Novel Prehospital Phenotypes and Outcomes in Adult Patients with Acute Disease

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Abstract
An early identification of prehospital phenotypes may allow health care workers to speed up and improve patients’ treatment. To determine emergency phenotypes by exclusively using prehospital clinical data, a multicenter, prospective, and observational ambulance-based study was conducted with a cohort of 3,853 adult patients treated consecutively and transferred with high priority from the scene to the hospital emergency department. Cluster analysis determined three clusters with highly different outcome scores and pathological characteristics. The first cluster presented a 30-day mortality after the index event of 45.9%. The second cluster presented a mortality of 26.3%, while mortality of the third cluster was 5.1%. This study supports the detection of three phenotypes with different risk stages and with different clinical, therapeutic, and prognostic considerations. This evidence could allow adapting treatment to each phenotype thereby helping in the decision-making process.

Keywords Clinical Decision-Making · Clinical Deterioration · Emergency Medical Services · Pre-hospital Care · Clinical Phenotypes

Introduction
Acute diseases present a wide clinical spectrum since critically ill patients are characterized by highly heterogeneous syndromes. Emergency medical services (EMS) face in their daily practice critical situations requiring precise responses to be performed usually in very short time windows [1, 2]. In these cases, the appearance of serious adverse events could account for a significant, non-negligible percentage of early mortality [3, 4].

Prehospital emergency care research has experienced remarkable advancements in the last years. For instance, huge efforts have been undertaken to improve classic scores by introducing point-of-care testing information [5–7]. Among all the scores, the National Early Warning Score 2 (NEWS2) is being used routinely in many EMS, based
mainly on the ample evidence in the literature supporting its use under different clinical conditions and its capability to predict the risk of deterioration hours before the appearance of serious adverse events [8–11].

These diagnostic aids together with the use of advanced life support maneuvers following defined protocols and guided by the identified symptoms (e.g., dyspnea, chest pain) and life-threatening problems (e.g., airway obstruction, tension pneumothorax, hemorrhage), certainly do have a direct influence on the final outcome [12, 13].

EMS represent the gateway for patients to receive health care. Getting first-hand information together with an early identification of time-dependent diseases can indeed improve the decision-making processes of EMS professionals [14, 15]. If specific individual phenotypes can be assessed from this prehospital information, either in the ambulance or later in the hospital, different management strategies to guide treatment can be customized to improve outcome and patient care [16–18].

The goal of the present study was to explore the possibility of developing a phenotyping classification for emergency patients based solely on the information available from prehospital care.

Methods

Study design

We conducted a prospective, multicenter, ambulance-based, EMS-delivery, observational study without intervention, in adults (> 18 years) treated consecutively and transferred with high-priority from the scene to the hospital emergency department (ED), between October 2018, and July 2020.

Ethics approval was granted by institutional review boards of each basic health zone involved in the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [19].

Study setting

The study was hosted by 5 ambulance (advanced life support -ALS-) stations (Burgos, Salamanca, Segovia, Valladolid I and II) and 5 hospitals (four tertiary university hospitals and one small general district hospital) of the Public Health System of Castilla-León (Spain) with a reference population of 1,364,952 inhabitants. Further details of the study settings can be found in Supplementary Text S1.

Participants

Adult patients (> 18 years) were identified and recruited from all calls for help (1-1-2 emergency phone) assigned to ALS and transferred with high priority to the EDs of the participating hospitals. Exclusion criteria were pregnancy, terminal illness (proven by reports from the medical specialist), cardiorespiratory arrest, situations with risk for the EMS healthcare personnel (e.g., assault, stabbing, gun shot, hazardous material), and cases in which informed consent was not obtained.

The patient, during the prehospital care, read and signed the informed consent that covered the whole study. If capacity was absent, a research associate from each hospital was in charge of following up on each pending case to obtain consent in the ED, or by a family member or legal guardian. If none of the above was possible, the patient was excluded from the study.

Outcomes

Primary outcomes included: cumulative in-hospital mortality at 1, 2, 3, 7, and 30 days since hospital admission. Secondary outcomes included: admission to intensive care unit (ICU) and necessity of prehospital advanced airway life support (pAALS) in one of the following forms: non-invasive ventilation, oro-tracheal intubation or video-laryngoscope. These maneuvers were performed after measurement of the principal respiratory variables. These outcomes are in line with previous similar studies [5, 20, 21]. An associate researcher from each hospital confirmed the result of death by following-up the patient’s electronic medical record.

Variables

The following twenty-three variables were selected because of their prehospital clinical importance: age (Age), arrival time (ArT), assistance time (AsT), transfer time (TrT), total time (ToT), respiratory rate (RR), pulse oximetry saturation (SpO2), fraction of inspired oxygen (FiO2), basal-previous to the EMS arrival-oxygen supply (O2.previous), pulse oximetry saturation/fraction of inspired oxygen ratio (SaFi), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), systolic-diastolic pressure ratio (PP), heart rate (HR), temperature (TT), ocular Glasgow coma scale (GCS.O), verbal Glasgow coma scale (GCS.V), motor Glasgow coma scale (GCS.M), lactate (Lac), glucose (Glu), sex (Sex), cardiac rhythm (CR), and ST segment (ST).

Data analysis

Two different kinds of analysis were performed on the data set. First, an unsupervised clustering was carried out on the complete data set of 3,853 patients with twenty-three variables. Because the patient database was composed of mixed variables (numerical and categorical), a mixed approach was conducted to perform an equivalent to a Principal Component/Multi Correspondence Analysis by using a
factor analysis of mixed data [22] (see also Supplementary Text S2). After this factorial analysis, a subsequent cluster analysis was performed on the selected first components with the aim of classifying patients according to their clinical characteristics or phenotypes. The optimal number of clusters/phenotypes was determined by merging numerical and clinical criteria. Further details on the methodology are described in Supplementary Text S2 and Supplementary eFigs. S1, S2 and S3.

Secondly, and with the objective of identifying variables with higher weight, or role played in the cluster classification, a supervised approach was conducted by using classification trees. We firstly used the classical classification tree algorithm rpart [23, 24] to gain some insight into the classification, but we thereafter completed the study of variable importance with the more robust, although less intuitive, method of Random Forests [25]. This last method allows to dig into the importance of certain variables in the phenotype classification. Further details on the methodology are described in Supplementary Text S3 and Supplementary eFig. S4.

All statistical analyses were performed using our own codes and base functions in R, version 4.0.3 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

In this study, 3,853 patients who met the inclusion criteria were included (Fig. 1). Median age was 69 years (Interquartile range [IQR]: 54–81 years), and 1,597 of them (41.4%) were women. In-hospital mortality at 30 days was 10.9% (420 cases) with an ICU admission rate of 10.4% (399 cases); 7.1% of patients required pAALS (275 cases). Demographic data and the outcomes 1, 2, 3, 7 and 30-day mortality, ICU admission, and necessity of pAALS are displayed for the study population in Table 1 (also plotted in Supplementary eFig. S5).

Prehospital clinical phenotypes

Three clusters were obtained including the following number of patients: cluster #1 (305 patients), cluster #2 (459), and cluster #3 (3,089). A qualitative characteristic of the clusters of patient variables is depicted in Fig. 2 where mean values of the numerical variables in each cluster are compared with their mean values across the whole cohort (for Fig. 2 interpretation see Supplementary Text S4). A quantitative description of the numerical variables in each cluster can be observed in the boxplots of Supplementary eFigs. S6 and S7, and in the Table 1. Also, the distribution of the categorical variables ST, CR, O2.previous, and Sex across the clusters is shown in the bar plots of Supplementary eFig. S8. Demographic characteristics and clinical data according to the cluster’s distribution are detailed in Table 1.

At first sight the disproportion among the three cluster sizes may seem surprising, with the third cluster encompassing almost 80% of the patients’ sample. However, this is readily understandable considering that this percentage is approximately the same as that of non-severe cases transferred by the ALS; the remaining 20% of severe cases can be considered as “outliers”. These cases, contrary to
| Phenotypes | Total | #1 (high_1) | #2 (high_2) | #3 (low) |
|------------|-------|------------|------------|---------|
| No. (%) with data | 3853 (100) | 305 (7.9) | 459 (11.9) | 3089 (80.2) |
| Age, median (IQR), years | 69 (54–81) | 68 (51–82) | 79 (67–86) | 67 (52–80) |
| Sex, No. (%) | | | | |
| Female | 1597 (41.4) | 135 (44.3) | 184 (40.1) | 1278 (41.4) |
| Male | 2256 (58.6) | 170 (55.7) | 275 (59.9) | 1811 (58.6) |
| Time, median (IQR), minutes | | | | |
| Arrival | 10 (8–14) | 10 (7–13) | 10 (8–14) | 10 (8–14) |
| Assistance | 28 (22–35) | 33 (24–45) | 31 (25–37) | 28 (22–35) |
| Transfer | 10 (7–14) | 10 (7–15) | 10 (7–15) | 10 (7–14) |
| Total | 50 (42–60) | 55 (46–70) | 53 (45–63) | 49 (41–59) |
| RR, median (IQR), bpm | 18 (14–23) | 18 (10–25) | 30 (22–36) | 17 (14–20) |
| SpO2, median (IQR), % | 96 (93–98) | 90 (76–95) | 86 (77–92) | 97 (95–98) |
| FiO2, median (IQR), % | 0.21 (0.21–0.21) | 0.21 (0.21–0.21) | 0.26 (0.24–0.31) | 0.21 (0.21–0.21) |
| SO2, No. (%) | 459 (11.9) | 50 (16.4) | 386 (84.1) | 23 (0.7) |
| SaFi, median (IQR) | 457 (438–466) | 416 (333–452) | 321 (250 (366) | 461 (450–466) |
| AP, median (IQR), mmHg | | | | |
| Systolic | 137 (118–155) | 128 (96–149) | 139 (127–162) | 138 (120–155) |
| Diastolic | 80 (68–91) | 73 (56–90) | 79 (65–92) | 80 (69–91) |
| Systolic-diastolic | 55 (42–70) | 50 (34–68) | 58 (43–74) | 55 (43–70) |
| HR, median (IQR), bpm | 85 (70–104) | 96 (77–115) | 100 (83–120) | 82 (70–100) |
| TT, median (IQR), ºC | 36.2 (36–36.8) | 36.1 (35.2–36.9) | 36.7 (36–37.5) | 36.2 (36–36.7) |
| GCS, median (IQR), points | | | | |
| Ocular | 4 (4–4) | 1 (1–2) | 4 (4–4) | 4 (4–4) |
| Verbal | 5 (5–5) | 1 (1–2) | 5 (5–5) | 5 (5–5) |
| Motor | 6 (6–6) | 2 (1–4) | 6 (6–6) | 6 (6–6) |
| Lac, median (IQR), mmol/L | 2.8 (1.8–3.9) | 4.9 (3.1–8.4) | 3.3 (2.3–4.6) | 2.5 (1.7–3.6) |
| Glu, median (IQR), mg/dL | 127 (106–162) | 146 (111–203) | 143 (114–190) | 124 (105–154) |
| Cardiac rhythm, No. (%) | | | | |
| Sinus | 2000 (51.9) | 98 (32.1) | 130 (28.3) | 1772 (57.4) |
| Tachycardia a | 1526 (39.6) | 175 (57.4) | 299 (65.1) | 1052 (34.1) |
| Bradycardia b | 249 (6.5) | 28 (9.2) | 19 (4.1) | 202 (6.5) |
| Pacemaker | 78 (2) | 4 (1.3) | 11 (2.4) | 63 (2) |
| ST elevation c, No. (%) | 242 (6.3) | 29 (9.5) | 9 (2) | 204 (6.6) |
| Outcomes, No. (%) | | | | |
| pAALS d | 275 (7.1) | 164 (53.8) | 81 (17.6) | 30 (1) |
| ICU admission e | 399 (10.4) | 149 (48.9) | 62 (13.5) | 188 (6.1) |
| 1-day mortality | 140 (3.6) | 65 (21.3) | 41 (8.9) | 34 (1.1) |
| 2-day mortality | 176 (4.6) | 81 (26.6) | 51 (11.1) | 44 (1.4) |
| 3-day mortality | 191 (5) | 87 (28.5) | 52 (11.3) | 52 (1.7) |
| 7-day mortality | 270 (7) | 106 (34.8) | 73 (15.9) | 91 (2.9) |
| 30-day mortality | 420 (10.9) | 140 (45.9) | 121 (26.4) | 159 (5.1) |

RR respiratory rate, SpO2 pulse oximetry saturation, FiO2 fraction of inspired oxygen, SO2 supplemental oxygen in the scene, SaFi pulse oximetry saturation/fraction of inspired oxygen ratio, AP arterial pressure, HR heart rate, TT temperature, GCS Glasgow coma scale, pNEWS2 prehospital National Early Warning Score 2, Lac lactate, Glu glucose, pAALS prehospital advanced airway life support, ICU intensive care unit

aTachycardia rhythm includes sinus tachycardia (821, 21%), atrial fibrillation (575,15%), atrial flutter (27, 1%), supraventricular tachycardia (71, 2%) and ventricular tachycardia (32, 1%)

bBradycardia rhythm includes sinus bradycardia (131, 3%), first-degree atrioventricular (AV) block (47, 1%), Mobitz type I 2nd-degree AV block (11, 0.3%), Mobitz type II 2nd-degree AV block (9, 0.2%), third-degree AV block (41, 1%), junctional rhythm (6, 0.1%) and idioventricular rhythm (4, 0.1%)

cNormal ST (3256, 85%), ST segment depression (111, 3%), peaked T wave (45,1%), negative T wave (132,3%), Q wave (63, 2%) and non-specific repolarization changes (4, 0.1%)

dpAALS includes non-invasive ventilation (100, 37%), orotracheal intubation (152, 55%) and difficult airway that requires the use of a video-laryngoscope (23, 8%)
the common notion attributed to this word, should not be discarded but instead treated with highly special care; see also Supplementary Text S5 and Supplementary eFig. S9 for a technical justification and validation.

To summarize the clinical characteristics of all the variables (numerical and categorical), we calculated a v-test and represented only the significant test values in Fig. 3. See Supplementary Text S6 for a further explanation of the v-test and Fig. 3 interpretation. The v-test plot shows that CR = Ventricular tachycardia is the only variable category associated to cluster #1, whereas high levels of Lactate, Glucemia, Heart Rate, and Atrial tachycardia are common to clusters #1 and #2, as well as, lower values of SaFI and SpO2. Moreover, higher values of Respiratory Rate, Age, and FiO2 are exclusively associated to cluster #2 as they are also the previous-to-attendance oxygen supply and Atrial fibrillation.

All these characteristics of clusters #1 and #2 are in accordance with the previous analysis displayed in Fig. 2 (also in eFigs. S6, S7 and S8) pointing out that both clusters represent groups of patients with serious conditions, although with different characteristics. In particular, cluster #2 seems to be more oriented toward aged patients with respiratory problems, whereas patients of cluster #1 suffer from other pathologies related with low values of Glasgow Coma Scale, as confirmed in Fig. 2 with the low levels of either GCS.M, GCS.O or GCS.V, associated to conditions such as traumatic injuries and nervous system related pathologies.

**Phenotypes and outcomes**

With the objective of exploring how well the clustering partition represents groups of patients with defined clinical characteristics and risk, we evaluated how many positive outcomes (mortalities, ICU or pAALS) were included in each cluster. This is displayed in Supplementary eFig. S10 where for each particular outcome (x-axis), the percentage of positive outcomes in each cluster is calculated, also displayed in eTable S1. Cluster #1 (in green) showed the highest percentage of cases in every outcome. Cluster #2 (blue) also showed elevated percentages of outcomes. Moreover, the percentage of cases rose moving from the first outcome, one-day mortality, to the last one, pAALS. Although cluster #1 contained the highest proportion of patients with positive outcomes, this cluster was also the one with the smallest number (305) of patients. Conceivably, the high proportion of outcomes in this cluster may be solely due to its small number of patients. However, calculating the rate of outcomes in each group relative to the total number of outcomes, cluster #1 still maintained the highest percentage compared to the other clusters (Supplementary eFig. S11).

Yet, another view of the outcomes can be seen in Supplementary eFig. S12 where the percentage of deaths along time is represented for each cluster.

**Patients’ risk within clusters**

As a result of the previous analysis, it was straightforward to assign a “risk” category to each of the clusters. For instance, cluster #3, the one with the highest number of patients (3,089, 80% of patients) was the cluster with the lowest percentage of outcomes, so it could be considered as the cluster or group with the lowest risk. On the other
hand, in cluster #2 and especially in cluster #1, a higher proportion of patients presented positive outcomes than in cluster #3. Accordingly, the risk phenotypes of clusters #1, #2, and #3 were labeled as high_1, high_2, and low, respectively. The chord diagrams in Fig. 4 show how pathologies are distributed across the clusters. In this figure, the upper left panel shows the association of certain pathologies with cluster #1, marked in red. In a similar fashion, the right upper panel shows those pathologies associated with cluster #2 in green and the lower panel shows those pathologies associated with cluster #3, in blue. This diagram describes the most common pathologies found in the cohort (more than 1% in the respective cluster).

Importance of variables in phenotyping

By using Random Forests, it is rather straightforward quantifying the variable importance at the time of constructing the decision trees. This is displayed in Supplementary eFig. S13 in the Supplement, for the case of 2-day mortality, using the training set. As shown, Lactate is the most important variable, followed in importance by SpO2, SaFi, Age, among others. The predictive validity of the random forest on the validation cohort (1,284 patients) presented an Area Under the Curve of the Receiving Operating Characteristic curve of 0.937, as displayed in Supplementary eFig. S14 in the Supplement.

Discussion

In this prospective, multicenter, ambulance-based, EMS-delivery study we have found that patients with acute disease transferred from ALS to ED can be rearranged, following a well-defined clinical characterization, into three phenotypes, each with an associated risk level. These three phenotypes were obtained by analyzing twenty-three variables collected during the first EMS contact with the patient, either on scene or en route. The phenotypes differ in their pathophysiological characteristics and final outcomes, with significant differences in the rates of advanced airway management, ICU-inpatients, and mortality rates. This classification can aid in an early decision-making process by focusing the professionals’ attention on the patients’ risk level.

The use of phenotypes has begun to spread among the medical community and, in certain acute pathologies such as sepsis, chronic obstructive pulmonary disease, heart failure or coronavirus disease 2019 (COVID-19), the identification of the clinical phenotypes is one of the first steps performed with the aim of helping in the subsequent decision-making process [26–29].
Phenotype #1 had an overall 30-day all-cause mortality in almost half of the patients, and one third of the patients in this group died within the first three days since the index event. Furthermore, it represents the largest group of patients with ICU-admission. This phenotype was characterized by greater neurological impairment, with significantly lower Glasgow Coma Scale levels and patients with an elevated lactate level (median 4.9 mmol/L) [30], a pathophysiological situation that suggests the presence of a certain degree of tissue hypoperfusion; that is, these patients present a shock, with lower blood pressure. Moreover, the high presence of ST-segment abnormalities is noteworthy in this cluster. This group included neurocritical patients (stroke, cerebral hemorrhage, seizures, traumatic brain injury) [31, 32], polytraumatized (in which the highest mortality occurs among patients with a low level of consciousness) [33], conditions of shock (bleeding, septic) [34, 35] and severe forms of myocardial dysfunction (cardiogenic shock, malignant arrhythmias) [36]. In short, this phenotype is composed of patients with a reduced level of consciousness and tissue hypoperfusion with abrupt onset where the most severe forms require a high level of advanced life support and are directly correlated with a significant degree of complications and high complexity and co-morbidity.

Phenotype #2 patients were older adults with overall 30-day mortality lower than phenotype #1, being the group that globally presented less ICU-admission. This cluster specifically exhibited a pattern of respiratory distress (tachypnea, desaturation, low SaFi, and use of supplemental oxygen upon ambulance arrival on scene), along with a model of ischemia on demand (tachycardia, elevated blood pressure) and some degree of continued tissue hypoperfusion (median lactate levels of 3.3 mmol/L), including decompensated respiratory and chronic cardiac pathology (chronic obstructive pulmonary disease, asthmatic crisis, heart failure, atrial fibrillation) [37, 38], as well as infectious pathology (respiratory infection and sepsis) [39]. This group is mainly composed of older adults with co-morbidities who suffer exacerbations of their chronic processes, with significant mortality and few ICU-admissions [40, 41].

Phenotype #3 included the majority of patients, with 80.2% of all the cohort patients. This was a very heterogeneous cluster, with pathologies in many cases with a very expressive symptomatology that generate considerable social alarm (syncope, chest pain, abdominal pain, minor trauma), but with clearly lower ICU-admissions and 30-day mortality rates than the other phenotypes.
From a clinical point of view, the pathophysiological, clinical, and prognostic implications of each phenotype could help EMS at the scene, or in the first moments of emergency care, to make decisions based on the characteristics of each phenotype. In this sense, detecting time-dependent pathologies in the shortest possible time, which is the most fundamental challenge of prehospital care, could benefit from this in situ phenotyping or characterization of patients.

Limitations

The present study has several limitations. Firstly, the cohort may have a selection bias since the sample was collected by opportunity criteria, including only patients attended and transferred by ALS. Patients evacuated in basic life support units or walking were not included. To reduce bias, patients were gathered from urban and rural areas, 24/7 during the entire study period and with assignment to hospitals with different training. Secondly, there is a high proportion of older adults, however, this is in line with similar studies [42, 43], suggesting how representative is our cohort of the population transferred by ALS. Thirdly, during the final period of data collection, the current COVID-19 pandemic had a direct impact on our region, disrupting the normal running of health systems, especially in EMS, ED, and ICU. The preponderance in the months of March to June of respiratory/infectious pathologies is a fact, but we believe that it has not altered the final sample of the analysis. Finally, the study was conducted in only one country; therefore, in order to be able to extend the phenotyping to areas outside Spain, future studies should expand the database with participants from different countries and treated by different health systems.

Conclusions

In summary, patients managed by EMS and transferred with high-priority discharge to ED can be categorized into three phenotypes with different clinical, therapeutic, and prognostic considerations.

Applying these phenotypes through bedside phenotyping, healthcare workers can begin to discriminate the real risk and future implications, and assist in the decision-making process at critical points, such as, at the level of monitoring, the intensity of advanced life support or the requirement for hospital referral.

Future studies are required to clarify every phenotype, and to identify which pathophysiological conditions contribute to a particular outcome.

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Author contributions Drs Martin-Rodríguez and López-Izquierdo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors. Acquisition, analysis, or interpretation of data: Ortega Rabbone; del Pozo Vegas; Castro Villamor; Martín-Conty. Drafting of the manuscript: Ortega Rabbone; Martin-Rodríguez and Sanz-García. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Mayo-Iscar; Sanz García and Ortega Rabbone. Obtained funding: Martin-Rodríguez Administrativa, technical, or material support: del Pozo Vegas; Castro Villamor; Martín-Conty. Study supervision: Castro Villamor.

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Data availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Code availability The code supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval Ethics approval was granted by institutional review boards of each basic health zone involved in the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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