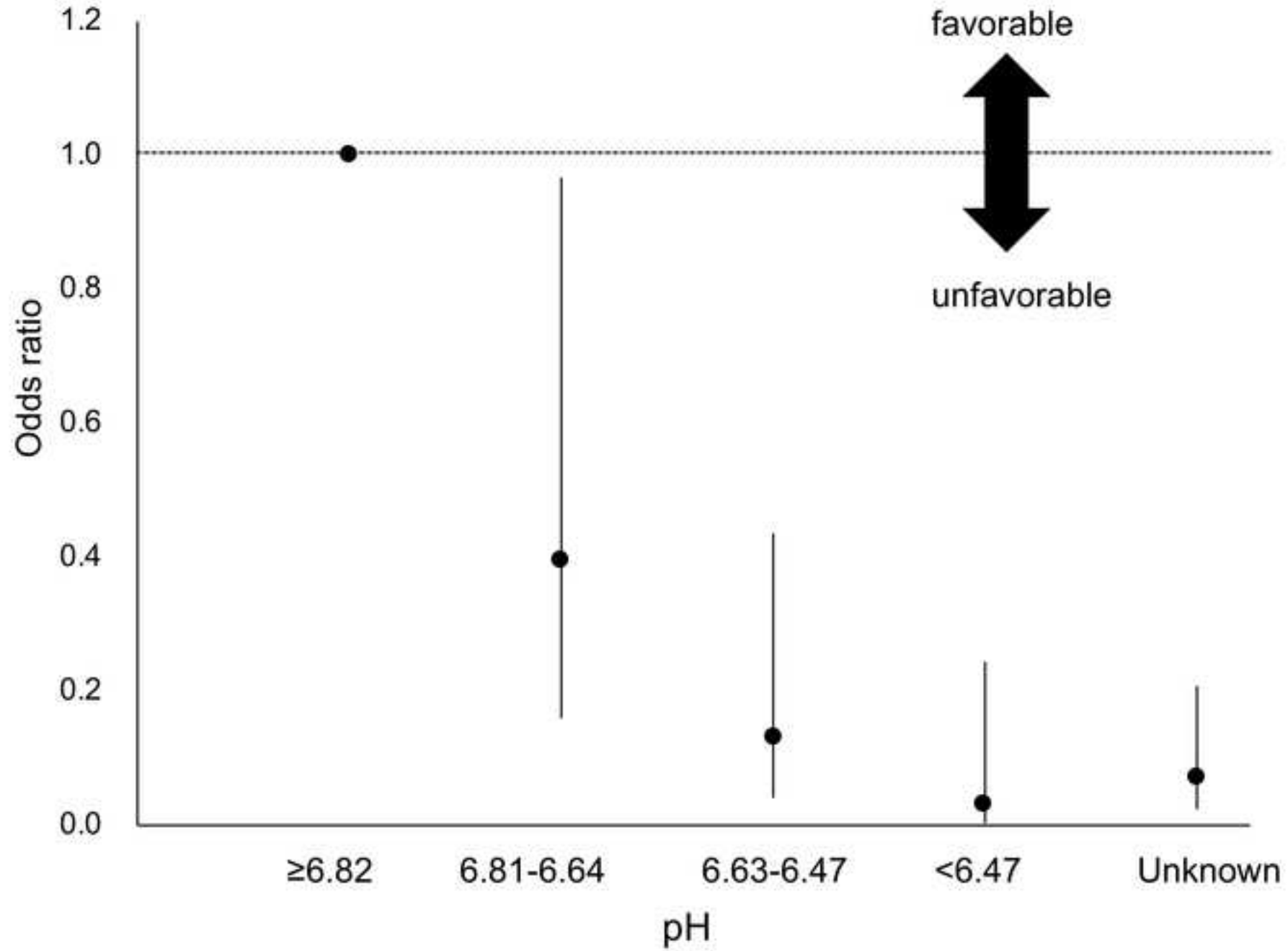
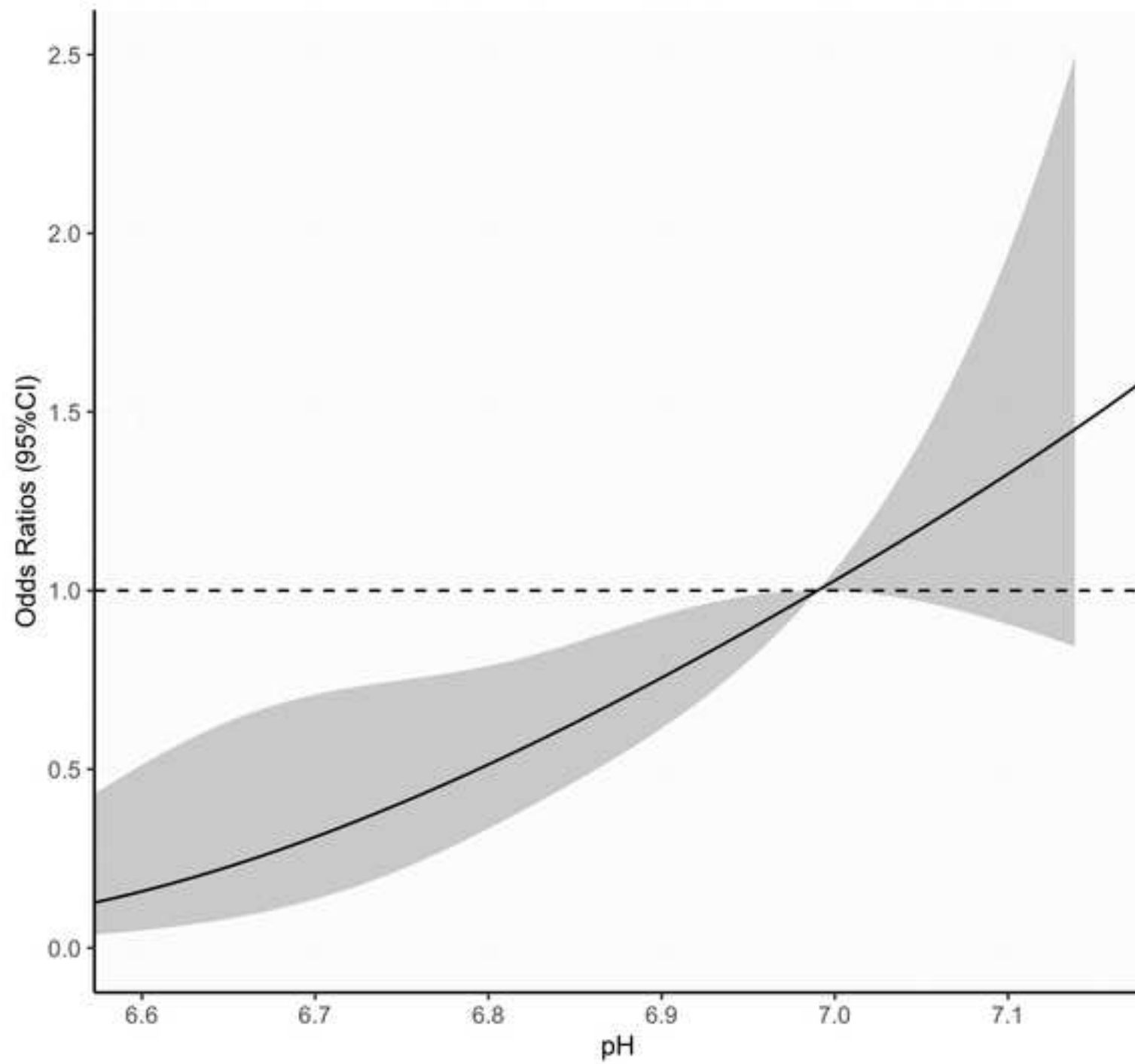
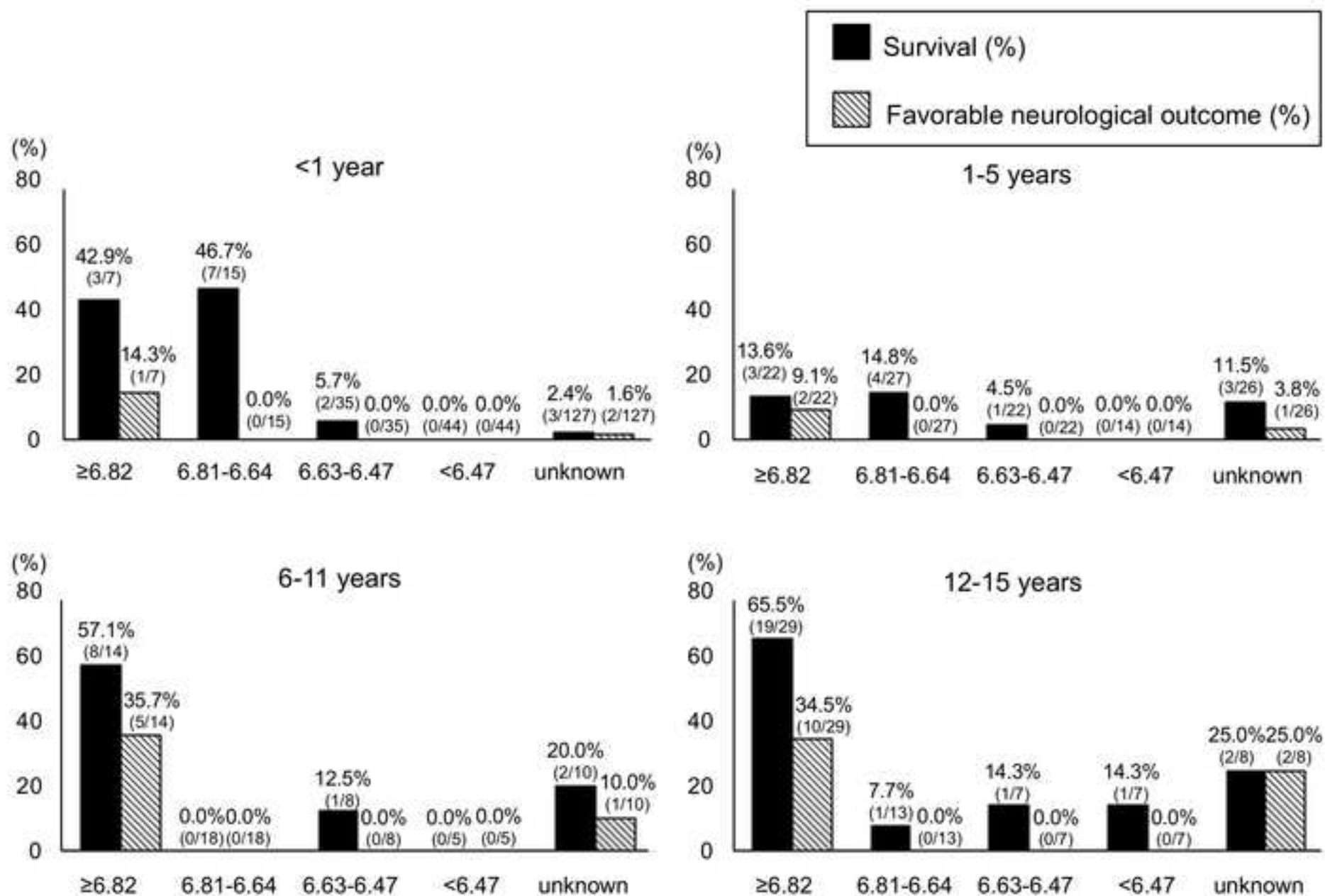


Figure4





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4 **TABLE LEGENDS**

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9 **Table 1. Characteristics of the study participants**

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11 IQR: interquartile range, CPR: cardio pulmonary resuscitation, PEA: pulseless electrical activity, pVT: pulseless

12 ventricular tachycardia, VF: ventricular fibrillation.

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18 **Table 2. Primary outcome and secondary outcome**

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20 *Note:* Favorable neurological outcome is a Pediatric Cerebral Performance Category score $\geq$ 1-2.

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24 **Table 3. Analysis of the association between pH and primary outcome**

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26 OR: odds ratio, CI: confidence interval.

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