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Initial arterial pH predicts survival of out-of-hospital cardiac arrest in South Korea

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Background: Arterial pH reflects both metabolic and respiratory distress in cardiac arrest and has prognostic implications. However, it was excluded from the 2024 update of the Utstein out-of-hospital cardiac arrest (OHCA) registry template. We investigated the rationale for including arterial pH into models predicting clinical outcomes.

Methods: Data were sourced from the Korean Cardiac Arrest Research Consortium, a nationwide OHCA registry (NCT03222999). Prediction models were constructed using logistic regression, random forest, and eXtreme Gradient Boosting frameworks. Each framework included three model types: pH, low-flow time, and combined models. Then the area under the receiver operating characteristic curve (AUROC) of each predicting model was compared. The primary outcome was 30-day death or neurologically unfavorable status (cerebral performance category ≥3).

Results: Among the 15,765 patients analyzed, 92.2% experienced death or unfavorable neurological outcomes. The predicting performance of the models including pH (AUROC, 0.92–0.94) were comparable to the models including low-flow time in all frameworks (0.93–0.94) (all P>0.05). Inclusion of pH into low-flow time models consistently showed higher AUROCs than individual models in all frameworks (AUROC, 0.93–0.95; all P<0.05).

Conclusions: The predicting performance of models including arterial pH was comparable to models including low-flow time, and addition of arterial pH into low-flow time models could increase the performance of the models.

Key Words: blood pH; hydrogen-ion concentration; machine learning; out-of-hospital cardiac arrest; prognosis; resuscitation

Original Article

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INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is characterized by high mortality and morbidity rates and continues to be a significant global health concern [1,2]. Despite advances in resuscitation and post-arrest care, survival rates remain low, averaging approximately 10% in Europe, America, and East Asia [3-5]. Hypoxic ischemic brain injury presents a significant challenge in OHCA, highlighting the need of predicting neurological outcomes to guide clinical decision-making and facilitate timely interventions [6,7]. Arterial pH reflects the metabolic and respiratory aspects of cardiac arrest and has been extensively explored for its association with clinical outcomes [8-10]. Acidosis is recognized for its harmful effects, including decreased cardiac output, vasodilation, impaired immune response, and progression to multi-organ failure [11-13]. Arterial pH has been included in various clinical prediction scoring systems such as Nonshockable rhythm, Unwitnessed arrest, Long no-flow or Long low-flow period, blood pH <7.2, Lactate >7.0 mmol/L, End-stage renal disease on dialysis, Age ≥85 years, Still resuscitation, and Extracardiac cause (NULL-PLEASE), Cardiac Arrest Hospital Prognosis (CAHP), Coronary artery disease, Glucose level ≥200 mg/dl, Rhythm of arrest other than ventricular tachycardia/fibrillation, Age >45 years, blood pH ≤7.0 (C-GRApH), and metabolic derangement score [14-17].

However, the 2024 update of the Utstein template by the International Liaison Committee on Resuscitation excluded arterial pH, citing its limited utility as a single measurement due to its variability over time and dependence on clinical factors such as ventilation parameters [7]. Although this change aims to streamline data collection, it highlights the importance of reevaluating the role of arterial pH in predicting outcomes of OHCA. This study evaluated the predictive value of arterial pH for clinical outcomes in patients with OHCA by comparing the performance of prediction models with and without arterial pH.

KEY MESSAGES

- Despite its well-known prognostic implication of arterial pH in out-of-hospital cardiac arrest (OHCA) patients, it was removed from the updated Utstein template for OHCA.
- In this retrospective analysis of 15,765 patients of Korean Cardiac Arrest Research Consortium, a nationwide OHCA registry in Korea, the performance of models incorporating arterial pH was comparable to those utilizing low-flow time for predicting clinical outcomes of OHCA.
- Arterial pH enhanced the predictive performance when added to the models that included low-flow time.
- The potential benefits of incorporating arterial pH measurement into the Utstein template for OHCA should be considered.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Samsung Medical Center (No. 2025-01-057). The study design was retrospective analysis of anonymized data and informed consent was waived.

Study Population and Definitions

We conducted a retrospective study using data from the Korean Cardiac Arrest Research Consortium (KoCARC) registry, a nationwide multicenter OHCA research network based on previous Utstein templates and a collaborative network of 65 hospitals (ClinicalTrials.gov identifier: NCT03222999). Patients with OHCA who were transferred to emergency departments by emergency medical services following resuscitation efforts and had a medical cause between October 2015 and June 2023 were included. Exclusion criteria were pregnancy, terminal illness or receiving hospice care, OHCA due to non-medical causes such as trauma or hanging, and advanced directives or documented "do not resuscitate" orders. Patients with age ≤18 years or missing arterial pH measurement were also excluded. A quality management committee monitored registry data quality [18].

Primary Outcome and Variables for Prediction Models

The primary outcome was 30-day death or neurologically unfavorable survival defined as cerebral performance category ≥3. The variables for the prediction models were selected based on existing evidence and clinical relevance from the KoCARC registry, and included patient demographics (age and sex), arrest characteristics (witnessed arrest, bystander cardiopulmonary resuscitation (CPR), arrest location, and low-flow time), initial shockable rhythm, and prehospital ROSC [14,15,19-21].

Statistical Analysis

Categorical data are presented as counts and percentages (%), and continuous data are presented as medians with interquartile ranges. Comparisons were made using the chi-square test or Kruskal-Wallis test. The entire dataset was randomly divided into a training set (70%) and a test set (30%). Variable importance analysis was performed on the training set using standardized logistic regression, random forest, and eXtreme Gradient Boosting (XGBoost). The prediction models were developed using three frameworks to improve the generalizability of predictions. All models were adjusted for seven variables: age, sex, arrest location, bystander CPR, witnessed arrest, prehospital ROSC, and initial shockable rhythm. Logistic regression was used to provide interpretable model. For the logistic regression analysis, continuous predictors were standardized to facilitate comparability of coefficients. A correlation matrix was used to visually present pairwise linear relationships, while the variance inflation factor was employed exclusively for the logistic regression model to quantitatively assess multicollinearity. Based on these analyses, potential multicollinearity issues were minimized to enhance the stability and reliability of the logistic regression frameworks. Random forest and XGBoost were employed to capture non-linear relationships and complex interactions between predictors and outcomes [22]. For the random forest and XGBoost models, hyperparameter tuning was performed using 5-fold cross-validation within the training set to optimize performance. Within each framework, three model variations were created: (1) model with arterial pH, (2) model with low-flow time, and (3) model with both arterial pH and low-flow time.

All models were validated on a test set using bootstrap resampling with 1,000 iterations. In each iteration, the models were refitted, and predictions were generated to calculate the area under the receiver operating characteristic curve (AUROC), positive predictive value, and negative predictive value. The resulting bootstrap distributions were summarized as means with 95% CIs. AUROCs were plotted and compared using the DeLong test to assess the discriminative performance of the models. Calibration plots were generated to assess the agreement between predicted probabilities and observed outcomes by grouping predicted probabilities into deciles and comparing the mean predicted values with observed proportions. A reference line indicating perfect calibration served as the benchmark. Statistical significance was set at $P<0.05$. All analyses were performed using the R version 4.4.2 (R Foundation for Statistical Computing).

RESULTS

Patients and Clinical Characteristics

A total of 21,273 adult patients were retrieved from the KoCARC registry. After excluding 5,508 patients lacked pH measurement, 15,765 patients were included for analysis (Figure 1, Supplementary Table 1). The mean age of the patients was of 68±15 years, with 66.7% male. Witnessed cardiac arrest, bystander CPR, and initial shockable rhythm occurred in 63.3%, 52.3%, and 21.8% of cases, respectively. The mean low-flow time was 37.0±23.9 minutes, whereas the average pH was 6.95. ROSC was achieved in 54.8% of cases. By day 30, 14,537 patients (92.2%) had either died or experienced neurologically unfavorable outcomes. Detailed baseline clinical characteristics are provided in Table 1 and Supplementary Table 2.

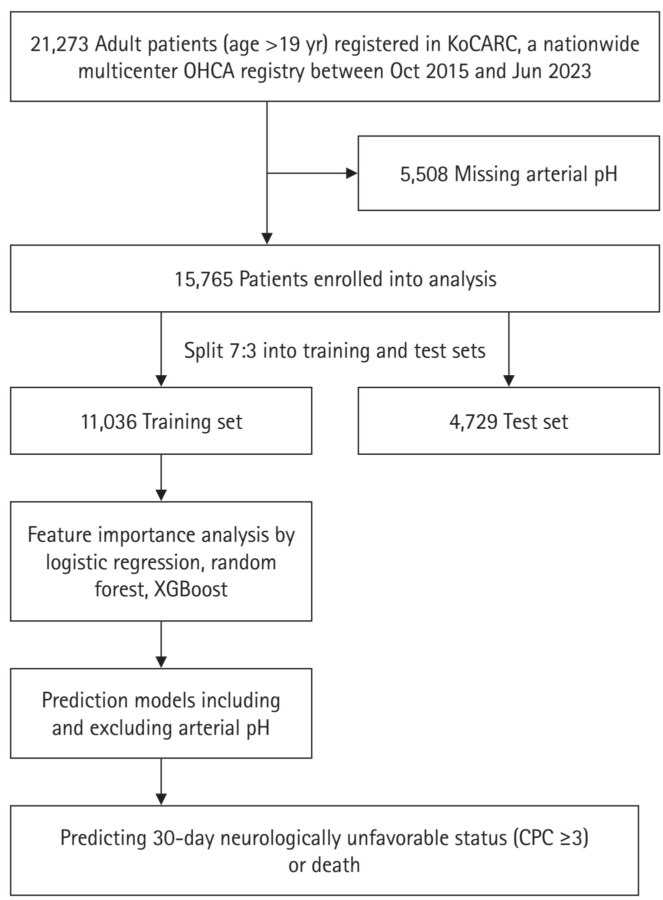

Figure 1. Study flow. KoCARC: Korean Cardiac Arrest Research Consortium; OHCA: out-of-hospital cardiac arrest; XGBoost: eXtreme Gradient Boosting; CPC: cerebral performance category.

Table 1. Baseline characteristics

Clinical characteristics	Value (n=15,765)	No. of measurements
Age (yr)	68.3±15.4	15,765
Male sex	10,510 (66.7)	15,765
Hypertension	6,092 (38.6)	15,765
Diabetes	4,124 (26.2)	15,765
Chronic renal disease	816 (5.2)	15,765
Witnessed arrest	9,975 (63.3)	15,765
Arrest at public location	6,236 (39.6)	15,765
Bystander CPR	8,242 (52.3)	15,765
Shockable rhythm	3,441 (21.8)	15,765
Low-flow time (min)	37.0±23.9	15,765
Prehospital ROSC	2,250 (14.3)	15,765
Arterial pH	6.95±0.21	15,765
Potassium (mmol/L)	5.84±2.21	13,655
PaO_2 (mm Hg)	72±81	15,402
$PaCO_2$ (mm Hg)	76±37	15,587
Hemoglobin (g/dl)	11.7±3.2	13,172
Creatinine (mg/dl)	2.0±2.1	9,392
Lactate (mmol/L)	12.3±5.2	12,180
Glucose (mg/dl)	263±157	13,422
Targeted temperature management	1,688 (10.7)	15,765
ECMO application attempted	582 (3.7)	15,765
ECMO successful application	516 (3.3)	15,765
Death or CPC ≥3 within 30 days	14,537 (92.2)	15,765
ROSC	8,635 (54.8)	15,765

Values are presented as mean±standard deviation or number (%).
CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; ECMO: extracorporeal membrane oxygenation; CPC: cerebral performance category.

Table 2. Multivariable logistic regression analysis

Variable	aOR	95% CI	P-value
Arterial pH	0.47	0.42–0.53	<0.001
Low-flow time	2.11	1.84–2.44	<0.001
Age	1.66	1.51–1.83	<0.001
Arrest at public location	0.70	0.58–0.84	<0.001
Male sex	0.79	0.63–0.99	0.041
Witnessed arrest	0.67	0.53–0.84	<0.001
Bystander CPR	1.06	0.88–1.28	0.550
Pre-hospital ROSC	0.41	0.33–0.51	<0.001
Shockable rhythm	0.20	0.16–0.24	<0.001

aOR: adjusted odds ratio; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation.

Important Features

Important features were extracted in the training dataset. In the logistic regression analysis, pH was negatively associated with poor neurological outcomes (adjusted odds ratio, 0.47; 95% CI, 0.42–0.53) (Table 2). The important features derived from the logistic regression, random forest, and XGBoost models for 30-day neurologically unfavorable outcomes are shown in Figure 2. Arterial pH, low-flow time, initial shockable rhythm, age, and prehospital ROSC were identified as important predictors. Correlations among the variables were minimal (Supplementary Table 3, Supplementary Figure 1).

Prediction of Neurologically Unfavorable Outcome

The predicting performance for death or 30-day neurologically unfavorable outcomes in each model was assessed in the test set. In the logistic regression frameworks, the AUROC of the low-flow time, pH, and combined models were 0.93 (95% CI, 0.92–0.95), 0.94 (95% CI, 0.92–0.95), and 0.94 (95% CI, 0.93–0.95), respectively (Figure 3A). In the random forest frameworks, the AUROC of the low-flow time, pH, and combined models were 0.93 (95% CI, 0.91–0.94), 0.92 (95% CI, 0.90–0.93), and 0.94 (95% CI, 0.93–0.95), respectively (Figure 3B). In the XGBoost frameworks, the AUROC of the low-flow time, pH, and combined models were 0.94 for both the low-flow time (95% CI, 0.93–0.95) and pH models (95% CI, 0.93–0.95), and 0.95 for the combined model (95% CI, 0.94–0.95) (Figure 3C). The prediction models showed fair calibration (Supplementary Figure 2). The DeLong test was used to assess differences in AUROCs among the three models. The low-flow time and pH models did not show a significant difference across the logistic regression, random forest, and XGBoost frameworks, whereas the combined model outperformed the individual models (Supplementary Tables 4 and 5).

DISCUSSION

In this study, we evaluated the predicting performance of the arterial pH and low-flow time for death or unfavorable neurological outcomes in patients with OHCA. Within three distinct frameworks, the predicting performance of arterial pH was comparable to that of low-flow time. When evaluated alongside low-flow time, arterial pH could enhance the predicting performance. Accurate prognostication is crucial to avoid pursuing futile treatments or inappropriately withdrawing treatment in patients with OHCA who might have a chance

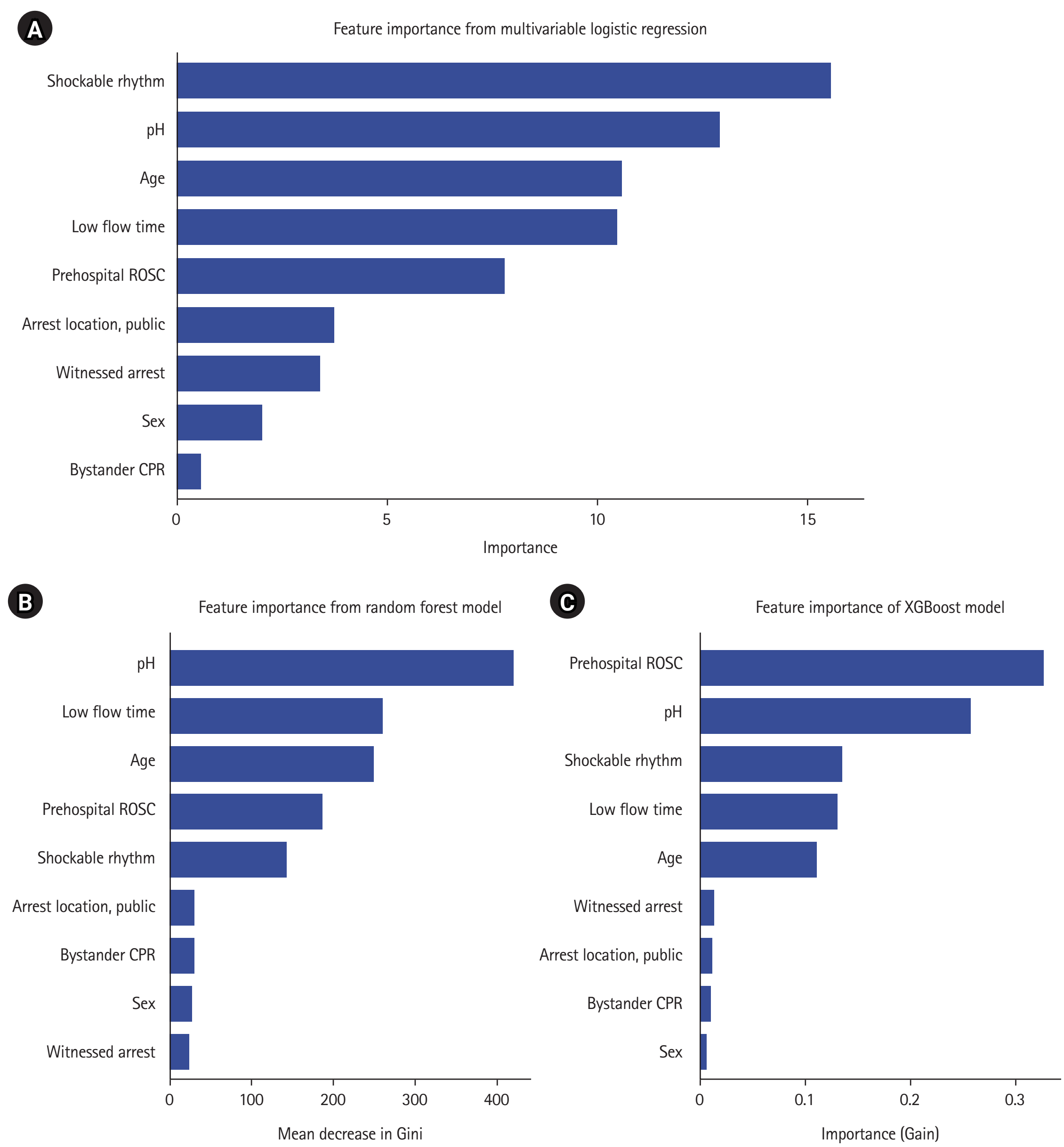

Figure 2. Feature importances from three frameworks. (A) Feature importance from the logistic regression frameworks. (B) Feature importance from the random forest frameworks. (C) Feature importance of the eXtreme Gradient Boosting (XGBoost) frameworks. ROSC: return of spontaneous circulation; CPR: cardiopulmonary resuscitation.

of recovery. Arterial pH is a key indicator of respiratory and metabolic acidosis, as well as hypoperfusion, all of which can significantly impact outcomes after cardiac arrest [17,23,24]. The prognostic value of arterial pH has been extensively investigated [10,17,25-27]. The statements from the Society for Cardiovascular Angiography & Interventions and the Extracorporeal Life Support Organization incorporate arterial pH as one of major prognostic factors in OHCA [28,29].

Since its introduction in 1990, the term "Utstein style" has been regarded as the consensus reporting guidelines for cardiac arrest [30]. In the 2024 update of the Utstein template, arterial pH was excluded, and greater emphasis was placed on the precise reporting of time intervals [7]. This decision reflects the findings that the survival after cardiac arrest heavily depends on the duration of the arrest, with each additional minute of no- or low-flow time associated with a 7%–10% increase in

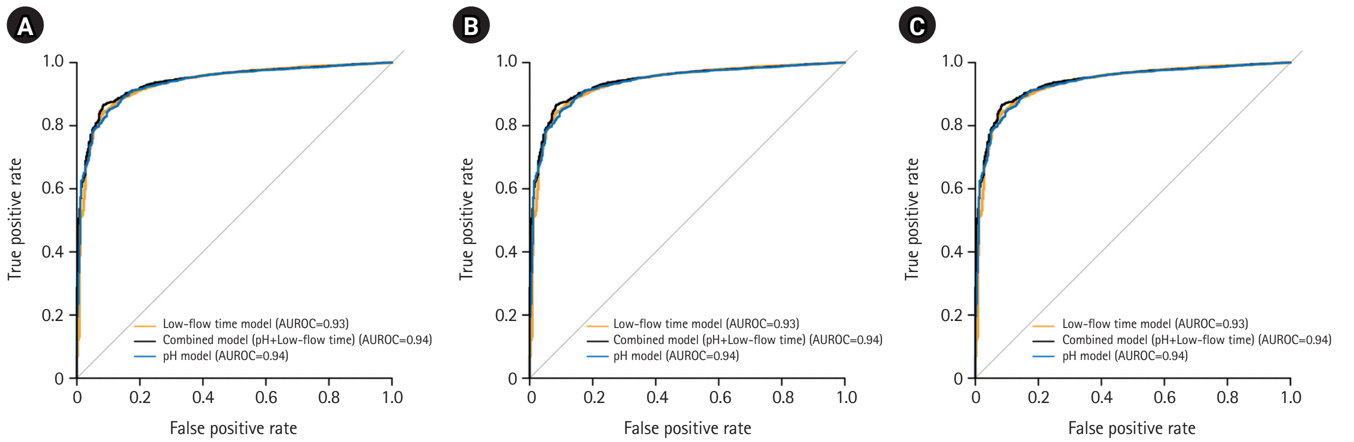

Figure 3. Area under the receiver operating characteristic curve (AUROC) curves of prediction models across frameworks. ROC curves for (A) logistic regression, (B) random forest, and (C) eXtreme Gradient Boosting frameworks.

poor outcomes [31].

This exclusion of arterial pH may reflect the fact that pH levels can fluctuate over time and are influenced by various clinical factors, such as blood pressure, oxygenation, and ventilation status, complicating its utility in predicting outcomes [7]. However, accurate recording timestamps may be also challenging, particularly in out-of-hospital settings, where they are prone to recall bias [31]. In our study, the pH models across all frameworks showed predictive performance comparable to the low-flow time models. Moreover, inclusion of pH in the low-flow time models significantly enhanced their predictive performance. These findings support the consideration of arterial pH as a valuable factor for predicting neurological outcomes in OHCA patients.

Clinical scoring systems including NULL-PLEASE and CAHP scores included arterial pH as a critical component alongside intra-arrest factors, including low-flow time, which are recognized as key prognostic indicators in OHCA [14,15,28,29]. Given its ability to reflect respiratory and metabolic acidosis, as well as hypoperfusion during resuscitation, arterial pH may serve as a valuable reference when low-flow time measurements are not available or imprecise. Therefore, incorporating arterial pH measurement into the Utstein template would enhance the overall quality of registry data. Although collecting arterial pH data from OHCA patients may require additional resources and costs, its potential benefit could outweigh these challenges.

This study had several limitations. First, our results are subject to the inherent limitations of retrospective study design, although efforts were made to reduce potential bias through quality control. Second, patients with missing arterial pH values were excluded, which may have introduced selection bias. Additionally, some measurements may have been derived from venous samples, potentially introducing further variability and measurement bias. Third, a limited number of predictor variables, manually selected based on existing evidence and clinical relevance, were used for the modeling. Fourth, the timestamp data of arterial pH was not available in the KoCARC registry, which may have contributed to variability and limited the interpretability of pH as a prognostic marker. Fifth, clinical parameters potentially affecting the arterial pH measurement, such as systemic metabolic status, cardiac or respiratory function, or the quality of chest compression, were not assessed. Given that these parameters could change rapidly, further research would be required to explore the implication of arterial pH in dynamic clinical scenarios. Finally, this study is the lack of external validation. Further validation in independent, multicenter cohorts is needed to confirm the generalizability and clinical applicability of the results.

Arterial pH measurement could added predictive neurological outcomes in patients with OHCA. Incorporating arterial pH into the Utstein template may enhance outcome prediction, despite potential resource challenges.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: DJ, JHC. Methodology: DJ, JHC. Formal analysis: DJ, JHC. Data curation: DJ, SDS, TGS, GTL, JEP, SYH, JHC. Visualization: DJ, JHC. Project administration: DJ, JHC. Writing - original draft: DJ, JHC. Writing - review & editing: DJ, SDS, TGS, GTL, JEP, SYH, JHC. All authors read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.001050.

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