Original research article

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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*** A complete list of the SEMI-COVID-19 Network members is provided in the Appendix.
Abstract: (1) Background: 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 March 1, to July 31, 2020, from the nationwide Spanish SEMI-COVID-19 Registry. (3) Results: Of the total of 12,066 patients included in the study, most were males (7,052, 58.5%) and Caucasian (10,635, 89.5%), with a mean age at diagnosis of 67 years (SD 16). The main pre-admission comorbidities were arterial hypertension (6,030, 50%), hyperlipidemia (4,741, 39.4%) and diabetes mellitus (2,309, 19.2%). The average number of days from COVID-19 symptom onset to hospital admission was 6.7 days (SD 7). The triad of fever, cough, and dyspnea was present almost uniformly in all 4 clinical phenotypes identified by clustering. Cluster C1 (8,737 patients, 72.4%) was the largest, and comprised patients with the triad alone. Cluster C2 (1,196 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 (1,253 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 phenotypic clusters as an independent factor for in-hospital death. (4) Conclusion: 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 August 13th, 2020, 20,624,830 people have been infected worldwide and 749,424 people have died. Numerous studies have highlighted the clinical characteristics of the disease [1-3]. From the beginning, different clinical forms in presentation and prognosis have been intuited; however, these clinical forms have not been defined yet. Although some factors associated with poor prognosis are known [4], it is not clear which patients may present a worse evolution during hospitalization and why.

The present study aimed to identify clinical phenotypes by cluster analysis in our large nationwide series of COVID-19 pneumonia and to create a predictive model related to a 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. From March 1, to July 31, 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 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 outcome was the requirement of mechanical ventilation or intensive care unit (ICU) admission.

2.4. Statistical analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables are expressed as mean plus standard deviation (SD) in case of parametric distribution or median [IQR] in the case of non-parametric distribution. Differences among groups were assessed using the chi-square test for categorical variable and 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 a visual distance criterion of the dendrogram. The cluster analysis model was included in a binary logistic regression, taking the two above-mentioned outcomes as dependent variables. Mortality among the groups was represented by the Kaplan-Meier curves with their logarithmic range test.

Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: 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 (7,052, 58.5%) and Caucasian (10,635, 89.5%). The mean age at diagnosis was 67 years (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 (6,030, 50%), hyperlipidemia (4,741, 39.4%) and diabetes mellitus (2,309, 19.2%). The mean Charlson index among patients was 1.2 (SD 1.8). The most common symptoms (Table 2) were fever 10,346 (85.7%), cough (9,142, 75.8%), dyspnea (7,205, 59.7%), arthromyalgia (3,794, 31.4%), diarrhea (2,943, 24. 4%), headache (1,402, 11.6%), sore throat (1,191, 9.9%), ageusia (992, 8.2%), vomiting (891, 7.4%), anosmia (879, 7.3%), and abdominal pain (738, 6.1%).

3.2. Clustering analysis.

Despite most patients presenting with fever, cough, and/or dyspnea, 4 different clusters were identified. The main characteristics of each are shown in Tables 1-5. Cluster C1 (8,737 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 ten 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 (1,196 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 9.7% of C3 patients required ICU admission and 14.5% died. Finally, subjects grouped in cluster C4 (1,253 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 286 mmHg [229-338], being highest in the C2 cluster (281 mmHg vs. 305 vs. 295 vs. 295; 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), interleukin-6 (IL-6) (37 pg/ml vs. 26 vs. 27 vs. 24; p<0.001), and D-dimer (680 ng/ml vs. 594 vs. 595 vs. 608; p<0.001).

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) (7,894, 65.7%), azithromycin (7,558, 62.9%) and remdesivir (60, 0.5%). As immunomodulatory treatments, they received corticosteroids (4,343, 36.2%), interferon (1,496, 12.5%) and tocilizumab (1,121, 9.3%). As anticoagulant treatment, patients received oral anticoagulation (384, 3.18%) or low-molecular-weight heparin (LMWH) at prophylactic doses (7,903, 65.9%), intermediate doses (815, 6.8%) or full doses (1,305, 10.9%).

Of the total 12,066, 1,038 (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 1,120 patients (9.3%). Overall, the mortality rate was 20.9% (2,522 patients). The outcomes are shown in Table 5.

3.4 Predictive model for mortality

A predictive study of uni- and multivariate logistic regression using in-hospital death as a dependent variable was performed. The predictors of mortality in the multivariate study were as follows: age [OR 1.07 (1.04-1.11)], gender (female) [OR 0.24 (0.10-0.56)], BMI [OR 1.09 (1.02-1.17)], Charlson index [OR 1.52 (1.30-1.78)], respiratory rate upon admission >20 bpm [OR 2.84 (1.33-6.05)], PaO2/FiO2 upon admission [OR 0.99 (0.98-1.00)], CRP [OR 0.99 (0.99-1.00)], LDH [OR 1.00 (1.00-1.00)], ferritin [OR 1.00 (1.00-1.00)], IL-6 [OR 1.00 (1.00-1.00)], and the phenotypic cluster. The C1 cluster was chosen as a reference. Clusters C2 [OR 0.91 (0.30-2.31)] and C3 [OR 0.18 (0.04-0.96)] had a better prognosis in the multivariate study. The C4 cluster was also observed to have a poor prognosis [OR 2.85 (0.88-9.22)].
3.5 Figures, Tables and Schemes

Figure 1. Dendrogram.
Table 1. General data between clusters

|                      | All patients | C1          | C2          | C3          | C4          | p-value   |
|----------------------|--------------|-------------|-------------|-------------|-------------|-----------|
|                      | N=12,066     | N=8,737     | N=1,196     | N=880       | N=1,253     |           |
| Age yr, median [IQR]| 68 [56-79]   | 70 [57-80]  | 61 [51-71]  | 64 [52-75]  | 67 [53-77]  | <0.001    |
| Gender, males n (%) | 7,052 (58.5) | 5,303 (60.8)| 643 (53.8)  | 507 (57.6)  | 599 (47.9)  | <0.001    |
| Race                 |              |             |             |             |             |           |
| Caucasian            | 10,635 (89.5)| 7,820 (90.9)| 1,023 (86.7)| 738 (84.7)  | 1,054 (86)  |           |
| Black                | 43 (0.4)     | 35 (0.4)    | 3 (0.3)     | 1 (0.1)     | 4 (0.3)     |           |
| Hispanic             | 1,041 (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 behaviour, n (%) |          |             |             |             |             |           |
| Never                | 8,035 (69.7) | 5,761 (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        | 2,930 (25.4) | 2,153 (25.9)| 297 (25.7)  | 218 (25.8)  | 262 (21.8)  |           |
| Comorbidity, n(%)    |              |             |             |             |             |           |
| Arterial hypertension| 6,030 (50)   | 4,571 (52.4)| 468 (39.1)  | 386 (43.9)  | 605 (48.4)  | <0.001    |
| Diabetes mellitus    | 2,309 (19.2) | 1,774 (20.4)| 177 (14.8)  | 156 (17.8)  | 202 (16.2)  | <0.001    |
| Hyperlipidemia       | 4,741 (39.4) | 3,527 (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     |
| Ischaemic 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    |
| Chronic hepatopathy  | 440 (3.7)    | 330 (3.8)   | 46 (3.8)    | 22 (2.5)    | 42 (3.4)    | <0.001    |
| Active cancer        | 1,196 (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 index, median [IQR] | 1 [0-2] | 1 [0-2] | 0 [0-1] | 0 [0-1] | 0 [0-2] | <0.001 |

BMI: body mass index. COPD: chronic obstructive pulmonary disease. OSAS: obstructive sleep apnea syndrome.
Table 2. Symptoms and physical examination between clusters

|                      | All patients | C1          | C2          | C3          | C4          | p-value |
|----------------------|--------------|-------------|-------------|-------------|-------------|---------|
|                      | N=12,066     | N=8,737     | N=1,196     | N=880       | N=1,253     |         |
| Symptoms n(%)        |              |             |             |             |             |         |
| High-grade fever ≥38°C| 7,915 (65.6) | 5,672 (64.9)| 843 (70.5)  | 598 (68)    | 802 (64)    | <0.001  |
| Low-grade fever <38°C| 2,431 (20.1) | 1,723 (19.7)| 238 (19.9)  | 194 (22)    | 276 (22)    | <0.001  |
| Cough                | 9,142 (75.8) | 6,501 (74.4)| 993 (83)    | 766 (87)    | 882 (70.4)  | <0.001  |
| Dyspnea              | 7,205 (59.7) | 5,340 (61.1)| 727 (60.8)  | 492 (55.9)  | 646 (51.6)  | <0.001  |
| Arthromyalgia        | 3,794 (31.4) | 2,432 (27.8)| 569 (47.6)  | 370 (42)    | 423 (33.8)  | <0.001  |
| Sore throat          | 1,191 (9.9)  | 0           | 186 (15.6)  | 880 (100)   | 125 (10)    | <0.001  |
| Headache             | 1,402 (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             | 2,943 (24.4) | 1,654 (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 >20x', n(%) | 3,833 (32.5) | 2,939 (34.4)| 304 (26.1)  | 249 (28.9)  | 341 (28)    | <0.001  |

Table 3. Lab tests between clusters

|                      | All patients | C1          | C2          | C3          | C4          | p-value |
|----------------------|--------------|-------------|-------------|-------------|-------------|---------|
|                      | N=12,066     | N=8,737     | N=1,196     | N=880       | N=1,253     |         |
| PaO2/FiO2 upon admission, mmHg median [IQR] | 286 [229-338] | 281 [224-333] | 305 [254-355] | 295 [238-352] | 295 [238-348] | <0.001  |
| Lymphocytes x10^9/l | 910 [680-1,280] | 900 [660-1,270] | 1,000 [700-1,310] | 1,000 [715-1,300] | 900 [630-1,210] | <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 [324-1,281] | 669 [330-1,320] | 634 [291-1,172] | 587 [310-1,167] | 620 [326-1,265] | 0.051  |
| IL6 pg/ml            | 33 [13-69]   | 37 [14-73]   | 26 [9-54]    | 27 [12-70]   | 24 [10-58]   | <0.001  |
| D-dimer ng/ml        | 654 [370-1,204] | 680 [382-1,290] | 594 [346-980] | 595 [347-1,023] | 608 [350-1,152] | <0.001  |

ALT: alanine transaminase. CRP: C-reactive protein. IL6: interleukin6. LDH: lactate dehydrogenase
### Table 4. Treatments between clusters

|                     | All patients N=12,066 | C1 N=8,737 | C2 N=1,196 | C3 N=880 | C4 N=1,253 | p-value |
|---------------------|-----------------------|------------|------------|----------|------------|---------|
| **HCQ, n (%)**      | 10,665 (88.6)         | 7,564 (87.9) | 1,130 (94.5) | 770 (87.6) | 1,111 (88.8) | <0.001  |
| **LPV/r, n (%)**    | (88.6)                | 5,640 (64.8) | 783 (65.5)  | 610 (69.5) | 861 (69)   | 0.002   |
| **Azithromycin, n (%)** | 7,894 (65.7)       | 5,407 (62.2) | 835 (69.8)  | 510 (58)  | 806 (64.5) | <0.001  |
| **Remdesivir, n (%)** | 7,558 (62.9)       | 36 (0.4)    | 10 (0.8)    | 5 (0.6)   | 9 (0.7)    | 0.150   |
| **Interferon, n (%)** | 1,496 (12.5)      | 1,122 (13)  | 68 (5.7)    | 141 (16.1) | 165 (13.2) | <0.001  |
| **Tocilizumab, n (%)** | 1,121 (9.3)       | 810 (9.3)   | 110 (9.2)   | 93 (10.6) | 108 (8.7)  | 0.487   |
| **Corticosteroids, n (%)** | 4,343 (36.2)    | 3,254 (37.5) | 399 (33.5)  | 273 (31.2) | 417 (33.4) | <0.001  |
| **Heparin, n (%)**  | 1,496 (12.5)         | 1,122 (13)  | 68 (5.7)    | 141 (16.1) | 165 (13.2) | <0.001  |
| **Prophylactic LMWH** | 7,903 (65.9)       | 5,633 (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** | 1,305 (10.9)        | 997 (11.5)  | 120 (10.1)  | 90 (10.3) | 98 (7.9)   |         |
| **Oral anticoagulation, n (%)** | 189 (1.6)        | 156 (1.8)   | 10 (0.8)   | 7 (0.8)   | 16 (1.3)   | 0.004   |
| **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=8,737 | C2 N=1,196 | C3 N=880 | C4 N=1,253 | p-value |
|---------------------|-----------------------|------------|------------|----------|------------|---------|
| **Oxygenation/ventilation, n (%)** | 1,038 (8.7)       | 757 (8.8)  | 82 (6.9)   | 75 (8.5)  | 124 (10)   | 0.053   |
| **HFNC**            | 641 (5.3)            | 485 (5.6)  | 46 (3.9)   | 44 (5)    | 66 (5.3)   | 0.094   |
| **NIMV**            | 906 (7.5)            | 694 (8)    | 49 (4.1)   | 75 (8.6)  | 88 (7.1)   | <0.001  |
| **ICU admission, n (%)** | 1,120 (9.3)       | 847 (9.7)  | 71 (5.9)   | 95 (10.8) | 107 (8.5)  | <0.001  |
| **Death, n (%)**    | 2,522 (20.9)         | 2,109 (24.1) | 51 (4.3)   | 129 (14.7) | 233 (18.6) | <0.001  |

HFNC: high-flow nasal cannula. ICU: intensive care unit. IMV: invasive mechanical ventilation. NIMV: non-invasive mechanical ventilation.
Table 6. Risk factors of in-hospital mortality.

|                        | Univariate analysis | p-value | Multivariate analysis | p-value |
|------------------------|---------------------|---------|-----------------------|---------|
|                        | OR (95%CI)          |         | OR (95%CI)            |         |
| Age/year               | 1.09 (1.09-1.10)    | <0.001  | 1.07 (1.04-1.11)      | <0.001  |
| Gender (female)        | 0.78 (0.71-0.86)    | <0.001  | 0.24 (0.10-0.56)      | 0.001   |
| BMI                    | 1.02 (1.01-1.04)    | <0.001  | 1.09 (1.02-1.17)      | 0.014   |
| Comorbidity            |                     |         |                       |         |
| Arterial hypertension  | 3.07 (2.79-3.38)    | <0.001  | NS                    |         |
| Diabetes mellitus      | 2.07 (1.87-2.29)    | <0.001  | NS                    |         |
| Hyperlipidemia         | 1.80 (1.64-1.96)    | <0.001  | NS                    |         |
| COPD                   | 2.82 (2.43-3.27)    | <0.001  | NS                    |         |
| Ischaemic cardiopathy  | 2.67 (2.32-3.07)    | <0.001  | NS                    |         |
| Chronic heart failure  | 3.74 (3.23-4.32)    | <0.001  | NS                    |         |
| Chronic kidney disease | 3.18 (2.72-3.72)    | <0.001  | NS                    |         |
| Chronic hepatopathy    | 1.57 (1.27-1.94)    | <0.001  | NS                    |         |
| Active cancer          | 2.23 (1.96-2.53)    | <0.001  | NS                    |         |
| Charlson index         | 1.37 (1.34-1.41)    | <0.001  | 1.52 (1.30-1.78)      | <0.001  |
| Heart rate upon admission | 1.00 (0.99-1.00) | 0.278   |                       |         |
| Respiratory rate upon admission >20x' | 4.48 (4.08-4.92) | <0.001  | 2.84 (1.33-6.05)      | 0.007   |
| PaO2/FiO2 upon admission | 0.99 (0.99-0.99) | <0.001  | 0.99 (0.98-1.00)      | 0.001   |
| Lab test upon admission |                     |         |                       |         |
| Lymphocytes x10⁶/l     | 1.00 (1.00-1.00)    | 0.768   |                       |         |
| CRP mg/l               | 1.01 (1.01-1.01)    | <0.001  | 0.99 (0.99-1.00)      | 0.034   |
| LDH U/l                | 1.00 (1.00-1.00)    | <0.001  | 1.00 (1.00-1.00)      | 0.032   |
| ALT U/l                | 1.00 (0.99-1.00)    | 0.792   |                       |         |
| Ferritin mcg/l         | 1.00 (1.00-1.00)    | <0.001  | 1.00 (1.00-1.00)      | 0.001   |
| IL6 pg/ml              | 1.00 (1.00-1.00)    | <0.001  | 1.00 (1.00-1.00)      | 0.020   |
| D-dimer ng/ml          | 1.00 (1.00-1.00)    | <0.001  | 1.00 (1.00-1.00)      | 0.054   |
| Treatments during admission |                     |         |                       |         |
| Remdesivir             | 1.16 (0.64-2.12)    | 0.623   |                       |         |
| Tocilizumab            | 1.24 (1.07-1.43)    | 0.004   | NS                    |         |
| Corticosteroids        | 2.06 (1.89-2.26)    | <0.001  | NS                    |         |
| Clusters               |                     |         |                       |         |
| C1                     | 1 ref.              |         | 1 ref.                |         |
| C2                     | 0.14 (0.11-0.19)    | <0.001  | 0.91 (0.30-2.75)      | 0.865   |
| C3                     | 0.54 (0.45-0.66)    | <0.001  | 0.18 (0.04-0.96)      | 0.044   |
| C4                     | 0.72 (0.62-0.84)    | <0.001  | 2.85 (0.88-9.22)      | 0.082   |

BMI: body mass index. COPD: chronic obstructive pulmonary disease.
Figure 2. In-hospital mortality between clusters. Kaplan-Meier. Log-rank test p<0.001

4. Discussion

The present investigation shows data from the first study of phenotypic clusters in COVID-19 pneumonia. The source of data was the Spanish registry SEMI-COVID-19, whose characteristics have recently been published [13]. 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. 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 crude survival study identified the C2 cluster as a cluster of good prognosis. The multivariate regression study showed a non-significant trend to better prognosis. Also identified the C3 cluster as another good prognostic subgroup, in addition to C2. In contrast, the C1 and C4 clusters were identified as the poorest prognosis clusters.

The risk factors recognized so far for poor prognosis have been repeated in several studies. 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 diabetes mellitus, arterial hypertension, or hyperlipidemia have also been suggested as poor prognostic factors but not identified to date.

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, in 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 out-of-hospital population can be found in the medRxiv repository [14]. It is based on an app in which patients enter their symptoms. With these data and some other clinical data provided by the patient, a risk of respiratory support (defined as the need for oxygen therapy or mechanical ventilation) is deduced. It is therefore 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 is 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, specially 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 [15]. 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 [16,17]. It would be interesting to combine all methods of phenotyping.

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. In this regard, we also believe that identification of phenotypes can serve as a guide for clinical trials, not evaluating new treatments in general, since not all subgroups of COVID-19 patients may benefit from the same therapeutic strategies. On the other hand, drugs previously discarded, but with a rational pathophysiological basis to be tested, should be reanalyzed to clarify their real efficacy, taking into account the different clinical spectrum of COVID-19 patients.

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.

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.

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Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used “Conceptualization, M.R.-R., X.C and J.M. M.-L.; methodology, M.R.; software, M.R.; validation, M.R.-R., X.C.; formal analysis, M.R.-R.; investigation, M.R.-R., X.C.; resources, R.G.-H., J.M.R.-R.; data curation, M.R.-R., X.C, J.M. M.-L., J.L.A., A.L.S., C.Y.B., V.G.G., L.F.D.G., R.G.F., S.P.C., S.F.C., B.C.R., L.J.V., I.P.C., M.L.T., J.A.M.O., M.C.M.G., J.L.S.C., E.G.S., J.N.A.P., A.M.-U.D.-C., M.J.E.G., P.T.G., R.G.-H., J.M.R.-R.; writing—original draft preparation, M.R.-R., X.C.; writing—review and editing, M.R.-R., X.C.; visualization M.R.-R., X.C.; supervision, M.R.-R., X.C, R.G.-H., J.M.R.-R.; project administration, J.M.R.-R. All authors have read and agreed to the published version of the manuscript.,” please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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