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Predicting Clinical Outcome with Phenotypic Clusters in COVID-19 Pneumonia: An Analysis of 12,066 Hospitalized Patients from the Spanish Registry SEMI-COVID-19

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Abstract: (1) Background: Different clinical presentations in COVID-19 are described to date, from mild to severe cases. This study aims to identify different clinical phenotypes in COVID-19 pneumonia using cluster analysis and to assess the prognostic impact among identified clusters in such patients. (2) Methods: Cluster analysis including 11 phenotypic variables was performed in a large cohort of 12,066 COVID-19 patients, collected and followed-up from 1 March to 31 July 2020, from the nationwide Spanish Society of Internal Medicine (SEMI)-COVID-19 Registry. (3) Results: Of the total of 12,066 patients included in the study, most were males (7052, 58.5%) and Caucasian (10,635, 89.5%), with a mean age at diagnosis of 67 years (standard deviation (SD) 16). The main pre-admission comorbidities were arterial hypertension (6030, 50%), hyperlipidemia (4741, 39.4%) and diabetes mellitus (2309, 19.2%). The average number of days from COVID-19 symptom onset to hospital admission was 6.7 (SD 7). The triad of fever, cough, and dyspnea was present almost uniformly in all 4 clinical phenotypes identified by clustering. Cluster C1 (8737 patients, 72.4%) was the largest, and comprised patients with the triad alone. Cluster C2 (1196 patients, 9.9%) also presented with ageusia and anosmia; cluster C3 (880 patients, 7.3%) also had arthromyalgia, headache, and sore throat; and cluster C4 (1253 patients, 10.4%) also manifested with diarrhea, vomiting, and abdominal pain. Compared to each other, cluster C1 presented the highest in-hospital mortality (24.1% vs. 4.3% vs. 14.7% vs. 18.6%; $p < 0.001$). The multivariate study identified age, gender (male), body mass index (BMI), arterial hypertension, chronic obstructive pulmonary disease (COPD), ischemic cardiopathy, chronic heart failure, chronic hepatopathy, Charlson's index, heart rate and respiratory rate upon admission >20 bpm, lower PaO2/FiO2 at admission, higher levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH), and the phenotypic cluster as independent factors for in-hospital death. (4) Conclusions: The present study identified 4 phenotypic clusters in patients with COVID-19 pneumonia, which predicted the in-hospital prognosis of clinical outcomes.

Keywords: COVID-19; cluster analysis; prognosis; phenotype

1. Introduction

Since January 2020, the COVID-19 pneumonia pandemic has spread across the globe. As of 6 October 2020, 35 million people have been infected worldwide and 1 million people have died. Numerous studies have highlighted the clinical characteristics of the disease, showing that 80% of COVID-19 patients present a low-mild disease with an overall case mortality rate of 2–3%. However, a worrying subset of 15% of patients presented with lung involvement of moderate severity requiring hospital admission, and 5% with severe respiratory failure and systemic host-immune response resulting in fatality in half of such cases [1–3].

Although some factors associated with poor prognosis (advanced age, male gender, higher body mass index (BMI), and some analytical parameters such as PaO2/FiO2, lymphocyte count, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, interleukin-6 (IL-6), and D-dimer) are

known [4], it is not clear which patients may present a worse evolution during hospitalization and why. Therefore, the search for clinical patterns of observed phenotypic variables might help physicians in care management in those patients with COVID-19. Interestingly, in recent years, cluster analysis has been increasingly used to investigate the heterogeneity of some diseases to identify different clinical phenotypes with similar combinations of traits. Performed either by hypothesis- or data-driven methods, this technique has been shown to offer a feasible approach to stratify entities with high clinical variability. Consequently, we hypothesized that within large cohorts of COVID-19 which include the wide spectrum of the disease and long-term follow-up, cluster analysis could reveal subsets of patients with similar clinical patterns that might help physicians in disease stratification and improve targeted care management.

The present study aimed to identify clinical phenotypes by cluster analysis in our large nationwide series of COVID-19 illness and to create a predictive model related to poor outcome.

2. Materials and Methods

2.1. Study Design, Patient Selection, and Data Collection

A cluster analysis was performed in the large cohort of consecutive patients included in the Spanish registry SEMI-COVID-19, created by the Spanish Society of Internal Medicine (SEMI). This is a multicenter, nationwide registry with 109 hospitals registered so far (the hospitals and collaborators are shown in Appendix A). The data in this study come from all the centers in the registry. From 1 March to 31 July 2020, 12,066 hospitalized patients providing data of symptoms of COVID-19 upon admission were included in the registry. All included patients were diagnosed by polymerase chain reaction (PCR) test taken from a nasopharyngeal sample, sputum or bronchoalveolar lavage. All data presented in this work (demographic data, symptoms, comorbidities, lab data, treatments, and outcomes derived from the SEMI-COVID-19 register. The symptoms of all patients were collected upon admission. Likewise, the analytical data collected in the present study correspond to the analysis upon admission as well. The collection of data from each patient in terms of laboratory data, treatments, and outcomes was verified by the principal investigator of each center through the review of clinical records.

All participating centers in the register received confirmation from the relevant ethics committees, including Bellvitge University Hospital (PR 128/20).

2.2. Treatments Prescribed

The treatments received were in accordance with the medical guidelines available at the time of the pandemic [5–11]. In the absence of clinical evidence of any of the treatments at the initial time of the pandemic, their use was allowed off-label.

2.3. Outcomes Definition

The primary outcome of the study was in-hospital mortality. The secondary outcomes were the requirement of mechanical ventilation or intensive care unit (ICU) admission, and the length of stay (from admission to discharge).

2.4. Statistical Analysis

The clinical variables did not present missing data and the demographic variables presented <1%, so it was decided not to perform any specific treatment of them. As for the analytical data, they presented between 5–30% of missing data, so multiple imputation was made accordingly.

Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as median [IQR]. Differences among groups were assessed using the chi-square test for categorical variable and analysis of variance (ANOVA) or Kruskal–Wallis test as appropriate for continuous variables. p-values < 0.05 indicated statistical significance.

The cluster analysis was performed by ascendant hierarchical clustering on the 11 variables previously selected by using Ward's minimum variance method with Euclidean squared distance [12]. Results are graphically depicted by a dendrogram. The number of clusters was estimated by the k-means method. The cluster analysis model was included in a binary logistic regression, taking in-hospital mortality, mechanical ventilation, and intensive care unit (ICU) admission as dependent variables. We introduced in the multivariate model those variables with a p-value < 0.10 in the univariate model. To avoid the so-called "Table 2 fallacy" we also made the multivariate model including all variables of the univariate model regardless of their significance [13]. Mortality among the groups was represented by the Kaplan-Meier curves with their logarithmic range test (event: death; censored data: hospital discharge).

Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA: IBM Corp.

3. Results

3.1. General Data and Symptoms

A total of 12,066 patients were included in the study. General data of the whole cohort are summarized in Table 1. Patients were mostly males (7052, 58.5%) and Caucasian (10,635, 89.5%). The mean age at diagnosis was 67 years (standard deviation (SD) 16). The average number of days from symptom onset to hospital admission was 6.7 days (SD 7). The main pre-admission comorbidities were arterial hypertension (6030, 50%), hyperlipidemia (4741, 39.4%) and diabetes mellitus (2309, 19.2%). The mean Charlson's index among patients was 1.2 (SD 1.8). The most common symptoms (Table 2) were fever 10,346 (85.7%), cough (9142, 75.8%), dyspnea (7205, 59.7%), arthromyalgia (3794, 31.4%), diarrhea (2943, 24. 4%), headache (1402, 11.6%), sore throat (1191, 9.9%), ageusia (992, 8.2%), vomiting (891, 7.4%), anosmia (879, 7.3%), and abdominal pain (738, 6.1%).

Table 1. General data of all patients.

	All Patients n = 12,066
Age yr., median (IQR)	68 (56–79)
Gender, males n (%)	7052 (58.5)
Race	
Caucasian	10,635 (89.5)
Black	43 (0.4)
Hispanic	1041 (8.8)
Asian	59 (0.5)
Others	100 (0.8)
BMI, median (IQR)	28 (25–31)
Days from onset to admission, median (IQR)	7 (4–9)
Smoking behavior, n (%)	
Never	8035 (69.7)
Current smoker	567 (4.9)
Former smoker	2930 (25.4)
Comorbidity, n (%)	
Arterial hypertension	6030 (50)
Diabetes mellitus	2309 (19.2)
Hyperlipidemia	4741 (39.4)
COPD	786 (6.5)
Asthma	869 (7.2)
OSAS	751 (6.3)
Ischemic cardiopathy	931 (7.7)

Table 1. *Cont.*

	All Patients n = 12,066
Chronic heart failure	809 (6.7)
Chronic kidney disease	696 (5.8)
Chronic hepatopathy	440 (3.7)
Active cancer	1196 (9.9)
Autoimmune disease	277 (2.3)
Charlson's index, median (IQR)	1 (0–2)

BMI: body mass index. COPD: chronic obstructive pulmonary disease. OSAS: obstructive sleep apnea syndrome. IQR: interquartile range.

3.2. Clustering Analysis

Despite most patients presenting with fever, cough, and/or dyspnea, 4 different clusters were identified (Figure 1). The main characteristics of each are shown in Tables 2 and 3. Cluster C1 (8737 patients, 72.4%) comprised patients with the triad of fever, cough, and dyspnea, with no other predominant symptoms. Subjects grouped in cluster C1 tended to be elderly males with a higher prevalence of comorbidities. The time between symptom onset and admission was also shorter in this subgroup of patients, in comparison with the other identified clusters. One in 10 C1 patients required ICU admission and a quarter of them died, representing the highest mortality rate among the 4 clusters. Patients in the C2 cluster (1196 patients, 9.9%) comprised patients predominantly presenting with ageusia and/or anosmia, often accompanied by fever, cough, and/or dyspnea. Subjects grouped in the C2 cluster showed the lowest percentage of ICU admission and mortality rate. Cluster C3 (880 patients, 7.3%) included patients predominantly with arthromyalgia, headache, and/or sore throat presentations, often also accompanied by fever, cough, and/or dyspnea. Up to 10.8% of C3 patients required ICU admission and 14.7% died. Finally, subjects grouped in cluster C4 (1253 patients, 10.4%) presented predominantly with diarrhea, vomiting, and/or abdominal pain, also often accompanied by fever, cough, and/or dyspnea. Of these, 8.5% required ICU admission and 18.6% died. This mortality rate of cluster C4 was second only to the C1.

Analytical results among clusters showed that PaO2/FiO2 at entry was a median 294 mmHg (292–296), being highest in the C2 cluster (289 mmHg vs. 311 vs. 305 vs. 301; $p < 0.001$). Cluster C1 showed the highest values of C-reactive protein (CRP) (78 mg/L vs. 69 vs. 63 vs. 66; $p < 0.001$), lactate dehydrogenate (LDH) (332 U/L vs. 309 vs. 330 vs. 331; $p < 0.001$), ferritin (669 mcg/L vs. 634 vs. 587 vs. 620; $p = 0.051$), and D-dimer (680 ng/mL vs. 594 vs. 595 vs. 608; $p < 0.001$).

Table 2. Symptoms and physical examination between clusters.

	All Patients n = 12,066	**C1 n = 8737**	**C2 n = 1196**	**C3 n = 880**	**C4 n = 1253**	***p*-Value**
Symptoms n (%)						
High-grade fever ≥ 38 °C	7915 (65.6)	5672 (64.9)	843 (70.5)	598 (68)	802 (64)	<0.001
Low-grade fever < 38 °C	2431 (20.1)	1723 (19.7)	238 (19.9)	194 (22)	276 (22)	<0.001
Cough	9142 (75.8)	6501 (74.4)	993 (83)	766 (87)	882 (70.4)	<0.001
Dyspnea	7205 (59.7)	5340 (61.1)	727 (60.8)	492 (55.9)	646 (51.6)	<0.001
Arthromyalgia	3794 (31.4)	2432 (27.8)	569 (47.6)	370 (42)	423 (33.8)	<0.001
Sore throat	1191 (9.9)	0	186 (15.6)	880 (100)	125 (10)	<0.001
Headache	1402 (11.6)	730 (8.4)	292 (24.4)	202 (23)	178 (14.2)	<0.001
Anosmia	879 (7.3)	0	879 (73.5)	0	0	<0.001
Ageusia	992 (8.2)	0	988 (82.6)	0	4 (0.3)	<0.001
Diarrhea	2943 (24.4)	1654 (18.9)	473 (39.5)	181 (20.6)	635 (50.7)	<0.001
Vomiting	891 (7.4)	0	110 (9.2)	0	781 (62.3)	<0.001
Abdominal pain	738 (6.1)	0	79 (6.6)	0	659 (52.6)	<0.001
Heart rate upon admission, bpm median (IQR)	88 (77–100)	87 (76–100)	89 (79–100)	89 (78–100)	87 (77–100)	0.001
Respiratory rate upon admission > 20 bpm, n (%)	3833 (32.5)	2939 (34.4)	304 (26.1)	249 (28.9)	341 (28)	<0.001

IQR: interquartile range.

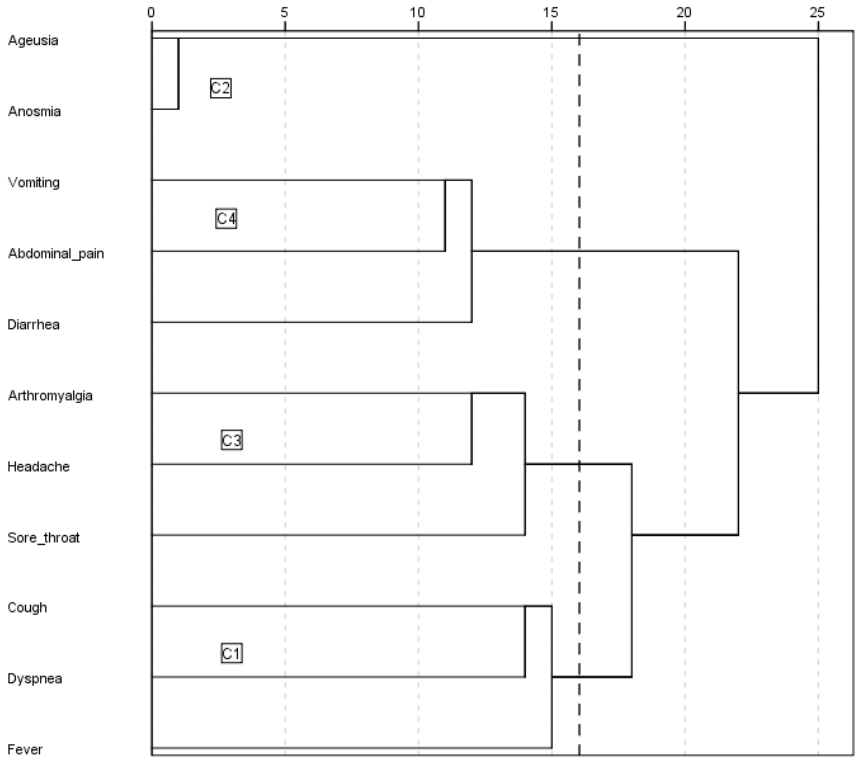

Figure 1. Dendrogram. Clusters 1 to 4.

Table 3. General data and lab tests between clusters.

	All Patients n = 12,066	C1 n = 8737	C2 n = 1196	C3 n = 880	C4 n = 1253	p-Value
Age yr, median (IQR)	68 (56–79)	70 (57–80)	61 (51–71)	64 (52–75)	67 (53–77)	<0.001
Gender, males n (%)	7052 (58.5)	5303 (60.8)	643 (53.8)	507 (57.6)	599 (47.9)	<0.001
Race						
Caucasian	10,635 (89.5)	7820 (90.9)	1023 (86.7)	738 (84.7)	1054 (86)	
Black	43 (0.4)	35 (0.4)	3 (0.3)	1 (0.1)	4 (0.3)	
Hispanic	1041 (8.8)	643 (7.5)	137 (11.6)	117 (13.4)	144 (11.7)	<0.001
Asian	59 (0.5)	41 (0.5)	2 (0.2)	6 (0.7)	10 (0.8)	
Others	100 (0.8)	62 (9.7)	15 (1.3)	9 (1)	14 (1.1)	
BMI, median (IQR)	28 (25–31)	28 (25–31)	28 (25–31)	28 (25–31)	28 (25–31)	0.426
Days from onset to admission, median (IQR)	7 (4–9)	6 (3–9)	8 (6–10)	7 (4–10)	7 (4–9)	<0.001
Smoking behavior, n (%)						
Never	8035 (69.7)	5761 (69.2)	793 (68.7)	587 (69.4)	894 (74.3)	
Current smoker	567 (4.9)	414 (5)	64 (5.5)	41 (4.8)	48 (4)	0.027
Former smoker	2930 (25.4)	2153 (25.9)	297 (25.7)	218 (25.8)	262 (21.8)	
Comorbidity, n (%)						
Arterial hypertension	6030 (50)	4571 (52.4)	468 (39.1)	386 (43.9)	605 (48.4)	<0.001
Diabetes mellitus	2309 (19.2)	1774 (20.4)	177 (14.8)	156 (17.8)	202 (16.2)	<0.001
Hyperlipidemia	4741 (39.4)	3527 (40.4)	420 (35.1)	325 (37)	469 (37.5)	0.001
COPD	786 (6.5)	649 (7.4)	44 (3.7)	43 (4.9)	50 (4)	<0.001
Asthma	869 (7.2)	630 (7.2)	90 (7.5)	57 (6.5)	92 (7.4)	0.827
OSAS	751 (6.3)	574 (6.6)	57 (4.8)	48 (5.5)	72 (5.8)	0.057
Ischemic cardiopathy	931 (7.7)	722 (8.3)	49 (4.1)	65 (7.4)	95 (7.6)	<0.001
Chronic heart failure	809 (6.7)	660 (7.6)	41 (3.4)	42 (4.8)	66 (5.3)	<0.001
Chronic kidney disease	696 (5.8)	550 (6.3)	36 (3)	36 (4.1)	74 (5.9)	<0.001

Table 3. *Cont.*

	All Patients n = 12,066	C1 n = 8737	C2 n = 1196	C3 n = 880	C4 n = 1253	p-Value
Chronic hepatopathy	440 (3.7)	330 (3.8)	46 (3.8)	22 (2.5)	42 (3.4)	<0.001
Active cancer	1196 (9.9)	916 (10.5)	94 (7.9)	72 (8.2)	114 (9.1)	0.005
Autoimmune disease	277 (2.3)	195 (2.2)	33 (2.8)	19 (2.2)	30 (2.4)	0.701
Charlson's index, median (IQR)	1 (0–2)	1 (0–2)	0 (0,1)	0 (0,1)	0 (0–2)	<0.001
PaO2/FiO2 at admission, mmHg median (95%CI)	294 (292–296)	289 (287–292)	311 (306–317)	305 (298–312)	301 (296–307)	<0.001
Lab test upon admission, median (IQR)						
Lymphocytes $\times 10^6$/L	910 (680–1280)	900 (660–1270)	1000 (700–1310)	1000 (715–1300)	900 (630–1210)	<0.001
CRP mg/L	74 (30–141)	78 (30–146)	69 (29–130)	63 (26–135)	66 (27–129)	<0.001
LDH U/L	329 (253-444)	332 (255–450)	309 (247–412)	330 (248–446)	331 (256–439)	<0.001
ALT U/L	30 (19-47)	29 (19–46)	32 (21–52)	31 (21–49)	30 (20–48)	<0.001
Ferritin mcg/L	655 (324-1281)	669 (330–1320)	634 (291–1172)	587 (310–1167)	620 (326–1265)	0.051
D-dimer ng/mL	654 (370-1204)	680 (382–1290)	594 (346–980)	595 (347–1023)	608 (350–1152)	<0.001

BMI: body mass index. COPD: chronic obstructive pulmonary disease. OSAS: obstructive sleep apnea syndrome. ALT: alanine transaminase. CRP: C-reactive protein. LDH: lactate dehydrogenase. IQR: interquartile range.

3.3. Treatments and Outcomes

The treatments received are shown in Table 4. As antiviral treatment, patients were treated with hydroxychloroquine (HCQ) (10,665, 88.6%), lopinavir/ritonavir (LPV/r) (7894, 65.7%), azithromycin (7558, 62.9%) and remdesivir (60, 0.5%). As immunosuppressive/immunomodulatory treatments, they received corticosteroids (4343, 36.2%), interferon (1496, 12.5%) and tocilizumab (1121, 9.3%). As anticoagulant treatment, patients received oral anticoagulation (384, 3.18%) or low-molecular-weight heparin (LMWH) at prophylactic doses (7903, 65.9%), intermediate doses (815, 6.8%) or full doses (1305, 10.9%).

Of the total 12,066, 1038 (8.7%) patients required high-flow nasal cannula (HFNC), 641 (5.3%) non-invasive mechanical ventilation (NIMV), and 906 (7.5%) invasive mechanical ventilation (IMV). Admissions to the ICU numbered 1120 patients (9.3%). Overall, the mortality rate was 20.9% (2522 patients). The outcomes are shown in Table 5 and Figure 2.

Table 4. Treatments between clusters.

	All Patients n = 12,066	C1 n = 8737	C2 n = 1196	C3 n = 880	C4 n = 1253	p-Value
HCQ, n (%)	10,665 (88.6)	7654 (87.9)	1130 (94.5)	770 (87.6)	1111 (88.8)	<0.001
LPV/r, n (%)	7894 (65.7)	5640 (64.8)	783 (65.5)	610 (69.5)	861 (69)	0.002
Azithromicin, n (%)	7558 (62.9)	5407 (62.2)	835 (69.8)	510 (58)	806 (64.5)	<0.001
Remdesivir, n (%)	60 (0.5)	36 (0.4)	10 (0.8)	5 (0.6)	9 (0.7)	0.150
Interferon, n (%)	1496 (12,5)	1122 (13)	68 (5.7)	141 (16.1)	165 (13.2)	<0.001
Tocilizumab, n (%)	1121 (9.3)	810 (9.3)	110 (9.2)	93 (10.6)	108 (8.7)	0.487
Corticosteroids, n (%)	4343 (36.2)	3254 (37.5)	399 (33.5)	273 (31.2)	417 (33.4)	<0.001
Heparin, n (%)						<0.001
Prophylactic LMWH	7903 (65.9)	5633 (65)	817 (68.5)	584 (66.6)	869 (69.7)	
Middle doses LMWH	815 (6.8)	589 (6.8)	97 (8.1)	49 (5.6)	80 (6.4)	
High doses LMWH	1305 (10.9)	997 (11.5)	120 (10.1)	90 (10.3)	98 (7.9)	
Oral anticoagulation, n (%)						0.004
Oral anti-vitamin K drugs	189 (1.6)	156 (1.8)	10 (0.8)	7 (0.8)	16 (1.3)	
DOACs	195 (1.6)	157 (1.8)	10 (0.8)	10 (1.1)	18 (1.4)	

DOACs: direct oral anticoagulants. HCQ: hydroxychloroquine. LPV/r: lopinavir/ritonavir. LMWH: low-molecular weight heparin.

Table 5. Outcomes between clusters.

	All Patients n = 12,066	C1 n = 8737	C2 n = 1196	C3 n = 880	C4 n = 1253	p-Value
Death, n (%)	2522 (20.9)	2109 (24.1)	51 (4.3)	129 (14.7)	233 (18.6)	<0.001
Length of stay, days mean (range)	11.3 (1–141)	11.6 (1–141)	9.6 (1–100)	11.4 (1–74)	11.4 (1–102)	0.407
Oxygenation/ventilation, n (%)						
HFNC	1038 (8.7)	757 (8.8)	82 (6.9)	75 (8.5)	124 (10)	0.053
NIMV	641 (5.3)	485 (5.6)	46 (3.9)	44 (5)	66 (5.3)	0.094
IMV	906 (7.5)	694 (8)	49 (4.1)	75 (8.6)	88 (7.1)	<0.001
ICU admission, n (%)	1120 (9.3)	847 (9.7)	71 (5.9)	95 (10.8)	107 (8.5)	<0.001

HFNC: high-flow nasal cannula. ICU: intensive care unit. IMV: invasive mechanical ventilation. NIMV: non-invasive mechanical ventilation.

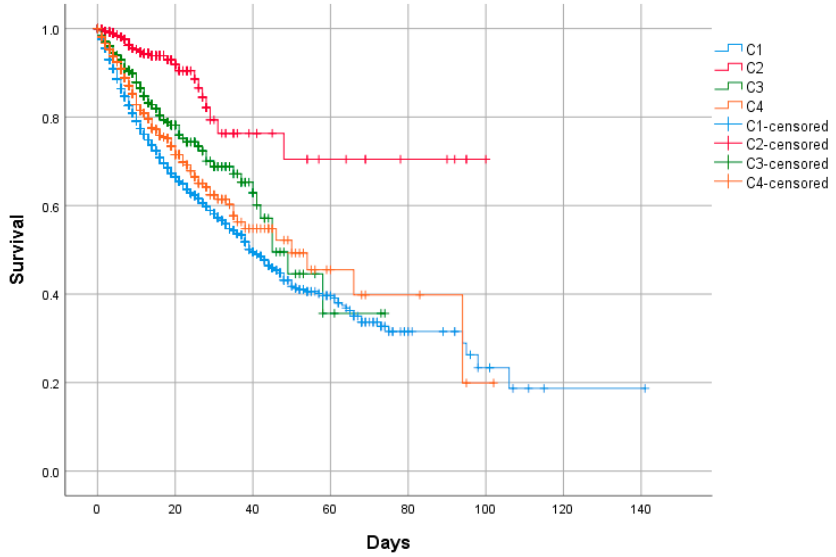

Figure 2. In-hospital mortality between clusters. Kaplan–Meier. Log-rank test $p < 0.001$.

3.4. Primary and Secondary Outcomes

A predictive study of uni- and multivariate logistic regression using in-hospital death as a dependent variable was performed (Table 6). The predictors of mortality in the multivariate study were as follows: age [odds ratio (OR) = 1.08 (95% confidence interval (CI) 1.07–1.08)], gender (female) [OR = 0.64 (95% CI 0.59–0.70)], body mass index (BMI) [OR = 1.04 (95% CI 1.03–1.05)], arterial hypertension [OR = 1.13 (95%CI 1.04–1.23)], chronic obstructive pulmonary disease (COPD) [OR = 1.36 (95%CI 1.21–1.53)], ischemic cardiopathy [OR = 1.19 (95%CI 1.06–1.34)], chronic heart failure [OR = 1.16 (95%CI 1.02–1.32)], chronic hepatopathy [OR = 1.20 (95%CI 1.00–1.44)], Charlson's index [OR = 1.18 (95%CI 1.15–1.20)], heart rate upon admission [OR = 1.01 (95%CI 1.01–1.01)], respiratory rate upon admission >20 bpm [OR = 2.88 (95%CI 2.66–3.11)], PaO2/FiO2 upon admission [OR = 0.99 (95%CI 0.99–0.99)], CRP level [OR = 1.01 (95%CI 1.01–1,01)], LDH level [OR = 1.01 (95%CI 1.01–1,01)], and the phenotypic cluster. The C1 cluster was chosen as a reference. Clusters C2 [OR = 0.22 (95%CI 0.18–0.27)] and C3 [OR = 0.57 (95%CI 0.48–0.67)] had a better prognosis in the multivariate study. The C4 cluster was also observed to have a poor prognosis [OR = 1.15 (95%CI 1.01–1.31)].

The phenotypic cluster was found to be an independent predictor of ICU admission, along with age, gender, BMI, diabetes mellitus, ischemic cardiopathy, chronic heart failure, Charlson's index, the respiratory rate upon admission, PaO2/FiO2, and LDH level (Supplemental Table S1).

The phenotypic cluster was also found to be an independent predictor of MV, along with age, gender, BMI, diabetes mellitus, COPD, ischemic cardiopathy, chronic hepatopathy, Charlson's index, the respiratory rate upon admission, PaO2/FiO2, and LDH level (Supplemental Table S2).

Table 6. Risk factors of in-hospital mortality.

	Univariate Analysis OR (95%CI)	*p*-Value	Multivariate Analysis * OR (95%CI)	*p*-Value	Multivariate Analysis ** OR (95%CI)	*p*-Value
Age/year	1.09 (1.09–1.10)	<0.001	1.08 (1.07–1.08)	<0.001	1.09 (1.07–1.09)	<0.001
Gender (female)	0.78 (0.71–0.86)	<0.001	0.64 (0.59–0.70)	<0.001	0.62 (0.51–0.75)	<0.001
BMI	1.02 (1.01–1.04)	<0.001	1.04 (1.03–1.05)	<0.001	1.04 (1.03–1.06)	<0.001
Clusters						
C1	1 ref.		1 ref.		1 ref.	
C2	0.14 (0.11–0.19)	<0.001	0.22 (0.18–0.27)	<0.001	0.22 (0.14–0.34)	<0.001
C3	0.54 (0.45–0.66)	<0.001	0.57 (0.48–0.67)	<0.001	0.56 (0.37–0.83)	0.004
C4	0.72 (0.62–0.84)	<0.001	1.15 (1.01–1.31)	0.035	1.15 (0.85–1.54)	0.362
Comorbidity						
Arterial hypertension	3.07 (2.79–3.38)	<0.001	1.13 (1.04–1.23)	0.006	NS	
Diabetes mellitus	2.07 (1.87–2.29)	<0.001	NS		NS	
Hyperlipidemia	1.80 (1.64–1.96)	<0.001	NS		NS	
COPD	2.82 (2.43–3.27)	<0.001	1.36 (1.21–1.53)	<0.001	1.36 (1.04–1.78)	0.024
Ischemic cardiopathy	2.67 (2.32–3.07)	<0.001	1.19 (1.06–1.34)	0.005	NS	
Chronic heart failure	3.74 (3.23–4.32)	<0.001	1.16 (1.02–1.32)	0.027	NS	
Chronic kidney disease	3.18 (2.72–3.72)	<0.001	NS		NS	
Chronic hepatopathy	1.57 (1.27–1.94)	<0.001	1.20 (1.00–1.44)	0.048	NS	
Active cancer	2.23 (1.96–2.53)	<0.001	NS		NS	
Charlson's index	1.37 (1.34–1.41)	<0.001	1.18 (1.15–1.20)	<0.001	1.20 (1.14–1.25)	<0.001
Heart rate upon admission	1.00 (0.99–1.00)	0.278	1.01 (1.01–1.01)	<0.001		
Respiratory rate upon admission > 20 bpm	4.48 (4.08–4.92)	<0.001	2.88 (2.66–3.11)	<0.001	3.09 (2.59–3.70)	<0.001
PaO2/FiO2 upon admission	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
Lab test upon admission						
Lymphocytes $\times 10^6$/L	1.00 (1.00–1.00)	0.768	NS			
CRP mg/L	1.01 (1.01.1.01)	<0.001	1.01 (1.01.1.01)	<0.001	NS	
LDH U/L	1.00 (1.00–1.00)	<0.001	1.01 (1.01.1.01)	<0.001	1.01 (1.01–1.01)	<0.001
ALT U/L	1.00 (0.99–1.00)	0.792	NS			
Ferritin mcg/L	1.00 (1.00–1.00)	<0.001	NS		NS	
D–dimer ng/mL	1.00 (1.00–1.00)	<0.001	NS		NS	
Treatments during admission						
Remdesivir	1.16 (0.64–2.12)	0.623	NS			
Tocilizumab	1.24 (1.07–1.43)	0.004	1.66 (1.47–1.88)	<0.001	1.71 (1.29–2.25)	<0.001
Corticosteroids	2.06 (1.89–2.26)	<0.001	1.21 (1.11–1.31)	<0.001	1.24 (1.04–1.49)	0.020

BMI: body mass index. COPD: chronic obstructive pulmonary disease. ALT: alanine transaminase. CRP: C-reactive protein. LDH: lactate dehydrogenase. NS: non-significant. * All variables included. ** Only variables with $p < 0.10$ in the univariate analysis included.

4. Discussion

The present investigation shows data from the first study of phenotypic clusters in COVID-19 pneumonia. The source of the data was the Spanish registry SEMI-COVID-19, whose characteristics have recently been published [14]. Our analysis showed the existence of 4 clusters with differentiated clinical peculiarities and different prognoses.

The general characteristics of age, gender, and comorbidities found in our study are consistent with those already described in the literature [1–4,14]. Likewise, the treatments administered are in accordance with the study period covered by the record.

The triad of fever, cough, and dyspnea was present almost uniformly in all patients with COVID-19 pneumonia grouped in the 4 phenotypes. However, other particular symptoms may help clinicians to differentiate them. Cluster C1 does not usually present symptoms in addition to the triad of fever, cough, and dyspnea. Subjects grouped in the C2 cluster usually present with ageusia and/or anosmia in addition to the triad. Cluster C3 is characterized by the presence of concomitant arthromyalgia, headache, and/or sore throat. Finally, the C4 cluster also manifests with digestive symptoms such as diarrhea, vomiting, and/or abdominal pain.

In terms of prognosis, the C1 cluster showed the highest mortality rate (24.1%) in this large Spanish nation-wide series. It was followed by C4 (18.6%), C3 (14.7%), and finally C2 (4.3%). The multivariate regression also identified clusters C1 and C4 as clusters of bad prognosis (in terms of in-hospital mortality) in contrast with the good prognosis of clusters C2 and C3

The risk factors recognized so far for poor prognosis have been repeated in several studies [1,4]. The mainly reported risk factors are advanced age, male gender, higher BMI, and some analytical parameters such as PaO2/FiO2, lymphocyte count, CRP, LDH, ferritin, IL-6, and D-dimer. Certain comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease have also been suggested as poor prognostic factors [15].

This study has not been designed to evaluate the efficacy of treatments and, therefore, the findings regarding remdesivir, steroids, and tocilizumab from the multivariate study should be taken with caution. They have been introduced into the regression model because of their importance as confounding variables. In addition, since these treatments are indicated for more severe patients, it is not uncommon for them to be associated with poor prognostic outcomes.

Interestingly, the study presented here identifies the cluster phenotype as a new prognostic factor. Since clusters share common characteristics, sometimes it can be difficult to recognize which cluster a patient belongs to. However, on other many occasions, the clinical profile may be sufficiently evident to recognize the cluster, helping physicians to make clinical decisions based on prognostic information of the identified cluster.

To date, there are no published, peer-reviewed phenotypic cluster studies in the medical literature on COVID-19. A study of clusters in the out-of-hospital population can be found in the medRxiv repository [16]. It is based on an app in which patients enter their symptoms. With these data and some other clinical data provided by the patient, risk of respiratory support (defined as the need for oxygen therapy or mechanical ventilation) is deduced. Therefore, it is a predictor of hospitalization, we could say. We have some doubts as to whether the source of the data can be considered reliable since the data are not introduced by a doctor but by the patient himself. On the other hand, the fact that it is based on an app may represent a bias against the elderly population not accustomed to electronic devices. They identify 6 phenotypic clusters, with some similarity and overlap with the clusters presented in our study. It is an interesting tool, especially designed for general practitioners.

As for the generalization of our results, it should be noted that the data come from a developed European western country with a mostly Caucasian population and little representation of other ethnicities. Furthermore, it should also be taken into account that Spain has a universal-coverage public healthcare system, not comparable with some other developed and developing countries. On the other hand, proportionally speaking, Spain has one of the largest elderly populations in the world and, as is well known, age has been described as a fundamental factor in the poor prognosis of COVID-19 pneumonia [4]. These characteristics could influence the outcomes shown.

In order to speak properly, the definition of a true phenotype requires a consistent natural history, similar clinical and physiological characteristics, underlying pathobiology with identifiable biomarkers and genetics, and predictable response to general and specific therapies [17]. Accordingly, it would be necessary to study each of the present clinical clusters genetically and to verify that each cluster has a differentiated genetic background. In the literature, some studies attempted to phenotype patients with COVID-19 as a function of the immune response, and others suggested phenotyping as a function of pathophysiology [18,19]. It would be interesting to combine all methods of phenotyping. However, the clinical phenotype alone does not account for the severity of COVID-19. Recently, inborn errors of type I interferon (IFN) immunity underlying life-threatening COVID-19 have been described [20].

We believe that the identification of the present clusters may be of great help to clinicians in order to identify those cases with a better or worse prognosis, and thus direct more individualized therapeutic strategies.

The main strength of this study is the identification of different phenotypic clusters in COVID-19 pneumonia from a very large sample of more than 12,000 patients from more than 100 hospitals.

Among limitations, data were obtained from a retrospective register of a sole country, which means that some specific data could be missing or collected with some grade of heterogeneity. Secondly, the data source of the present study seems to us to be sufficiently reliable to give validity to the data obtained. However, we cannot rule out certain variability when collecting all the patients' symptoms, but in any case, the missing data should be residual. Finally, another limitation of the study that deserves comment is that the treatments among the 4 clusters differ. If we look at the treatments that have shown effectiveness in COVID-19 we only find differences in the use of steroids. In any case, the C1 cluster was the one that received the most steroids (and even so this effect does not mask the poor prognosis of this cluster), the C2 and C4 clusters received a similar percentage of steroids and the C3 cluster was the one that received the least steroids (possibly because they were not so severely affected).

5. Conclusions

In conclusion, the present study identified 4 phenotypic clusters that predicted in-hospital prognosis of clinical outcome in a large nationwide series of patients with COVID-19 pneumonia. Clusters associated with bad in-hospital prognosis were C1, in which subjects presented with the isolated triad of fever, cough, and dyspnea, and C4 also manifested with diarrhea, vomiting, and/or abdominal pain. In contrast, subjects grouped in the C2 cluster (manifested also with ageusia and/or anosmia) showed the best prognosis, together with cluster C3 (adding arthromyalgia, headache, and/or sore throat), which was second only to C2 showing a good outcome.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/11/3488/s1, Table S1: Risk factors of ICU admission, Table S2: Risk factors of mechanical ventilation.

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Appendix A

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