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Clinical paper

Factors associated with neurological outcomes in patients experiencing out-of-hospital cardiac arrest and severe acidaemia: retrospective analysis of a nation-wide registry

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ABSTRACT

Background and objective: Acidaemia is common among individuals who experience out-of-hospital cardiac arrest (OHCA). While severe acidaemia is a strong predictor of unfavourable outcomes, a subset of patients exhibits dramatic recovery. Despite these conflicting outcomes, little is known about the factors associated with neurological outcomes in those who experience OHCA with severe acidaemia.
Methods: This retrospective analysis used data from a Japanese multicentre nationwide database, the Japanese Association for Acute Medicine OHCA Registry. The analysis included data from adult patients with OHCA for whom blood pH data were available upon arrival to hospital. The primary outcome was 30-day survival with favourable neurological outcomes, defined as a Glasgow-Pittsburgh cerebral performance category score of 1 or 2. Patients were categorised with severe acidaemia if their blood pH was $\leq$ 6.8. Factors associated with favourable outcomes were investigated using multiple logistic regression analysis.
Results: Data from 49,044 patients were included in the analysis, of whom 16,620 exhibited severe acidaemia with a median pH of 6.70 (interquartile range [IQR] 6.61–6.76], and 0.5% (86/16,620) experienced a neurologically favourable outcome. After adjustment for important prognostic factors, witnessed status exhibited a strong association with favourable neurological outcome (adjusted odds ratio [aOR] 6.46 [95% confidence interval (CI) 2.64–15.8]), while initial blood pH exhibited no significant association (aOR 0.90 with every 0.1 unit increase [95% CI 0.71–1.14]).
Conclusion: Although the number is small, a notable number of patients with severe acidaemia exhibited good neurological recovery. Witness status was critical for the prognosis of these patients.

Introduction

Acidaemia is common among individuals who experience out-of-hospital cardiac arrest (OHCA),[1–5] and its presence is a strong predictor of unfavourable patient outcomes, particularly when pH levels become severe (i.e., $\leq$ 6.8).[3] Simultaneously, severe acidaemia can be a reversible cause of cardiac arrest as listed in the mnemonic “5Hs” in some resuscitation guidelines.[6,7]

Severe acidaemia among patients with OHCA has at least two pathophysiological interpretations that are contradictory from a prognostic perspective. It may represent an irreversible status following a prolonged no-flow time with the accumulation of carbon dioxide (CO_2) and lactate.[8] In other cases, worsening acidaemia, regardless of cause, could be the “last push” before cardiac arrest due to its cardiopulmonary decompression effects, such as vasodilation, arrhythmia, decreased catecholamine reactivity, and cardiac contractility.[9–11] Because patients with slowly progressive acidaemia do not experience cardiac arrest–-even at pH $\leq$ 6.8–and peri-arrest pH also affects acidaemia in patients with OHCA,[12,13] acidaemia may be a treatable cause rather than a result of a long no-flow time. In these cases, severe acidaemia may be an easy breakthrough during resuscitation because small changes in bicarbonate (HCO_3^-) or CO_2 levels can have large pH effects at very low pH.

Due to the particularity of the subset of patients with OHCA and severe acidaemia, whose condition is treatable,[13,14] their

Abbreviations: OHCA, out-of-hospital cardiac arrest; EMS, emergency medical services; JAAM-OCHA, Japanese Association for Acute Medicine OHCA Registry.

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prognostication requires special consideration. Although identifying the aetiology of acidaemia and cardiac arrest is important, detailed patient information is often not readily available during resuscitation in many cases. Instead, prognostication using generalised, easily available, and objective information is a feasible goal. However, little is known about the characteristics and outcomes of patients with OHCA and severe acidaemia, and furthermore, conventional prognostication may not be appropriate for this population.

The aim of this study, therefore, was to investigate the characteristics and factors associated with outcomes of patients with concurrent OHCA and severe acidaemia using the database of the Japanese Association for Acute Medicine (JAAM)-OHCA Registry, a multicentre prospective registry that includes Utstein-style patient demographic data and blood gas analysis data upon arrival to hospital.

Methods

Design, setting, and patient selection

The present study was a retrospective analysis of the JAAM-OHCA registry, a nationwide, multicentre, prospective database of individuals who experienced OHCA. The database houses pre- and in-hospital information, as well as information regarding outcomes among individuals who experienced OHCA and were transported to emergency departments. The registry started in June 2014, is ongoing without setting an end date, and currently consists of 160 institutions.

All patients with OHCA who were transported to participating institutions and underwent resuscitation by emergency medical services (EMS) were included. Patients with OHCA, in whom resuscitation was not attempted by a physician(s) after hospital arrival, were transported from institutions that did not participate in this registry, or refused (either personally or by family members) to participate in the registry, were excluded. Notably, in Japan, almost all patients with OHCA cared for by EMS personnel are transported to hospitals because EMS personnel are not permitted to terminate resuscitation at the scene.

For this analysis, data from patients with OHCA and $>$ 18 years of age, who were transported to the participating hospitals between June 2014 and December 2020, were included. Patients for whom the blood gas pH data were unavailable were excluded.

This registry was approved by the Ethics Committee of Kyoto University, and each hospital approved the JAAM-OHCA registry protocol, as necessary.

Data collection

The dataset consisted of prehospital information registered by paramedics in accordance with the international Utstein style,[15] and in-hospital information registered by medical staff at each institution using a standardised format in an Internet-based system. These were integrated by the JAAM-OHCA Registry Committee as previously described.[16]

The following resuscitation-related covariates were used for this analysis: patient age; sex; cause of arrest; presence of a bystander who witnessed collapse of the patient; initially documented rhythm at the scene, EMS response time (time from call to arrival at the hospital); initially documented rhythm upon hospital arrival; and initial blood gas data (pH, partial pressure of CO_2 [pCO_2]), lactate, and HCO_3^- obtained after hospital arrival. Data collected as outcome measures included neurological outcomes 30 days after cardiac arrest evaluated according to the Glasgow-Pittsburgh cerebral performance category (CPC) scale as follows: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death/brain death.[17]

Statistical analysis

In this study, severe acidaemia was defined as pH $\leq$ 6.8 based on a previous study.[2,3] Favourable neurological outcomes were defined as a Glasgow-Pittsburgh cerebral performance category score of 1 or 2. The impact of each covariate on favourable neurological outcomes in patients with severe acidaemia were investigated. Baseline patient characteristics and outcomes were compared using Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney U test for continuous variables after verifying normality using the Kolmogorov–Smirnov test. Crude odds ratio (OR), adjusted odds ratio (aOR), and corresponding 95% confidence interval (CI) were calculated using univariate and multivariate logistic regression analyses by forced entry. We adjusted for preliminary selected factors that were essential and considered to be associated with clinical outcomes based on previous studies,[2,18] including age, sex (male or female), cause of arrest (cardiac or non-cardiac aetiology), bystander witness (yes or no), initially documented rhythm at the scene (shockable, pulseless electrical activity [PEA], asystole, unknown), EMS response time (from call to arrival of the hospital), initially documented rhythm at the hospital arrival (shockable, PEA, asystole, presence of pulse), and blood gas data upon arrival to hospital (pH, pCO_2, lactate, HCO_3^-). Sensitivity analysis evaluated the association of these factors with neurological outcomes among patients with different definitions of severe acidaemia (pH $\leq$ 6.9, 7.0, 7.1, and 7.2) and the overall cohort, using the same model as in the main analysis. All statistical tests were two-sided, and differences with $P < 0.05$ were considered to be statistically significant. All statistical analyses were performed using R version 4.03 (R Foundation for Statistical Computing, Vienna, Austria) and EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which are graphical user interfaces for R.[19]

Results

Enrolled patients

Data from 68,110 patients with OHCA were registered in the JAAM-OHCA registry between June 2014 and December 2020. Patients were excluded for the following reasons: not resuscitated by a physician(s) (n=1637); prehospital data not available (n=6094); $<$ 18 years of age (n=1271); and blood gas data unavailable (n=10,064). As such, data from 49,044 patients were eligible for the final analysis (Figure 1), of whom 16,620 (33.9%) presented with severe acidaemia and 86 (0.5%) experienced favourable neurological outcomes.

Baseline data

Baseline characteristics of patients with and without severe acidaemia according to outcomes are summarized in Table 1. Among patients with severe acidaemia, compared to those with unfavourable outcomes, those with favourable neurological outcomes were younger, more likely to have experienced a witnessed collapse, and more likely to have a presumed cardiac cause of arrest; these differences were statistically significant. The initially documented rhythms were significantly different in accordance with the neurological outcome because Vf, PEA, and the presence of pulses are mainly documented in patients with favourable outcomes, while asystole is mainly documented in patients with unfavourable outcomes. The EMS response time was not significantly different between the two groups, whereas the EMS call for the first blood gas analysis was longer among patients with favourable neurological outcomes. According to blood gas data, patients with favourable neurological outcomes were more likely to exhibit higher blood pH, and lower HCO_3^-, pCO_2, and lactate levels. These trends were similar in patients without severe acidaemia. However, the presence of a pulse or Vf was mainly documented on arrival to hospital, accounting for $>$ 90% of patients. In addition, patients with favourable neurological

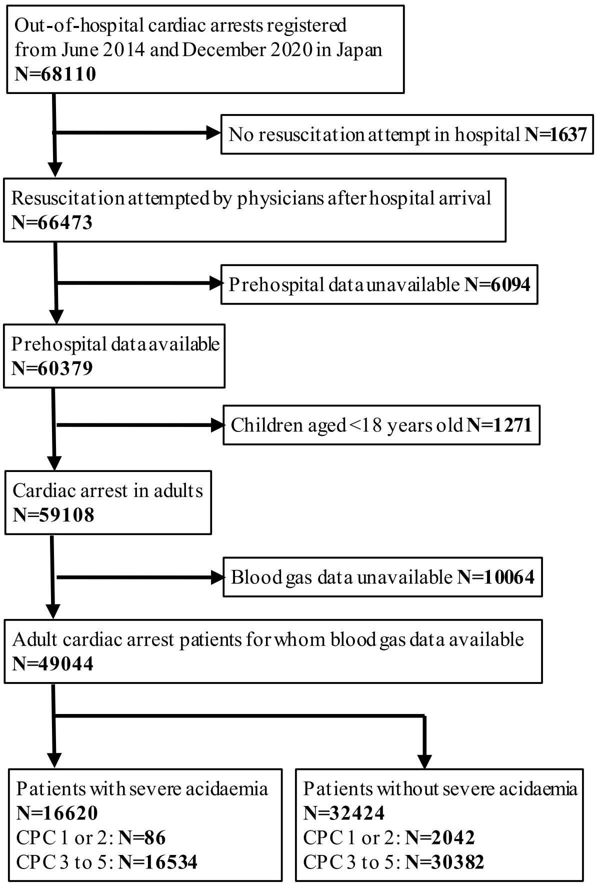

Fig. 1. Study flow chart. CPC, cerebral performance category.

outcomes were more likely to be male, have a shorter EMS response time, and exhibit higher HCO_3^- levels on blood gas analysis.

Outcomes

Results of univariate and multivariate logistic regression analyses for favourable outcomes are summarised in Table 2. Among patients with severe acidaemia, factors associated with favourable neurological outcome included age (aOR with every 1 year increase, 0.96 [95% CI 0.95–0.97]), presence of bystander witness (aOR 6.46 [95% CI 2.64–15.8]), initial PEA at the scene (aOR compared with shockable rhythm, 0.44 [95% CI 0.21–0.93]), initial asystole at the scene (aOR compared with shockable rhythm, 0.14 [95% CI 0.06–0.36]), initial PEA at hospital arrival (aOR compared with shockable rhythm, 0.34 [95% CI 0.16–0.72]), initial asystole on arrival to hospital (aOR compared with shockable rhythm, 0.07 (95% CI 0.03–0.18]), HCO_3^- (aOR with every 1 mEq increase, 1.07 [95% CI 1.01–1.13]), and pCO_2 (aOR with every 1 mmHg increase, 0.98 [95% CI 0.97–0.99]). Although factors associated with outcomes were similar among patients without severe acidaemia, a shorter time from EMS call to hospital arrival, presence of pulse at hospital arrival, cardiac aetiology of cardiac arrest, higher blood pH, and lower lactate levels were significantly associated with favourable outcomes, whereas HCO_3^- exhibited no significant association.

Results of sensitivity analysis for different definitions of severe acidaemia (pH $\leq$ 6.8, $\leq$ 6.9, $\leq$ 7.0, $\leq$ 7.1, and $\leq$ 7.2), and for the overall cohort are summarised in Table 3. The result was consistent when the pH cut-off was $\leq$ 6.9; however, the trend in the association between covariates and outcome approached that of patients without severe acidaemia with an increase in pH.

Discussion

In this study, we evaluated the characteristics and factors associated with neurological outcomes of patients with OHCA and concurrent extreme acidaemia. We found that, although their prognosis was poor, the number of patients who exhibited good neurological recovery was non-negligible. Witnessed status may be a critical prognostic factor, whereas pH, which has been listed as an important prognostic factor in previous studies, is no longer reliable for these patients.

The strength of this study, compared to previous research, lies in the large number of included patients. Several studies have reported pH cut-off values that can predict with reasonable sensitivities,[1,3,20,21] while others have reported complete recovery of patients from far lower arterial pH,[14] necessitating further insight for these patients to prevent inappropriate cessation of resuscitation or intensive care. However, due to the small number of patients with severe acidaemia included in previous studies and widely varying inclusion criteria,[2,3,20] little is known about the characteristics of and factors associated with favourable outcomes among these patients. Our trial, using a nationwide registry that includes virtually all patients with OHCA with the potential for favourable outcomes, is the first to focus on this issue with the largest number of patients–as large as 16,000 with OHCA and severe acidaemia–including 86 with favourable neurological outcomes.

Consistent with previous trials, our study demonstrated that the outcomes of patients with OHCA and severe acidaemia were dismal given that approximately 0.5% experienced good neurological recovery.[2,3] Simultaneously, according to previous studies and our study, approximately one-quarter to one-third of patients with OHCA present with severe acidaemia.[3] Since severe acidaemia is a biomarker of the duration of CPR and concurrent cardiogenic shock, it is not surprising that patients present with severe acidaemia upon arrival. These findings suggest that a significant number of OHCA patients included in this group.

Patients with severe acidaemia and favourable neurological outcomes appear to have distinctive demographics in terms of the initial rhythm and the presumed cause of cardiac arrest. Of note, initial PEA at hospital arrival accounts for one-quarter of the patients, and non-cardiac causes of arrest account for one-third, while these patients account for 7% and 15%, respectively, of those with favourable neurological outcomes among patients without severe acidaemia. A previous trial reported that PEA is associated with a noncardiac cause of arrest,[22] and several previous trials have reported favourable neurological outcomes in patients with severe acidaemia, primarily in those with non-cardiovascular triggers of arrest.[13,14] These results, along with our findings, suggest the need for specific prognostic models for OHCA patients with severe acidaemia, which take into account the potential differences in the aetiologies of cardiac arrest.

Bystander witnesses appear to be crucial in the prognosis of patients with severe acidaemia. Our study revealed a stronger association between the presence of a bystander witness and favourable neurological outcomes, with an aOR of 6.5, compared with an aOR of 1.6 in patients without severe acidaemia, and an aOR of 1.9 in a recent large observational study.[23] Witness status and blood pH are directly associated with no- or low-flow duration, which is a major factor contributing to its predictive value for good neurological outcomes.[8] However, among patients with severe acidaemia, witnessed arrest means not only shorter duration of no-flow time but also suggests that the acidaemia may be no-flow time independent and reversible, as described in the "5Hs" in the guidelines.[6,7] Due to this composite predictive significance, witness status may be strongly associated with outcomes among these patients.

Our study contributes to the literature regarding the association between pH and outcomes. Recently developed and validated prognostic models give important weight to pH in different ways, including a cut-off value for c-GRApH,[24] several cut-off values in the TTM risk

Table 1
Baseline characteristics of patients with and without severe acidaemia according to outcomes.

	patients with severe acidaemia (pH ≤ 6.8)					patients without severe acidaemia (pH > 6.8)				
	All patients	Missing	unfavourable outcome	favourable outcome	P values[b]	All patients	Missing	unfavourable outcome	favourable outcome	P values[b]
	n=16620		n=16534	n=86		n=32424		n=30382	n=2042	
Baseline characteristics										
Male	9844 (59.2)	0 (0.0)	9788 (59.2)	56 (65.1)	0.274	20081 (61.9)	0 (0.0)	18516 (60.9)	1565 (76.6)	<0.001
Age, y, median (IQR)	73 (61–82)	0 (0.0)	74 (60–84)	55 (47–65)	<0.001	76 (64–85)	0 (0.0)	77 (66–85)	63 (51–73)	<0.001
Bystander witness	4776 (28.7)	0 (0.0)	4698 (28.4)	78 (90.7)	<0.001	18609 (57.4)	0 (0.0)	16871 (55.5)	1738 (85.1)	<0.001
Initially documented rhythm at the scene		0 (0.0)			<0.001		0 (0.0)			<0.001
Ventricular fibrillation	591 (3.6)		557 (3.4)	34 (39.5)		3995 (12.3)		2894 (9.5)	1101 (53.9)	
Pulseless ventricular tachycardia	15 (0.1)		14 (0.1)	1 (1.2)		85 (0.3)		62 (0.2)	23 (1.1)	
Pulseless electric activity	2321 (14.0)		2297 (13.9)	24 (27.9)		10467 (32.3)		10135 (33.4)	332 (16.3)	
Asystole	13289 (80.0)		13279 (80.3)	10 (11.9)		15775 (48.7)		15709 (51.7)	66 (3.2)	
Unknown	404 (2.0)		387 (2.3)	17 (19.8)		2102 (6.5)		1582 (5.2)	520 (25.5)	
EMS call to hospital arrival, min, median (IQR)[a]	35 (29–43)	74 (0.4)	35 (29–43)	33 (28–44)	0.594	32 (26–39)	91 (0.3)	32 (27–39)	30 (24–38)	<0.001
Initially documented rhythm at the hospital		0 (0.0)			<0.001		0 (0.0)			<0.001
Ventricular fibrillation	391 (2.4)		362 (2.2)	29 (33.7)		1816 (5.6)		1504 (5.0)	312 (15.3)	
Pulseless ventricular tachycardia	30 (0.2)		30 (0.2)	0 (0.0)		145 (0.5)		130 (0.4)	15 (0.7)	
Pulseless electric activity	2303 (13.9)		2281 (13.8)	22 (25.6)		8463 (26.1)		8328 (27.4)	135 (6.6)	
Asystole	13060 (75.6)		13051 (78.9)	9 (10.5)		17747 (54.7)		17682 (58.2)	65 (3.2)	
Presence of pulse	836 (5.0)		810 (4.9)	26 (30.2)		4253 (13.1)		2738 (9.0)	1515 (74.2)	
Cause of arrest		0 (0.0)			0.021		0 (0.0)			<0.001
Cardiac	9043 (54.4)		8986 (54.3)	57 (66.3)		17640 (54.4)	0 (0.0)	15895 (52.3)	1745 (85.5)	
Cerebrovascular	586 (3.5)		585 (3.5)	1 (1.2)		1175 (3.6)		1165 (3.8)	10 (0.5)	
Respiratory	1004 (6.0)		998 (6.0)	6 (7.0)		1736 (5.4)		1694 (5.6)	42 (2.1)	
Malignancy	329 (2.0)		329 (2.0)	0 (0.0)		636 (2.0)		632 (2.1)	4 (0.2)	
External	3587 (21.6)		3579 (21.6)	8 (9.3)		6770 (20.9)		6626 (21.8)	144 (7.1)	
Other	2071 (12.5)		2057 (12.4)	14 (16.3)		4467 (13.8)		4370 (14.4)	97 (4.8)	
EMS call to blood gas test, min, median (IQR)[a]	44 (37–55)	578 (3.5)	44 (37–55)	47 (38–68)	0.035	42 (34–53)	1064 (3.2)	42 (34–53)	43 (33–60)	<0.001
Blood gas parameters										
pH, median (IQR)	6.70 (6.61–6.76)	0	6.70 (6.60–6.76)	6.75 (6.70–6.78)	<0.001	6.98 (6.89–7.09)	0 (0.0)	6.97 (6.88–7.07)	7.26 (7.13–7.34)	<0.001
HCO3-, mEq/L, median (IQR)[a]	12.5 (9.2–15.4)	1190 (7.2)	12.5 (9.2–15.4)	10.4 (7.1–13.9)	<0.001	17.0 (13.4–20.5)	324 (1.0)	17.0 (13.3–20.5)	17.7 (14.4–20.9)	<0.001
pCO2, mmHg, median (IQR)[a]	114 (88–141)	330 (2.0)	114 (88–141)	84 (61–108)	<0.001	74 (54–92)	183 (0.6)	76 (58–94)	41 (34–51)	<0.001
Lactate, mg/dL, median (IQR)[a]	162 (134–189)	804 (4.8)	162 (134–190)	153 (121–176)	0.022	101 (75–129)	897 (2.8)	103 (78–130)	65 (43–94)	<0.001

Values are expressed numbers (percentages) unless indicated otherwise.
IQR, interquartile range; EMS, emergency medical service.
Favourable neurological outcomes were defined as a Glasgow-Pittsburgh cerebral performance category score of 1 or 2.
[a] Calculated for patients for whom data were available.
[b] Comparisons between the 2 groups were evaluated with Mann-Whitney U test for numeric variables and Fisher's exact test for categorical variables.

score,[25] and continuous values in the nomogram of the CAHP score.[26] However, no data are available regarding whether a decrease in pH is consistently associated with worse outcomes, whether a threshold exists below which outcomes remain unchanged, or whether resuscitation becomes impossible. Our data suggest that blood pH has no significant impact on the outcomes of patients with severe acidaemia, and similar trends have been reported in several trials. In an observational study of patients with OHCA, although low pH appears to be a predictor of worse outcome, it appears unlikely to be associated with outcome when the blood pH is < 7.0.[27] An observational study reported that blood pH was associated with outcomes in initially shockable patients but not in non-shockable patients.[28] Another observational study that included critically ill patients with pH < 6.8, reported that there was no difference in pH between the surviving and non-surviving patient groups, whereas patients with more readily reversible causes of acidaemia in the absence of other serious derangements survived.[12] Therefore, blood pH may no longer be linearly associated with patient outcomes when the pH is very low.

Blood pH, which is not specific but routinely available objective data, is used to select patients who are candidates for additional resuscitative methods such as extracorporeal life support and targeted temperature management.[29,30] Although our data, as well as those of previous trials, show that the prognosis of patients with severe acidaemia is dismal, results of this study suggest that withholding

Table 2
uni- and multivariate logistic regression analysis for favourable outcomes

	patients with severe acidaemia (pH ≤ 6.8)			patients without severe acidaemia (pH > 6.8)		
	patients with favourable outcome	univariable analysis	multivariable analysis[b]	patients with favourable outcome	univariable analysis	multivariable analysis[b]
	n, %	OR (95%CI)	AOR (95% CI)	n, %	OR (95%CI)	AOR (95% CI)
Sex						
Female	30/6776 (0.4)	ref	ref	477/12343 (3.9)	ref	ref
Male	56/9844 (0.6)	1.29 (0.83–2.01)	0.69 (0.41–1.17)	1565/20081 (7.8)	2.10 (1.89–2.34)	1.17 (1.00–1.38)
Age with every 1 year increase		0.96 (0.95–0.97)	0.96 (0.95–0.97)		0.96 (0.96–0.96)	0.95 (0.95–0.96)
Bystander witness						
no	8/11844 (0.1)	ref	ref	304/13815 (2.2)	ref	ref
yes	78/4776 (1.6)	24.6 (11.9–50.9)	6.46 (2.64–15.8)	1738/18609 (9.3)	4.58 (4.04–5.18)	1.55 (1.30–1.85)
Initially documented rhythm at the scene						
Ventricular fibrillation / Pulseless ventricular tachycardia	35/606 (5.8)	ref	ref	1124/4080 (27.5)		ref
Pulseless electric activity	24/2321 (1.0)	0.17 (0.10–0.29)	0.44 (0.21–0.93)	332/10467 (3.2)	0.09 (0.08–0.10)	0.39 (0.32–0.47)
Asystole	10/13289 (0.1)	0.01 (0.01–0.02)	0.14 (0.06–0.36)	66/15775 (0.4)	0.01 (0.01–0.01)	0.13 (0.09–0.17)
Unknown	17/404 (4.2)	0.72 (0.40–1.30)	1.33 (0.61–2.94)	520/2102 (24.7)	0.86 (0.77–0.98)	1.36 (1.10–1.67)
EMS call to hospital arrival with every 1 minute increase[a]		1.01 (1.00–1.02)	1.00 (0.98–1.02)		0.99 (0.99–0.99)	0.98 (0.98–0.99)
Initially documented rhythm at the hospital						
Ventricular fibrillation / Pulseless ventricular tachycardia	29/421 (6.9)	ref	ref	327/1961 (16.7)		ref
Pulseless electric activity	22/2303 (1.0)	0.13 (0.07–0.23)	0.34 (0.16–0.72)	135/8463 (1.6)	0.08 (0.07–0.10)	0.27 (0.21–0.34)
Asystole	9/13060 (0.1)	0.01 (0.00–0.20)	0.07 (0.03–0.18)	65/17747 (0.4)	0.02 (0.01–0.02)	0.12 (0.09–0.17)
Presence of pulse	26/836 (3.1)	0.43 (0.25–0.74)	1.91 (0.88–4.15)	1515/4253 (35.6)	2.76 (2.42–3.16)	4.35 (3.60–5.26)
Cause of arrest						
non cardiac cause	29/7577 (0.4)	ref	ref	297/14784 (2.0)	ref	ref
cardiac cause	57/9043 (0.6)	1.65 (1.05–2.58)	1.22 (0.69–2.16)	1745/17640 (9.9)	5.35 (4.73–6.07)	3.41 (2.84–4.09)
pH with every 0.1 unit increase		1.54 (1.21–1.97)	0.96 (0.75–1.22)		2.46 (2.38–2.54)	1.42 (1.29–1.56)
HCO3- with every 1 mEq/L increase[a]		0.93 (0.88–0.97)	1.07 (1.01–1.13)		1.02 (1.01–1.03)	0.99 (0.97–1.02)
pCO2 with every 1 mmHg increase[a]		0.98 (0.98–0.99)	0.98 (0.97–0.99)		0.95 (0.95–0.95)	0.98 (0.98–0.99)
Lactate with every 10mg/dL increase[a]		0.96 (0.92–1.00)	1.01 (0.96–1.06)		0.82 (0.81–0.83)	0.97 (0.95–0.99)

Values are expressed numbers (percentages) unless indicated otherwise.
Favourable neurological outcomes were defined as a Glasgow-Pittsburgh cerebral performance category score of 1 or 2.
EMS, emergency medical service; OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio.
[a] Calculated for patients for whom data were available.
[b] Shown is the AOR from the multivariable logistic regression analysis adjusted for sex, age, bystander witness, initially documented rhythm at the scene, time from EMS call to hospital arrival, initially documented rhythm at the hospital, cause of arrest, blood pH, HCO3-, pCO2, and lactate.

investment of resources for these patients is not necessarily appropriate when patients experience witnessed collapse. We believe that this study can inform care guidance and family expectations for OHCA patients with severe acidaemia.

Whether pH manipulation through bicarbonate administration impacts patient outcomes remains controversial. Our trial suggests that baseline characteristics of patients are highly heterogeneous, even among those with severe acidaemia, supporting current guideline recommendations against the routine use of bicarbonate. On the other hand, recent trials have demonstrated potential benefits of sodium bicarbonate in selected patients, such as those with an initial non-shockable rhythm and prolonged CPR.[31,32] Further studies are warranted to identify patients who may benefit from pH manipulation, considering not just the presence of acidaemia but a combination of several factors, including those mentioned above.

Limitations

The present study had some limitations. First, our datasets did not include information regarding the pre-arrest condition(s) of the patients. Although determining the aetiology of acidaemia is important, it is often difficult to determine the detailed preceding conditions in those with OHCA. Therefore, we collected Utstein-style data and simple in-hospital information to predict outcomes for better fit with resuscitation in real-world settings. Second, we did not have information regarding whether blood gas was obtained from arteries or veins. Blood samples obtained during cardiopulmonary resuscitation, particularly from the inguinal region, may be uncertain. Although venous and arterial pH and HCO_3^- levels demonstrated reasonable agreement,[33] pCO_2 and lactate levels should be interpreted with caution. Third, the accuracy of ventilation may be an essential determinant of pH on hospital arrival, and may constitute a treatment bias. However, in Japan, at least one emergency

Table 3
Multivariate logistic regression analysis for favourable neurological outcome at different pH cut off

cut off value of pH	pH ≤ 6.8	pH ≤ 6.9	pH ≤ 7.0	pH ≤ 7.1	pH ≤ 7.2	over all cohort
Sex						
Women	ref	ref	ref	ref	ref	ref
Men	0.69 (0.41–1.17)	0.84 (0.59–1.22)	0.94 (0.71–1.24)	0.91 (0.73–1.14)	1.08 (0.89–1.31)	1.12 (0.97–1.31)
Age with every 1 year increase	0.96 (0.95–0.97)	0.96 (0.95–0.97)	0.96 (0.95–0.97)	0.96 (0.95–0.96)	0.96 (0.95–0.96)	0.95 (0.95–0.96)
Bystander witness						
no	ref	ref	ref	ref	ref	ref
yes	6.46 (2.64–15.8)	3.58 (2.12–6.02)	2.51 (1.78–3.53)	2.07 (1.60–2.68)	1.91 (1.54–2.38)	1.68 (1.41–1.98)
Initially documented rhythm at the scene						
Ventricular fibrillation / Pulseless ventricular tachycardia	ref	ref	ref	ref	ref	ref
Pulseless electric activity	0.44 (0.21–0.93)	0.49 (0.30–0.81)	0.47 (0.33–0.67)	0.39 (0.29–0.52)	0.39 (0.31–0.50)	0.39 (0.32–0.46)
Asystole	0.14 (0.06–0.36)	0.11 (0.06–0.23)	0.13 (0.08–0.22)	0.10 (0.07–0.15)	0.12 (0.09–0.17)	0.13 (0.09–0.17)
Unknown	1.33 (0.61–2.94)	1.55 (0.91–2.64)	1.75 (1.18–2.60)	1.27 (0.92–1.77)	1.34 (1.02–1.77)	1.39 (1.14–1.69)
EMS call to hospital arrival with every 1 minute increase[a]	1.00 (0.98–1.02)	0.98 (0.97–1.00)	0.98 (0.97–0.99)	0.98 (0.98–0.99)	0.98 (0.98–0.99)	0.99 (0.98–0.99)
Initially documented rhythm at the hospital						
Ventricular fibrillation / Pulseless ventricular tachycardia	ref	ref	ref	ref	ref	ref
Pulseless electric activity	0.34 (0.16–0.72)	0.35 (0.21–0.56)	0.30 (0.21–0.44)	0.31 (0.23–0.42)	0.29 (0.22–0.38)	0.28 (0.23–0.36)
Asystole	0.07 (0.03–0.18)	0.05 (0.02–0.10)	0.08 (0.05–0.14)	0.11 (0.08–0.16)	0.11 (0.08–0.15)	0.12 (0.09–0.16)
Presence of pulse	1.91 (0.88–4.15)	1.82 (1.10–3.01)	2.47 (1.72–3.53)	3.76 (2.85–4.96)	4.34 (3.44–5.46)	4.38 (3.65–5.25)
Cause of arrest						
non cardiac cause	ref	ref	ref	ref	ref	ref
cardiac cause	1.22 (0.69–2.16)	1.22 (0.82–1.82)	1.45 (1.07–1.98)	1.89 (1.46–2.43)	2.16 (1.74–2.69)	3.19 (2.68–3.79)
pH with every 0.1 unit increase	0.96 (0.75–1.22)	0.96 (0.79–1.16)	1.00 (0.87–1.16)	1.12 (0.97–1.28)	1.29 (1.14–1.46)	1.34 (1.24–1.46)
HCO3- with every 1 mEq/L increase	1.07 (1.01–1.13)	1.03 (0.98–1.09)	1.02 (0.98–1.06)	0.99 (0.96–1.03)	0.98 (0.95–1.01)	1.00 (0.98–1.02)
pCO2 with every 1 mmHg increase	0.98 (0.97–0.99)	0.98 (0.97–0.99)	0.98 (0.98–0.99)	0.98 (0.98–0.99)	0.99 (0.98–0.99)	0.98 (0.98–0.99)
Lactate with every 10mg/dL increase	1.01 (0.96–1.06)	1.02 (0.99–1.06)	1.00 (0.97–1.03)	0.99 (0.97–1.02)	0.99 (0.97–1.01)	0.97 (0.96–0.99)

Favourable neurological outcomes were defined as a Glasgow-Pittsburgh cerebral performance category score of 1 or 2.
Shown is the AOR (95% CI) for the favourable neurological outcome from the multivariable logistic regression analysis adjusted for age, sex, bystander witness, initially documented rhythm at the scene, time from EMS call to hospital arrival, initially documented rhythm at the hospital, cause of arrest, blood pH, HCO3-, pCO2, and lactate.
EMS, emergency medical service; AOR, adjusted odds ratio; CI, confidence interval

life-saving technician, a highly trained pre-hospital emergency care provider permitted to provide advanced life support, including adjunct airways for patients with OHCA, is dispatched to each ambulance. Therefore, we believe that the heterogeneity in the quality of respiratory support is not significant. Fourth, the present study was a retrospective analysis of a database; hence, we could not avoid several biases. A significant number of patients from the registry who did not have any blood gas results available were excluded from our analysis, which limits our findings to those patients who were stable enough to have blood gases taken. Furthermore, although we have adjusted for possible confounding factors, residual confounding factors may still exist.

Conclusion

Although the number is small, a notable number of patients with severe acidaemia exhibited good neurological recovery. Witness status was critical for the prognosis of these patients.

CRediT authorship contribution statement

Makoto Watanabe: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Tetsuhisa Kitamura:** Writing – review & editing, Supervision. **Bon Ohta:** Supervision. **Tasuku Matsuyama:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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jaamohca-web.com/list/.

Appendix A. Supplementary data

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