Novel Prehospital Phenotypes and Outcomes in Adult-Patients with Acute Disease

Francisco Martín-Rodríguez[1,2] · Raúl López-Izquierdo[1,3] · Ancor Sanz-García[4] · Carlos del Pozo Vegas[1,5] · Miguel Ángel Castro Villamor[1] · Agustín Mayo-Iscar[6] · José L. Martín-Conty[7] · Guillermo José Ortega[4,8,9]

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

✉ Francisco Martín-Rodríguez
fmartin@saludcastillayleon.es

✉ Ancor Sanz-García
ancor.sanz@gmail.com

1 Advanced Clinical Simulation Center. Faculty of Medicine, Valladolid University, Valladolid, Spain

2 Advanced Life Support, Emergency Medical Services (SACYL), Valladolid, Spain

3 Emergency Department. Hospital, Universitario Rio Hortega, Valladolid, Spain

4 Data Analysis Unit, Health Research Institute, Hospital de La Princesa, Madrid (IIS-IP), Spain

5 Emergency Department. Hospital, Clínico Universitario, Valladolid, Spain

6 Department of Statistics and Operative Research. Faculty of Medicine, University of Valladolid, Valladolid, Spain

7 Facultad de Ciencias de La Salud, Universidad de Castilla La Mancha, Talavera de La Reina, Spain

8 Consejo Nacional de Investigaciones Científicas Y Técnicas (CONICET), Buenos Aires, Argentina

9 Science and Technology Department, Universidad Nacional de Quilmes, Bernal, Buenos Aires, Argentina

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, orotracheal 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 (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

Fig. 1 Patient selection flow chart. EMS: emergency medical services; BLS: basic life support unit
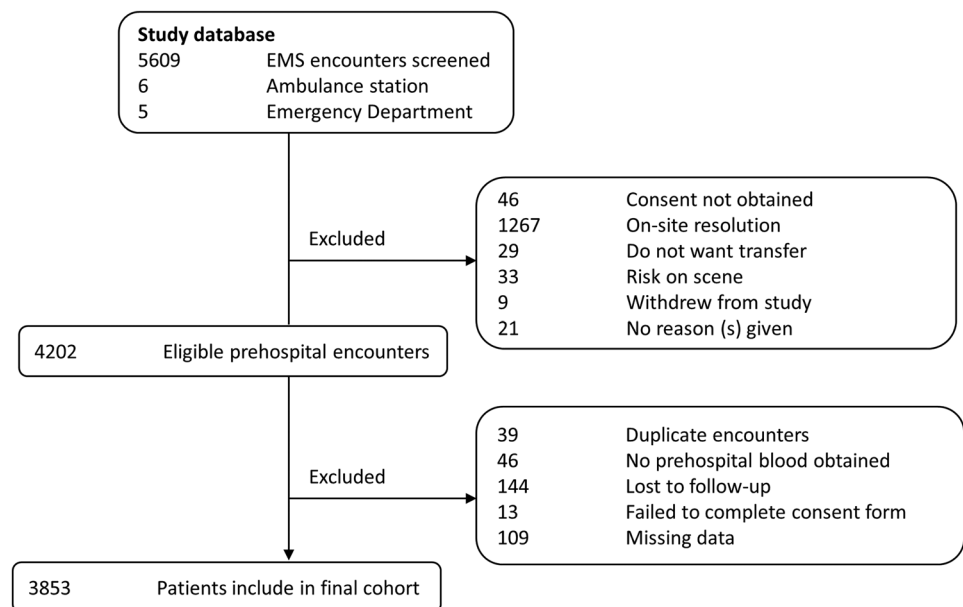
Table 1 Demographics and clinical characteristics of the phenotypes

|		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)
SpO_2, median (IQR), %	96 (93–98)	90 (76–95)	86 (77–92)	97 (95–98)
FiO_2, 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)
SO_2, 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

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

[b]Bradycardia 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%)

[c]Normal 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%)

[d]pAALS includes non-invasive ventilation (100, 37%), orotracheal intubation (152, 55%) and difficult airway that requires the use of a video-laryngoscope (23, 8%)
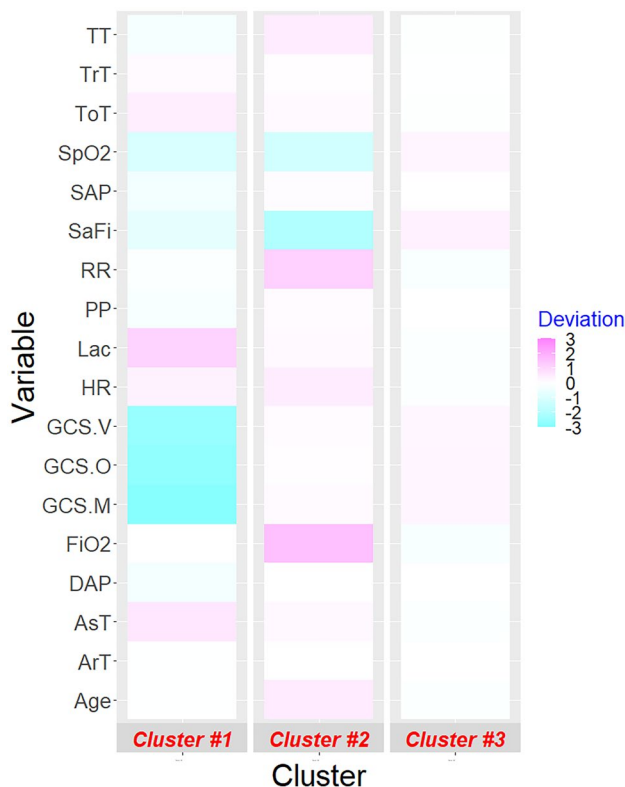
Fig. 2 Heatmap of the relative importance of continuous variables in each cluster. Intensity of colors represents the deviation, in terms of standard deviations, of the mean value of the variable in the cluster with respect to the mean value of that variable in the whole cohort. Reddish colors represent higher values and bluish colors represent lower values. Abbreviations: 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; ArT: arrival time; AsT: assistance time; TrT: transfer time; ToT total time; TrT: transfer time; TT: temperature; GCS.O: ocular Glasgow coma scale; GCS.V: verbal Glasgow coma scale; GCS.M: motor Glasgow coma scale; pNEWS2: prehospital National Early Warning Score 2; Lac: lactate; Glu: glucose; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; PP: systolic-diastolic pressure

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 Comma 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
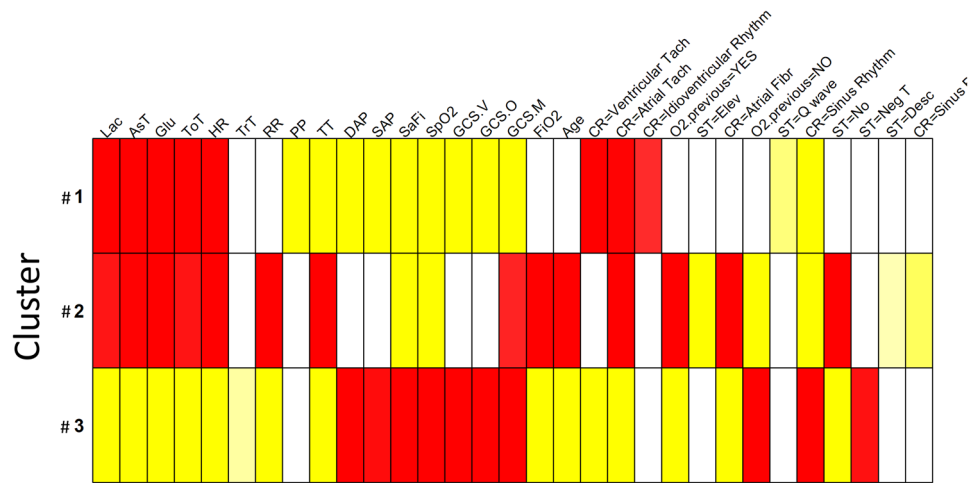
Fig. 3 Heatmap corresponding to the v-test applied to the whole set of 23 variables. For the case of numerical variables, red colors represent affinity or overrepresentation of high values with the corresponding cluster and yellow colors represent affinity of low values with the corresponding cluster. For the case of categorical variables, red colors represent the affinity or overrepresentation of the factor level with the corresponding cluster and the yellow colors represent an underrepresentation of the factor level with the corresponding cluster. Intensity of colors are proportional to the test significance, more intense, more significant. White colors represent non-significant values. Abbrevia-tions: 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; ArT: arrival time; AsT: assistance time; TrT: transfer time; ToT total time; TrT: transfer time; TT: temperature; GCS.O: ocular Glasgow coma scale; GCS.V: verbal Glasgow coma scale; GCS.M: motor Glasgow coma scale; pNEWS2: pre-hospital National Early Warning Score 2; Lac: lactate; Glu: glucose; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; PP: systolic-diastolic pressure

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].
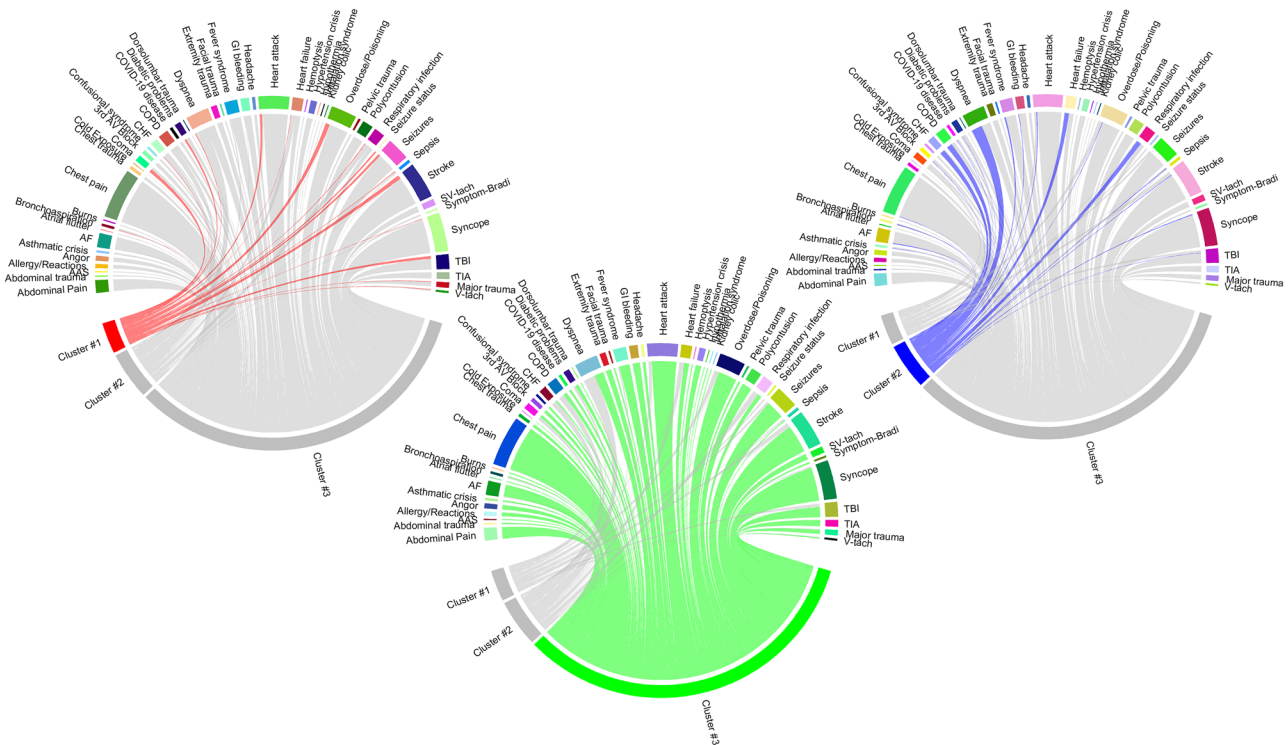
Fig. 4 Chord diagram of cluster distributions: Left upper panel. Distribution of patient's pathologies corresponding to cluster #1, in red. Right upper panel. Distribution of patient pathologies corresponding to cluster #2, in blue color. Lower panel. Distribution of patient's pathologies corresponding to cluster #3, in green

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.

Declarations

References

1. Holmberg M, Andersson H, Winge K, Lundberg C, Karlsson T, Herlitz J, et al. Association between the reported intensity of an acute symptom at first prehospital assessment and the subsequent outcome: a study on patients with acute chest pain and presumed acute coronary syndrome. BMC Cardiovasc Disord. 2018; 18(1): p. 216.

2. Shkirkova K, Saver JL, Starkman S, Wong G, Weng J, Hamilton S, et al. Frequency, Predictors, and Outcomes of Prehospital and Early Postarrival Neurological Deterioration in Acute Stroke: Exploratory Analysis of the FAST-MAG Randomized Clinical Trial. JAMA Neurol. 2018; 75(11): p. 1364-1374.

3. Jørgensen R, Brabrand M. Screening of the frail patient in the emergency department: A systematic review. Eur J Intern Med. 2017; 45: p. 71-73.

4. Hsia RY, Huang D, Mann NC, Colwell C, Mercer MP, Dai M, et al. A US National Study of the Association Between Income and Ambulance Response Time in Cardiac Arrest. JAMA Netw Open. 2018; 1(7): p. e185202.

5. Patel R, Nugawela MD, Edwards HB, Richards A, Le Roux H, Pullyblank A, et al. Can early warning scores identify deteriorating patients in pre-hospital settings? A systematic review. Resuscitation. 2018; 132: p. 101-111.

6. Goyder C, Tan PS, Verbakel J, Ananthakumar T, Lee JJ, Hayward G, et al. Impact of point-of-care panel tests in ambulatory care: a

systematic review and meta-analysis. BMJ Open. 2020; 10(2): p. e0321.

7. Swan KL, Avard BJ, Keene T. The relationship between elevated prehospital point-of-care lactate measurements, intensive care unit admission, and mortality: A retrospective review of adult patients. Aust Crit Care. 2019; 32(2): p. 100-105.

8. Pimentel MAF, Redfern OC, Gerry S, Collins GS, Malycha J, Prytherch D, et al. A comparison of the ability of the National Early Warning Score and the National Early Warning Score 2 to identify patients at risk of in-hospital mortality: A multi-centre database study. Resuscitation. 2019; 134: p. 147-156.

9. Gerry S, Bonnici T, Birks J, Kirtley S, Virdee PS, Watkinson PJ, et al. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. BMJ. 2020; 369: p. m1501.

10. Silcock DJ, Corfield AR, Staines H, Rooney KD. Superior performance of National Early Warning Score compared with quick Sepsis-related Organ Failure Assessment Score in predicting adverse outcomes: a retrospective observational study of patients in the prehospital setting. Eur J Emerg Med. 2019; 26(6): p. 433-439.

11. Gidari A, De Socio GV, Sabbatini S, Francisci D. Predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission in patients with SARS-CoV-2 infection. Infect Dis (Lond). 2020; 52(10): p. 698-704.

12. Grunau B, Kawano T, Scheuermeyer F, Tallon J, Reynolds J, Besserer F, et al. Early advanced life support attendance is associated with improved survival and neurologic outcomes after non-traumatic out-of-hospital cardiac arrest in a tiered prehospital response system. Resuscitation. 2019; 135: p. 137-144.

13. Fishe JN, Crowe RP, Cash RE, Nudell NG, Martin-Gill C, Richards CT. Implementing Prehospital Evidence-Based Guidelines: A Systematic Literature Review. Prehosp Emerg Care. 2018; 22(4): p. 511-519.

14. Ishak M, Ali D, Fokkert MJ, Slingerland RJ, Tolsma RT, Badings E, et al. Fast assessment and management of chest pain patients without ST-elevation in the pre-hospital gateway (FamouS Triage): ruling out a myocardial infarction at home with the modified HEART score. Eur Heart J Acute Cardiovasc Care. 2018; 7(2): p. 102-110.

15. Carroll G, Levy K, Pescatore R, Hong R. Examination of EMS Decision Making in Determining Suitability of Patient Diversion to Urgent Care Centers. Healthcare (Basel). 2019; 7(1): p. 24.

16. Ondrejka J, Giorgio G. The Emergency Physician\'s Role in Differentiating Brugada Syndrome from Brugada Phenotype. J Emerg Med. 2016; 50(5): p. 783.

17. Chang R, Fox EE, Greene TJ, Swartz MD, DeSantis SM, Stein DM, et al. Abnormalities of laboratory coagulation tests versus clinically evident coagulopathic bleeding: results from the prehospital resuscitation on helicopters study (PROHS). Surgery. 2018; 163(4): p. 819-826.

18. Yeates KO, Tang K, Barrowman N, Freedman SB, Gravel J, Gagnon I, et al. Derivation and Initial Validation of Clinical Phenotypes of Children Presenting with Concussion Acutely in the Emergency Department: Latent Class Analysis of a Multi-Center, Prospective Cohort, Observational Study. J Neurotrauma. 2019; 36(11): p. 1758-1767.

19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007; 370(9596): p. 1453-1457.

20. Stopyra JP, Harper WS, Higgins TJ, Prokesova JV, Winslow JE, Nelson RD, et al. Prehospital Modified HEART Score Predictive of 30-Day Adverse Cardiac Events. Prehosp Disaster Med. 2018; 33(1): p. 58-62.

21. Shaw J, Fothergill RT, Clark S, Moore F. Can the prehospital National Early Warning Score identify patients most at risk from subsequent deterioration? Emerg Med J. 2017; 34(8): p. 533-537.

22. Turcsanyi P, Kriegova E, Kudelka M, Radvansky M, Kruzova L, Urbanova R, et al. Improving risk-stratification of patients with chronic lymphocytic leukemia using multivariate patient similarity networks. Leuk Res. 2019; 79: p. 60-68.

23. Nilsen G, Borgan O, Liestøl K, Lingjærde OC. Identifying clusters in genomics data by recursive partitioning. Stat Appl Genet Mol Biol. 2013; 12(5): p. 637-652.

24. Hibbs MA, Dirksen NC, Li K, Troyanskaya OG. Visualization methods for statistical analysis of microarray clusters. BMC Bioinformatics. 2005; 6: p. 115.

25. Ramzan F, Gültas M, Bertram H, Cavero D, Schmitt AO. Combining Random Forests and a Signal Detection Method Leads to the Robust Detection of Genotype-Phenotype Associations. Genes (Basel). 2020; 11(8): p. 892.

26. Seymour CW, Kennedy JN, Wang S, Chang CCH, Elliott CF, Xu Z, et al. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. JAMA. 2019; 321(20): p. 2003-2017.

27. Castaldi PJ, Boueiz A, Yun J, Estepar RSJ, Ross JC, Washko G, et al. Machine Learning Characterization of COPD Subtypes: Insights From the COPDGene Study. Chest. 2020; 157(5): p. 1147-1157.

28. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017; 19(10): p. 1242-1254.

29. Rello J, Storti E, Belliato M, Serrano R. Clinical phenotypes of SARS-CoV-2: implications for clinicians and researchers. Eur Respir J. 2020; 55(8): p. 2001028.

30. Martín-Rodríguez F, López-Izquierdo R, Medina-Lozano E, Ortega Rabbione G, Del Pozo Vegas C, Carbajosa Rodríguez V, et al. Accuracy of prehospital point-of-care lactate in early in-hospital mortality. Eur J Clin Invest. 2020; 50(12): p. e13341.

31. Fassbender K, Walter S, Grunwald IQ, Merzou F, Mathur S, Lesmeister M, et al. Prehospital stroke management in the thrombectomy era. Lancet Neurol. 2020; 19(7): p. 601-610.

32. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. Med Clin North Am. 2020; 104(2): p. 213-238.

33. Carroll SL, Dye DW, Smedley WA, Stephens SW, Reiff DA, Kerby JD, et al. Early and prehospital trauma deaths: Who might benefit from advanced resuscitative care? J Trauma Acute Care Surg. 2020; 88(6): p. 776-782.

34. Pusateri AE, Moore EE, Moore HB, Le TD, Guyette FX, Chapman MP, et al. Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes: A Post Hoc Analysis of the PAMPer and COMBAT Clinical Trials. JAMA Surg. 2020; 155(2): p. e195085.

35. Jouffroy R, Gilbert B, Tourtier JP, Bloch-Laine E, Ecollan P, Bounes V, et al. Impact of Prehospital Antibiotic Therapy on Septic Shock Mortality. Prehosp Emerg Care. 2021; 25(3): p. 317-324.

36. Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, et al. Management of cardiogenic shock complicating myocardial infarction. Intensive Care Med. 2018; 44(6): p. 760-773.

37. Wu JR, Lee KS, Dekker RD, Welsh JD, Song EK, Abshire DA, et al. Prehospital Delay, Precipitants of Admission, and Length of Stay in PatientsWith Exacerbation of Heart Failure. Am J Crit Care. 2016; 26(1): p. 62-69.

38. Hodroge SS, Glenn M, Breyre A, Lee B, Aldridge NR, Sporer KA, et al. Adult patients with respiratory distress: current evidence-based recommendations for prehospital care. West J Emerg Med. 2020; 21(4): 849–857.

39. Wallgren UM, Sjölin J, Järnbert-Pettersson H, Kurland L. The predictive value of variables measurable in the ambulance and the development of the Predict Sepsis screening tools: a prospective cohort study. Scand J Trauma Resusc Emerg Med. 2020; 28(1): p. 59.

40. Martín-Rodríguez F, López-Izquierdo R, Del Pozo Vegas C, Delgado-Benito JF, Ortega GJ, Castro Villamor MA, et al. Association of Prehospital Oxygen Saturation to Inspired Oxygen Ratio With 1-, 2-, and 7-Day Mortality. JAMA Netw Open. 2021; 4(4): p. e215700.

41. Schulte PJ, Warner DO, Martin DP, Deljou A, Mielke MM, Knopman DS, et al. Association Between Critical Care Admissions and Cognitive Trajectories in Older Adults. Crit Care Med. 2019; 49(8): p. 116-1124.

42. Goldstein J, Jensen J, Carter A, Travers A, Rockwood K. The Epidemiology of Prehospital Emergency Responses for Older Adults in a Provincial EMS System. CJEM. 2015; 17(5): p. 491-496.

43. Miró Ò, Llorens P, Escalada X, Herrero P, Jacob J, Gil V, et al. Prehospital emergency care of patients with acute heart failure in Spain: the SEMICA study (Emergency Medical Response Systems for Patients with Acute Heart Failure). Emergencias. 2017; 29(4): p. 223-230.