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Clinical paper

Initial arterial pH as a predictor of neurologic outcome after out-of-hospital cardiac arrest: A propensity-adjusted analysis

Erich L. Kiehl[a], *Ram Amuthan*[b], *Mark P. Adams*[c], *Thomas E. Love*[d,e], *Kyle B. Enfield*[f], *Lawrence W. Gimple*[c], *Daniel J. Cantillon*[a], *Venu Menon*[a,*]

[a] Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA
[b] Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA
[c] Department of Cardiovascular Medicine, University of Virginia, Charlottesville, VA, USA
[d] Departments of Medicine and of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA
[e] Center for Health Care Research and Policy, MetroHealth Medical Center, Cleveland, OH, USA
[f] Department of Pulmonary and Critical Care Medicine, University of Virginia, Charlottesville, VA, USA

Abstract

Background: Lower pH after out-of-hospital cardiac arrest (OHCA) has been associated with worsening neurologic outcome, with <7.2 identified as an "unfavorable resuscitation feature" in consensus treatment algorithms despite conflicting data. This study aimed to describe the relationship between decremental post-resuscitation pH and neurologic outcomes after OHCA.

Methods: Consecutive OHCA patients treated with targeted temperature management (TTM) at multiple US centers from 2008 to 2017 were evaluated. Poor neurologic outcome at hospital discharge was defined as cerebral performance category ≥3. The exposure was initial arterial pH after return of spontaneous circulation (ROSC) analyzed in decremental 0.05 thresholds. Potential confounders (demographics, history, resuscitation characteristics, initial studies) were defined a priori and controlled for via ATT-weighting on the inverse propensity score plus direct adjustment for the linear propensity score.

Results: Of 723 patients, 589 (80%) experienced poor neurologic outcome at hospital discharge. After propensity-adjustment with excellent covariate balance, the adjusted odds ratios for poor neurologic outcome by pH threshold were: ≤7.3: 2.0 (1.0–4.0); ≤7.25: 1.9 (1.2–3.1); ≤7.2: 2.1 (1.3–3.3); ≤7.15: 1.9 (1.2–3.1); ≤7.1: 2.4 (1.4–4.1); ≤7.05: 3.1 (1.5–6.3); ≤7.0: 4.5 (1.8–12).

Conclusions: No increased hazard of progressively poor neurologic outcomes was observed in resuscitated OHCA patients treated with TTM until the initial post-ROSC arterial pH was at least ≤7.1. This threshold is more acidic than in current guidelines, suggesting the possibility that post-arrest pH may be utilized presently as an inappropriately-pessimistic prognosticator.

Keywords: pH, Out-of-hospital cardiac arrest, Targeted temperature management, Prognostication, Outcomes

* Corresponding author at: 9500 Euclid Avenue, J1-5, Cleveland, OH 44195, USA.
E-mail address: menonv@ccf.org (V. Menon).

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Introduction

The American Heart Association estimates 347,000 adults in the United States suffer out-of-hospital cardiac arrest (OHCA) annually. Reported survival to hospital discharge with favorable neurologic outcome, defined by cerebral performance category (CPC) <3/5, is only 8%.[1] While cerebral anoxia remains the leading cause of morbidity/mortality,[2] neurologic outcomes have improved with widespread integration of targeted temperature management (TTM) as standard of care for all comatose patients post-OHCA. TTM is recommended for 24 h at 32–36 °C regardless of arrest rhythm,[3] a guideline supported by randomized control trial[4–6] and meta-analysis[7–9] data.

In TTM-treated OHCA patients, current recommendations are to delay neurologic prognostication >72 h post-arrest,[3,10] a timeline consistent with reported average awakening 3.2 days post-OHCA.[11] Nevertheless, the majority of patients will not recover meaningful neurologic function. While premature withdrawal of care is literally life-changing, protracted, ultimately-futile hospitalizations also carry considerable emotional and financial costs for patients and their loved ones.[12,13]

As such, validated prediction models (*C-GRApH*,[14] *CAHP*,[15] *TTM risk score*[16]) have recently been developed in an effort to provide earlier neurologic stratification. Each scoring system includes initial arterial pH as a predictor with significant weight, with lower pH associated with poorer neurologic outcome. However, the relationship between initial pH and eventual neurologic outcome remains poorly characterized. It is not understood if pH decrements are associated with incrementally poor outcomes, or rather if a threshold exists, below which outcomes progressively worsen.

Based on nephrology and sepsis-centric literature,[17,18] pH < 7.2 has historically been considered severe acidosis. In a current consensus-care algorithm, post-arrest pH < 7.2 is identified as an "unfavorable resuscitation feature" and potential justification to forego coronary angiography.[19] However, the evidence supporting this threshold is unclear. The algorithm cites data from the PROCAT registry,[20] but *TTM risk score* and *C-GRApH* utilize pH cutoffs down to <6.9 and <7.0 respectively. In fact, 7.2 has been previously evaluated in cardiac arrest,[21–23] albeit in more heterogeneous populations (in-/out-of-hospital) with pH collected at differing time-points (peri-cardiopulmonary resuscitation [CPR], post-return of spontaneous circulation [ROSC]). The prior studies are conflicting, two showing no worsened neurologic outcomes <7.2, one showing improved outcomes >7.2 with shockable rhythms only.[22]

In this large, multi-center study spanning a decade of TTM-treated OHCA patients, propensity-adjustment for confounding was employed to better characterize the association of initial post-ROSC arterial pH and neurologic prognosis.

Methods

Study sample

Consecutive adult patients treated with TTM following OHCA with successful ROSC were prospectively included in institutional quality-improvement registries from 2008 to 14 at the University of Virginia and 2012 to 17 at Cleveland Clinic. Institutional review board approval was obtained for retrospective analysis. Informed consent waiver was granted. Patients were included whether ROSC was obtained pre- or in-hospital and if initially presenting or subsequently transferred to study sites. TTM goal was 32–34 °C for 24 h via external or intravascular techniques. Patient were not excluded from analysis if goal temperature or duration was not achieved (intention-to-treat).

Outcome variable

The outcome variable was neurologic classification at hospital discharge. As applied in landmark studies,[4–6] neurologic outcome was dichotomized by CPC: 1–2 favorable, 3–5 poor. There was logistical variability in CPC assignment between study sites. At University of Virginia, CPC was assigned retrospectively based on chart review by neurologists blinded to the study question. At Cleveland Clinic, CPC was assigned during the index hospitalization by consulting neurologists.

Exposure variable

The exposure variable was initial post-ROSC arterial pH. To restrict to the early post-arrest period, pH levels were only included if resulting ≤2 h after ROSC. In rare cases, pH was obtained pre-hospital by emergency medical services (EMS), but in the overwhelming majority was obtained by either the primary study sites or transferring hospitals. Neither venous pH nor peri-resuscitation (pre-ROSC) arterial pH were deemed adequate surrogates.

Covariates

Clinical information available at the time of initial pH were included as potential covariates for adjustment. This included patient demographics, medical history, arrest characteristics, and other laboratory studies. Covariate data was obtained via review of available EMS, transferring hospital, and study site documents via electronic medical record review. Of note, medical diagnosis were required to be known prior to OHCA. For example, if OHCA occurred due to myocardial infarction as the first presentation of coronary artery disease (CAD), this was not considered pre-arrest CAD.

Statistical analysis

Continuous variables are presented mean (standard deviation) and were compared via Student's t-test. Categorical variables are presented number (percentage) and were compared using Pearson's chi-squared test. By rule, missing data was not allowed for either the exposure or outcome variables. For covariates where missingness was present, simple random imputation was performed. Covariates for modeling were selected entirely *a priori* based on associations with neurologic outcome established in prior literature.[10] The exposure variable was created by applying recursive 0.05 pH decrements to generate a series of pH thresholds ranging 7.0–7.3. At each threshold, propensity scores were created from the covariates, as well as indicator variables for covariates with >10% missingness. A double-robust propensity weighting strategy was selected due to more effective covariate balance than alternative propensity approaches. This utilized average treatment effect in the treated (ATT)-weighting on the inverse propensity score, as well as direct adjustment for the linear propensity score in final logistic regression modeling. Odds ratios for poor neurologic outcome were estimated pre- and post-propensity adjustment at each pH threshold. All comparisons involved two-tailed tests at 5% significance level. The data was analyzed using R v3.3.2 statistical software (2016, Vienna, Austria, https://www.R-project.org/).

Results

From 2008 to 17, 723 patients were included, 540 from Cleveland Clinic and 183 from University of Virginia. Overall, 226 (31%) survived to hospital discharge, 141 (20%) with favorable neurologic outcome. For non-survivors, median time from ROSC to death was 92 h (IQR 53–161). Of 497 patients dying during the index post-OHCA hospitalization, 306 (62%) survived <72 h post-ROSC. Roughly half of 191 patients dying <72 h post-ROSC either re-arrested, met clinical criteria for brain death, or had high-risk findings for severe anoxic brain injury on neuroimaging. In the remaining half (19% composite), withdrawal of care occurred prior to current guidelines by directive of patients' medical power of attorney.

Baseline demographics, medical history, arrest characteristics, and initial laboratory studies are summarized in Table 1, stratified by neurologic outcome. Nearly all univariable analyses were strongly significant ($p < 0.05$). Poor neurologic outcome patients were older and disproportionately female. Unsurprisingly, patients with pre-existing CAD, congestive heart failure (CHF), or diabetes mellitus experienced worse outcomes. Nevertheless, nearly half the patients (n = 307, 42%) were not known to have cardiovascular disease pre-arrest, yet 72% went on to experience poor outcomes. The majority of patients suffered witnessed arrests. Bystander CPR, shockable rhythm (ventricular fibrillation/tachycardia [VT/VF]), and shorter ROSC times were identified as favorable resuscitation features, consistent with prior work.[10] Time to ROSC was not reliably known, however, in 36% (n = 257) of patients. As for initial post-ROSC laboratory studies, higher blood glucose and lactic acid and lower arterial pH were associated with poor neurologic outcomes.

Table 1 – Baseline characteristics, pre-arrest medical history, arrest characteristics, and initial post-resuscitation laboratory values for the study patients (n = 723) stratified by neurologic outcome (favorable: CPC 1–2; poor; CPC 3–5). Continuous variables are expressed as mean (standard deviation) and categorical variables as number (percentage).

	Favorable (n = 142)	Poor (n = 581)	P value
Age (years)	57 (15)	63 (15)	<0.001
Female	41 (29%)	271 (47%)	<0.001
Coronary artery disease	32 (23%)	205 (35%)	0.005
Congestive heart failure	26 (18%)	187 (32%)	0.002
Diabetes mellitus	27 (19%)	215 (37%)	<0.001
Witnessed arrest	119 (84%)	444 (76%)	0.07
Bystander CPR	89 (63%)	295 (51%)	0.01
Shockable rhythm	125 (88%)	175 (30%)	<0.001
Time to ROSC (min)	22 (16)	29 (17)	<0.001
Glucose (mg/dL)	233 (82)	277 (134)	<0.001
Lactic acid (mmol/L)	6.0 (3.3)	8.6 (4.4)	<0.001
Arterial pH	7.23 (0.11)	7.11 (0.18)	<0.001

The distribution of initial post-ROSC arterial pH stratified by neurologic outcome is shown in Fig. 1. As a continuous variable, pH was strongly associated with neurologic outcome ($p < 0.001$) with a C-statistic 0.68, but poor Nagelkerke R^2 0.125. The outcomes at decremental pH thresholds 7.0–7.3 are shown in Fig. 2. In general, as pH decreases, *favorable* neurologic outcome also decreases, and thus, in unadjusted analysis, odds ratios for *poor* neurologic outcome increase steadily until ≤7.1, below which this pattern amplifies (Table 2).

At baseline, covariate balance was poor at all pH thresholds. Rubin's balance criteria[24] were examined pre-adjustment at each pH threshold: (1) absolute value of the standardized differences of the logit of the propensity score– maximum allowable <50%, ideal <10%; (2) ratio of variances of the linear propensity score– required range 0.5–2.0, optimal 0.8–1.25. The calculations are summarized at each pH threshold in Table 2. Rubin's 1st balance criteria was violated at all thresholds, the 2nd at 7.30. As such, propensity adjustment was deemed necessary to adjust for confounding in the absence of randomization.

Density plots of the propensity score at several pH thresholds are displayed in Fig. 3. At the extremes of pH (7.0, 7.3), poor overlap accounts for weighting over matching as the preferred propensity adjustment. After ATT-weighting, the number of treatment patients (below pH threshold) versus weighted control patients (above pH

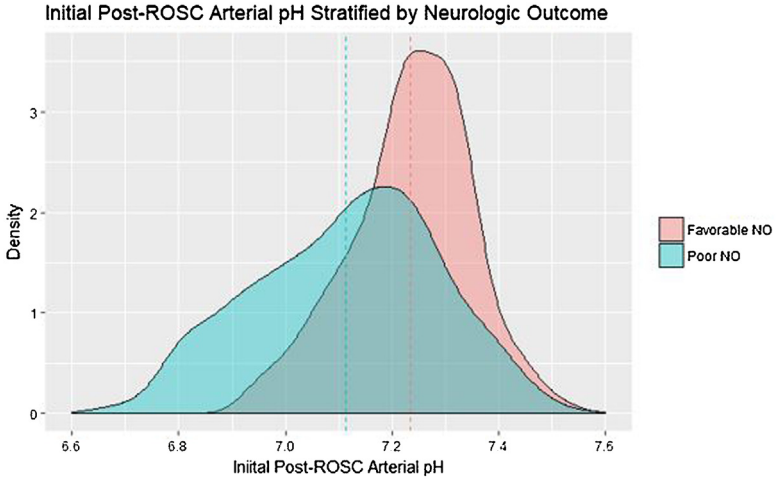
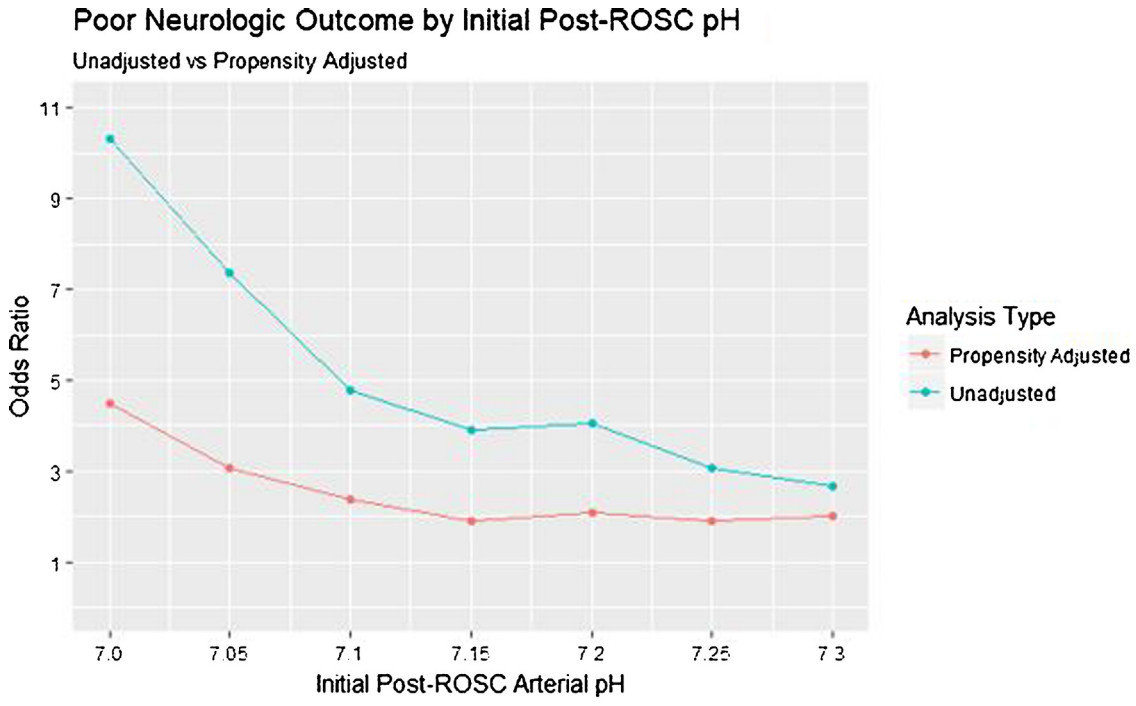


Fig. 1 – Distribution of initial post-ROSC arterial pH stratified by neurologic outcome. The dotted lines represent the mean pH values for the neurologic outcome groups: favorable 7.23 (95% CI 7.01–7.45), poor 7.11 (95% CI.6.76-7.46).

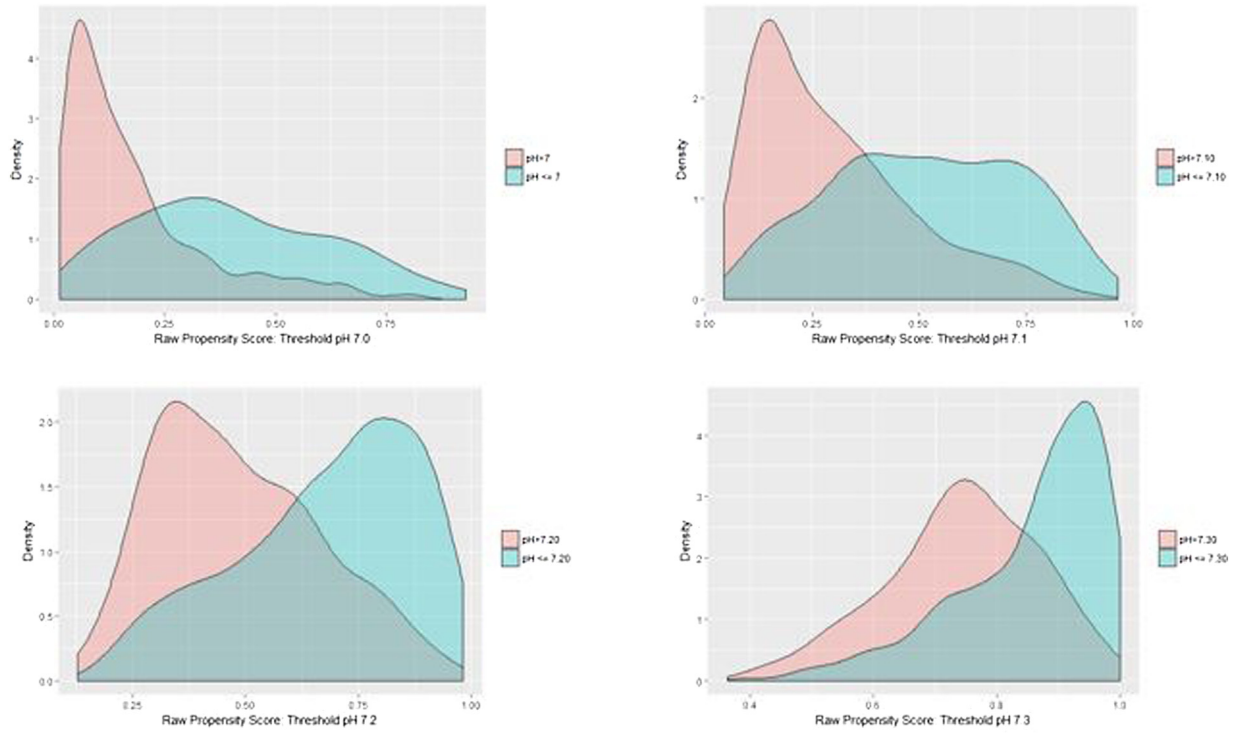


pH Threshold	Favorable Neurologic Outcome (n)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
7.30	16.7% (101/605)	2.7 (1.7-4.1)	2.0 (1.0-4.0)
7.25	14.4% (76/529)	3.1 (2.1-4.5)	1.9 (1.2-3.1)
7.20	10.8% (47/435)	4.1 (2.8-6.0)	2.1 (1.3-3.3)
7.15	9.6% (34/354)	3.9 (2.6-5.9)	1.9 (1.2-3.1)
7.10	7.3% (20/275)	4.8 (2.9-7.9)	2.4 (1.4-4.1)
7.05	4.6% (10/218)	7.4 (3.8-14)	3.1 (1.5-6.3)
7.00	3.0% (5/164)	10 (4.2-26)	4.5 (1.8-12)

Fig. 2 – Pre- and post-adjustment odds ratios for poor neurologic outcome, as well as *favorable* neurologic outcome rates, are shown, stratified by decremental thresholds of initial post-ROSC arterial pH. After adjustment, no significant additive hazard is observed until pH $\leq$ 7.10.

Table 2 – Absolute value of standardized differences of the logit of the propensity score (Rubin's 1st balance criteria) and ratio of variances of the linear propensity score (Rubin's 2nd balance criteria). The values are displayed pre-adjustment and after ATT-weighting on the inverse propensity score plus direct regression adjustment for the linear propensity score. <50% is required for the 1st criteria (ideal <10%) and 0.5-2 for the 2nd criteria (ideal 0.8-1.25). Pre-adjustment, the 1st criteria is violated at all thresholds, the 2nd criteria at the 7.30 threshold. Post-adjustment, there is marked improvement, with both criteria satisfied and nearly meeting ideal targets at all pH thresholds.

pH threshold	1st criteria pre (%)	1st criteria post (%)	2nd criteria pre	2nd criteria post
7.30	84	13	2.23	1.24
7.25	83	5	1.85	0.95
7.20	88	8	1.6	0.84
7.15	94	7	1.52	0.88
7.10	95	5	1.23	0.93
7.05	107	3	1.17	0.97
7.00	109	5	1.03	0.93



pH Threshold	Treatment	Unweighted Control	Weighted Control (%)
7.30	605	118	44 (37%)
7.25	529	194	60 (31%)
7.20	435	288	78 (27%)
7.15	354	369	90 (24%)
7.10	275	448	140 (31%)
7.05	218	505	124 (25%)
7.00	164	559	150 (27%)

Fig. 3 – Density plots of the propensity score at selected pH thresholds showing poor overlap at pH extremes. The resultant sample size of weighted versus unweighted controls after ATT-weighting are also displayed.

threshold) at each cutoff are also displayed. The sample size of weighted controls ranges 24–37% of the unweighted controls.

The standardized differences of the individual covariates pre-/post-weighting are shown in Love plots at several pH thresholds in Fig. 4. Following weighting and direct adjustment for the linear propensity score, Rubin's balance criteria post-adjustment are summarized in Fig. 3. At all pH thresholds, covariate balance is markedly improved and nearly satisfies ideal targets universally.

The odds ratios after ATT-weighting and direct regression adjustment for the linear propensity score are displayed in Fig. 2. No consistent increased hazard for poor neurologic outcome was observed until at least pH $\leq$ 7.10, more markedly $\leq$7.05. Additionally, after adjustment, the amplitude of the odds ratios were decreased at each pH threshold, at times by 50%. These trends were grossly reproducible when repeating propensity adjustment for subgroups restricted to each individual study site, as well as a subgroup restricted to patients surviving >72 h post-ROSC (Supplement Table 1).

Discussion

In this multi-center study spanning a decade of OHCA patients treated with TTM, we demonstrate that decrements in initial post-resuscitation arterial pH are only associated with progressively poorer neurologic outcomes at values $\leq$7.10. This is a lower level than currently advocated as an "unfavorable resuscitation feature" in consensus post-arrest treatment algorithms.[19]

Our study has several strengths. Prior work on post-arrest pH has not controlled as rigorously for confounding. Mechanistically, pH is not a criteria whose confounders can be readily randomized, and as such, propensity adjustment is likely the best alternative approach. Such an attempt has not been published previously. The study sample is large, diverse, and externally generalizable. It includes patients presenting initially to medical centers in rural, suburban, and urban environments of non-academic and academic classification with post-arrest care occurring in all subtypes of intensive care units. All rhythms of arrest

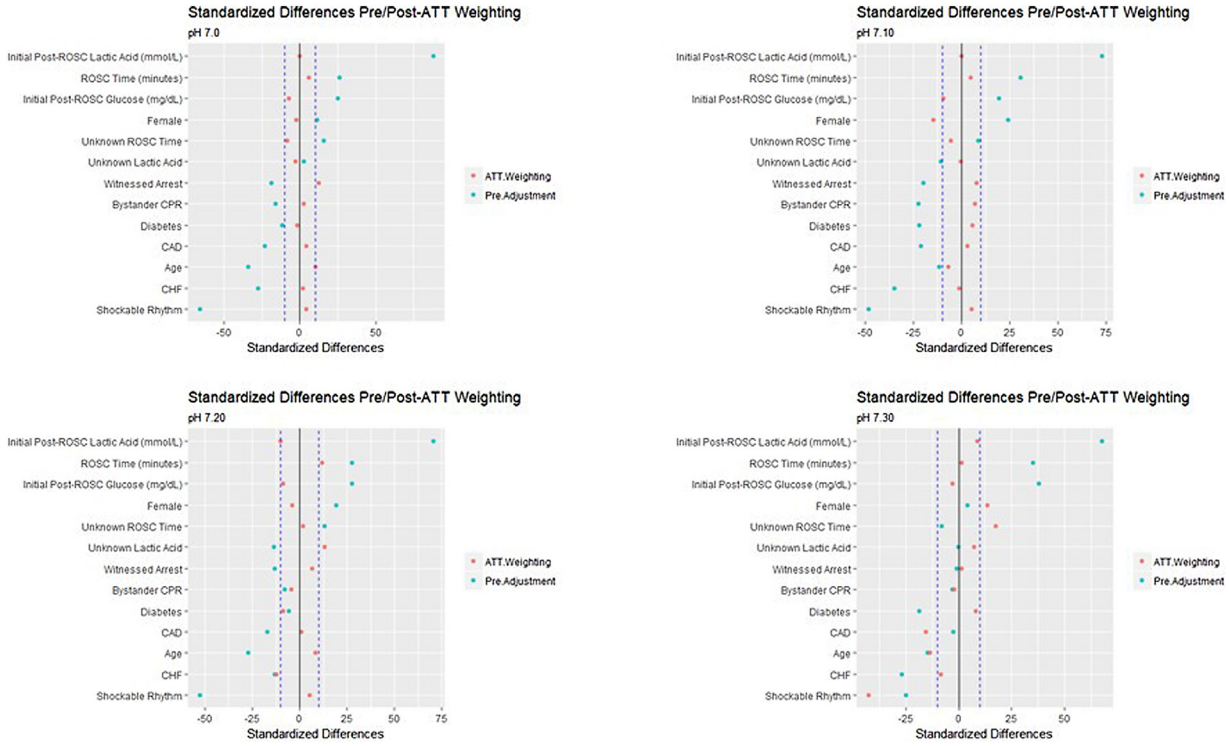


Fig. 4 – Love plots demonstrating marked improvement in covariate balance after propensity weighting.

are represented, with TTM administered in all patients, whether via external or intravascular approach.

Our primary findings are within the range of prior studies, which have yielded variable results likely due to variability in the type, setting, and timing of initial pH sampling. In one of the largest such studies,[25] Shin et al. analyzed peri-CPR pH, whether arterial or venous, in >2000 patients presenting with OHCA. The mean pH with poor neurologic outcome was 6.96 versus 7.11 with favorable ($p < 0.001$). No patients with pH < 6.8 survived with favorable neurologic outcome. However, outcomes were disproportionately poor (4% favorable) with only 16% receiving TTM. In a smaller (n = 135) emergency department (ED) study[26] of first arterial pH, whether pre- or post-ROSC, pH was 7.03 in poor versus 7.26 in favorable outcomes ($p < 0.001$). In Ganga et al.'s study investigating the 7.2 cutoff,[22] baseline blood gases were drawn post-ROSC but immediately prior to TTM initiation. Only in patients with shockable rhythms was pH < 7.2 associated with poor neurologic outcomes ($p < 0.001$). In the prediction models integrating pH thresholds as adverse prognostic factors, *C-GRApH*[14] utilizes 7.0 and *TTM risk score*[16] assigns -1 points for pH ≥ 7.35, 0 for 7.2–7.34, 1 for 7.05–7.19, 2 for 6.9–7.04, and 3 for <6.9 towards total score −2 to 35.

Interpreting pH in OHCA patients will always require contextualization. Lower pH is expected peri-arrest during ongoing CPR due to a no-flow/low-flow state. Higher pH is expected further after ROSC, due to improved hemodynamics and clinician's ability to optimize acid–base status via mechanical ventilation and medication administration. As such, transitive application of prior studies utilizing pH levels drawn peri-CPR versus post-ROSC is fraught with inappropriate pessimism or false optimism respectively. In a study examining OHCA pH at both ED and ICU presentations, the mean pH in favorable outcomes was 7.22 in the ED and 7.40 in the ICU versus 7.12 in the ED and 7.35 in the ICU in poor outcomes.[23] The interchangeability of arterial and venous pH in OHCA patients is also important. Though multiple studies[27,28] have described a +0.03 correction factor to convert venous to arterial pH in patients with normal cardiac output, peri-arrest venous pH has been shown 0.2–0.35 lower,[27,29,30] and post-ROSC >0.1 lower.[30,31] As such, if peri-CPR or post-ROSC, arterial and venous pH should not be considered interchangeable.

Given the myriad factors that affect generalizability of the initial post-arrest pH, clinical prognostication on pH alone should be limited in scope. Based on this data, there is a strong suggestion that current guidelines attribute inappropriate pessimism at a pH of 7.2. Instead, ≤7.1, or perhaps even ≤7.05 would be more appropriate as "unfavorable resuscitation features." Nevertheless, across studies, there is no consistent pH nadir below which favorable neurologic outcome is impossible. In our population, the lowest post-ROSC pH to experience favorable neurologic outcome was 6.94. However, full neurologic recovery has been reported at 6.33–6.85, primarily occurring in young patients with known non-cardiovascular triggers of arrest.[32]

Instead, the use of initial pH as part of a prediction model to direct prognostication and perhaps clinical decision-making is more appropriate, albeit still controversial. Whereas in our data set pH ≤ 7.10 as a univariable predictor produced a c-statistic of 0.65, *C-GRApH*, utilizing pH ≤ 7.0 as a component, generated a c-statistic of 0.88.

Limitations

Our study has several limitations. We cannot exclude the persistent influence of unmeasured confounding variables. Factors that directly affect pH are no longer readily accessible, including timing of

mechanical ventilation and the degree of associated respiratory acidosis, as well as the quantity of sodium bicarbonate administered. As for the exposure, though initial pH was homogenously arterial and resulted ≤2 h post-ROSC, the exact time and location of each pH measurement is no longer readily available and not controlled for. Patients whose initial ABG was obtained via EMS minutes post-ROSC compared to after an hour or more of reperfusion, ventilation, and critical care management may still be too clinically heterogeneous for comparison.

Future directions

Prior post-OHCA prognostication has regularly treated pH and lactic acid as interchangeable analogues. However, Makino et al. reported that only 50% of metabolic acidosis observed post-arrest is explained by lactic acid, [33] and in our study sample, the Pearson correlation coefficient between pH and lactic acid was only −0.48, likely attributable to concurrent respiratory acidosis from peri-arrest hypoventilation. In our population, initial lactic acid and pH perform similarly as univariable predictors, both continuously (C-statistic: 0.68 lactic, 0.71 pH) and at algorithm-identified binary thresholds[19] of >7 for lactic acid and <7.2 for pH respectively (C-statistic: 0.61 lactic, 0.67 pH). However, in a prior study comparing both simultaneously,[34] whereas pH was associated with poor neurologic outcome (6.93 poor, 7.26 favorable), lactic acid was not significantly different (9.6 poor, 8.2 favorable), the latter finding corroborated by Starodub et al.[35] In studies showing significant association between lactic acid and neurologic outcome, the mean lactic acid in poor outcome groups were consistently >7,[34,36,37] with Mullner et al. showing 100% specificity for poor neurologic outcome only at >16 mmol/L.[37] As such, a propensity-adjusted analysis of lactic acid in a similar fashion to pH, as well as an analysis of pH/lactic acid combinations is warranted.

Conclusions

Decrements in initial post-resuscitation arterial pH after OHCA are not associated with progressively poor neurologic outcomes until at least ≤7.10, below which, outcomes worsen. This threshold is lower than reported in consensus algorithms, a discrepancy which may result in overly pessimistic prognostication and/or inappropriate treatment withholding in actual clinical practice. Nevertheless, no consistent pH nadir has been identified to categorize further treatment as futile. As such, initial post-resuscitation pH remains more appropriately utilized as a component in prediction models rather than as a prognosticator in isolation.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.03.036.

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