ORIGINAL ARTICLE

Derivation and validation of new prehospital phenotypes for adults with COVID-19

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Objective. To characterize phenotypes of prehospital patients with COVID-19 to facilitate early identification of at-risk groups.

Methods. Multicenter observational noninterventional study of a retrospective cohort of 3789 patients, analyzing 52 prehospital variables. The main outcomes were 4 clusters of prehospital variables describing the phenotypes. Secondary outcomes were hospitalization, mechanical ventilation, admission to an intensive care unit, and cumulative mortality inside or outside the hospital on days 1, 2, 3, 7, 14, 21, and 28 after hospitalization and after start of prehospital care.

Results. We used a principal components multiple correspondence analysis (factor analysis) followed by decomposition into 4 clusters as follows: cluster 1, 1090 patients (28.7%); cluster 2, 1420 (37.4%); cluster 3, 250 (6.6%), and cluster 4, 1029 (27.1%). Cluster 4 was comprised of the oldest patients and had the highest frequencies of residence in group facilities and low arterial oxygen saturation. This group also had the highest mortality (44.8% at 28 days). Cluster 1 was comprised of the youngest patients and had the highest frequencies of smoking, fever, and requirement for mechanical ventilation. This group had the most favorable prognosis and the lowest mortality.

Conclusions. Patients with COVID-19 evaluated by emergency medical responders and transferred to hospital emergency departments can be classified into 4 phenotypes with different clinical, therapeutic, and prognostic characteristics. The phenotypes can help health care professionals to quickly assess a patient's future risk, thus informing clinical decisions.

Keywords: COVID-19. Phenotype. Prognosis. Emergency health services. Decision making.

Derivación y validación de nuevos fenotipos prehospitalarios en pacientes adultos con enfermedad por COVID-19

Objetivos. Desarrollar un fenotipado prehospitalario de pacientes con COVID-19 que permita una identificación temprana de los grupos de riesgo.

Método. Estudio observacional de cohorte retrospectivo multicéntrico, sin intervención con 3.789 pacientes y 52 variables prehospitalarias. Las variables de resultado principal fueron las cuatro agrupaciones prehospitalarios obtenidos, #1, #2, #3 y #4. Los resultados secundarios fueron: ingreso hospitalario, ventilación mecánica, ingreso en unidad de cuidados intensivos y mortalidad acumulada a los 1, 2, 3, 7, 14, 21 y 28 días desde el ingreso hospitalario (hospitalaria y extrahospitalaria).

Resultados. Por medio de una descomposición en componentes principales/correspondencia múltiple de datos mixtos (continuos y categóricos), seguido de una descomposición en agrupaciones, se obtuvo cuatro agrupaciones/fenotipos #1, #2, #3 y #4 de 1.090 (28,7%), 1.420 (37,4%), 250 (6,6%) y 1.029 (27,1%) pacientes, respectivamente. El grupo #4, compuesto por los pacientes de mayor edad, baja saturación de oxígeno e institucionalización es el que presenta la mayor mortalidad (44,8% de mortalidad a 28 días). El grupo #1, compuesto de pacientes de menor edad, con mayor porcentaje de tabaquismo, fiebre y necesidades de ventilación mecánica, es el de pronóstico más favorable con la menor tasa de mortalidad.

Conclusiones. Los pacientes con COVID-19 valorados por los servicios médicos de emergencias y transferidos al servicio de urgencias hospitalario se pueden clasificar en 4 fenotipos con diferentes consideraciones clínicas, terapéuticas y de pronóstico, y permite a los profesionales sanitarios discriminar rápidamente el nivel de riesgo futuro del paciente y ayuda por lo tanto en el proceso de toma de decisiones.

Palabras clave: COVID-19. Fenotipo. Pronóstico. Servicios de emergencias médicos. Toma de decisiones clínicas.

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Authors Contributions:
All the authors have confirmed their authorship in the document of author responsibilities, publication agreement and assignment of rights to EMERGENCIAS.

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Article Information:
Received: 20-2-2022
Accepted: 20-3-2022
Online: 23-5-2022

Editor in Charge:
Agustín Julián-Jiménez

Introduction

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) has had an extraordinary impact on the response capacity of the health systems of all nations due to the nature of the pandemic.[1,2] According to official data as of February 11, 2022 provided by the Ministry of Health of the Government of Spain, since the beginning of the pandemic, 10 604 200 confirmed cases had been detected in Spain, totaling 95 995 deaths, with 12 843 patients being ad-

mitted on that date, 1588 of them in intensive care units (ICU).[3]

The COVID-19 pandemic has destabilized health systems jeopardizing their sustainability and requiring the implementation of triage protocols and optimization of health resources at all levels[4], from primary health care through emergency medical services (EMS) to hospital centers.

In the era of precision medicine, it is important to identify the main phenotypes of severity and thus personalize care for each patient.[5,6] In the context of the current pandemic, research on the clinical phenotyping of patients infected with COVID-19 has been conducted mainly at the hospital level.[7-10] However, there are few studies in prehospital care systems and these focus on the clinical presentation and identification of cases with the disease[11,12] as well as the impact on the healthcare system.[13,14] The identification of these phenotypes and the application of a personalized approach would help to improve the decision-making process of EMS professionals, optimizing therapies and outcomes, particularly on patients with suspected COVID-19, indicating different pathophysiological pathways and outcomes.

The aim of this study was to explore the possibility of developing a phenotyping of COVID-19 infected patients through information available only in prehospital care (sociodemographic data, comorbidities, and signs and symptoms at presentation), evaluating its reproducibility and correlation with prognosis.

Methods

Scope of study and patients

Multicenter, non-intervention, retrospective, observational, retrospective cohort study conducted in the provinces of Palencia, Salamanca, Segovia and Valladolid (Spain). The study involved the Emergency Coordination Center (ECC), 8 advanced life support units (ALSU), 53 basic life support units (BLSU) of the Castilla y León Health Emergency Department (Spanish acronym, SACYL), and 8 hospital emergency departments (ED).

The study included patients over 18 years of age, seen consecutively between February 1, 2020, and December 31, 2020, who made an urgent call for assistance, and who, after interview and evaluation by the ECC, were classified as patients with suspected COVID-19 disease, who were subsequently evacuated to the reference ED and who presented a positive polymerase chain reaction for SARS-CoV-2. Patients who did not accept transfer, cases of death on arrival of the ambulance at the incident site, and those patients in whom follow-up was not possible were excluded.

Selection and collection of variables

The main outcome variables included: hospital admission, mechanical ventilation, ICU admission and cumulative mortality at 1, 2, 3, 7, 14, 21 and 28 days from hospital admission (in-hospital and out-of-hospital).

The covariates included information extracted from the incident management application in the ECC. Requests for assistance were made through the 1-1-2 telephone number, through a specific number when the call came from primary care, and ultimately when the warner contacted the system through the specific coronavirus hotline of Castilla y León. The operators or managers collected geolocation (urban or rural area), affiliation, age, gender and institutionalization. The call was then transferred to a physician or regulatory nurse who, through a telephone interview, asked about the guiding signs and symptoms (Table 1) and determined that this was a suspected case of COVID-19. During this clinical interview, the clinical manifestations, and the following vital signs were collected: desaturation (SaO_2 < 93%), tachypnea (respiratory rate > 18 brpm), fever (temperature > 37 °C), and tachycardia (heart rate > 100 bpm).

By means of an electronic medical record (EMR) query in the ECC, the regulating physician or nurse collected the patient's comorbidities, specified in Table 1, and by reviewing the EMR 30 days after the index event, an associate investigator from each hospital recorded: SARS-positive CoV-2 results, admission or discharge from the ED, need for mechanical ventilation and ICU, and mortality (both in-hospital and out-of-hospital).

Data analysis

An exploratory study based on the geometric analysis of the variables was carried out on the set of 3789 patients with 52 variables, of which 51 were categorical variables. For this purpose, a multiple correspondence analysis was performed on the n categorical variables, which basically studies the "distances" between the variables involved from the corresponding contingency table of the n categorical variables involved (Burt table) together with the distances of the numerical variables. From here, a decomposition into singular values is performed to obtain the most important dimensions to be analyzed,[15] which represent the greatest variability or inertia of the data, similar to what is done in a decomposition into principal components. The next step is to decompose the selected components into groups to classify patients according to their clinical and phenotypic characteristics. For this purpose, an agglomerative hierarchical grouping has been performed, cutting the tree in such a way that four phenotypes are obtained. Euclidean distance and agglomerative Ward's method were used to construct the dendrogram and the partition into four groups. The final phenotype partition was obtained by applying the k-means algorithm with Ward's partition as the initial solution. The number of four clusters was set a priori as the optimal number of clusters, taking into account both the numerical criterion as well as the clinical criterion of applicability, since in this way a balance can be obtained between too

Table 1. Clinical-epidemiological characteristics of patients with COVID-19

	Phenotype #1 N = 1090 n (%)	Phenotype #2 N = 1420 n (%)	Phenotype #3 N = 250 n (%)	Phenotype #4 N = 1029 n (%)	*P*
Epidemiology					
Sex: female	435 (39.9)	736 (51.8)	145 (58.0)	542 (52.7)	< **.001**
Age (years) [Median IQR]	67 [55-76]	79 [66-88]	74 [59-85]	86 [81-90]	< **.001**
Area: urban	648 (59.4)	649 (45.7)	139 (55.6)	512 (49.8)	< **.001**
Residences: yes	60 (5.5)	447 (31.5)	55 (22.0)	661 (64.2)	< **.001**
Clinical manifestations					
Anosmia or ageusia	16 (1.47)	1346 (94.8)	2 (0.80)	11 (1.07)	**.001**
Dyspnea	484 (44.4)	4 (0.3)	51 (20.4)	495 (48.1)	< **.001**
Desaturation	196 (18.0)	14 (1.0)	37 (14.8)	599 (58.2)	< **.001**
Cough	194 (17.8)	3 (0.2)	44 (17.6)	132 (12.8)	< **.001**
Hemoptysis	39 (3.6)	0 (0.0)	2 (0.80)	21 (2.04)	< **.001**
Crackles	125 (11.5)	3 (0.2)	23 (9.2)	145 (14.1)	< **.001**
Rhonchi	20 (1.8)	0 (0.0)	6 (2.4)	72 (7.0)	< **.001**
Wheezing	16 (1.5)	1 (0.1)	2 (0.8)	19 (1.85)	< **.001**
Tachypnea	98 (9.0)	1 (0.1)	15 (6.0)	210 (20.4)	< **.001**
Rib pain	76 (7.0)	0 (0.0)	6 (2.4)	32 (3.1)	< **.001**
Fever	489 (44.9)	12 (0.8)	91 (36.4)	334 (32.5)	< **.001**
Headache	41 (3.8)	2 (0.1)	8 (3.2)	18 (1.7)	< **.001**
Asthenia	228 (20.9)	29 (2.0)	55 (22.0)	160 (15.5)	< **.001**
Tachycardia	62 (5.7)	5 (0.3)	14 (5.6)	7 (5.5)	< **.001**
Precordial pain	88 (8.1)	0 (0.0)	10 (4.0)	22 (2.1)	< **.001**
Syncope	68 (6.2)	6 (0.4)	27 (10.8)	56 (5.4)	< **.001**
Abdominal pain	0 (0.0)	0 (0.0)	71 (28.4)	3 (0.3)	< **.001**
Diarrhea	2 (0.2)	0 (0.0)	149 (59.6)	9 (0.9)	**.001**
Nausea or vomiting	2 (0.2)	0 (0.0)	103 (41.2)	4 (0.4)	**.001**
Disturbance LC	55 (5.0)	3 (0.2)	27 (10.8)	223 (21.7)	**.001**
Urinary Clinic	28 (2.6)	13 (0.9)	9 (3.6)	73 (7.1)	**.001**
Familial Claudication	14 (1.3)	10 (0.7)	2 (0.8)	3 (0.3)	**.062**
Comorbidities					
Dyslipidemia	314 (28.8)	522 (36.8)	97 (38.8)	456 (44.3)	< **.001**
Hypertension	391 (35.9)	821 (57.8)	147 (58.8)	815 (79.2)	< **.001**
Mental illness	158 (14.5)	350 (24.6)	55 (22.0)	351 (34.1)	< **.001**
Smoking	111 (10.2)	127 (8.9)	18 (7.2)	57 (5.5)	< **.001**
Thyroid pathology	102 (9.4)	199 (14.0)	30 (12.0)	117 (11.4)	.004
Obesity	130 (11.9)	176 (12.4)	36 (14.4)	117 (11.4)	.593
AIDS	1 (0.1)	4 (0.3)	0 (0.0)	0 (0.0)	.349
Metastatic cancer	16 (1.4)	17 (1.2)	3 (1.2)	13 (1.3)	.947
Severe liver disease	24 (2.2)	32 (2.2)	4 (1.6)	26 (2.5)	.841
Neoplasm	117 (10.7)	188 (13.2)	31 (12.4)	153 (14.9)	.040
Leukemia	18 (1.6)	15 (1.1)	4 (1.6)	10 (1.0)	.407
Lymphoma	7 (0.6)	7 (0.5)	3 (1.2)	4 (0.4)	.376
Complicated DM	17 (1.6)	60 (4.2)	14 (5.6)	98 (9.5)	< **.001**
Renal disease	37 (3.4)	205 (14.4)	41 (16.4)	279 (27.1)	< **.001**
Hemiplegia	8 (0.7)	23 (1.6)	6 (2.4)	69 (6.71)	< **.001**
Uncomplicated DM	139 (12.8)	290 (20.4)	41 (16.4)	250 (24.3)	< **.001**
Mild liver disease	25 (2.3)	39 (2.7)	15 (6.0)	33 (3.2)	**.017**
Gastric ulcer	15 (1.4)	36 (2.5)	5 (2.0)	48 (4.7)	< **.001**
Connective tissue disease	32 (2.9)	63 (4.4)	10 (4.0)	38 (3.7)	.275
COPD	103 (9.4)	120 (8.4)	11 (4.4)	150 (14.6)	< **.001**
Dementia	16 (1.5)	318 (22.4)	31 (12.4)	458 (44.5)	< **.001**
Stroke	35 (3.2)	135 (9.5)	26 (10.4)	190 (18.5)	< **.001**
Peripheral venous disease	49 (4.5)	112 (7.9)	27 (10.8)	139 (13.5)	< **.001**
Heart failure	44 (4.1)	172 (12.1)	32 (12.8)	274 (26.6)	< **.001**
Ischemic heart disease	48 (4.4)	120 (8.4)	22 (8.8)	172 (16.7)	< **.001**

IQR: interquartile range; CRI: interquartile range; CPR: interquartile range; CPR: level of consciousness; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease.
Values in bold denote statistical significance.

many clusters with little help for healthcare personnel in making quick decisions and too low a partition (two, for example), with no relevant phenotypic characteristics.

Ethical aspects

The study was approved by the Ethics Committee on Drug Research (Spanish acronym, CEIm) of the

Valladolid West Health Area (code PI 38-20), which granted an exemption from the requirement to obtain the informed consent of the study participants due to the use of de-identified data. At all times, current legislation on data protection was respected and the national and international regulations for studies on human subjects included in the Declaration of Helsinki on Biomedical Research were complied with. The study was designed in accordance with the STROBE guidelines for observational studies.[16]

Results

A total of 3789 patients met the inclusion criteria (Figure 1). The median age was 78 years (IQR: 65-87 years), with 1,858 women (49.0%). The demographic and clinical characteristics of the phenotypes obtained can be seen in Table 1.

Mortality observed at 1, 2, 3, 7, 14, 21 and 28 days were: 5.0%, 7.2%, 9.4%, 16.3%, 21.9%, 23.7% and 25.0%, respectively. The total percentage of hospital admissions was 77.8%, while 6.1% of patients were admitted to the ICU and 6.0% received invasive mechanical ventilation. Table 2 shows the hospital follow-up variables broken down by group.

The phenotypes obtained in the analysis performed were 4 (Figure 2 and 3). Younger patients were grouped in phenotype #1 with a median age of 67 years (IQR: 55-76). In this phenotype arterial hypertension (AHT) (35.9%) and dyslipidemia (28.8%) were the most frequent personal history, while the most prevalent symptomatologies were the presence of fever (44.9%) and dyspnea (44.4%). Phenotype #2 included patients with a median age of 79 years (IQR: 66-88) and 31.5% institutionalized; the most common symptomatology was the presence of anosmia or ageusia in 94.8% of patients. In phenotype #3, the median age was 74 years (IQR: 59-85); AHT and dyslipidemia were the most common comorbidities with 57.8% and 36.8%, respectively.

In this group, the most common clinical manifestations were digestive, with 59.6% presenting diarrhea and 41.2% nausea or vomiting. Finally, phenotype #4 consisted of patients with the highest median age of 86 years (IQR: 81-90), with a high percentage of institutionalized patients (64.2%). AHT (79.2%), cognitive impairment (44.5%) and dyslipidemia (44.3%) were the most prevalent comorbidities. The predominant clinical manifestations in this group were respiratory: dyspnea was observed in 48.1% of the cases, and the presence of desaturation in 58.2%. It was also observed that this was the group with the highest proportion of altered level of consciousness (21.7%).

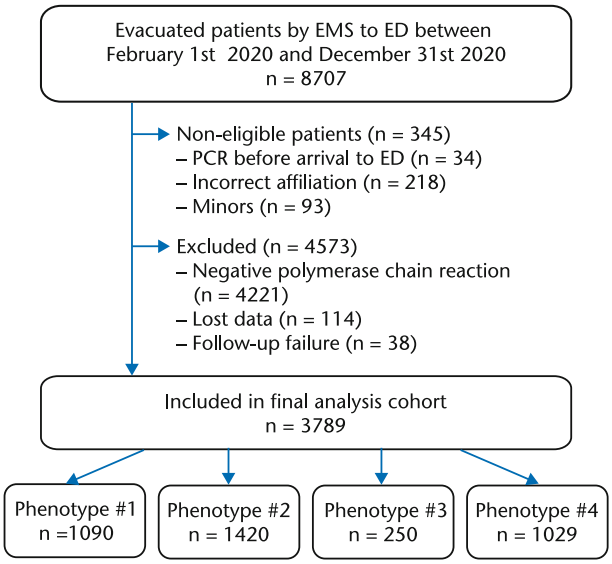

Figure 1. Flow diagram of the study participants.
EMS: emergency medical service; ED: hospital emergency department; CRA: cardiorespiratory arrest.

With respect to the severity of each phenotype, phenotype #1 presented the lowest mortality in all cases, from 1.9% on day 1 to 11.0% on day 28. However, this is the group that was admitted to the ICU the most (11.1%) and required mechanical ventilation the most (9.8%). In phenotypes #2 and #3 mortality on days 1 and 2 is similar, but on day 3 phenotype #2 already begins to present higher mortality (7.5% vs. 5.6%) and this increase in mortality is confirmed on day 7 where mortality in phenotype #2 rises to 13.5% and 23.3% on day 28, while in phenotype #3 it only reaches 8.4% at 7 days and 14.8% on day 28. With respect to admission to the ICU, phenotypes #2 and #3 have a similar

Table 2. Hospital follow-up variables

	Phenotype #1 N = 1090 n (%)	Phenotype #2 N = 1.420 n (%)	Phenotype #3 N = 250 n (%)	Phenotype #4 N = 1029 n (%)
Admission	774 (71.0)	1.094 (77.0)	179 (71.6)	901 (87.6)
Mechanic Ventilation	107 (9.8)	79 (5.6)	14 (5.6)	29 (2.8)
ICU	121 (11.1)	71 (5.0)	14 (5.6)	26 (2.5)
Mortality after 1 day	21 (1.9)	52 (3.7)	10 (4.0)	107 (10.4)
Mortality after 2 day	34 (3.1)	78 (5.5)	12 (4.8)	149 (14.5)
Mortality after 3 day	43 (3.9)	107 (7.5)	14 (5.6)	192 (18.7)
Mortality after 7 day	73 (6.7)	192 (13.5)	21 (8.4)	330 (32.1)
Mortality after 14 day	97 (8.9)	280 (19.7)	34 (13.6)	420 (40.8)
Mortality after 21 day	110 (10.1)	310 (21.8)	35 (14.0)	443 (43.1)
Mortality after 28 day	120 (11.0)	331 (23.3)	37 (14.8)	461 (44.8)

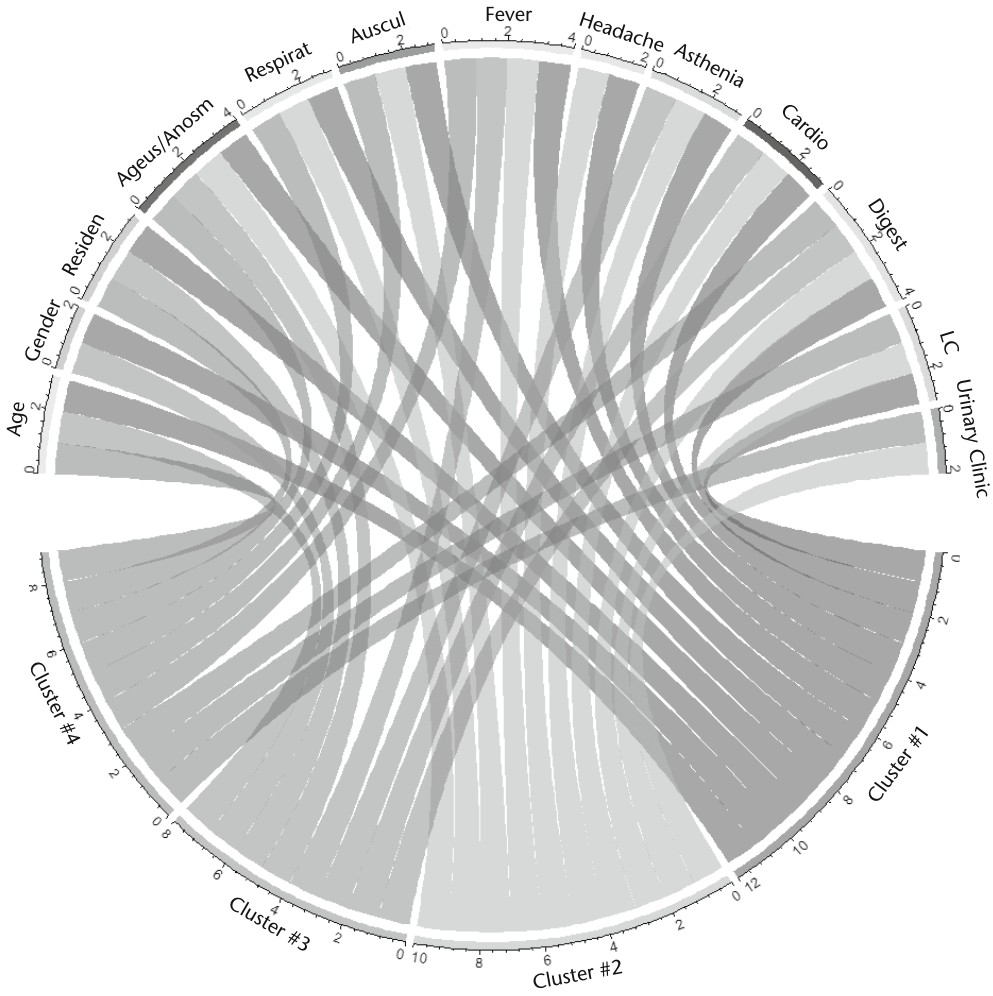

Figure 2. String diagram of the distribution of groups of variables in the phenotypes.
Variables are grouped into categories. Phenotypes are shown in different shades of grey. For each phenotype, if a variable mean (for continuous variables) or proportion (for categorical variables) is significantly different from the mean or proportion in the total, a ribbon connects the phenotype and the variable group. The width of the ribbons correlates with the number of variables that are significantly different from those in the derivation cohort for that phenotype. Residen: residences; Respirat: respiratory (includes: dyspnea, desaturation, rib pain, tachypnea, and hemoptysis); Auscul: pathologic auscultation (includes: rhonchi, wheezing, and crackles); Ageus/Anosm: ageusia or anosmia; Cardio: cardiologic (includes: tachycardia, chest pain and syncope); Digest: digestive (includes: abdominalgia, nausea, vomiting and diarrhea); LC: altered level of consciousness; Clin. Urin: urinary clinic.

proportion, 5% in phenotype #2 and 5.6% in phenotype #3, with the same proportion of ventilation in the ICU in both groups (5.6%). Phenotype #4 has the highest mortality from day 1 (10.4%), rising to 14.5% on day 2 and reaching 44.8% on day 28. In addition, it is the group with the lowest admission to the ICU (2.8%) and the lowest mechanical ventilation (2.5%) (Table 2).

Discussion

In the present study we have identified 4 bedside phenotypes based on the analysis of 52 epidemiological, clinical and comorbidity variables collected at the first EMS contact and without taking into account the outcome variable. To our knowledge, this is the first prehospital study describing different phenotypes of patients with COVID-19 referred to the ED.

In relation to COVID-19, phenotypes have been reported based on self-reporting of symptoms by non-hospitalized patients using a mobile app[17] and clinical phenotypes of disease and pneumonia during hospital admission have been investigated both on the inpatient ward and in the ICU.[7-10,18]

Our study has been able to find 4 phenotypes with clinical and prognostic peculiarities. Phenotype #4, which includes almost a third of the patients analyzed,

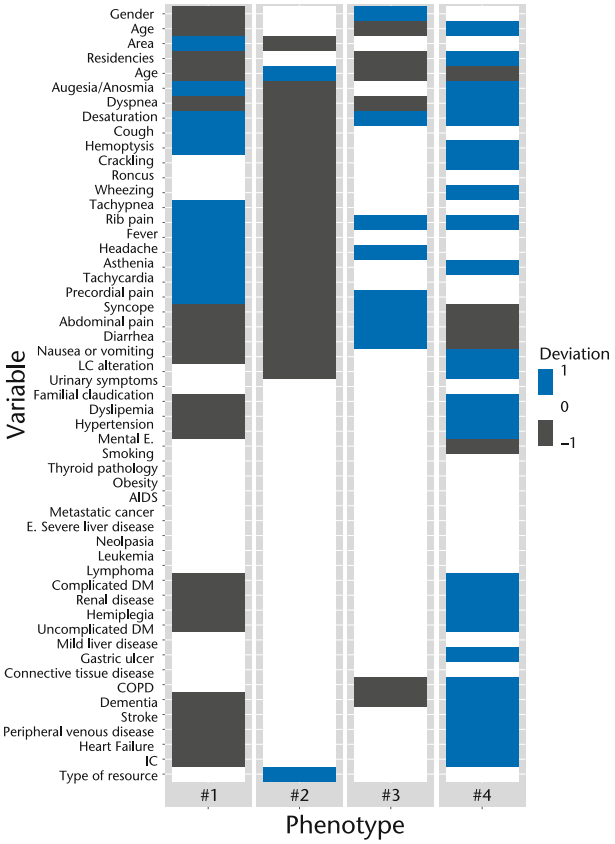

Figura 3. Heat map for variables according to phenotypes. For each phenotype, if the mean value of a variable (for continuous variables) or proportion (for categorical variables) in the group is significantly different from the mean or proportion, respectively, in the total cohort, the deviation, positive (blue) or negative (gray) of that variable in the group, with respect to the total cohort, is plotted.
COPD: chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; IHD: ischemic heart disease; DM: diabetes mellitus; LC: level of consciousness; IHD: ischemic heart disease.

has a very high mortality rate (10.4% at 24 hours and 45% at 28 days), so that belonging to this group is clearly a risk factor for a very poor prognosis. This phenotype groups patients with risk factors already described since the beginning of the pandemic, such as: advanced age,[19] institutionalization[20] and respiratory symptoms associated with desaturation.[21] Another factor that should be highlighted compared to the other phenotypes is the altered level of consciousness.[22] This coincides with the clinical presentations with worse prognosis obtained by other authors in hospital phenotyping studies.[8,9] In relation to personal history, institutionalization and the presence of major comorbidity factors such as cardiovascular, neurodegenerative or respiratory disease stand out.[9] This group of patients hardly generated ICU admissions, which can be explained by the high percentage of institutionalized and older patients in our group, since both factors have been a limitation for admission to this type of unit.[23]

Of the remaining phenotypes analyzed, the least adverse phenotype, #1, has been observed to correspond to the youngest age group with the lowest overall all-cause mortality in all the time periods analyzed.[24] This phenotype is characterized by fever, dyspnea, asthenia and desaturation being the most prevalent symptoms. There is a clear predominance of the male gender and it is characterized by low comorbidity. As a peculiarity, it is the one that generates the highest number of admissions to the ICU, which coincides with the analysis of other studies where 80% of the patients admitted to the ICU are male, young in age and with hardly any comorbidities.[25]

The most numerous phenotype is #2, with a median age close to 80 years, but, unlike phenotype #4, these patients have a more benign initial symptomatology. Characteristically, almost all patients present with anosmia or ageusia with almost no respiratory or systemic symptoms.[26] The exact pathogenesis of SARS-CoV-2 causing olfactory and gustatory disorders remains unknown, but appears to be related to prognosis.[26,27]

Anosmia has been described as a possible good predictive factor in relation to its pathophysiologic mechanism and seems to be confirmed in our study in the short term. However, it is noteworthy that the mortality of the group increases progressively to over 20% at 28 days, so there must be other characteristics, such as high comorbidity or unknown factors, in addition to age that imply the poor medium-term evolution of some of the individuals in this group.[19]

Finally, a phenotype (#3) has been identified that is very small in proportion to the other groups, grouped around 75 years of age and with digestive symptoms including diarrhea, nausea or vomiting and abdominal pain, with few respiratory symptoms, and a mild-moderate prognosis, with a 24-hour mortality of 4%. The literature reflects studies on the relationship between digestive symptoms and the severity of the clinical course of COVID-19, with variable results.[28,29]

#1. The short-term mortality associated with this group is very low, which distinguishes it from the rest, but, on the other hand, a high percentage of the patients included will require admission to the ICU. Likewise, patients with phenotype #4 should be closely monitored during admission, as they are at high risk of deterioration progressing to death from the very moment of first medical attention.

At the present time of the pandemic, in which cases continue to occur in epidemic waves, and in which there is great uncertainty about its future evolution, it is essential not only to know the individual risk of each patient by means of scores or severity scales[30] but also to identify the clinical groups at risk in the different health care settings. Although the pathophysiological mechanisms underlying each phenotype are unknown, belonging to one or the other leads to different outcomes.[9] This would allow strategies to be designed to deal with each patient individually depending on the patient's risk, the level of care at which care is provid-

ed, and the moment of saturation of the health care system. In prehospital care, early detection of time-dependent diseases is a fundamental challenge and allows individualization of monitoring, initial therapeutic measures and patient fate, which could potentially modify the course of the disease.

Our study has several limitations. First of all, our cohort may have a selection bias, since the sample was obtained by opportunity criteria, including only patients attended and transferred by the EMS, discarding patients who attended the ED by their own means. To reduce bias, patients were collected from urban and rural areas, 24 hours a day, 7 days a week throughout the study period and with assignment to hospitals of different training. In addition, this is a retrospective study, which may have meant the loss of some clinical variable that later proved to be important with the evolution of the disease and the clinical knowledge acquired. On the other hand, it should be noted that the clinical variable blood pressure was not included in our study, since when the patient was referred to the hospital in an ALSU, the reference vital signs were those transmitted by telephone, and in the case of transfer in an ALSU, it was not taken in all patients due to the high transmissibility of the disease added to the lack of knowledge about the risk of transmission by contact, giving priority to immediate transfer. Similarly, some clinical signs and manifestations (e.g. pulmonary auscultation) could only be evaluated when a physician was on the scene, which we consider to be an information bias. The problems of lack of information regarding some variables probably could have implied an underestimation of the true sensitivity of the prehospital COVID-19 suspicion. In addition, there is no information available on the status of patients' therapeutic effort limitation or palliative or terminal status, which may also have interfered with patient assessment. Finally, the data from this study, being from a single country, should be considered together with data collected in other settings to elucidate their clinical impact on prehospital care. Spain is undergoing a more rapid demographic aging than the rest of the countries in the European community, with Castilla y León being the community with the highest mean age, a fact that is in line with the data obtained in our study. The natural progression of COVID-19 over time could lead to changes in phenotypes and will require further studies.

In conclusion, patients with COVID-19 assessed by EMS and transferred to the ED can be classified into 4 phenotypes with different clinical and prognostic considerations. Through bedside phenotyping, healthcare professionals can discriminate at the prehospital level the risk and future implications with more robust data, which would help in the decision-making process with the appropriate use of resources, such as the level of monitoring, the need for mechanical ventilation or immediate transfer to the hospital.

Conflict of Interests Disclosure: None reported.

Funding/Support: This research has received support from the Gerencia Regional de Salud de Castilla y León (SACYL) for research projects in disease COVID-19, with registration number GRS COVID 7/A/20, PI: Francisco Martín-Rodríguez.

Ethical Responsibilities: The authors have confirmed the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS. The study was approved by the Drug Research Ethics Committee (CEIm) of the Valladolid West Health Area (code PI 38-20).

Article not commissioned by the Editorial Committee and with external peer review.

Addendum

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