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ORIGINAL ARTICLE

Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry☆

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Abstract:
Background: Spain has been one of the countries most affected by the COVID-19 pandemic.
Objective: To create a registry of patients with COVID-19 hospitalized in Spain in order to improve our knowledge of the clinical, diagnostic, therapeutic, and prognostic aspects of this disease.
Design: A multicenter retrospective cohort study that includes consecutive patients hospitalized with confirmed COVID-19 throughout Spain. Epidemiological and clinical data, additional tests at admission and at seven days, treatments administered, and progress at 30 days of hospitalization were collected from electronic medical records.
Results: Up to June 30 2020, 15,111 patients from 150 hospitals were included. Their median age was 69.4 years (range: 18–102 years) and 57.2% were male. Prevalences of hypertension, dyslipidemia, and diabetes mellitus were 50.9%, 39.7%, and 19.4%, respectively. The most frequent symptoms were fever (84.2%) and cough (73.5%). High values of ferritin (73.5%), lactate dehydrogenase (73.9%), and D-dimer (63.8%) as well as lymphopenia (52.8%) were frequent. The most used antiviral drugs were hydroxychloroquine (85.6%) and lopinavir/ritonavir (61.4%). 33.1% developed respiratory distress. Overall mortality rate was 21.0%, with a marked increase with age (50-59 years: 4.7%, 60—69 years: 10.5%, 70—79 years: 26.9%, ≥80 years: 46.0%).
Conclusion: The SEMI-COVID-19 Network provides data on the clinical characteristics of patients with COVID-19 hospitalized in Spain. Patients with COVID-19 hospitalized in Spain are mostly severe cases, as one in three patients developed respiratory distress and one in five patients died. These findings confirm a close relationship between advanced age and mortality.

PALABRAS CLAVE
2019-nCoV;
SARS-CoV-2;
Coronavirus;
COVID-19;
España

Características clínicas de los pacientes hospitalizados con COVID-19 en España: resultados del Registro SEMI-COVID-19

Resumen
Antecedentes: España ha sido uno de los países más afectados por la pandemia de COVID-19.
Objetivo: Crear un registro de pacientes hospitalizados en España por COVID-19 para mejorar nuestro conocimiento sobre los aspectos clínicos, diagnósticos, terapéuticos y pronósticos de esta enfermedad.
Métodos: Estudio de cohorte retrospectiva, multicéntrico, que incluye pacientes consecutivos hospitalizados con COVID-19 confirmada en toda España. Se obtuvieron los datos epidemiológicos y clínicos, las pruebas complementarias al ingreso y a los siete días de la admisión, los tratamientos administrados y la evolución a los 30 días de hospitalización de las historias clínicas electrónicas.
Resultados: Hasta el 30 de junio de 2020 se incluyeron 15.111 pacientes de 150 hospitales. Su mediana de edad fue 69,4 años (rango: 18-102 años) y el 57,2% eran hombres. Las prevalencias de hipertensión, dislipemia y diabetes mellitus fueron 50,9%, 39,7% y 19,4%, respectivamente. Los síntomas más frecuentes fueron fiebre (84,2%) y tos (73,5%). Fueron frecuentes los valores elevados de ferritina (73,5%), lactato deshidrogenasa (73,9%) y dímero D (63,8%), así como la linfopenia (52,8%). Los fármacos antivirales más utilizados fueron la hidroxicloroquina (85,6%) y el lopinavir/ritonavir (61,4%). El 33,1% desarrolló distrés respiratorio. La tasa de mortalidad global fue del 21,0%, con un marcado incremento con la edad (50-59 años: 4,7%, 60-69 años: 10,5%, 70-79 años: 26,9%, ≥80 años: 46%).
Conclusiones: El Registro SEMI-COVID-19 proporciona información sobre las características clínicas de los pacientes con COVID-19 hospitalizados en España. Los pacientes con COVID-19 hospitalizados en España son en su mayoría casos graves, ya que uno de cada tres pacientes desarrolló distrés respiratorio y uno de cada cinco pacientes falleció. Nuestros datos confirman una estrecha relación entre la edad avanzada y la mortalidad.

Introduction

Spain is one of the countries with the highest number of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the world. Since the first COVID-19 case was confirmed in the country on January 31, 2020, 253,908 cases have been diagnosed and 28,403 patients have died as of July 13, 2020.[1]

Current knowledge about COVID-19 is incomplete and fragmented. Cohort studies from various countries[2–7] suggest that the risk factors and prognosis of this disease may not be able to be extrapolated to other geographical areas, as they could be influenced by specific public health conditions or race-related issues. To date, there are no solid therapeutic recommendations, as the results from ongoing clinical trials on the efficacy of antiviral and immunosuppressant drugs are pending.[8–10]

The SEMI-COVID-19 Network arises as an initiative of the Spanish Society of Internal Medicine (SEMI) to improve the quality of treatment for SARS-CoV-2. The main objective of the registry is to generate, in a short period of time, a large, multicenter cohort with detailed information on the epidemiology, clinical progress, and treatment received by patients. This will allow for the development of prognostic models and the assessment of the efficacy of different treatment regimens used in real-world clinical practice.

Methods

Study design

Observational study

The SEMI-COVID Registry is an ongoing retrospective cohort comprising most consecutive patients with confirmed COVID-19 hospitalized and discharged in Spain from March 1, 2020 up to the end of the pandemic. Inclusion began on March 24 and is ongoing. Follow-up at one month was done via telephone.

Study population and participants

All consecutive patients with confirmed SARS-COV-2 infection who had been discharged or died after hospital admission were eligible for inclusion. COVID-19 was confirmed either by a positive result on real-time polymerase chain reaction (RT-PCR) testing of a nasopharyngeal or sputum sample or by a positive result on serological testing and compatible clinical presentation.

Inclusion criteria for the registry were: a) patient age$\geq$ 18 years, b) confirmed diagnosis of COVID-19, c) first hospital admission in a Spanish hospital participating in the study, d) hospital discharge or in-hospital death.

Exclusion criteria were subsequent admissions of the same patient and denial or withdrawal of informed consent.

Patients were treated at their attending physician's discretion, according to local protocols and clinical judgement. Patients included in open-label clinical trials could be included in the registry, provided that all information about treatment was available. Given its observational nature, inclusion in the registry entailed no further inconvenience to the patients included.

Registry information

An online electronic data capture system (DCS) has been developed, which includes a database manager along with procedures for the verification of data and contrasting of information against the original medical record in order to ensure the best possible quality of data collection.

Patient identifiable data are dissociated and pseudonymized. Direct identifiers are not collected in the DCS, but rather an alphanumeric sequence of characters that includes a code for identification of the researcher and a correlative number is used. Each researcher must maintain a protected registry (patient log) that is for his/her sole use. The purpose of this protected registry is to be able to confirm data with the medical records so that additional information may be gathered, if necessary, as well as to perform quality controls. This system allows for patient privacy to be respected, ethical considerations to be met, and data protection regulations to be complied with.

The database platform is hosted on a secure server. All information contained in the database, the configuration of the information within the database, as well as the database itself are fully encrypted. Every client-server data transfer is encrypted through a valid TLS certificate. Daily backups are performed in order to ensure data integrity.

Data collection

Data are collected retrospectively and include approximately 300 variables grouped under various headings: (1) inclusion criteria, (2) epidemiological data, (3) RT-PCR and serology data, (4) personal medical and medication history, (5) symptoms and physical examination findings at admission, (6) laboratory (blood gases, metabolic panel, complete blood count, coagulation) and diagnostic imaging tests, (7) additional data at seven days after admission or at admission to the intensive care unit (ICU), (8) pharmacological treatment during the hospitalization (antiviral drugs, immunomodulators, antibiotics) and ventilatory support, (9) complications during the hospitalization, and (10) progress after discharge and/or 30 days from diagnosis. A list of variables can be found in Appendix A.

Study management

The Spanish Society of Internal Medicine (SEMI, for its initials in Spanish) is the sponsor of this study. The researchers that coordinate the study from each hospital are SEMI members and were asked to participate in the study on a voluntary basis without receiving remuneration.

Database monitoring is performed by the study's scientific steering committee and an independent external agency. Logistics coordination and data analysis are also carried out by external independent agencies.

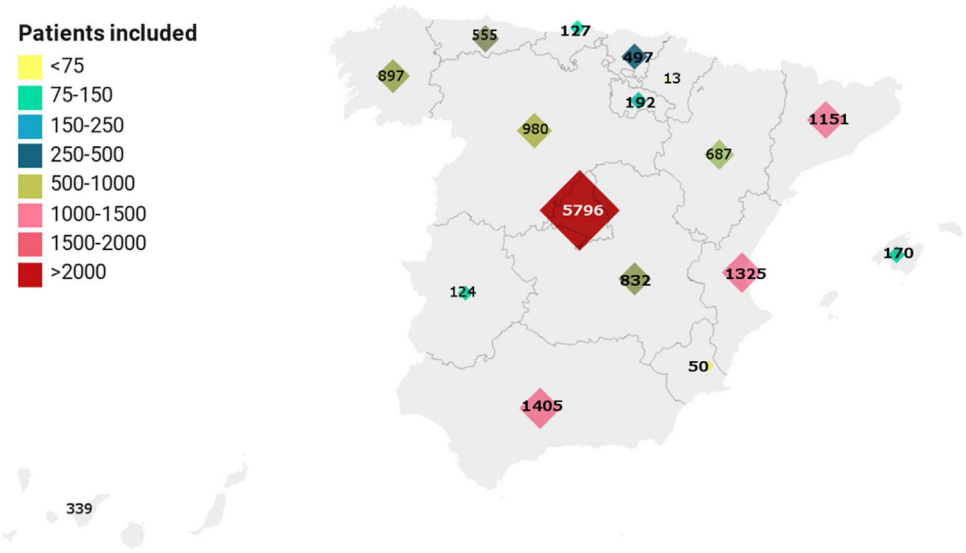

Fig. 1 Geographical origin of patients, by Autonomous Community.

Data analysis

Participating patients' demographic, clinical, epidemiological, laboratory, and diagnostic imaging data were analyzed as well as their clinical progress. Quantitative variables are expressed as median [interquartile range]. Categorical variables are expressed as absolute frequencies and percentages. Mortality is expressed as case fatality rate (CFR).

Ethical aspects

Personal data are processed in strict compliance with Spanish Law 14/2007, of July 3, on Biomedical Research; Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation); and Spanish Organic Law 3/2018, of December 5, on the Protection of Personal Data and the Guarantee of Digital Rights.

The SEMI-COVID-19 Registry has been approved by the Provincial Research Ethics Committee of Malaga (Spain).

In accordance with applicable regulations, the Spanish Agency of Medicines and Medical Products (AEMPS, for its initials in Spanish) has ruled that due to its nature, the study only required the approval of the Ethics Committee and not the Autonomous Community, as in other studies.

Informed consent was obtained from all the patients. When it was not possible to obtain informed consent in writing due to biosafety concerns or if the patient had already been discharged, informed consent was requested verbally and noted on the medical record.

The STROBE statement guidelines were followed in the conduct and reporting of the study.

Results

As of June 30, 2020, 15111 patients hospitalized in 150 hospitals throughout Spain were included in the registry (Fig. 1). The epidemiological characteristics of population studied are described in Table 1. The median age was 69.4 years (range: 18–102 years) and 57.2% were male. Male gender was predominant in all age ranges except for patients $\geq$90 years, in which females accounted for 56.7% of the total.

A high level of comorbidity was observed (61.4% with moderate or severe Charlson Comorbidity Index scores). Furthermore, 16.5% of patients had moderate or severe dependency for activities of daily living (Barthel index score <60). The most common comorbidities were hypertension (50.9%), dyslipidemia (39.7%), obesity (21.2%), and diabetes mellitus (19.4%).

Table 2 summarizes the clinical and radiological findings upon admission to the emergency department. The most common clinical manifestations were fever (84.2%), cough (73.5%), dyspnea (57.6%), and asthenia (43.6%). Anosmia, dysgeusia, and hyporexia were less common. Gastrointestinal manifestations were quite common, especially diarrhea. At triage, only 52.1% of patients were febrile and almost half showed some degree of respiratory failure (oxygen saturation <90% in 17.9%, respiratory rate >20 breaths per minute in 31.1%). Lung involvement was less common upon examination than in the radiographic findings: crepitant rales were present in 53.2% of patients whereas pneumonia or interstitial infiltrates were observed on chest X-rays in 86.8% of patients.

Laboratory findings at admission are also shown in Table 2. Decreased lymphocytes and eosinophil counts were of note: the median values were 940 and 0 $\times$ 10^6/L, respectively. High lactate dehydrogenase (LDH), D-dimer, and ferritin levels were observed in 73.9%, 63.8%, and 73.5%, respectively.

Treatment and complications during hospitalization are summarized in Table 3. A wide variety of drugs with purported antiviral effects have been used, the most frequent of which were hydroxychloroquine (85.6%) and lopinavir/ritonavir (61.4%). Remdesivir was only used in 68 patients (0.5%). Antibiotics were also widely indicated, mainly beta-lactam antibiotics (71.7%) and azithromycin

Table 1 Demographic and comorbidity data.

Variable	Absolute frequency (%). *Median [Interquartile range]	N
Age (years)	69.4 [56.4;79.9] *	15111
18−29	250 (1.7%)	
30−64	6027 (39.9%)	
65−79	5096 (33.7%)	
≥80	3738 (24.7%)	
Gender		15111
Male	8643 (57.2%)	
Female	6478 (42.8%)	
Race/Ethnicity		14889
Caucasian	13437 (90.2%)	
Other	1452 (9.8%)	
Healthcare worker	608 (4%)	15093
Age-adjusted Charlson Comorbidity Index		14733
No comorbidities	1753 (11.9%)	
Mild	3927 (26.7%)	
Moderate	4115 (27.9%)	
Severe	4938 (33.5%)	
Degree of dependency		14938
Independent or mild	12460 (83.4%)	
Moderate	1410 (9.4%)	
Severe	1068 (7.1%)	
Tobacco use		14419
Has never smoked	9995 (69.3%)	
Former smoker	3659 (25.4%)	
Smoker	765 (5.3%)	
Alcohol use disorder	690 (4.7%)	14631
Obesity (BMI $\geq 30\,kg/m^2$)	2910 (21.2%)	13758
Hypertension	7689 (50.9%)	15111
Dyslipidemia	5990 (39.7%)	15104
Diabetes mellitus	2924 (19.4%)	15095
Cancer (solid tumor, leukemia, lymphoma)	1610 (10.7%)	15078
Cardiovascular disease (atrial fibrillation, angina pectoris, heart failure)	3001 (19.9%)	15076
Angina pectoris	534 (3.5%)	15107
Atrial fibrillation	1687 (11.2%)	15095
Heart failure	1086 (7.2%)	15107
Myocardial infarction	894 (5.9%)	15111
Obstructive lung disease (COPD, asthma)	2071 (13.7%)	15091
COPD	1038 (6.9%)	15106
Asthma	1098 (7.3%)	15101
Obstructive sleep apnea/hypopnea syndrome	903 (6.0%)	15038
Known HIV infection (with or without AIDS criteria)	103 (0.7%)	15075
Moderate-severe chronic kidney disease	917 (6.1%)	15102

(60.8%). Immunomodulatory drugs were also common, principally corticosteroids (35.2%), beta-interferon (11.3%), and tocilizumab (8.4%). Low-molecular-weight heparin was used in 83.4% of patients, generally at prophylactic doses.

Many patients required support: high flow nasal cannula was used in 8.0% of patients, noninvasive positive-pressure ventilation in 4.9%, and invasive mechanical ventilation in 6.6%. The main complication was acute respiratory distress syndrome (ARDS), which 33.1% of patients developed, fol-

Table 2 Clinical, laboratory, and diagnostic imaging findings upon admission.

Variable	Absolute frequency (%). *Median [Interquartile range]	N
Clinical presentation		
Fever or low-grade fever		15081
None	2388 (15.8%)	
Low-grade fever (<38 °C)	3131 (20.8%)	
Fever (> = 38 °C)	9562 (63.4%)	
Cough		15079
No	3997 (26.5%)	
Yes, dry	8751 (58%)	
Yes, with expectoration	2331 (15.5%)	
Fatigue	6507 (43.6%)	14915
Diarrhea	3554 (23.7%)	14991
Anorexia	2915 (19.6%)	14845
Shortness of breath	8684 (57.6%)	15067
Anosmia	1040 (7.1%)	14710
Physical Examination		
Oxygen saturation (pulse oximetry, %)	94 [91;97]	14705
<90	2628 (17.9%)	
≥ 90	12077 (82.1%)	
Oxygen saturation/FiO_2 ratio (%)	442.9 [404.8;457.1] *	14411
Temperature, ºC	37 [36.3;37.8] *	14646
<37 °C	7026 (48%)	
37-37.9 °C	4520 (30.9%)	
≥ 38 °C	3100 (21.2%)	
Hypotension (systolic blood pressure <100 mmHg)	907 (6.3%)	14464
Tachycardia (>100 beats per minute)	3751 (24.8%)	15140
Tachypnea (>20 breaths per minute)	4590 (31.1%)	14769
Confusion	1803 (12%)	14992
Crackles	7854 (53.2%)	14754
Chest x-ray		14949
No pulmonary infiltrates	1973 (13.2%)	
Unilateral pulmonary infiltrates	3058 (20.5%)	
Bilateral pulmonary infiltrates	9918 (66.3%)	
Complete blood count		
White blood cell count, ($x10^6$/L)	6300 [4780;8520] *	15015
Absolute count ($x10^6$/L)		
Neutrophils	4600 [3200;6700] *	14944
Lymphocytes	940 [690;1300] *	14990
>1200	4818 (32.1%)	
1000-1200	2249 (15%)	
800-1000	2729 (18.2%)	
<800	5194 (34.6%)	
Eosinophils	0 [0;20] *	14786
Monocytes	400 [300;600] *	14866
Hemoglobin (g/dL)	13.9 [12.6;15] *	15016
Platelets ($x10^6$/L)	190000 [148000;247000] *	15012
Arterial Blood Gases		
pH	7.5 [7.4;7.5] *	7764
PCO_2 (mmHg)	34 [30.7;39] *	7851
PO_2 (mmHg)	66 [56;77.6] *	7509
pO_2/FiO_2 ratio (%)	288.6 [233.3;342.9] *	7203
Basic metabolic panel		
Glucose (mg/dL)	112 [98;136] *	14547
Serum creatinine (mg/dL)	0.9 [0.7;1.2] *	14977
Urea (mg/dL)	37 [27;55] *	12095

Table 2 (*Continued*)

Variable	Absolute frequency (%). *Median [Interquartile range]	N
Lactate dehydrogenase (U/L)	321 [246;432] *	13053
<250	3410 (26.1%)	
250-400	5634 (43.2%)	
>400	4009 (30.7%)	
Aspartate aminotransferase (U/L)	35 [25;52] *	11974
Alanine aminotransferase (U/L)	29 [19;46] *	14145
C-reactive protein (mg/L)	60.2 [19;127.9] *	14483
Lactate (mmol/L)	1.6 [1.1;2.4] *	6824
Procalcitonin (ng/mL)	0.1 [0.1;0.2] *	7159
Interleukin-6 (IL-6) (pg/mL)	29.8 [11.5;65.4] *	1993
D-dimer (ng/mL)		11749
< 500	4251 (36.2%)	
500-1000	3610 (30.7%)	
> 1000	3888 (33.1%)	
Serum ferritin (μg/L)		5978
<300	1584 (26.5%)	
300-650	1583 (26.5%)	
>650	2811 (47%)	
qSOFA index	0 [0;1] *	14129
Low risk ≥1	12817 (90.7%)	
High risk ≥2	1312 (9.3%)	

lowed by bacterial pneumonia and sepsis. Although 2680 patients developed severe ARDS, only 1255 (8.3%) were transferred to an intensive care unit.

The median follow-up period was 40 days (range: 0–102 days). At the end of follow-up, 78.8% had been discharged, 21.0% had died, and 0.2% continued hospitalized (after readmission). The average length of hospital stay for discharged patients was 10.4 days (range: 1–62 days). The rate of readmission within 30 days was 3.9% (573 patients).

Discussion

In this study, we analyze a large series of patients hospitalized with COVID-19 in Spain who have been included in the SEMI-COVID-19 Registry. This first cohort includes consecutive patients admitted to hospitals throughout Spain who were discharged or died. Similar to almost all Western series, our patients were predominantly male, elderly, and with multiple comorbidities.

Recently, the first conclusions about the impact of COVID-19 in Madrid, the epicenter of the pandemic in Spain, were drawn from a large cohort of 2226 patients from La Paz University Hospital of Madrid.[11] The strengths and weaknesses of this study both arise from its single-center design: the data are more consistent and able to be analyzed, but are also less able to be extrapolated to the general population and prone to local biases, such as different population demographics or features specific to that particular hospital.

Our series has a higher proportion of males, as has been described in most multicenter cohorts and contrary to the work by Borobia et al.[11] The higher proportion of females at La Paz University Hospital may be a result of the specific demographic features of its reference population and thus does not reflect the differences according to sex previously described in other viral infections in general and specifically in COVID-19.

In addition, our cohort includes older patients with a greater number of comorbidities. In our series, the median age was 69 years (61 in Madrid cohort[11]), which is clearly higher than Guan et al.'s Chinese series,[4] moderately higher than Richardson et al.'s New York series,[7] and lower than Docherty et al.'s UK series.[8] The most frequent comorbidities (hypertension, diabetes, obesity, dementia, and others) are similar to those that have been previously described, but all were more prevalent among our patients. They are summarized in Table 4.

In our cohort, the main symptoms reported upon admission (fever, cough, dyspnea, and asthenia) were similar to those reported in other studies,[4–8] although myalgia and anosmia were less common. This could potentially be explained by a difference in admission criteria: patients without lung involvement were managed as outpatients from emergency departments and, therefore, only the most severe cases were admitted.

In our series, mortality, as defined by CFR, was similar to what was observed in the Madrid cohort,[11] some Chinese series,[2–6] and the USA cohort,[7] but was much higher than the Italian cohort[9] and lower than what has been described in the UK.[8]

The difference between our series and the Italian series warrants some explanation, as we share many demographic features with Italy and the timing and magnitude of the COVID-19 pandemic have been similar. The difference in

Table 3 Treatment and complications during hospitalization.

Variable	Absolute frequency (%)	N
Antimicrobial therapy		
Hydroxychloroquine	12915 (85.6%)	15084
Lopinavir/Ritonavir (LPV/r)	9254 (61.4%)	15072
Azithromycin	9146 (60.8%)	15036
Beta-lactam antibiotics	10795 (71.7%)	15050
Remdesivir	68 (0.5%)	14968
Immunomodulatory therapy		
Systemic corticosteroids	5287 (35.2%)	15034
Interferon Beta-1B (IFNb)	1689 (11.3%)	15008
Tocilizumab	1276 (8.5%)	15038
Anakinra	91 (0.6%)	14939
Immunoglobulin	70 (0.5%)	14821
Ventilatory support		
High flow nasal cannula	1197 (8.0%)	14989
Invasive mechanical ventilation (IMV)	998 (6.6%)	15057
Non-invasive mechanical ventilation (NIMV)	733 (4.9%)	15051
Anticoagulant therapy		
Low-molecular-weight heparin during hospitalization		15016
No	2645 (17.6%)	
Low (prophylactic) dose	9713 (64.7%)	
High (anticoagulant) dose	1648 (11%)	
Intermediate dose	1010 (6.7%)	
Complications		
Acute respiratory distress syndrome (ARDS)		15057
No	10077 (66.9%)	
Mild	1203 (8.0%)	
Moderate	1097 (7.3%)	
Severe	2680 (17.8%)	
Bacterial pneumonia	1680 (11.1%)	15075
Sepsis	937 (6.2%)	15080
Intensive Care Unit admission	1255 (8.3%)	15129
Outcome		
Discharge	11928 (78.8%)	15140
Death	3181 (21.0%)	15140
Readmission	573 (3.9%)	14709
Not discharged at the end of follow-up (after readmission)	31 (0.2%)	15140

mortality may reflect different study inclusion criteria or different hospital admission criteria. Less strict admission or inclusion criteria yield a greater number of patients included in the registry, thus lowering the CFR. Indeed, population-based studies, which include more patients with milder disease, have lower CFRs than hospital-centered series.[9] Conversely, stricter admission or inclusion criteria lead to greater severity among the patients analyzed and an increase in the CFR.

Another explanation could be that these observational works could not control for factors related to race, including the percentage and origin of immigrant populations or healthcare-system disparities. In fact, racial and demographic factors may in part explain the differences in severity and mortality between Chinese and Western series.[2–8]

Demographic factors, such as age or comorbidities, may partially explain the differences in mortality and can be controlled for by means of multivariate analysis. Pressure on the healthcare system can result in different mortality rates, as was shown in China by Liang et al.,[12] who compared the CFR both within and outside of Hubei province (CFR of 7.3% vs. 0.3%, respectively).

In Italy,[9] the pandemic placed the greatest pressure on the region of Lombardy whereas in Spain, it has been more widely distributed. Nevertheless, the majority of patients in our series are from hospitals in Madrid, which has been one of the most affected regions and where the situation is comparable to that of northern Italy. Whether there is a geographical influence will be further explored in additional studies.

As has been shown in all series, a high percentage of patients had abnormal laboratory values that were consistent with an abnormal inflammatory profile.[2–8] In our series, lymphopenia and elevated levels of D-dimer, LDH, and ferritin were the most frequent findings. Also, a large part of our patients received treatment that has purported antiviral activity against SARS-CoV-2. Our multicenter registry has

Table 4 Comparison of baseline characteristics and outcome of patients with COVID-19 included in series from different countries.

	Guan et al.[4]	Zhou et al.[6]	Docherty et al.[8]	Onder et al.[9]		Richardson et al.[7]		Borobia et al.[11]		SEMI-COVID-19	
City/Country/Type of study	Wuhan / China / multicenter cohort	Wuhan / China / multicenter cohort	UK / multicenter cohort	Italy / Italian National Institute of Health		New York / USA / multicenter cohort		Spain / single-center cohort		Spain / multicenter cohort	
Number of cases	1099	191	20133	22512		5700		2226		15111	
Median age in years [IQR]	47 [35-58]	56 (46-67)	73 [58-82]	–		63 [52-75]		61 [46–78]		69.4 [56.4-79.9]	
Male sex	58.1%	62.0%	59.9%	–		60.3%		48.2%		57.2%	
Comorbidity											
Hypertension	15.0%	30.0%	–			56.0%		41.3%		50.9%	
Obesity	–	–	10.5%	–		41.7%		10.9%		21.2%	
Diabetes	7.4%	19.0%	24.6%	–		33.8%		17.1%		19.4%	
Abnormal chest x-ray	59.0%	59%-75%	–	–		–		–		86.8%	
Clinical outcomes											
Acute Respiratory Distress Syndrome	3.4%	31.0%	–	–		–		4.9%		33.1%	
ICU admission	5.0%	26.0%	17.0%	–		12.2%		10.6%		8.3%	
Mortality	1.4%	28.3%	26.0%	7.2%		21.0%		20.7%		21.0%	
Mortality by age group (years)				No (%)	CFR %	No (%)	CFR %	No (%)	CFR %	No (%)	CFR %
<30	–	–	–	0	0	97 (3.7)	4.1%	1 (0.2)	0.6%	7 (0.2)	2.8%
30-39	–	–	–	4 (0.3)	0.3	211 (8.1)	3.8%	0 (0.0)	0.0%	7 (0.2)	1.0%
40-49	–	–	–	10 (0.6)	0.4	353 (13.5)	6.2%	4 (0.9)	1.5%	38 (1.2)	2.6%
50-59	–	–	–	43 (2.7)	1.0	515 (19.8)	10.3%	14 (3.0)	3.8%	114 (3.6)	4.7%
60-69	–	–	–	139 (8.6)	3.5	533 (20.5)	15.8%	36 (7.8)	11.0%	311 (9.8)	10.5%
70-79	–	–	–	578 (25.6)	12.8	451 (17.3)	32.1%	122 (26.5)	34.1%	975 (30.7)	26.9%
≥80	–	–		850 (52.3)	20.2	441 (16.9)	53.7%	283 (61.5)	55.4%	1719 (54.2)	46.0%

IQR: interquartile range; ICU: intensive care unit; CFR%: case fatality rate percentage: SEMI: Spanish Society of Internal Medicine.

been designed to allow for multivariate analysis of the prognostic value of these abnormal laboratory findings as well as treatment received during hospitalization.

Notably, in our series, there was a much higher proportion of patients with ARDS (moderate or severe: 25.1% or 3777 patients) than patients who were admitted to an ICU (8.3%, 1255 patients). This suggests that only approximately one out of every three patients with ARDS was admitted to an ICU.

We have discussed this finding in detail and have evaluated some possible confounding factors and biases. On the one hand, patients admitted directly to an ICU or who died in an ICU may have not been included in our cohort and thus altered our ICU admission rate. Patients who have still not been discharged have not been included in our cohort. Therefore, patients who are currently hospitalized in the ICU thus also falsely lower our ICU admission rate. Patients with ARDS may have died before being transferred to an ICU or have presented with criteria that is not compatible with treatment in an ICU, but even still, this does not explain how 2522 out of 3777 patients with moderate or severe ARDS were discharged without having been admitted to an ICU.

Another plausible explanation could be the overloading of the healthcare system, at least in the most affected regions of the country. It is known that the number of ICU beds has increased substantially during the COVID-19 pandemic in Spain. It is likely that in addition to increasing the number of ICU beds, some semi-intensive care areas were established within hospitals. In our personal experience, many hospitals have designed ''semi-intensive'' or ''intermediate care'' wards in order to provide ventilatory support to patients when ICU expansion was no longer feasible. This finding warrants further examination.

The collaborative effort of the SEMI-COVID-19 Network Group has provided us with a large amount of data from a sizeable number of patients. Among the strengths of our registry are its multicenter design; its wide geographical dispersion, which limits local biases (selection, admission, treatment availability, ICU availability, etc.) and increases its external validity; and its large size, which provides statistical power for confirming hypotheses.

This study also has limitations. First, data are collected by a large number of researchers from different centers, which could lead to heterogeneity in data collection and validation. Second, the registry includes consecutive patients from participating centers, which limits patient selection bias but introduces another selection bias according to participating centers. Third, our registry, though extensive (more than 300 variables), collects only basic data for enhancing our knowledge of COVID-19, but lacks the level of detail required for deeper analysis of very specific aspects. Lastly, the main limitation of this study is its observational design, which does not allow for establishing causal relationships.

This is the largest reported series of hospitalized patients in Spain with confirmed COVID-19 disease and one of the largest registries in the world to date. Though our findings are currently preliminary and must be explored in greater detail, the SEMI-COVID-19 Network working group and the SEMI-COVID-19 Registry will surely become a key tool for helping clinicians and researchers improve knowledge of this novel disease which has threatened not only the lives of many patients and the proper functioning of our healthcare systems, but also the foundations of our economy and way of life.

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Conflicts of interest disclosure

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.rceng.2020.07.003.

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