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# Clustering patients with COVID-19 according to respiratory support requirements, and its impact on short- and long-term outcome (RECOVID study)

Rosario Menéndez[a,b*], Raúl Méndez[a,b*], Ana Latorre[b], Paula González-Jiménez[a,b], Germán Peces-Barba[c*], María Molina-Molina[d*], Pedro Pablo España[e], Estela García[f], Angélica Consuegra-Vanegas[g], Marta María García-Clemente[h], Carolina Panadero[i], Juan Marco Figueira-Gonçalves[j], David De la Rosa-Carrillo[l], Oriol Sibila[k], María Dolores Martínez-Pitarch[m], Nuria Toledo-Pons[n], Cecilia López-Ramírez[o], Wanda Almonte-Batista[p], Abigail Macías-Paredes[q], Mercedes Villamon[r], Marisol Domínguez-Álvarez[s], Eli Nancy Pérez-Rodas[t], Javier Lázaro[u], Sarai Quirós[v], Rosa Cordovilla[w], Irene Cano-Pumarega[x*], Antoni Torres[k*] and on behalf of RECOVID

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**ABSTRACT**

**Introduction:** The Spanish Society of Pulmonology and Thoracic Surgery created a registry for hospitalised patients with COVID-19 and the different types of respiratory support used (RECOVID). Objectives. To describe the profile of hospitalised patients with COVID-19, comorbidities, respiratory support treatments and setting. In addition, we aimed to identify varying profiles of patients according to outcomes and the complexity of respiratory support needed.

**Methods:** Multicentre, observational study in 49 Spanish hospitals. A protocol collected demographic data, comorbidities, respiratory support, treatment setting and 1-year follow-up. Patients were described using either frequency and percentages or median and interquartile range, as appropriate. A cluster analysis made it possible to identify different types of profile among the patients.

**Results:** In total, 2148 of 2454 hospitalised patients (87.5%) received care in the conventional ward, whilst 126 in IRCU and 180 in ICU. In IRCU, 30% required high-flow nasal oxygen whilst 25%, non-invasive mechanical ventilation and 17%, mechanical ventilation. Four clusters of patients were identified. Two clusters were more likely to require IRCU/ICU admission, although primarily Cluster 2: Cluster (C) 1 consisted of patients without comorbidities and C2, those with comorbidities. Both presented higher inflammatory levels and lower lymphocyte count and SpO2/FiO2; however, C2 showed worse values. Two different clusters identified patients requiring less complex respiratory support. C3 presented higher comorbidities and elevated lymphocyte count, SpO2/FiO2 and low C-reactive protein (CRP). C4 included those without comorbidities except for arterial hypertension, lymphopenia and an intermediate CRP. In-hospital mortality and subsequent 1-year mortality were greater for C2 (28.6% and 7.1%) and C1 (11.1%, 8.3%) than for C4 (3.3%, 1.8%) and C3 (0%, 0%).

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**KEYWORDS**
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**Conclusions:** The cluster analysis identified four clinical phenotypes requiring distinct types of respiratory support, with great differences present per characteristics and outcomes.

## Introduction

The start of SARS-CoV-2 outbreak in Spain took place at the end of February two months later after the virus's initial appearance in China.[1–3] The first epidemic wave happened in March 2020, which, by then, had underpinned the spread of the virus across the Spanish region. The rapid overload of hospitalisations arising in both the conventional ward and intensive care unit (ICU) made it necessary to administer more complex respiratory support treatments in intermediate care or even in conventional ward outside of ICU.[4–7]

The clinical picture of the SARS-CoV-2 infection requiring hospitalisation showed bilateral pulmonary involvement (20%), which would lead to respiratory insufficiency, distress and progression.[8–12] Treatment of respiratory insufficiency proved key to mitigating the effects caused by SARS-CoV-2. Although the use of non-invasive respiratory support in acute respiratory failure due to viral infection is still debated, non-invasive respiratory support strategies were widely and variably used during the early phase of the pandemic. Meanwhile, several randomised trials were conducted to better understand the impact of these strategies on patient outcomes.[13,14]

Therefore, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) created its own registry: RECOVID. The aim of this initiative was to obtain data from different hospitals throughout Spain to assess acute episodes and subsequent evolution,[15,16] thereby shedding light on respiratory support provided to patients during the pandemic.

We believe that more complex types of respiratory support provided in intermediate respiratory care unit (IRCU) could help treat different patients outside of ICUs, including those with either more severe profiles or many comorbidities. Today, COVID-19 remains in wide circulation; a considerable amount of the population faces a high risk of developing acute respiratory failure and severe outcomes. As stated by Christopher Murray,[17] COVID-19 will continue despite the end of the pandemic.

The overall objective of RECOVID was to understand patient profiles, risk factors, diagnosis, therapeutic response, evolution and respiratory support treatments administered by pneumologists. Furthermore, using cluster analyses, we aimed to identify the different patient profiles who would require more or less complex respiratory support treatments, and assess its potential impact on mortality and one-year outcome.

## Patients and methods

### *Design*

Multicentre, observational study that retrospectively collected data on acute COVID-19 episodes and follow-up visits for up to a year in survivors. The study received approval by the Ethics Committee (Comité Ètic d'Investigació Clínica, Hospital San Pau, Barcelona) on 29 April 2020, and locally in the varying participating centres.

With the aim to include patients from many centres, we designed a randomly stratified sample. We identified patients with COVID-19 registered in the pneumology service or attended by a pneumologist on call and admitted to ICU of each participating centre (stratum). Each centre recruited a group of 50 patients randomly selected from those who fulfilled eligibility criteria, except for three hospitals. The latter recruited consecutive patients attended by pneumologists involved in the study.

Eligibility criteria for the RECOVID registry included those patients admitted to a Spanish hospital after receiving a confirmed diagnosis of SARS-CoV-2 infection via reverse transcription polymerase chain reaction (RT-PCR) testing. Patients with a do-not-resuscitate order were not included. Due to the nature of the retrospective study, signed informed consent was not required; consent obtained prospectively was done either orally or signed. This registry has been previously used for other published studies.[18–20]

## Electronic databases

A data collection sheet agreed upon by the different areas of SEPAR involved with the disease was designed to prepare a set of general and common data, as well as specific sections designed in the form of sub-notebooks. The web platform XOLOMON hosted the electronic database. In accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016, and Organic Law 3/2018 of 5 December, measures regarding patient confidentiality and identity were taken, protected by a code.

The platform had limitations in terms of error detection in variables. The study included monitoring via a data monitor to review inconsistencies and missing data, as well as pre-defined follow-up questions for each hospital. To deem each case as valid, a minimum of 70% of completed data on fundamental variables was considered.

The general notebook included general demographic data, smoking habit, comorbidities (chronic obstructive pulmonary disorder [COPD], asthma, liver disease, chronic kidney disease, dementia, hypertension, heart disease, diabetes mellitus and other), and previous treatments. Data included initial symptoms, analytical data, radiologic pattern and treatments used for COVID-19. To assess initial severity, the CURB-65 scale was used; for respiratory insufficiency, data on oxygen saturation and FiO2 and/or arterial blood gas, if available. Follow-up folders consisted of clinical check-up visits at 6 and 12 months. These contained a description of symptoms, radiologic findings, diffusion impairment and mortality.

## Statistical analysis

The nature of RECOVID – as a registry created during a pandemic – entails the existence of lost data. A descriptive analysis of the qualitative and quantitative variables was carried out, without any imputation made for missing data.

Categorical variables were expressed as absolute and relative frequency, whilst quantitative variable as medians with interquartile range (IQR). For univariate comparisons between Ward, IRCU and ICU patients we used the Chi-squared test in the case of categorical variables, and the Kruskal-Wallis test in the case of continuous variables.

To define factor patterns, a cluster analysis was performed. This approach allowed for the designed inclusion of demographic and previous comorbidities, respiratory support and biochemical data. Variables were selected according to clinical experience and previously identified factors associated with different outcomes: age, smoking, comorbidities (diabetes, arterial hypertension, asthma, COPD, heart disease, renal disease, liver disease and Charlson comorbidity index), prior treatments (statins and antiplatelets), symptom duration, some initial analytical parameters (D-dimer, C-reactive protein, lymphocyte count and platelet count), SpO2/FiO2 (oxygen saturation/fraction of inspired oxygen), respiratory support and initial care setting (conventional ward, IRCU and ICU). For the cluster analysis, qualitative variables dichotomised as yes/no (smoking, diabetes, arterial hypertension, asthma, COPD, heart disease, renal disease, liver disease, CCI, statins, antiplatelets, initial ward admission, initial IRCU admission, initial ICU admission, no oxygen, low-flow oxygen, reservoir oxygen, HFNO/CPAP/NIMV, IMV); continuous variables were included as numerical. The clustering method used was k-means. The Gower distance was used as the distance measure, as categorical and continuous variables had both been included. The so-called elbow method was used to select the number of clusters. All analyses were performed with STATA/SE v.16.0; all p-values below 0.05 were considered significant.

## Results

### *General cohort characteristics*

Forty-nine hospitals across all of Spain's autonomous communities participated in RECOVID. RECOVID represented approximately 10% of hospitals from the National Health System (NHS): based on the 2016 Annual Report on The National Health System, 451 comprise the 791 health institutions registered in Spain.

The study enrolled 2500 hospitalised patients (February 2020 - January 2021). Of these, 2454 (46 with missing fundamental variables) were included in the analyses (Figure 1, Table 1). The most frequent comorbidities were those cardiovascular-related (49.7%), diabetes mellitus (19.4%) and, to a lesser extent, COPD (6.2%) and asthma (7.6%). Initial presentation showed bilateral infiltrates in 69.9% of patients, with a median SpO2/FiO2 index of 409; 77.2% had a low CURB65 score (0–1). With respect to the place of

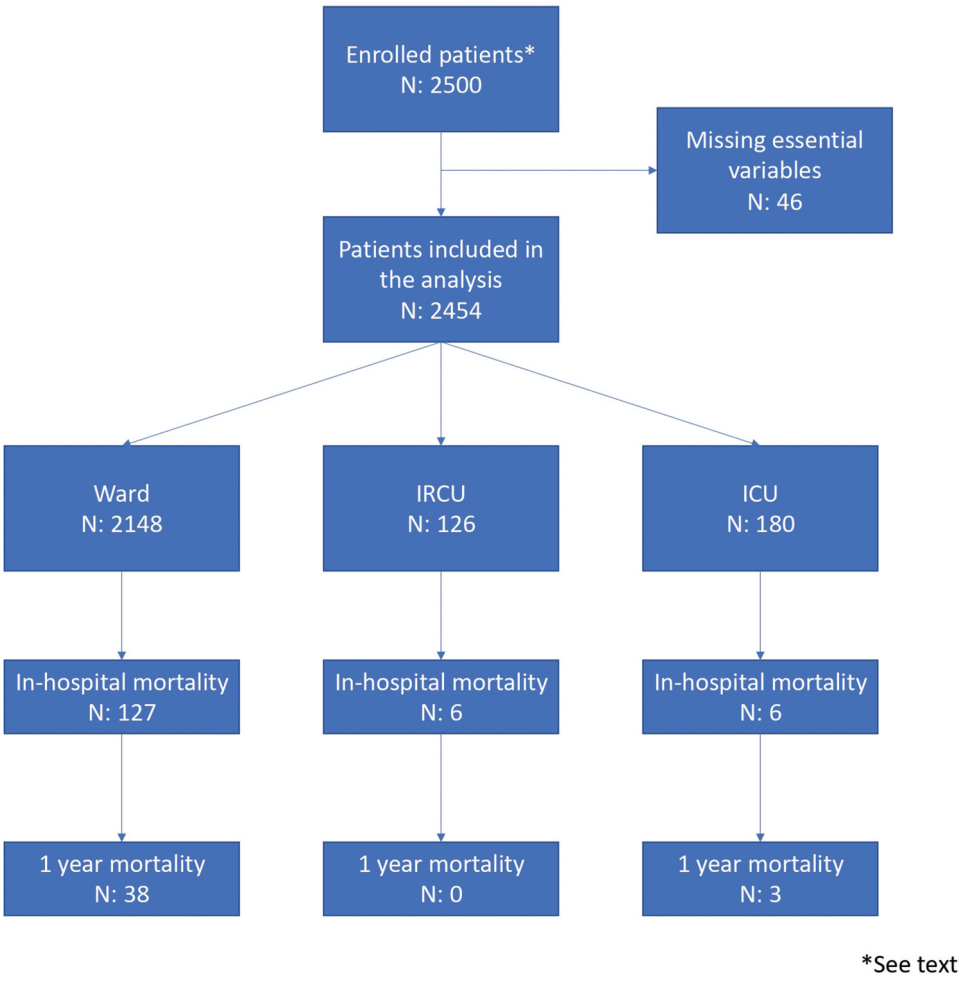


**Figure 1.** Flowchart.

hospitalisation, 2148 (85.9%) patients were initially admitted to conventional ward, whilst 126 (5.1%) to IRCU and 180 (7.3%) to ICU.

### *Demographic characteristics and comorbidities: conventional ward, IRCU and ICU*

Table 1 shows demographic data, smoking habit and comorbidities per hospitalisation at different levels of care. In the conventional ward, 34.5% of patients had no comorbidities; 39.1%, one comorbidity; 20.5%, two comorbidities; and 5.9%, three or more. In IRCU, 28.9% had no comorbidities; 34.9%, one comorbidity; 27.7%, two comorbidities; and 8.4%, three or more. In ICU, 40.9% had no comorbidities; 38.6%, one comorbidity; 18.2%, two comorbidities; and 2.3%, three or more.

The CURB-65 scale showed a low severity score (0–1) in 77.2% of patients, with differences presenting at varying levels of care ($p < 0.001$). A CURB-65 score ≥ 2 was more frequent in patients admitted to ICU (38.8%). Respiratory failure, as measured by SpO2/FiO2, showed significantly lower values in patients treated in either ICU or IRCU ($p < 0.01$). The analytical results showed higher leucocytosis and neutrophilia in patients admitted to ICU compared to those hospitalised in the ward ($p = 0.001$). Figures were similar in patients from IRCU and ICU, yet lower than those in patients in ward. C-reactive protein (CRP) levels were higher in IRCU- and ICU-admitted patients compared to those of patients hospitalised in ward ($p < 0.001$).

Table 2 shows initial respiratory support treatments per levels of care (conventional ward, IRCU and ICU). In the conventional room, 10% received oxygen therapy with a reservoir mask; 7%, high-flow nasal oxygen (HFNO) therapy or CPAP; 3%, non-invasive mechanical ventilation (NIMV); and 1%, IMV. Of those patients

**Table 1.** Description of patient characteristics and analytical data according to care setting (conventional ward, IRCU and ICU) at admission.

| | Available data (N) | Ward (N: 2148) | IRCU (N: 126) | ICU (N: 180) | Total (N: 2454) |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Sex | 2454 | | | | |
| Male | | 1268 (59) | 88 (69.8) | 114 (63.3) | 1470 (59.9) |
| Female | | 880 (41) | 38 (30.2) | 66 (36.7) | 984 (40.1) |
| Age (years) | 2454 | 64 (53–74) | 63 (53–69) | 61 (53–69) | 63 (51–74) |
| Smoking | 2388 | | | | |
| Never smoker | | 1358 (65.1) | 70 (55.6) | 106 (60.2) | 1534 (64.2) |
| Current/Former smoker | | 728 (34.9) | 56 (44.4) | 70 (39.8) | 854 (35.8) |
| **Comorbidities and treatments** | | | | | |
| COPD | 2258 | 125 (6.4) | 9 (7.2) | 6 (3.3) | 140 (6.2) |
| Asthma | 2276 | 155 (7.9) | 9 (7.1) | 9 (5) | 173 (7.6) |
| Cardiovascular disease | 2454 | 1060 (60.3) | 69 (55.7) | 88 (52.4) | 1217 (49.6) |
| Renal disease | 2203 | 118 (6.2) | 8 (6.5) | 4 (2.2) | 130 (5.9) |
| Liver disease | 2417 | 69 (3.7) | 12 (9.4) | 6 (3.4) | 87 (3.6) |
| Arterial hypertension | 2049 | 786 (44.7) | 57 (46) | 73 (43.7) | 916 (44.7) |
| Diabetes | 2088 | 342 (19) | 27 (22) | 36 (20.9) | 405 (19.4) |
| CCI | 2454 | 0 (0–1) | 0 (0–2) | 0 (0–1) | 0 (0–1) |
| Statins | 2167 | 531 (28.5) | 32 (25.2) | 48 (27.1) | 611 (28.2) |
| Antiplatelets | 2150 | 245 (13.2) | 14 (11) | 14 (8) | 273 (12.7) |
| **Analytical data** | | | | | |
| Lymphocytes (cells/mL) | 2082 | 960 (660–1340) | 840 (520–1070) | 780 (550–1138) | 930 (630–1300) |
| Platelets (cells/mL) | 2111 | 194000 (152000–254000) | 236000 (182000–307000) | 224000 (168000–289000) | 197000 (155000–262000) |
| CRP (mg/L) | 2097 | 22.8 (5.2–83.2) | 96 (33.2–178.9) | 83.1 (19.6–178.3) | 27.5 (6.6–96.2) |
| D-dimer (ng/mL) | 2051 | 500 (211.8–999) | 339 (249–778) | 533 (208–1315) | 491 (212–999) |
| **Severity** | | | | | |
| CURB-65 | 1905 | | | | |
| 0 | | 664 (40.8) | 38 (32.5) | 40 (25) | 742 (39) |
| 1 | | 617 (37.9) | 53 (45.3) | 58 (36.3) | 728 (38.2) |
| 2 | | 259 (15.9) | 21 (17.9) | 38 (23.8) | 318 (16.7) |
| 3 | | 72 (4.4) | 4 (3.4) | 20 (12.5) | 96 (5) |
| 4 | | 14 (0.9) | 1 (0.9) | 4 (2.5) | 19 (1) |
| 5 | | 2 (0.1) | 0 (0) | 0 (0) | 2 (0.1) |
| SpO2 baseline | 1938 | 97 (96–98) | 90 (85–96) | 88 (80–93) | 94 (91–96) |
| SpO2/FiO2 | 1938 | 454 (348–466) | 316 (168–448) | 196 (160–424) | 409 (98–410) |

Data are presented as n (%) or median (interquartile range). Abbreviations: IQR, interquartile range; SpO2/FiO2, oxygen saturation/fraction of inspired oxygen; CCI, Charlson comorbidity index; CRP, C-reactive protein; CPAP, continuous positive airway pressure; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation; COPD, chronic obstructive pulmonary disease; IRCU, intermediate respiratory care unit; ICU, intensive care unit; HFNO, high-flow nasal oxygen.

**Table 2.** Oxygen and respiratory support treatments according to initial care setting: conventional ward, IRCU and ICU.

| Respiratory support | Ward | IRCU | ICU | Total |
|---|---|---|---|---|
| Nasal cannula | 848 (79) | 16 (14) | 3 (2) | 867 (59) |
| Reservoir oxygen therapy | 167 (10) | 17 (14) | 3 (2) | 187 (13) |
| HFNO/CPAP | 118 (7) | 36 (30) | 7 (5) | 161 (11) |
| NIMV | 46 (3) | 31 (25) | 16 (9) | 93 (6) |
| IMV | 13 (1) | 22 (17) | 128 (82) | 163 (11) |

Data are presented as n (%). Abbreviations: IRCU, intermediate respiratory care unit; ICU, intensive care unit; HFNO, high-flow nasal oxygen; CPAP, continuous positive airway pressure; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation.

admitted to conventional ward, 96 required an IRCU transfer and 199, an ICU transfer due to disease progression. In IRCU, 25% required NIMV; 17%, IMV; and 30%, HFNO. In ICU, the percentages were lower for HFNO/CPAP and NIV, and higher for IMV (82%) (Table 2).

### *Clusters for identifying patients' phenotypes with different respiratory support treatments*

The total number of patients included in the cluster analysis was 1938. Four patient phenotype clusters with distinct complexity of respiratory support – low-flow, high-flow, NIMV or IMV – were identified. In Table 3, variables for each cluster are detailed as frequencies (%) for qualitative

**Table 3.** Cluster analysis. Description of individual variables in the four clusters.

| Variable | C1 N = 638 | C2 N = 369 | C3 N = 680 | C4 N = 251 |
|---|---|---|---|---|
| Age (years) | 65 (55–72) | 66 (59–75) | 63 (59–68) | 78 (59–83) |
| Smoking | 237 (37.2) | 182 (49.1) | 251 (36.9) | 115 (45.8) |
| Diabetes | 3 (0.5) | 197 (53.4) | 188 (27.7) | 11 (4.2) |
| Arterial hypertension | 87 (13.6) | 209 (56.6) | 398 (58.5) | 202 (80.6) |
| Asthma | 17 (2.7) | 24 (6.6) | 118 (17.4) | 4 (1.4) |
| COPD | 0 (0.0) | 31 (8.5) | 56 (8.2) | 0 (0.0) |
| Heart disease | 24 (3.8) | 52 (14.1) | 178 (26.1) | 24 (9.7) |
| Renal disease | 3 (0.5) | 66 (17.9) | 90 (13.3) | 0 (0.0) |
| Liver disease | 3 (0.5) | 59 (16.0) | 38 (5.6) | 0 (0.0) |
| CCI | 0 (0–1) | 2 (1–3) | 3 (2–3) | 0 (0–1) |
| Number of comorbidities | 0 (0–1) | 1 (0–1) | 2 (1–2) | 0 (0–1) |
| Treatment with statins | 17 (2.7) | 153 (41.5) | 258 (37.9) | 146 (58.3) |
| Treatment with antiplatelets | 10 (1.6) | 66 (17.9) | 160 (23.6) | 28 (11.1) |
| Symptoms duration (days) | 8 (6–10) | 8 (5–9) | 9 (7–10) | 10 (7–12) |
| SpO2/FiO2 ratio | 442 (433–447) | 438 (412–452) | 442 (424–457) | 442 (419–460) |
| Platelets (cells/mL) | 175500 (143000–196500) | 183500 (171500–202500) | 270000 (253000–314000) | 310000 (265500–332500) |
| D-dimer (ng/mL) | 510 (327–707) | 810 (480–1100) | 819 (424–1160) | 945 (367–3480) |
| Lymphocytes (cells/mL) | 1145 (740–1375) | 830 (660–1260) | 1110 (790–1460) | 1230 (900–1560) |
| CRP (mg/L) | 64.8 (28.2–110.4) | 107.9 (9.5–177.5) | 52.9 (25.65–135.1) | 85.4 (36.8–158.1) |
| Initial ward admission | 481 (75.4) | 199 (53.8) | 659 (96.9) | 209 (83.3) |
| Initial IRCU admission | 105 (16.4) | 97 (26.4) | 14 (2.0) | 24 (9.7) |
| Initial ICU admission | 52 (8.2) | 73 (19.8) | 7 (1.0) | 17 (6.9) |
| No oxygen | 119 (18.6) | 0 (0.0) | 139 (20.5) | 28 (11.1) |
| Low flow oxygen | 223 (35.0) | 21 (5.7) | 520 (76.4) | 178 (70.8) |
| Reservoir oxygen | 171 (26.8) | 206 (55.7) | 18 (2.6) | 21 (8.3) |
| HFNO/CPAP/NIMV | 126 (19.7) | 143 (38.7) | 3 (0.5) | 24 (9.7) |
| IMV | 10 (1.5) | 9 (2.3) | 5 (0.8) | 3 (1.2) |

Data are presented as n (%) or median (interquartile range). Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; SpO2/FiO2, oxygen saturation/fraction of inspired oxygen; CRP, C-reactive protein; IRCU, intermediate respiratory care unit; ICU, intensive care unit; HFNO, high-flow nasal oxygen; CPAP, continuous positive airway pressure; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation.

variables and for quantitative variables as median (IQR). Clusters C1 ($N = 638$, 32.9%) and C2 ($N = 369$, 19%) grouped patients who may require more respiratory support and IRCU/ICU admission compared to C3 ($N = 680$, 35.1%) and C4 ($N = 251$, 13%). Cluster 1 consisted of younger patients without comorbidities, albeit with higher levels of CRP and D-dimer and a low median of lymphocytes. Cluster 2 grouped patients with more comorbidities, prior treatments with statins/antiplatelets and higher CRP, D-dimer and a lower count of lymphocytes. Clusters C3 and C4 grouped patients who mainly received care in conventional ward and required less complex respiratory support, such as low-flow oxygen or a reservoir. C3 represented a group of older patients with several comorbidities, a high Charlson score and prior treatment with statins/antiplatelets. However, they also presented lower SpO2/FiO2 and median levels of CRP and lymphocytes. C4 also grouped older patients characterised by very few comorbidities, except for those with arterial hypertension and an analytical pattern comparable to that of C3: high SpO2/FiO2, a median count of lymphocytes and median CRP <100 mg/L.

### *In-hospital mortality and one-year follow-up*

In the overall cohort, 139 patients died during hospitalisation, with great differences present among clusters: 11.1%, 18.6%, 0% and 3.3% for C1, C2, C3 and C4, respectively (Figure 2). In the subsequent year, 41 more patients died: 26.8%, 31%, 0% and 6.2% for C1, C2, C3 and C4, respectively. Clusters C2, C1 and C3 showed greater impairment of diffusion capacity for carbon monoxide (DLCO <80%) and more persistent infiltrates.

## Discussion

Characteristics gathered on patients hospitalised for the RECOVID Registry showed that: 1) patients were primarily male, with a median age of 63 years, presenting cardiovascular disease and associated diabetes; 2) 5.1% of patients received care in IRCU. Of these, 25% required NIMV; 17%, IMV; and 30%, HFNO; 3) there were four identifiable

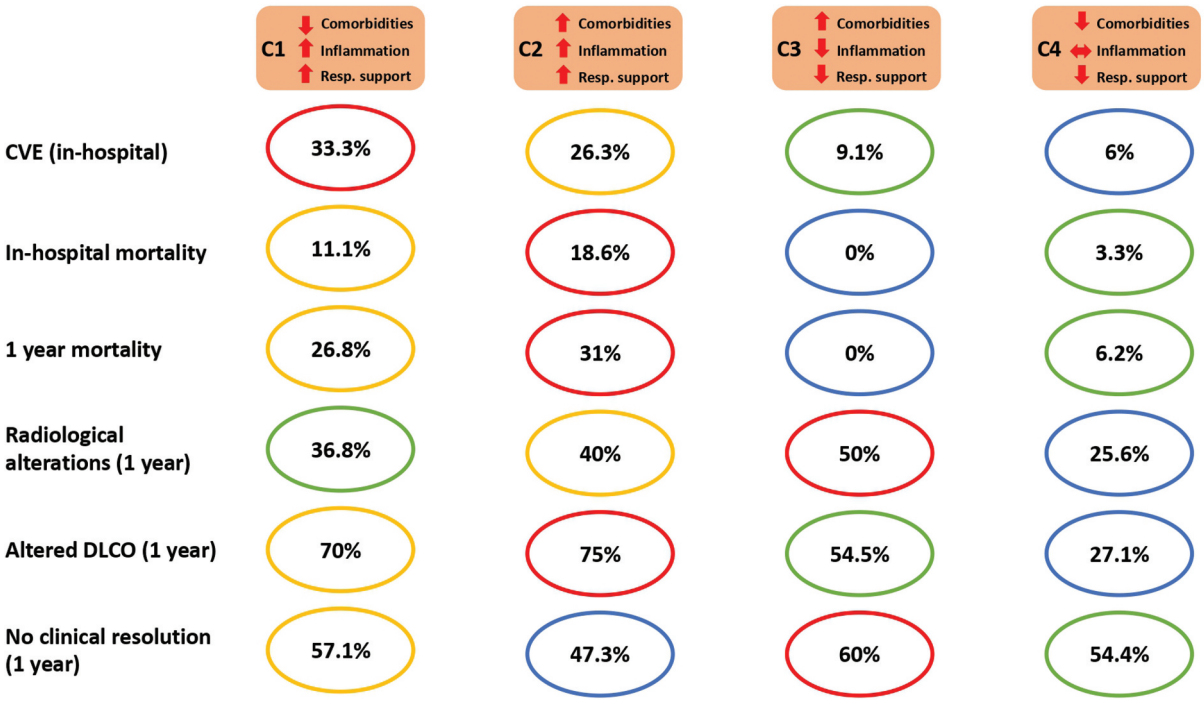


**Figure 2.** Mortality and one-year evolution in survivors from the four clusters.

clusters: C1 and C2 required more complex types of respiratory support, whereas C3 and C4 mainly received care in conventional ward; 4) In-hospital mortality was greater in C2 (28.6%) and C1 (11.1%) than in C4 (3.3%) and C3 (0%).

Demographics and comorbidity characteristics in the RECOVID Registry – principally male with cardiovascular comorbidity – are similar to those described in Europe,[21] Italy,[22] China,[1] and the United States.[23] The balanced recruitment design allowed us to depict a comprehensive picture of respiratory support treatments required during hospitalisation and acute and long-term consequences in a Spanish cohort. Concerning respiratory failure, in a previous RECOVID study we found a greater need for prescription home oxygen at discharge in COPD patients compared to those without COPD, as well as a greater risk for re-admission due to respiratory complications.[20]

To achieve patient survival during the pandemic and, even nowadays, it has proven pivotal to treat respiratory insufficiency. Pneumology services increased the number of IRCU beds to provide complex respiratory support treatments outside of ICU,[4–6] including HFNO and NIMV, which had been shown to decrease intubation.[7,24] The profile of a patient receiving care in IRCU was more similar to that of patients in ICU when compared to those admitted to conventional ward, albeit with a lower CURB-65 score.[25,26] It is worth noting that CURB-65 May underestimate severity:[27] 72% of IRCU-admitted patients presented a score <2 and required respiratory support. In IRCU, 30% of patients received HFNO and 25% NIMV. However, for those hospitalised in ward, percentages were lower: 7% and 3% for HFNO and NIMV, respectively. Ospina-Gascon et al. have reported that the use of HFNO compared with conventional low-flow oxygen therapy significantly decreased the need for mechanical ventilation support and, thereby, time to clinical recovery.[28] Perkins et al. found that when compared with conventional oxygen therapy, an initial strategy using CPAP significantly reduced the risk of tracheal intubation or mortality. They did not, however, observe a significant difference with HFNO when compared with conventional oxygen therapy.[29] Nevertheless, this study may have been underpowered for the later comparison and other characteristics such as a high requirement of FiO2 May have conferred an effect. In this aspect, in a randomised trial, Crimi et al. found that the use of HFNO vs. conventional therapy did not significantly decreased the need of respiratory escalation in patients with mild hypoxaemia.[30]

Using cluster analyses, four groups of patients with different respiratory support treatments required were identified. Our findings could be useful for risk stratification of these patients and help to identify specific profiles that could benefit from admission to specific units. In fact, C1 and C2 patients were more likely to progress, need more complex respiratory support and, therefore, require IRCU/ICU admission. On the contrary, patients from C3 and C4 did not require an escalation in respiratory treatment support and received care in conventional ward.

Interestingly, the two profiles of patients requiring NIMV/IMV showed different characteristics among them. For instance, C1 comprised younger adults than other groups with no comorbidities; however, they presented higher levels of CRP, D-dimer and a lower count of lymphocytes and SpO2/FiO2. On the other hand, C2 comprised older adults with comorbidities and similar initial analytical parameters. The two profile of clusters who did not experience an escalation in respiratory support yet required low-flow oxygen also showed different characteristics. C3 comprised a group of patients with a high number of comorbidities, current smoking habit, and a higher Charlson score. These patients presented a higher count of lymphocytes and lower levels of CRP and D-dimer, whereas those in C4 had very few comorbidities, except for hypertension and a similar analytical pattern: high SpO2/FiO2 and lymphocyte count and lower CRP. The four clusters of patients identified by their requirement of less-to-highly complex respiratory support treatments make clinical sense. Irrespective of whether they had comorbidities, they presented a different combination of analytical alterations that would make them more susceptible to progress to respiratory failure.

In-hospital mortality and mortality in the subsequent first year showed important differences among the four phenotypes. Concerning in-hospital mortality, Cluster C2 experienced the highest mortality, as well as the highest initial inflammation, hypoxaemia and a requirement of more complex respiratory support treatment. On the contrary, C3 —which comprised patients with some comorbidities – presented the lowest mortality; they also had lower initial inflammation. This same cluster only required low-flow oxygen.

One-year mortality was low in the whole cohort, although with significant differences among the four phenotypes. In a previous study from RECOVID registry, we compared COVID-19 one-year mortality to that of community-acquired pneumonia, and found that it was similar after adjusting for potential confounders.[19] The cluster analyses allowed us to recognise phenotypes with the greatest risk for 1-year mortality (C2 and C1), while C4 and C3 exhibited low mortality. Interestingly, in patients with severe COVID-19 (ICU-admitted), Cidade et al. identified three phenotypes. The lowest mortality reported was that in the phenotype comprising patients with lower CRP and higher PCT and IL-6.[31]

Concerning lung residual infiltrates and reduction of diffusion capacity, C4 exhibited the lowest percentage. It comprised patients with low inflammation who did not require complex respiratory support.[32–34] However, C1 and C3 phenotypes presented more reduction of DLCO. Interestingly, at one-year follow-up, around 50% of survivors presented some persistent symptoms across the four phenotypes. In a previous study from the RECOVID registry, we evaluated in patients discharged alive what factors were associated to residual infiltrates, DLCO reduction and symptom persistence; unlike that study, the cluster analyses allowed us to identify phenotypes with different trajectories.[18] In one meta-analysis, factors related with symptoms were more associated with gender, smoking and vaccination status; symptom persistence was lower in those vaccinated.[35,36]

There is still a concern related to the burden of long COVID and potential sequelae. The identified four phenotypes showed different clinical trajectories, not only during hospital stay, but also after hospital discharge. The current cluster analyses and recognised phenotypes with simple variables – comorbidities, analytical parameters and respiratory support – may have clinical utility for clinical decision-making processes, follow-up and patient recruitment in future clinical trials aiming to reduce long COVID.

The RECOVID registry does have some limitations, though. First, like all registries, criteria for admission and administered treatments during the pandemic were not set forth in protocol and may differ among the various hospitals. Second, each hospital and centre had different access to IRCU or ICU resources. This means they followed varying criteria according to hospital capacity or care models implemented throughout the pandemic. Third, as patients were recruited from the pneumology service where post-ICU survivors were admitted, ICU mortality was underestimated and unassessed by pneumologists. Fourth, there is incomplete data due to overburdened care. The strengths of our study were as follows: 1) to guarantee data quality, a data monitor was made available to generate and resolve queries with investigators; 2) our design provided a balanced recruitment with a large sample size and nationwide representation from many hospitals of different geographic areas. As COVID-19 variants are evolving and vaccination status/waning protection varies, the profiles of clusters and respiratory support may differ.

In conclusion, four phenotypes of patients were identified according to requirements for less-to-highly complex respiratory support and with different in-hospital mortality and long-term outcome. Two clusters clearly identified patients with multiple comorbidities or even only hypertension, who would eventually require more complex respiratory support in IRCU/ICU. Two more clusters profiled those not requiring such type of treatment and only needing care in conventional ward. Profiling patients per requirements for more/less complex respiratory support

is useful for risk stratification, monitoring and follow-up. Such an approach could benefit decision-making processes related to admission to specific units. In hospitalised patients with SARS-CoV-2, age, comorbidities and initial parameters might help identify patients for selection in clinical trials exploring potential new treatments to modify early and long-term outcomes.

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