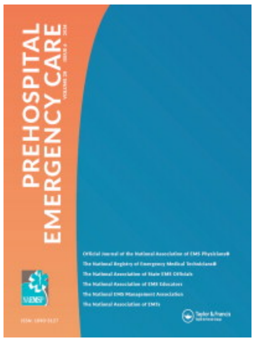

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Prehospital Post-Resuscitation Vital Sign Phenotypes are Associated with Outcomes Following Out-of-Hospital Cardiac Arrest

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ABSTRACT

Objectives: The use of machine learning to identify patient 'clusters' using post-return of spontaneous circulation (ROSC) vital signs may facilitate the identification of patient subgroups at high risk of rearrest and mortality. Our objective was to use k-means clustering to identify post-ROSC vital sign clusters and determine whether these clusters were associated with rearrest and mortality.

Methods: The ESO Data Collaborative 2018–2022 datasets were used for this study. We included adult, non-traumatic OHCA patients with >2 post-ROSC vital sign sets. Patients were excluded if they had an EMS-witnessed OHCA or were encountered during an interfacility transfer. Unsupervised (*k*-means) clustering was performed using minimum, maximum, and delta (last minus first) systolic blood pressure (BP), heart rate, SpO_2, shock index, and pulse pressure. The assessed outcomes were mortality and rearrest. To explore the association between rearrest, mortality, and cluster, multivariable logistic regression modeling was used.

Results: Within our cohort of 12,320 patients, five clusters were identified. Patients in cluster 1 were hypertensive, patients in cluster 2 were normotensive, patients in cluster 3 were hypotensive and tachycardic ($n = 2164$; 17.6%), patients in cluster 4 were hypoxemic and exhibited increasing systolic BP, and patients in cluster 5 were severely hypoxemic and exhibited a declining systolic BP. The overall proportion of patients who experienced mortality stratified by cluster was 63.4% (c1), 68.1% (c2), 78.8% (c3), 84.8% (c4), and 86.6% (c5). In comparison to the cluster with the lowest mortality (c1), each other cluster was associated with greater odds of mortality and rearrest.

Conclusions: Unsupervised k-means clustering yielded 5 post-ROSC vital sign clusters that were associated with rearrest and mortality.

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Introduction

Following the return of spontaneous circulation (ROSC), out-of-hospital cardiac arrest (OHCA) patients are commonly unstable and exhibit vital sign abnormalities including hypotension and hypoxia. A growing body of evidence suggests that post-ROSC vital signs are strongly associated with outcomes following resuscitation from out-of-hospital cardiac arrest (1–7). The majority of studies on this topic focus on individual vital signs (i.e., hypotension alone, hypoxia alone, etc.) or the interaction of a limited set (3) of vital signs (i.e., combined hypotension and hypoxia). However, it is possible that complex interactions between multiple vital signs, as well as trends in vital signs across time, may better predict outcomes following OHCA. One method that may be useful in understanding this complex problem is the use of machine learning techniques, such as unsupervised clustering to identify patient subgroups that present with distinct vital sign patterns following resuscitation.

Unsupervised clustering algorithms allow for the automated identification of subgroups based on underlying patterns within datasets. In a clinical context, this may translate to the identification of subgroups or phenotypes within established disease categories. For example, previous studies have suggested that phenotypes of critical illness defined by clinical and demographic variables may be associated with outcomes and responsiveness to therapy in the context of sepsis (8), trauma (9, 10), and acute respiratory distress syndrome (11). Identifying phenotypes of vital sign derangement following resuscitation from out-of-hospital cardiac arrest may have important implications for personalized delivery of therapeutics, adaptive clinical trial design, prognostication, and triage.

We aimed to use unsupervised clustering techniques to discern phenotypes of post-ROSC vital sign abnormalities. As a secondary aim, we planned to explore the relationship between cluster membership, patient factors, clinical treatments, and patient outcomes.

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Methods

Study Setting and Inclusion Criteria

The 2018–2022 ESO Data Collaborative public use research datasets were used for this study. The ESO company provides electronic health record (EHR) software to >2000 EMS agencies across the United States for patient care documentation and billing purposes. Agencies agreeing to participate in the Data Collaborative have their EHR data deidentified and compiled into annual datasets without data abstraction. These data are available for research purposes at no cost following approval by an independent review committee. All data are collected and stored in accordance with the National Emergency Medical Services Information System (NEMSIS) v3 data standard. All unresponsive (maximum prehospital Glasgow Coma Scale = 3) adults (>18 years of age), non-traumatic OHCA patients with a documented ROSC time were evaluated for inclusion in this study. Patients were excluded if they were encountered during an interfacility transfer, had an EMS witnessed OHCA or if they did not have documentation of >2 sets of all vital signs of interest. The use of this deidentified dataset was classified as 'Not Human Subjects Research' by an institutional review board (protocol 2202524583).

Variable Definitions

For clustering analyses, the maximum, minimum, and delta (last minus first post-ROSC measurement) systolic blood pressure (SBP), heart rate (HR), pulse oximetry (SpO_2), pulse pressure (SBP minus DBP; PP), and shock index (SI = HR/SBP) values were calculated for each patient. These values were then converted to z-scores before clustering analyses.

Patients were classified as having an initially shockable rhythm if their initial electrocardiogram (ECG) showed ventricular fibrillation or ventricular tachycardia or if the first rhythm was automated external defibrillator (AED)-shockable. Pre-first responder cardiopulmonary resuscitation (CPR) was defined as any CPR delivered before the arrival of professional rescuers (fire department personnel, law enforcement officers, or EMS). The airway management strategy for each patient was defined by the initial airway attempt. Patients were classified as receiving no advanced airway attempt or as having an initial endotracheal intubation, supraglottic airway, or surgical airway attempt. The location of OHCA was stratified by residential, public, or institutional setting. The remaining variables of interest were derived from preexisting EHR elements. For descriptive purposes, hypoxemia was defined as an $SpO_2 < 90\%$, and hypotension was defined as an SBP < 100 mmHg.

Fluid resuscitation was defined as >250 mL of crystalloid solution administered following the first documented ROSC time in the prehospital setting. Vasopressor administration was defined as the administration of an infusion (dose units expressed as rate) of epinephrine, norepinephrine, vasopressin, or phenylephrine, or a bolus dose of <300 μg of 'push dose' epinephrine.

Outcomes and Clinical Variables

Among patients who were transported to an emergency department (ED) and had hospital discharge disposition data available, patients were classified as deceased at discharge or discharged to home, a rehabilitation facility, a skilled nursing facility, a long-term acute care facility, a psychiatric facility, law enforcement, or hospice. Patients were classified as surviving to discharge if they were not discharged to hospice or deceased.

Patients were classified as experiencing a rearrest if they had 1 mg of epinephrine administered, defibrillation delivered, or CPR initiated following the first documented ROSC time. In addition, patients were classified as experiencing a rearrest if they had a documented ROSC and a pulseless rhythm at the receiving facility (12).

Statistical Analysis

The k-means clustering method facilitates the sorting of units into groups, or clusters, using continuous data points associated with each unit. First, you provide the k-means algorithm with an estimate of the number of cluster centers (centroids) that exist within the population of units. Then, the algorithm randomly places the centroids in n-dimensional space (n = number of variables, each unit has n coordinates) and assigns each unit to the nearest centroid as determined by Euclidian distance. The centroids then reposition to the mathematical center of the units assigned to each centroid. This process repeats until either the centroids stop changing significantly or a maximum number of iterations is reached. The *k*-means clustering (13) technique was performed using the R function *kmeans* (14). The optimal cluster number for *k*-means clustering was determined using the distortion elbow method using the Scikit-Learn and Yellowbrick Python libraries. The categorical baseline characteristics of each cluster were reported using percentages with frequencies. Continuous baseline characteristics of each cluster were reported using medians with interquartile ranges. To explore the association between cluster membership and our outcomes of interest, multivariable logistic regression was employed. Separate regression models were used for the outcomes of rearrest and mortality. Rearrest was not included as a variable in the modeling of mortality due to the likelihood that rearrest is a mediating variable between vital sign patterns and mortality. All regression models were performed as complete case analyses and adjusted for age, sex, witnessed status, pre-first responder CPR, initial ECG rhythm, downtime (dispatch to ROSC), airway management strategy, and location type. Stata 18 SE (Stata LLC; College Station, TX, USA) and R (R Foundation for Statistical Computing; Vienna, Austria) were used for all data management and statistical analyses.

Secondary Analyses

To determine what non-vital sign factors influenced cluster membership, we performed ordinal regression using the same covariables we used for our multivariable logistic regression modeling of mortality and rearrest. Ordinal regression was chosen because we ordered our clusters using mortality (lowest to highest mortality rate), and therefore 'illness severity' increases as cluster number increases.

To determine how early cluster membership may be identified following ROSC, we repeated our method for k-means clustering for the subgroups of patients with at least two sets of vital signs acquired within 5, 10, 15, or 20 min of the first documented ROSC time.

To determine if there was heterogeneity of treatment effect by phenotype, logistic regression analysis was repeated for each cluster using a four-level factor variable describing post-ROSC treatment (no treatment; fluid resuscitation, no vasopressor; vasopressor, no fluid resuscitation; both fluid resuscitation and vasopressor). The association between these treatment levels and survival to discharge was explored for each cluster.

Kaplan–Meier time-to-rearrest curves were generated for each cluster. Time zero was defined as the time of the first documented ROSC. The time of rearrest was defined as the time of the first CPR start, defibrillation, or 1 mg epinephrine administration following the first ROSC time.

Results

Baseline Cohort Characteristics

Overall, 415,055 OHCA patients were assessed for inclusion, and of these, 82,957 had at least one post-ROSC vital sign documented. Following the application of exclusion criteria, 12,320 post-ROSC OHCA patients treated by 1207 EMS agencies were eligible for analysis (Supplemental File Figure 1). The baseline characteristics of all patients are displayed in Table 1. Overall, 2937/12,320 (23.8%) patients experienced at least one rearrest event. Among transported patients with available ED and hospital disposition data, 24.8% (699/2816) survived to hospital discharge.

Characteristics of Vital Sign Phenotypes

Five vital sign phenotypes were identified within the overall cohort (Supplemental File Figure 2) They were identified as clusters 1–5, ordered by increasing mortality rate. Patients in cluster 1 ($n = 2861$; 23.2% of cohort) were hypertensive during the entire prehospital interval. Patients in cluster 2 ($n = 3206$; 26.0% of cohort) were normotensive during the entire prehospital interval. Patients in cluster 3 were hypotensive and tachycardic ($n = 2164$; 17.6% of cohort). Patients in cluster 4 ($n = 1856$; 15.1% of cohort) experienced initial hypoxemia that resolved and an increase in SBP. Patients in cluster 5 ($n = 2233$; 18.1% of cohort) experienced severe, prolonged hypoxemia and exhibited a decrease in SBP before hospital arrival. The proportion of patients who experienced mortality stratified by cluster was 63.4% (c1), 68.1% (c2), 78.8% (c3), 84.8% (c4), and 86.6% (c5). The proportion of patients who experienced rearrest stratified by cluster was 16.3% (c1), 18.8% (c2), 20.3% (c3), 32.5% (c4), and 36.9% (c5). Because cluster membership appeared to be driven by differences in BP and pulse oximetry values, Figure 1 displays the trends in SBP and SpO_2 for each cluster during the first 20 min of monitoring. The median time between the first and last documented systolic blood pressure for our sample was 15.6 min. Supplemental File Figure 3 displays the distribution of each variable included in our clustering analysis, subdivided by cluster membership.

Association of Vital Sign Phenotypes with Outcome

The prevalence of mortality and rearrest varied between vital sign clusters (Table 1). In comparison to the cluster with the lowest mortality (cluster 1), each cluster was associated with greater adjusted odds of mortality (c2 aOR: 1.42 [1.04, 1.93]; c3 aOR: 2.32 [1.62, 3.31]; c4 aOR: 3.52 [2.38, 5.19]; c5 aOR: 2.60 [1.77, 3.82]) and rearrest (c2 aOR: 1.20 [1.03, 1.40]; c3 aOR: 1.42 [1.21, 1.68]; c4 aOR: 2.60 [2.21, 3.04]; c5 aOR: 2.89 [2.48, 3.36]) (Figure 2). This result was consistent when both multivariable logistic regression and multi-level mixed effects logistic regression using EMS agency as a random effect were used (Supplemental File Table 1).

Non-Vital Sign Factors Associated with Cluster Membership

Ordinal regression demonstrated that increasing downtime, an initial non-shockable ECG rhythm, presumed cardiac etiology, unwitnessed OHCA, a private/residential OHCA location, and the use of a supraglottic airway device as the initial airway management strategy were associated with increased odds of membership in a 'higher' cluster with worse mortality (Supplemental File Table 6). The dispatch to ROSC interval (down time) was the strongest predictor of membership in a cluster that ranked higher in terms of mortality.

Time to Identification of Clusters

Clusters 1, 2, and 3 were identifiable within 5 min of ROSC (Supplemental File Figure 4), and all clusters identified in the total cohort were also identified at the 20-min timepoint (Supplemental File Figure 5). The optimal number of clusters for the subgroups of patients with at least two sets of prehospital vital signs acquired within 5, 10, and 15 min of ROSC was 4. The optimal number of clusters for the subgroup of patients with at least two sets of prehospital vital signs acquired within 20 min of ROSC was 5. The baseline characteristics of the clusters derived from these subgroups are displayed in Supplemental File Tables 2–5.

Treatment Effect Heterogeneity between Phenotypes

Sequential multivariable logistic regression analyses were performed using the patients within each phenotype to examine the association between the delivery of prehospital fluid resuscitation and/or vasopressors and mortality. No statistically significant difference in mortality was noted for any treatment strategy in any cluster when treatment was

Table 1. Baseline characteristics of each cluster and overall patient sample.

	Overall cohort						
Cluster #	c1 Hypertensive	c2 Normotensive	c3 Elevated SI	c4 Increasing SBP, hypoxemia	c5 Decreasing SBP, hypoxemia	Total	Test
N	2861 (23.2%)	3206 (26.0%)	2164 (17.6%)	1856 (15.1%)	2233 (18.1%)	12,320 (100.0%)	
Age	65.0 (53.0–75.0)	64.0 (52.0–74.0)	59.0 (43.0–71.0)	62.0 (49.0–73.0)	68.0 (57.0–78.0)	64.0 (51.0–75.0)	<0.001
Response time	6.0 (4.3–8.4)	6.6 (4.7–9.5)	6.3 (4.5–8.9)	6.7 (4.8–9.5)	6.8 (4.8–9.6)	6.4 (4.6–9.2)	<0.001
Dispatch to ROSC	18.6 (13.2–24.9)	21.9 (15.4–29.0)	21.9 (16.5–28.6)	22.5 (17.0–29.2)	24.4 (18.6–31.9)	21.7 (15.8–28.7)	<0.001
Epinephrine dose	1.0 (0.0–2.0)	2.0 (0.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	3.0 (1.0–4.0)	2.0 (1.0–3.0)	<0.001
Total fluid (mL)	0.0 (0.0–20.0)	0.0 (0.0–100.0)	0.0 (0.0–50.0)	0.0 (0.0–110.0)	0.0 (0.0–10.0)	0.0 (0.0–30.0)	<0.001
Max. SBP	187.0 (168.0–209.0)	137.0 (120.0–154.0)	112.0 (94.0–132.0)	158.0 (135.0–184.0)	149.0 (129.0–171.0)	149.0 (124.0–177.0)	<0.001
Min. SBP	139.0 (120.0–159.0)	101.0 (84.0–118.0)	76.0 (61.0–92.0)	77.0 (61.0–97.0)	86.0 (68.0–107.0)	97.0 (74.0–124.0)	<0.001
Max. DBP	109.0 (93.0–131.0)	88.0 (74.0–105.0)	71.0 (59.0–88.0)	99.5 (82.0–124.5)	96.0 (77.0–118.0)	93.0 (75.0–115.0)	<0.001
Min. DBP	77.0 (62.0–92.0)	60.0 (47.0–74.0)	44.0 (33.0–58.0)	44.0 (34.0–59.0)	50.0 (37.0–65.0)	56.0 (41.0–74.0)	<0.001
Max. SPO_2	99.0 (97.0–100.0)	99.0 (97.0–100.0)	98.0 (95.0–100.0)	99.0 (94.0–100.0)	91.0 (85.0–96.0)	98.0 (94.0–100.0)	<0.001
Min. SPO_2	93.0 (84.0–97.0)	94.0 (89.0–98.0)	90.0 (80.0–96.0)	83.0 (76.0–92.0)	76.0 (72.0–80.0)	89.0 (79.0–96.0)	<0.001
Max. pulse rate	128.0 (110.0–147.0)	105.0 (88.0–122.0)	141.0 (124.0–163.5)	140.0 (118.0–168.0)	120.0 (100.0–145.0)	124.0 (104.0–147.0)	<0.001
Min. pulse rate	86.0 (68.0–104.0)	70.0 (55.0–86.0)	101.0 (83.0–117.0)	73.0 (50.0–93.5)	59.0 (41.0–78.0)	77.0 (58.0–98.0)	<0.001
Max. SI	0.8 (0.6–0.9)	0.9 (0.8–1.1)	1.5 (1.3–1.8)	1.4 (1.2–1.7)	1.0 (0.8–1.3)	1.0 (0.8–1.4)	<0.001
Min. SI	0.6 (0.4–0.7)	0.6 (0.5–0.7)	1.0 (0.9–1.2)	0.6 (0.5–0.7)	0.6 (0.4–0.7)	0.6 (0.5–0.8)	<0.001
Max. PP	86.0 (74.0–100.0)	54.0 (44.0–65.0)	45.0 (36.0–56.0)	65.0 (51.0–81.0)	61.0 (47.0–75.0)	62.0 (47.0–79.0)	<0.001
Min. PP	49.0 (37.0–62.0)	31.0 (25.0–39.0)	25.0 (20.0–32.0)	25.0 (21.0–32.0)	26.0 (21.0–34.0)	30.0 (23.0–41.0)	<0.001
Delta SBP	−22.0 (−53.0–1.0)	−1.0 (−20.0–16.0)	−4.0 (−25.0–10.5)	50.0 (26.0–74.0)	−30.0 (−58.0 to −1.0)	−5.0 (−33.0–20.0)	<0.001
Delta DBP	−7.0 (−26.0–10.0)	−2.0 (−18.0–12.0)	−3.0 (−19.0–8.0)	26.0 (4.0–47.0)	−15.0 (−37.0–6.0)	−2.0 (−21.0–16.0)	<0.001
Delta pulse rate	−13.0 (−33.0–2.0)	−5.0 (−22.0–8.0)	−10.0 (−30.0–5.0)	−25.0 (−54.0 to −2.0)	−12.0 (−38.0–8.0)	−11.0 (−33.0–5.0)	<0.001
Delta SPO_2	1.0 (−1.0–5.0)	0.0 (−1.0–3.0)	1.0 (−1.0–7.0)	2.0 (−1.0–10.0)	2.0 (−3.0–10.0)	1.0 (−1.0–6.0)	<0.001
Delta SI	0.0 (−0.1–0.1)	−0.0 (−0.2–0.1)	−0.0 (−0.3–0.2)	−0.6 (−0.9 to −0.4)	0.1 (−0.1–0.3)	−0.0 (−0.3–0.1)	<0.001
Delta PP	−17.0 (−37.0–0.0)	0.0 (−12.0–11.0)	−2.0 (−13.0–8.0)	20.0 (5.0–37.0)	−13.0 (−31.0–2.0)	−3.0 (−20.0–11.0)	<0.001
Sex							
Male	1706 (59.8%)	1874 (58.6%)	1171 (54.3%)	1090 (58.9%)	1350 (60.5%)	7191 (58.5%)	<0.001
Female	1148 (40.2%)	1325 (41.4%)	987 (45.7%)	762 (41.1%)	880 (39.5%)	5102 (41.5%)	
Etiology							
Presumed cardiac	2042 (71.4%)	2392 (74.6%)	1426 (66.0%)	1264 (68.1%)	1737 (77.8%)	8861 (72.0%)	<0.001
Respiratory/ asphyxia	580 (20.3%)	499 (15.6%)	463 (21.4%)	384 (20.7%)	348 (15.6%)	2274 (18.5%)	
Drug overdose	127 (4.4%)	169 (5.3%)	190 (8.8%)	113 (6.1%)	75 (3.4%)	674 (5.5%)	
Other	110 (3.8%)	145 (4.5%)	83 (3.8%)	95 (5.1%)	73 (3.3%)	506 (4.1%)	
Witnessed							
No	767 (30.3%)	908 (32.0%)	793 (41.6%)	605 (37.3%)	689 (35.5%)	3762 (34.7%)	<0.001
Yes	1762 (69.7%)	1933 (68.0%)	1111 (58.4%)	1017 (62.7%)	1251 (64.5%)	7074 (65.3%)	
Location							
Home	1951 (68.2%)	2343 (73.1%)	1602 (74.0%)	1434 (77.3%)	1659 (74.3%)	8989 (73.0%)	<0.001
Public	578 (20.2%)	481 (15.0%)	291 (13.4%)	219 (11.8%)	273 (12.2%)	1842 (15.0%)	
Institutional	272 (9.5%)	341 (10.6%)	238 (11.0%)	175 (9.4%)	276 (12.4%)	1302 (10.6%)	
Other	60 (2.1%)	41 (1.3%)	33 (1.5%)	28 (1.5%)	25 (1.1%)	187 (1.5%)	
Pre-EMS CPR							
No	1553 (58.1%)	1752 (58.4%)	1213 (59.7%)	1069 (60.3%)	1236 (58.6%)	6823 (58.9%)	0.548
Yes	1121 (41.9%)	1247 (41.6%)	818 (40.3%)	705 (39.7%)	875 (41.4%)	4766 (41.1%)	
Initial rhythm							
Asystole	878 (31.3%)	1090 (34.6%)	940 (43.8%)	799 (43.4%)	996 (44.8%)	4703 (38.7%)	<0.001
PEA	854 (30.4%)	745 (23.6%)	591 (27.6%)	486 (26.4%)	562 (25.3%)	3238 (26.6%)	
AED non-shockable	132 (4.7%)	119 (3.8%)	74 (3.4%)	32 (1.7%)	54 (2.4%)	411 (3.4%)	
VF/VT	942 (33.6%)	1197 (38.0%)	540 (25.2%)	522 (28.4%)	613 (27.6%)	3814 (31.3%)	
Primary airway							
No advanced airway	561 (19.6%)	535 (16.7%)	281 (13.0%)	225 (12.1%)	260 (11.6%)	1862 (15.1%)	<0.001
Tracheal intubation	1130 (39.5%)	1440 (44.9%)	1014 (46.9%)	830 (44.7%)	947 (42.4%)	5361 (43.5%)	
Supraglottic airway	1170 (40.9%)	1231 (38.4%)	865 (40.0%)	801 (43.2%)	1022 (45.8%)	5089 (41.3%)	
Surgical airway	0 (0.0%)	0 (0.0%)	4 (0.2%)	0 (0.0%)	4 (0.2%)	8 (0.1%)	
Treatment group							
Neither	2345 (82.0%)	2291 (71.5%)	1416 (65.4%)	1109 (59.8%)	1515 (67.8%)	8676 (70.4%)	<0.001
Fluid only	380 (13.3%)	512 (16.0%)	290 (13.4%)	297 (16.0%)	275 (12.3%)	1754 (14.2%)	
Vasopressors only	117 (4.1%)	315 (9.8%)	352 (16.3%)	356 (19.2%)	374 (16.7%)	1514 (12.3%)	
Both	19 (0.7%)	88 (2.7%)	106 (4.9%)	94 (5.1%)	69 (3.1%)	376 (3.1%)	
Rearrest							
No	2394 (83.7%)	2603 (81.2%)	1724 (79.7%)	1253 (67.5%)	1409 (63.1%)	9383 (76.2%)	<0.001
Yes	467 (16.3%)	603 (18.8%)	440 (20.3%)	603 (32.5%)	824 (36.9%)	2937 (23.8%)	
Mortality							
No	230 (36.6%)	223 (31.9%)	103 (21.2%)	74 (15.2%)	69 (13.5%)	699 (24.8%)	<0.001
Yes	399 (63.4%)	477 (68.1%)	383 (78.8%)	414 (84.8%)	444 (86.5%)	2117 (75.2%)	

ROSC: return of spontaneous circulation; mL: milliliters; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; SI: shock index; EMS: emergency medical services; AED: automated external defibrillator; PEA: pulseless electrical activity; VF/VT: ventricular fibrillation/ventricular tachycardia.

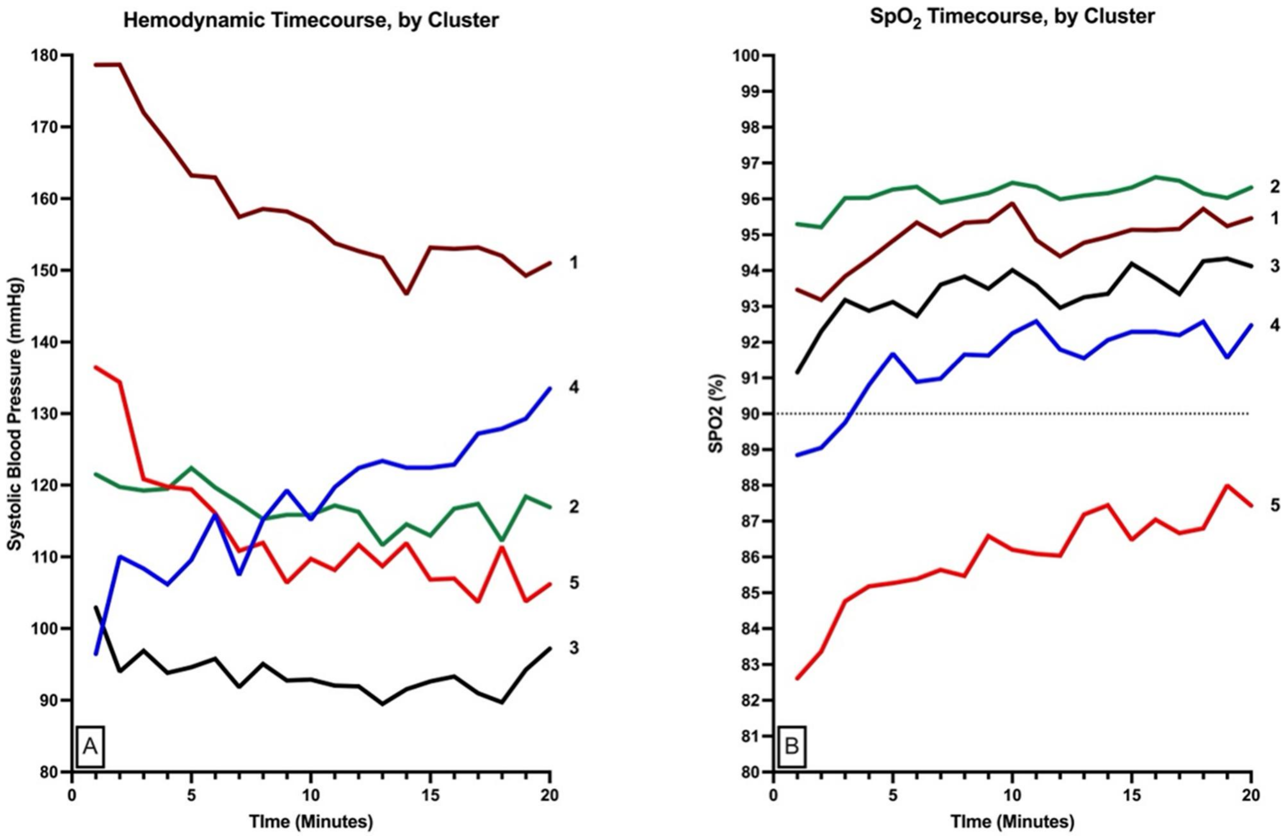

Figure 1. Vital signs *vs.* time, stratified by cluster. (A) Systolic blood pressure values were averaged over twenty sequential 1 min windows using the time of the first documented blood pressure as time zero. (B) Pulse oximetry values were averaged over twenty sequential 1 min windows using the time of the first documented SpO_2 as time zero.

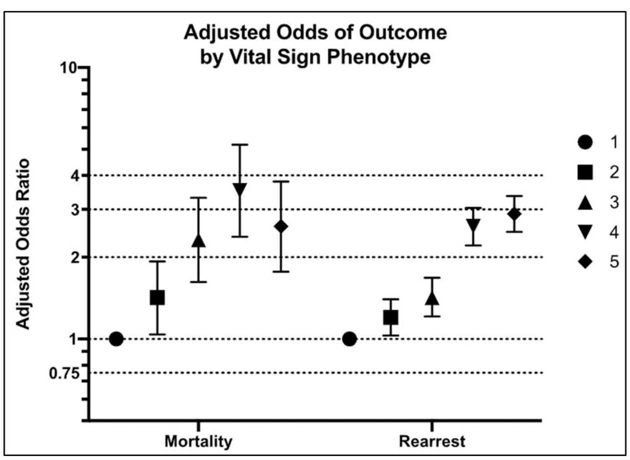

Figure 2. Adjusted odds of mortality and rearrest by cluster. This figure displays the adjusted odds of mortality and rearrest for patients in clusters 2–5 relative to the cluster with the lowest prevalence of mortality and rearrest (cluster 1). The logistic regression models used to calculate the values displayed in this figure included age, sex, witnessed status, pre-first responder CPR, initial electrocardiogram (ECG) rhythm, downtime (dispatch to ROSC), airway management strategy, and location type. Symbols represent the point estimates of adjusted odds ratios, and the error bars represent 95% confidence intervals.

defined as displayed in Figure 3. However, some heterogeneity existed between clusters with respect to treatment effect.

Vital Sign Phenotype and Time to Rearrest

Overall, 23% of patients had a timestamped rearrest event (epinephrine, defibrillation, or CPR start time following ROSC time). The ROSC to rearrest interval for the entire cohort (median [IQR]) was 9.0 [2.9, 16.3] min. The ROSC to rearrest interval stratified by cluster was 7.0 [1.6, 14.4] (c1), 8.3 [2.4, 16.5] (c2), 7.7 [2.9, 14.1] (c3), 10.6 [4.0, 17.8] (c4), and 10.0 [3.6, 17.0] (c5) min (Figure 4).

Discussion

Using a large, multi-agency dataset, we identified post-ROSC vital sign clusters, or phenotypes, that were associated with both clinical factors and patient outcomes. The existence of these phenotypes has relevance for both prognostication of outcomes from OHCA and future studies of post-resuscitation care.

These phenotypes derived from an unsupervised machine learning technique appeared to be driven by changes in BP across the prehospital interval in addition to the maximum and minimum observed BP values. Previous studies have suggested that post-ROSC BP is associated with outcome (1, 4–6, 15), and this study underscores the importance of this vital sign while also suggesting the importance of changes in BP across time.

In our cohort, the group of patients with early and persistent hypertension had the lowest prevalence of rearrest and mortality. It is possible that early post-ROSC hypertension is a marker of a healthy or minimally injured cardiovascular system that is capable of producing high cardiac output and vascular tone following resuscitation.

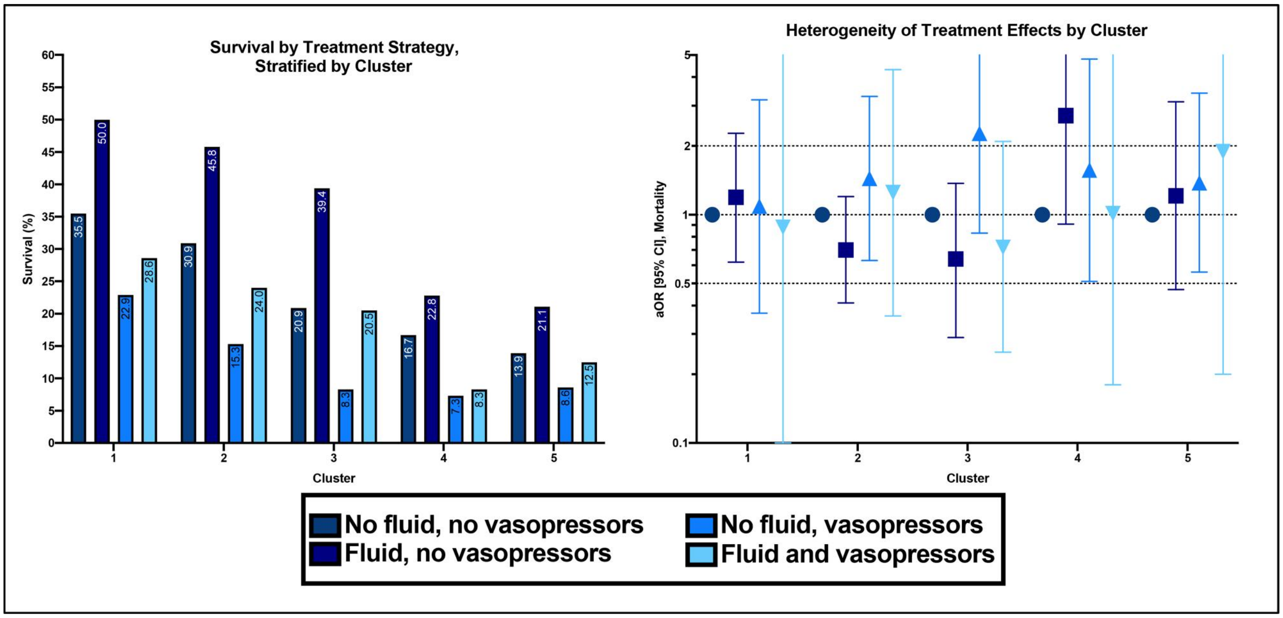

Figure 3. Treatment effects, stratified by cluster. (A) Displays the unadjusted probability of survival to hospital discharge for patients in each treatment category. (B) Displays the adjusted odds of mortality of patients in each treatment category in comparison to patients who received no post-ROSC fluid or vasopressors.

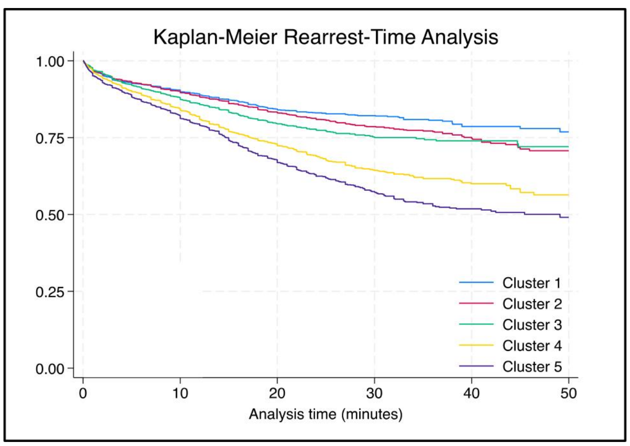

Figure 4. Kaplan–Meier analysis of time to rearrest, stratified by cluster. Time zero was defined as the first documented ROSC time. The time of rearrest was defined as the documented time of CPR, defibrillation, or the administration of 1 milligram of epinephrine. Patients were censored at the time of hospital arrival if rearrest did not occur. The prevalence of rearrest mirrored the probability of mortality (cluster 1 = lowest, cluster 5 = highest).

Alternatively, hypertension may improve cerebral perfusion during a critical period of altered cerebral autoregulation (16), or prevent the development of the 'no reflow' phenomenon (17, 18). Animal studies conducted in canine models of cardiac arrest have suggested that hypertensive post-ROSC BP targets improve neurological outcomes as well as surrogate measures of brain injury including histopathological markers and electroencephalogram (EEG) normalization times (19, 20).

The clusters of patients exhibiting dynamic changes in blood pressure across the prehospital interval (clusters 4 and 5) had the worst outcomes, regardless of the direction of the change. Interestingly, there was no significant difference in outcomes between the cluster of patients who experienced a decline in SBP during EMS care (cluster 4) and the cluster of patients who experienced an increase in SBP during EMS care (cluster 5). It is possible that interventions deployed to increase BP in this patient population do not influence long-term outcomes. Alternatively, because these two subgroups experienced more hypoxemia than the other clusters, it is possible that the deleterious effects of prehospital hypoxemia (2, 3) outweighed the effects of hemodynamic changes and prevented the observation of a difference in outcomes.

The analysis of the association between post-ROSC fluid and vasopressor administration did not reveal statistically significant differences with respect to mortality in any subgroup. However, there was some evidence of heterogeneity of treatment effect. For example, there was a trend favoring fluid administration post-ROSC in clusters 2 and 3, and a trend suggesting harm from fluid administration in cluster 4. This observation deserves further study because it suggests specific vital sign patterns (i.e., persistently elevated shock index in the case of cluster 3) may predict responsiveness to therapy and allow EMS clinicians to tailor treatment to patient physiology.

Limitations

Our findings are vulnerable to the biases inherent to all retrospective observational studies, including the presence of confounding variables that distort the relationship between cluster membership and outcome. We attempted to account for confounding by adjusting our logistic regression models for clinical variables known to predict outcomes following OHCA. However, the possibility of residual confounding or the existence of unknown or unmeasured confounders still exists. One factor not explored in this study was the influence of EMS system factors, such as the level of care provided by each EMS agency. This may be important because agencies that do not provide advanced life support would have been unable to administer fluid boluses or vasopressors, which may have influenced cluster membership.

Out-of-hospital cardiac arrest is a heterogeneous disease process, and many patient factors are known to influence outcome. With respect to prognostication, it is undoubtedly important that vital sign patterns are considered in combination with factors of known prognostic significance, including initial rhythm, downtime, and witnessed status.

Due to the pragmatic nature of data collection, encounters within the ESO annual datasets have missing data in some variable fields. This missingness may be due to a myriad of factors, including a true lack of knowledge regarding clinical characteristics (i.e., whether bystander CPR was initiated before EMS arrival), variable EMS documentation practices, requirement of completeness by the NEMSIS data standard, or patient characteristics (i.e., inability to obtain post-ROSC BP or rearrest after the first set of vital signs was acquired). As a result, some patients did not have documentation of vital signs required for k-means clustering or covariables necessary for our multivariable logistic regression analyses. The exclusion of these patients may have introduced selection bias and reduced the generalizability of our results. However, given that the ESO dataset is the largest outcome-linked prehospital dataset available, it provided a pragmatic way to pursue our aims.

The vital signs used for this investigation were obtained either manually acquired or automatically acquired using cardiac monitor/defibrillators. It is possible that some of the documented vital signs were inaccurate due to patient or clinician factors. For example, BP cuff size and positioning are known to be important to the accuracy of BP readings, but neither were standardized in this study. Similarly, patient factors, such as peripheral perfusion and skin color may influence SpO_2 readings.

For this study, we used an operational definition of rearrest that relied on documentation of CPR initiation, defibrillation, or administration of 1 milligram of epinephrine following a documented ROSC time. This may have led to the potential for misclassification of patients with respect to rearrest occurrence. For example, if EMS clinicians documented the initiation of CPR following ROSC in a free text field but did not specifically enter this time-stamped intervention into the EHR, we may have erroneously classified this patient as not experiencing a rearrest. In the future, the use of continuous waveform data may provide a more objective method to derive rearrest prevalence and incidence.

The outcome of survival to hospital discharge was only available from this data source for transported patients. Because the standard of care for OHCA patients is termination of resuscitation in the field unless specific favorable prognostic characteristics are present (21), the population of transported OHCA patients may have been subject to selection bias and experienced better outcomes than the overall population of OHCA patients. However, because all patients included in this study experienced ROSC, they would not have qualified for standard ALS (22) or BLS (23, 24) termination of resuscitation criteria.

For our secondary analyses of treatment effects within clusters, we focused on interventions intended to manage hemodynamics (fluid resuscitation, vasopressor administration). We did not choose to repeat this analysis for airway management strategy based on the assumption that the majority of patients in this cohort received airway management before ROSC and the acquisition of vital signs. The study of treatment effect heterogeneity of other interventions, such as post-ROSC antiarrhythmic medications or vasopressor types are important areas of future study.

Based on this retrospective study, we can make no specific recommendations for change in the clinical management of post-ROSC patients in the prehospital setting. However, the implication that SpO_2 and SBP patterns are associated with outcomes is consistent with prior literature. Aggressive treatment of hypotension and hypoxia may improve outcomes, but prospective work is needed to determine optimal methods and quantify potential benefits. In the future, if cluster membership is shown to be associated with responsiveness to clinical treatment, early identification of cluster may guide the application of therapies, such as fluid resuscitation and/or vasopressor administration.

The median duration between the first and last documented SBP for patients in our sample was $\sim$16 min. Considering previously published data that suggests the majority of rearrests occur in the first 10 minutes following ROSC (25), tailored prehospital treatment guided by cluster membership may not be feasible if patients cannot be sorted into clusters faster. Our secondary analysis that repeated *k*-means clustering for the subgroup of patients with two sets of vital signs acquired within 5 min of ROSC suggested that identification of major subgroups was possible within this time frame. Furthermore, the BP and SpO_2 trends displayed in Figure 1 demonstrate clear separation immediately following ROSC. Together, these data suggest that cluster membership may be determined quickly after resuscitation.

Conclusions

Unsupervised clustering yielded phenotypes of post-OHCA vital sign abnormalities that are associated with both prehospital and long-term outcomes. Future work validating these phenotypes and determining optimal treatment strategies may be warranted.

Declaration of Generative AI in Scientific Writing

The authors did not use a generative artificial intelligence (AI) tool or service to assist with the preparation or editing of this work. The author(s) take full responsibility for the content of this publication.

Disclosure Statement

RPC is an employee of ESO. The aims of this investigation were reviewed by an independent committee before access to the data was granted. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the results reported in this paper.

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