Association between pH and neurological outcome among cardiac arrest patients treated by extracorporeal CPR: a prospective observational cohort study in Japan

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Research

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Abstract

Background

We aimed to identify the association of pH value in blood gas assessment with neurological outcome among out-of-hospital cardiac arrest (OHCA) patients treated by extracorporeal cardiopulmonary resuscitation (ECPR).

Methods

We retrospectively analysed the database of a multicentre prospective observational study to collect pre-hospital and in-hospital data among OHCA patients in Osaka prefecture, Japan (CRITICAL study), from 1 July 2012 to 31 December 2016. We included the adult OHCA patients treated by ECPR with blood gas assessment before starting ECPR. Patients with OHCA of external causes, such as trauma, were excluded. The patients were divided into three approximately equal groups based on the pH values. We conducted logistic regression analysis to identify the odds ratio (OR) and 95% confidence interval (CI) of the groups for the 1-month neurological favourable outcome adjusted by the potential confounders of sex, age, witnessed by bystander, CPR by bystander, pre-hospital initial cardiac rhythm, and cardiac rhythm on hospital arrival.

Results

Among the 9,822 patients in the database, 260 patients were finally included in the analysis. The three groups were Tertile 1: pH ≥7.030, Tertile 2: pH 6.875-7.029, and Tertile 3: pH<6.875. The adjusted OR of Tertiles 2 and 3 compared with Tertile 1 for 1-month favourable neurological outcome were 0.26 (95% CI: 0.10-0.63) and 0.24 (95% CI: 0.09-0.61), respectively.

Conclusion

This multi-institutional observational study showed that low pH value (<7.03) before the implementation of ECPR was associated with 1-month unfavourable neurological outcome among OHCA patients treated with ECPR. It may be helpful to consider the candidate for ECPR.

Background

Extracorporeal cardiopulmonary resuscitation (ECPR) is a mechanical haemodynamic support for out-of-hospital cardiac arrest (OHCA) patients using veno-arterial extracorporeal membrane oxygenation (V-A ECMO). Although this advanced resuscitation is expected to improve outcomes among patients with refractory cardiac arrest, it is invasive and expensive and requires huge human resources.[1–3] Therefore, it is important to judge whether this is appropriate for a patient immediately after hospital arrival, based on the available information associated with neurological outcome.[4,5]

Blood gas assessment (BGA) is performed easily and commonly to identify the treatable causes and predict prognosis in resuscitation for OHCA.[6–10] Of the factors assessed in BGA, pH value in particular is influenced by metabolic and respiratory acidosis and is representative of haemodynamic and respiratory conditions.[11] Some observational studies show that the pH value after the return of spontaneous circulation (ROSC) is associated with neurological outcome among OHCA patients.[6–8] These results may be helpful in considering the indication of intensive care admission or targeted temperature management after ROSC; however, the decision to start ECPR needs to be made before ROSC. Thus, these results may not be generalisable to ECPR candidates. One other observational study indicated that the pH value during resuscitation was related to neurological outcome; however, this study did not include patients with ECPR.[6] Currently, little is known about the association between pH value before the implementation of ECPR and neurological outcome among OHCA patients treated by ECPR. Our study aimed to determine the association between the pH value before implementation of ECPR and neurological outcome, among OHCA patients treated with ECPR.

Methods

We have reported the methodology of this study according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[12] The Ethics Committee of Kyoto University and each participating institution approved this study protocol (R1045), and written informed consent was waived.

Study design and settings

We performed retrospective analysis of the database of the Comprehensive Registry of Intensive Care for OHCA Survival (CRITICAL) study. This is a multicentre prospective observational study to collect pre-hospital and in-hospital data among OHCA patients in Osaka prefecture, Japan. The pre-hospital data was obtained from the All-Japan Utstein Registry of the Fire and Disaster Management Agency (FDMA).[13–16] In-hospital data were from 13 tertiary critical care medical centres (CCMCs) and 1 non-CCMC community hospital with an emergency department, all in Osaka prefecture in Japan. Osaka prefecture is an urban area of 1,905 km^2, and it had a residential population of about 8.8 million in 2015.[17] In Osaka Prefecture, a total of 7,500 OHCA cases occur every year,[18] and approximately 1 in 4 OHCA patients (approximately 2,000 cases or more) have been registered every year from 2012 to 2016. This registry is still ongoing, with an undefined study period. In-hospital data were recorded by the physicians in charge of the patients and registered by the physicians or medical administrators using a predefined online form. Finally, the working group checked and confirmed the quality of data. If the data were incomplete, they were returned to each institution, and then the data were completed.[16] A detailed description of the All-Japan Utstein Registry of FDMA and the CRITICAL study were previously published.[16]

Study patients

From the CRITICAL database, we included all adult (aged ≥ 18 years) patients with OHCA due to internal medical causes, who were treated with ECPR, between 1 July 2012 and 31 December 2016. We defined ECPR as initiation of cardiopulmonary bypass using V-A ECMO with the emergency cannulation of a large vein and artery for OHCA patients on hospital arrival during the resuscitation.[19] We excluded patients as follows: those who did not receive any resuscitation or treatment in the hospital, whose pre-hospital record was unavailable, whose age was 17 years or less or unknown, or who collapsed with cardiac arrest due to external causes such as trauma, drowning, or hanging and those who did not undergo ECPR. We also excluded those without available BGA results before implementation of ECPR. In this cohort, the implementation of ECPR was decided by the physicians in charge of the patients or by each institution's protocol.

Outcome

The primary outcome of our study was 1-month survival with favourable neurological outcome, defined as Cerebral Performance Category (CPC) 1 or 2. CPC is most commonly used to evaluate neurological status 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.[15]

Data measurement and collection

From the CRITICAL database, we obtained clinical information as follows: sex, age (< 65, 65–74, ≥ 75), cause of cardiac arrest (cardiac, others), witnessed by bystander (yes, no), CPR performed by bystander (yes, no), pre-hospital initial cardiac rhythm (shockable, non-shockable), cardiac rhythm on hospital arrival (shockable, non-shockable, ROSC), pH in the BGA before the implementation of ECPR, resuscitation time course, and outcomes. Age categories were defined on the basis of a government reference.[17] The pH value in venous BGA can be used interchangeably with that in arterial BGA because they are well related to each other.[20,21] Thus, we treated them as the same. The resuscitation time courses were defined as the time from emergency call (E-call) for ambulance to hospital arrival, BGA, and start of ECPR in the hospital. The included patients were divided into three groups of approximately equal size, based on the pH value in the BGA (Tertiles 1 to 3).

Potential bias

We excluded patients who lacked BGA data from the main analysis (complete case analysis). If data are missing completely at random, excluding patients with missing data does not lead to biased results; thus, it can be acceptable.[22] However, if the missing happens not at random and depends on the outcome and exposure, then it would introduce selection bias.[22] Therefore, to demonstrate the robustness of our results and compensate for the risk of selection bias, we described the characteristics of patients with missing data and performed a sensitivity analysis using the scenario that missing depended on exposure and outcome, described in additional file1. (The details of the sensitivity analysis are also described in additional file1.)

Statistical analysis

We described the patients' characteristics in each patient group. To identify the associations of the pH with the primary outcome, we calculated crude odds ratios (OR) and adjusted OR with 95% confidence intervals (CI) of each patient group for the outcome, using a logistic regression model. We adjusted for potential confounders as follows: sex (male, female), age (< 65, 65–74, ≥ 75), witnessed by bystander, CPR by bystander, pre-hospital initial cardiac rhythm (shockable, non-shockable), and cardiac rhythm on hospital arrival (shockable, non-shockable, ROSC). Moreover, for better understanding of the results, we described the characteristics of those who had favourable neurological outcomes in each group.

We did not estimate a sample size because our analysis was secondary usage on already available data.[12] All statistical results were considered significant at a two-sided P-value of < 0.05. All statistical analyses were performed using JMP Pro® 14 software (SAS Institute Inc., Cary, NC, USA).

Results

Study participants

Among the 9,822 patients in the CRITICAL database, 260 patients were finally included in the analysis (Fig. 1). The three groups into which the included patients were divided were Tertile 1: pH ≥ 7.03, Tertile 2: pH 6.875–7.029, and Tertile 3: pH < .875. The characteristics of the patients are shown in Table 1. In summary, the patients in Tertile 3 (pH < 6.875) were relatively young (age, median, [IQR]: 55.5, [46–66] years), compared with those in Tertile 1 (pH ≥ 7.03) (67 [56.8–75.3] years) and Tertile 2 (pH 6.875–7.029) (63.5 [49.0-69.8] years). The other parameters were substantially similar among groups.

Table 1

The characteristics

	Total	pH on Blood gas analysis before ECPR started		
		Tertile 1	Tertile 2	Tertile 3
Parameters		(≥ 7.03)	(7.029–6.875)	(< 6.875)
	(N = 260)	(N = 86)	(N = 88)	(N = 86)
Men	197 (75.8%)	63 (73.3%)	65 (73.9%)	69 (80.2%)
Age, y	62.5 (49–71)	67 (56.8–75.3)	63.5 (49-69.8)	55.5 (46–66)
18–65	146 (56.2%)	38 (44.2%)	48 (54.5%)	60 (69.8%)
65–74	72 (27.7%)	22 (25.6%)	30 (34.1%)	20 (23.3%)
≥ 75	42 (16.2%)	26 (30.2%)	10 (11.4%)	6 (7.0%)
Cause of cardiac arrest				
Cardiac	245 (94.2%)	81 (94.2%)	83 (94.3%)	81 (94.2%)
Pre-hospital information				
Bystander witness	206(79.2%)	66(76.7%)	71(80.7%)	69(80.2%)
Bystander CPR	120(46.2%)	36(41.9%)	42(47.7%)	42(48.8%)
Shockable on initial rhythm	175(67.3%)	58(67.4%)	63(71.6%)	54(62.8%)
Advanced airway	110 (69.6%)	33 (67.3%)	32 (69.6%)	45 (71.4%)
In-hospital information				
Cardiac rhythm on arrival				
ROSC	22(8.5%)	14(16.3%)	6(6.8%)	2(2.3%)
Shockable	121(46.5%)	39(45.3%)	41(46.6%)	41(47.7%)
Non-shockable	117(45%)	33(38.4%)	41(46.6%)	43(50%)
pH value before ECPR start	6.95 (6.83–7.08)	7.13 (7.08–7.20)	6.95 (6.91–6.99)	6.78 (6.72–6.83)

Continuous value is described as median and IQR. Categorical variables are number and percentage.

No missing value in these parameters.

IQR: Interquartile range, CPR: Cardio-pulmonary resuscitation, ROSC: Return of spontaneous circulation, PEA: Pulseless electrical activity, BGA: Blood gas analysis, E-Call: call to the emergency service, ECPR: Extra-corporeal circulatory support during the CPR

	Total	pH on Blood gas analysis before ECPR started		
Time course, min				
E-call to Hospital arrival	31 (25–38)	30 (22–36)	30 (26-37.5)	35 (28–44)
E-call to collect BGA	39 (32–48)	35 (29–45)	39.5 (33.3–46.0)	43.5 (36.0–54.0)
E-call to start ECPR	60 (51–79)	60 (50.8–90.5)	61.5 (51.3–82)	59 (51.0-71.8)
Continuous value is described as median and IQR. Categorical variables are number and percentage.				
No missing value in these parameters.				
IQR: Interquartile range, CPR: Cardio-pulmonary resuscitation, ROSC: Return of spontaneous circulation, PEA: Pulseless electrical activity, BGA: Blood gas analysis, E-Call: call to the emergency service, ECPR: Extra-corporeal circulatory support during the CPR				

Primary outcome

The primary outcome (1-month survival with favourable neurological outcome) was 27.9% (24/86) in Tertile 1 (pH ≥ 7.03), 10.2% (9/88) in Tertile 2 (pH 6.875 to 7.029), and 9.3% (8/86) in Tertile 3 (pH < 6.875).

The crude OR with 95% CI for primary outcome of Tertiles 2 and 3, compared with Tertile 1 for reference, were 0.29 (95% CI: 0.13–0.68) and 0.26 (95% CI: 0.11–0.63), respectively (Fig. 2). Adjusted OR with 95% CI for primary outcome of Tertiles 2 and 3 compared with Tertile 1 were 0.26 (95% CI: 0.10–0.63) and 0.24 (95% CI: 0.09–0.61), respectively (Fig. 2). According to these results, Tertile 2 (pH 6.875–7.029) and Tertile 3 (pH < 6.875) were associated with unfavourable neurological outcome, compared with Tertile 1 (pH ≥ 7.03).

The characteristics of patients with favourable neurological outcome

The characteristics of patients with favourable neurological outcome are shown in Table 2. Those in Tertiles 2 and 3 were more likely to be young, have OHCA witnessed by bystanders, and have ECPR implemented early after arrival.

Table 2

The characteristics in the patients with neurological favourable outcome

	pH on Blood gas analysis before ECPR started		
	Tertile 1	Tertile 2	Tertile 3
Parameters	(≥ 7.03)	(7.029–6.875)	(< 6.875)
	(N = 24)	(N = 9)	(N = 8)
Men	19 (79.2%)	5 (55.6%)	7 (87.5%)
Age, y	62.5 (51.5–68.8)	58.0 (51.5–69.5)	50.5 (33.0–60.0)
18–65 y	13 (54.2%)	6 (66.7%)	7 (87.5%)
65–74	8 (33.3%)	3 (33.3%)	1 (12.5%)
≥ 75	3 (12.5%)	0 (0.0%)	0 (0.0%)
Cause of cardiac arrest			
Cardiac	21(87.5%)	7(77.8%)	8(100%)
Pre-hospital information			
Bystander witness	14(58.3%)	9(100%)	7(87.5%)
Bystander CPR	10(41.7%)	5(55.6%)	4(50%)
Shockable on initial rhythm	18(75%)	6(66.7%)	7(87.5%)
Advanced airway	6 (54.5%)	0 (0.0%)	4 (80.0%)
In-hospital information			
Cardiac rhythm on arrival			
ROSC	6(25%)	2(22.2%)	0(0%)
Shockable	15(62.5%)	4(44.4%)	6(75%)
Non-shockable	3(12.5%)	3(33.3%)	2(25%)
pH value before ECPR start	7.14 (7.10–7.26)	6.96 (6.93-7.00)	6.75 (6.71–6.83)
Time course, min			
E-call to Hospital arrival	29.5 (19.3–35.0)	27.5 (19.5–38.8)	25.5 (19.3–33.0)

Continuous value is described as median and IQR. Categorical variables are number and percentage.

IQR: Interquartile range, CPR: Cardio-pulmonary resuscitation, ROSC: Return of spontaneous circulation, PEA: Pulseless electrical activity, BGA: Blood gas analysis, E-Call: call to the emergency service, ECPR: Extra-corporeal circulatory support during the CPR

	pH on Blood gas analysis before ECPR started		
E-call to collect BGA	33 (26.8–41.3)	43 (31–51)	36 (32.3–45.8)
E-call to start ECPR	63 (51-191.5)	48 (45.5–65.0)	49 (46.3–58.5)
Continuous value is described as median and IQR. Categorical variables are number and percentage.			
IQR: Interquartile range, CPR: Cardio-pulmonary resuscitation, ROSC: Return of spontaneous circulation, PEA: Pulseless electrical activity, BGA: Blood gas analysis, E-Call: call to the emergency service, ECPR: Extra-corporeal circulatory support during the CPR			

Sensitivity analysis

Under this assumption, Tertile 2 (pH 6.875–7.029) and Tertile 3 (pH < 6.875) were also independently associated with neurological outcome (Additional file 1). This result demonstrates the robustness of this association, despite the exclusion of the patients with missing BGA.

Discussion

Key observations

This multi-institutional observational study including 14 emergency departments showed that the pH value before the implementation of ECPR was associated with 1-month neurological outcome among OHCA patients treated with ECPR. It may be helpful to consider the candidate for ECPR.

Interpretation of the results

We suggest that our results may be explained as follows: severe acidaemia, including metabolic and respiratory acidosis, is representative of the severe conditions of hypoperfusion of vital organs and insufficient discharge of carbon dioxide during resuscitation, and these conditions may lead to cerebral injury or multiple organ failure and unfavourable outcomes. Metabolic acidosis, especially lactic acidosis, is caused by inadequate oxygen delivery, impaired tissue oxygenation, and anaerobic glycolysis.[24] In cardiac arrest patients, it may be affected by low cardiac output by chest compression during resuscitation.[25] Some observational studies have reported that metabolic acidosis after ROSC is correlated with the duration from arrest to ROSC and associated with neurological outcome among OHCA patients.[8,26–29] Respiratory acidosis, the other cause of severe acidaemia, indicates inadequate discharge of carbon dioxide and is mostly caused by low venous return by chest compression and insufficient alveolar ventilation during resuscitation.[25,30] Previous observational studies also reported that respiratory acidosis is associated with cerebral injury and unfavourable neurological outcome among post-cardiac arrest patients or those with head trauma injury.[31,32] Thus, it is reasonable that lower pH values may represent the severe conditions of longer duration of cardiac arrest, lower cerebral blood flow and venous return, and insufficient ventilation, and these conditions are associated with unfavourable neurological outcome.

Clinical implication

We conclude that pH measurement may be helpful to judge the indication of ECPR. If OHCA patients have a pH value higher than 7.03, they have a higher probability of favourable neurological outcome. The results of BGA are objective, reproductive, and available as soon as a blood sample is collected. Further, when ECPR is attempted, obtaining access to the femoral artery enables continual collection of blood samples. Therefore, pH measurement can be easily applied to real clinical settings.

It should be noted that in our results, some patients with severe acidaemia did survive with favourable neurological outcome. These patients were relatively young, with shockable rhythm and OHCA witnessed by bystanders. A previous case series also reported that some patients with severe acidaemia could achieve good recovery from OHCA in some situations.[33] According to these findings, physicians considering the indication of ECPR should not jump to conclusions too quickly based only on the pH value.

Strengths and limitations

The strength of our study compared with previous studies was that we could identify the association between pH value and neurological outcome adjusting for potential confounders. Among ECPR patients, a previous systematic review reported that witnessed cardiac arrest, CPR performed by bystander, initial shockable rhythm, arrest to ECPR duration, and higher pH value during resuscitation can be potential predictors for survival.[23] In the meta-analysis including five observational studies in this review, there were statistical differences between survivors and non-survivors based on pH value (7.16 ± 0.04 vs 7.01 ± 0.06, mean difference 0.14 [95% CI: 0.08–0.21]) during resuscitation.[23] However, this analysis did not consider the effect of confounding. Further, it did not identify an association with neurological outcome. On the other hand, our analysis adjusted for several major confounders using a logistic regression model and showed the association with neurological outcome. Therefore, our results showed a more robust association than previous studies.

Our study also has several limitations. First, the timing of collecting blood sample and the collecting site (arterial or venous) were not strictly defined, which might have caused measurement bias. Second, our sample size and the number of events were limited. For more precise estimation, a larger sample size would be better. Third, some potential unmeasured confounders might influence on the results. Fourth, the indication of ECPR was decided by each physician or according to each institution’s protocol. Thus, there might be selection bias. Finally, this registry was derived from critical care centre in Osaka, Japan; it is unclear to what extent the results can be generalised to other populations or other settings.

Conclusions

Our study showed that lower pH value (< 7.03) was associated with unfavourable neurological outcome among OHCA patients treated by ECPR. Our results may be helpful in deciding the indication of ECPR.

Abbreviations

BGA
blood gas assessment
CCMC
critical care medical centre
CPC
Cerebral Performance Category
CRITICAL
Comprehensive Registry of Intensive Care for OHCA Survival
ECPR
extracorporeal cardiopulmonary resuscitation
FDMA
Fire and Disaster Management Agency
OHCA
out-of-hospital cardiac arrest
ROSC
return of spontaneous circulation
STROBE
STrengthening the Reporting of OBservational studies in Epidemiology
V-A ECMO
veno-arterial extracorporeal membrane

Declarations

Ethics approval and consent to participate:

The Ethics Committee of Kyoto University and each participating institution approved this study protocol (R1045), and written informed consent was waived.

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

YO: Conceptualization, Validation, Verification, Visualization, Formal analysis, Methodology, Writing - Original Draft, Takeyuki K: Conceptualization, Methodology, Validation, Verification, Formal analysis, Writing - Review & Editing, Takuya I, KY, TY, KH, KN, TN, TI, YY, MK, HS, YH, TS, TM, HS, KS, FN, NN, TM, JS, SM: Resource, Data Curation, TS: Supervision, KK: Writing - Review & Editing, Supervision, Takashi K: Methodology, Writing - Review & Editing, Tetsuhisa K: Methodology Resource, Data Curation, Supervision, Project administration, Funding acquisition, Taku I: Methodology, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. All authors approved final manuscript.

References

1. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. Resuscitation. 2014;85:762-8.
2. Ortega-Deballon I, Hornby L, Shemie SD, Bhanji F, Guadagno E. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: A systematic review of international practices and outcomes. Resuscitation. 2016;101:12-20.
3. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, et al. Coronary Artery Disease in Patients With Out-of-Hospital Refractory Ventricular Fibrillation Cardiac Arrest. J Am Coll Cardiol. 2017;70:1109-17.
4. Dennis M, Zmudzki F, Burns B, Scott S, Gattas D, Reynolds C, et al. Cost effectiveness and quality of life analysis of extracorporeal cardiopulmonary resuscitation (ECPR) for refractory cardiac arrest. Resuscitation. 2019;139:49-56.
5. Kawashima T, Uehara H, Miyagi N, Shimajiri M, Nakamura K, Chinen T, et al. Impact of first documented rhythm on cost-effectiveness of extracorporeal cardiopulmonary resuscitation. Resuscitation. 2019;140:74-80.
6. Shin J, Lim YS, Kim K, Lee HJ, Lee SJ, Jung E, et al. Initial blood pH during cardiopulmonary resuscitation in out-of-hospital cardiac arrest patients: a multicenter observational registry-based study. Crit Care. 2017;21:322.
7. Takaki S, Kamiya Y, Tahara Y, Tou M, Shimoyama A, Iwashita M. Blood pH is a useful indicator for initiation of therapeutic hypothermia in the early phase of resuscitation after comatose cardiac arrest: a retrospective study. J Emerg Med. 2013;45:57-64.
8. Momiyama Y, Yamada W, Miyata K, Miura K, Fukuda T, Fuse J, et al. Prognostic values of blood pH and lactate levels in patients resuscitated from out-of-hospital cardiac arrest. Acute Med Surg. 2017;4:25-30.
9. Hope Kilgannon J, Hunter BR, Puskarich MA, Shea L, Fuller BM, Jones C, et al. Partial pressure of arterial carbon dioxide after resuscitation from cardiac arrest and neurological outcome: A prospective multi-center protocol-directed cohort study. Resuscitation. 2019;135:212-20.

10. Truhlar A, Deakin CD, Soar J, Khalifa GE, Alfonzo A, Bierens JJ, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances. Resuscitation. 2015;95:148-201.
11. Cowley NJ, Owen A, Bion JF. Interpreting arterial blood gas results. BMJ. 2013;346:f16.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Ann Intern Med. 2007;147:573-7.
13. Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Hiraide A; Implementation Working Group for the All-Japan Utstein Registry of the Fire and Disaster Management Agency. Nationwide public-access defibrillation in Japan. N Engl J Med. 2010;362:994-1004.
14. Kitamura T, Kiyohara K, Sakai T, Matsuyama T, Hatakeyama T, Shimamoto T, et al. Public-Access Defibrillation and Out-of-Hospital Cardiac Arrest in Japan. N Engl J Med. 2016;375:1649-59.
15. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). Circulation. 2004;110:3385-97.
16. Yamada T, Kitamura T, Hayakawa K, Yoshiya K, Irisawa T, Abe Y, et al. Rationale, design, and profile of Comprehensive Registry of In-Hospital Intensive Care for OHCA Survival (CRITICAL) study in Osaka, Japan. J Intensive Care. 2016;4:10.
17. Statistics Bureau (Japan). https://www.stat.go.jp/english/. Accessed 17 Nov 2019.
18. Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications (Japan). http://www.fdma.go.jp/neuter/topics/fieldList9_3.html. Accessed 7 Jun 2018.
19. Brooks SC, Anderson ML, Bruder E, Daya MR, Gaffney A, Otto CW, et al. Part 6: Alternative Techniques and Ancillary Devices for Cardiopulmonary Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132:S436-43.
20. Malatesha G, Singh NK, Bharija A, Rehani B, Goel A. Comparison of arterial and venous pH, bicarbonate, PCO2 and PO2 in initial emergency department assessment. Emerg Med J. 2007;24:569-71.
21. Kelly AM, McAlpine R, Kyle E. Venous pH can safely replace arterial pH in the initial evaluation of patients in the emergency department. Emerg Med J. 2001;18:340-2.
22. Hughes RA, Heron J, Sterne JAC, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. Int J Epidemiol. 2019;48:1294-304.

23. Wang J, Ma Q, Zhang H, Liu S, Zheng Y. Predictors of survival and neurologic outcome for adults with extracorporeal cardiopulmonary resuscitation: A systemic review and meta-analysis. Medicine (Baltimore). 2018;97:e13257.
24. Reddy AJ, Lam SW, Bauer SR, Guzman JA. Lactic acidosis: Clinical implications and management strategies. Cleve Clin J Med. 2015;82:615-24.
25. Magliocca A, Olivari D, De Giorgio D, Zani D, Manfredi M, Boccardo A, et al. LUCAS Versus Manual Chest Compression During Ambulance Transport: A Hemodynamic Study in a Porcine Model of Cardiac Arrest. J Am Heart Assoc. 2019;8:e011189.
26. Takasu A, Sakamoto T, Okada Y. Arterial base excess after CPR: the relationship to CPR duration and the characteristics related to outcome. Resuscitation. 2007;23:394-9.
27. Orban JC, Novain M, Cattet F, Plattier R, Nefzaoui M, Hyvernat H, et al. Association of serum lactate with outcome after out-of-hospital cardiac arrest treated with therapeutic hypothermia. PLoS One. 2017;12:e0173239.
28. Jamme M, Ben Hadj Salem O, Guillemet L, Dupland P, Bougouin W, Charpentier J, et al. Severe metabolic acidosis after out-of-hospital cardiac arrest: risk factors and association with outcome. Ann Intensive Care. 2018;8:62.
29. Carden DL, Martin GB, Nowak RM, Foreback CC, Tomlanovich MC. Lactic acidosis as a predictor of downtime during cardiopulmonary arrest in dogs. Am J Emerg Med. 1985;3:120-4.
30. Sandroni C, De Santis P, D'Arrigo S. Capnography during cardiac arrest. Resuscitation. 2018;132:73-7.
31. McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. Resuscitation. 2017;111:116-26.
32. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of Hypercapnia and Hypercapnic Acidosis With Clinical Outcomes in Mechanically Ventilated Patients With Cerebral Injury. JAMA Neurol. 2018;75:818-26.
33. Ilicki J, Djarv T. Survival in extremely acidotic cardiac arrest patients depends on etiology of acidosis. Resuscitation. 2017;113:e25.

Additional Files

File name: Additional file 1
File format PDF

Title of data: Sensitivity analysis

Description of data: The details of sensitivity analysis and the results

Figures

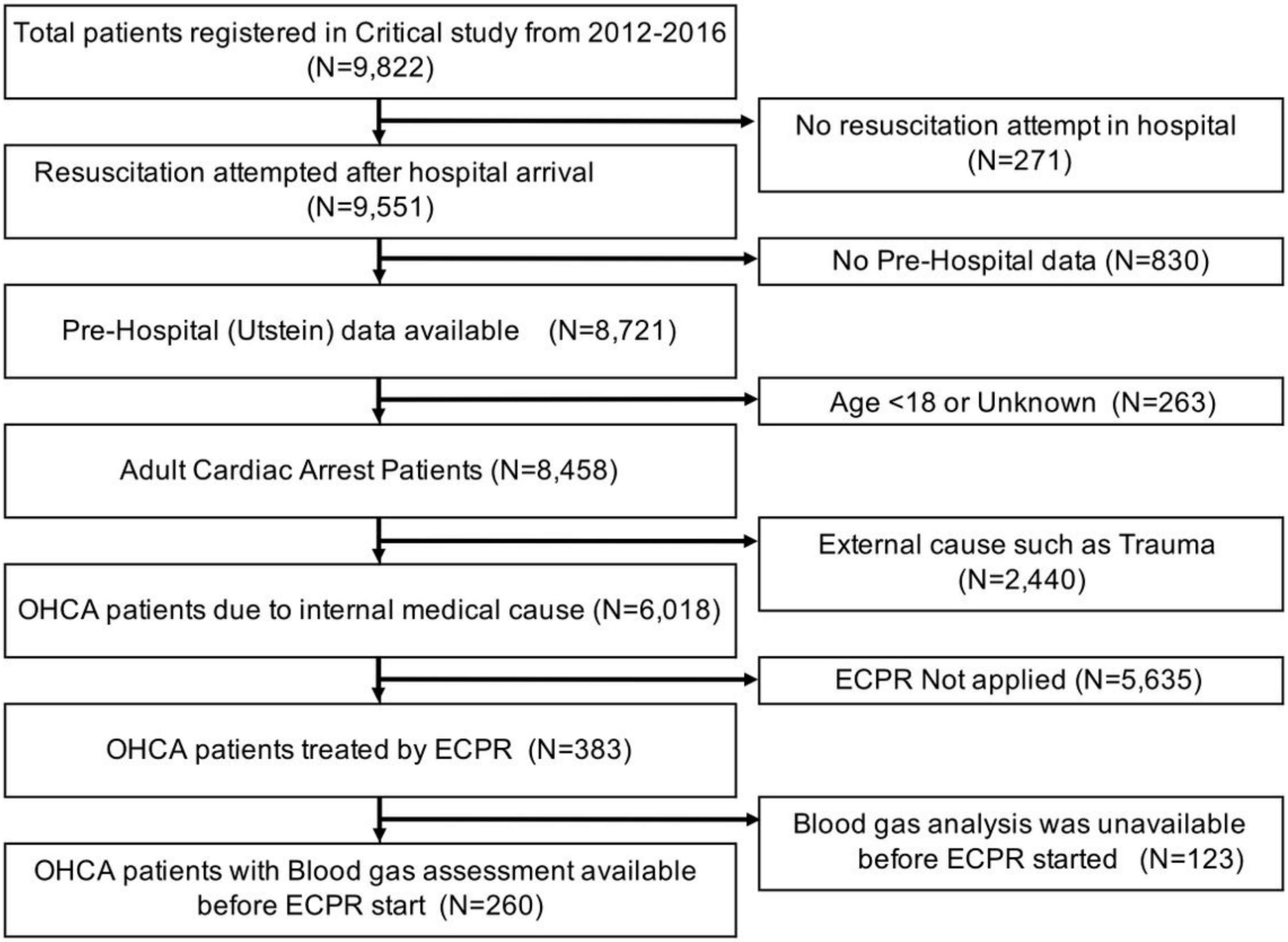

Figure 1

Study flow chart

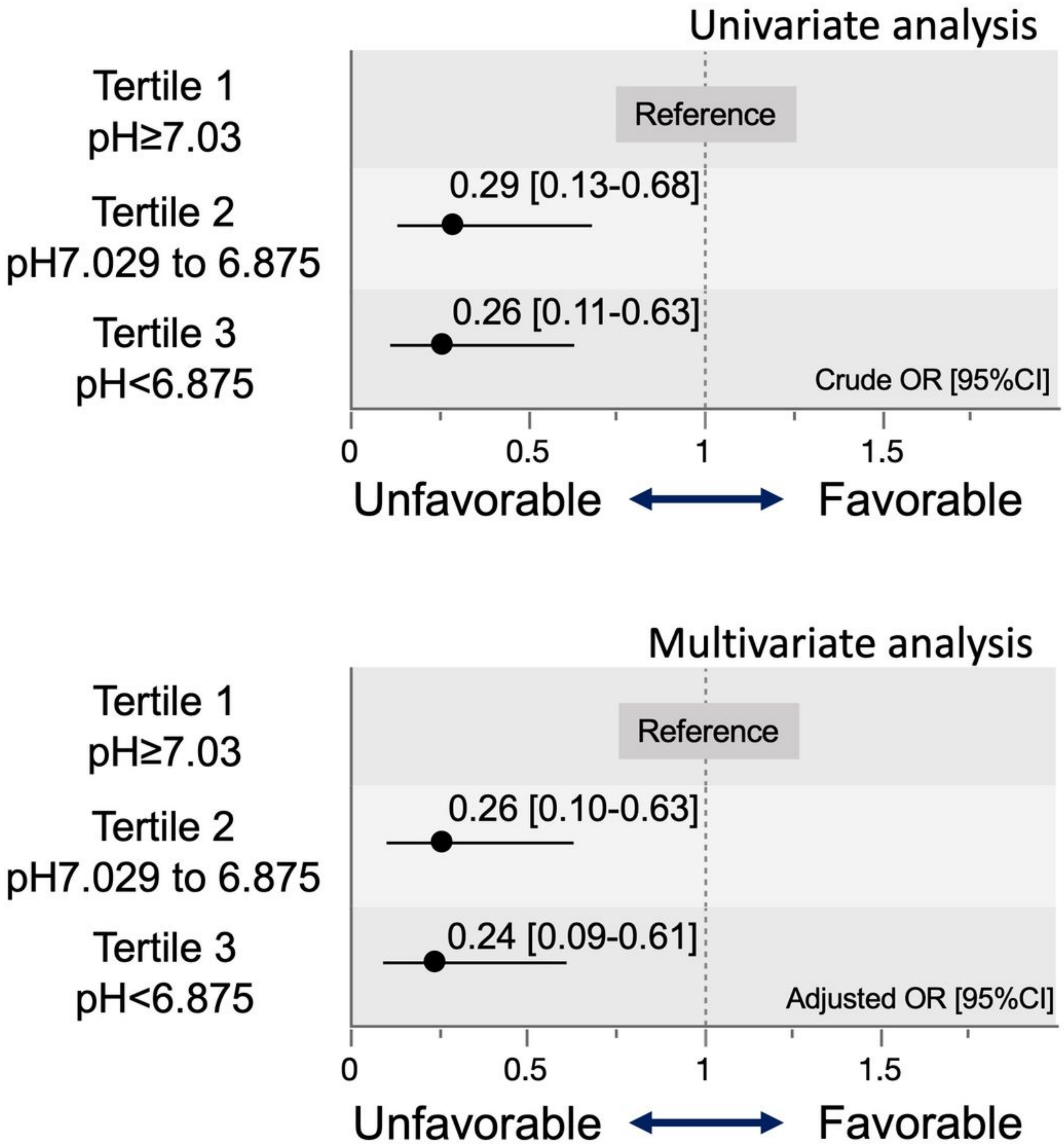

Figure 2

Crude and adjusted odds ratios and 95% CI of Tertiles 2 and 3 for the primary outcome. Adjusted by sex, age, witness of collapse, bystander CPR, prehospital initial rhythm, and initial rhythm on hospital arrival. OR: odds ratio, CI: confidence interval

Supplementary Files

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