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Characteristics, Complications and Outcomes Among 1,549 Patients Hospitalized with COVID-19 in a Secondary Hospital

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KEYWORDS: COVID-19, secondary-level hospital, epidemiology.

ABSTRACT

Background: The rapid global spread of COVID-19 has caused a public health emergency with major international repercussions. Information on patient profiles and outcomes in secondary hospitals is limited. We aimed to describe demographic, clinical, radiological and laboratory characteristics, as well as outcomes, of patients admitted for COVID-19 in a secondary hospital. **Methods:** Retrospective case series of sequentially hospitalized patients with confirmed SARS-CoV-2, at Infanta Leonor University Hospital in Madrid, Spain from the beginning of the outbreak until 28 May 2020. **Results:** A total of 1,549 COVID-19 cases were included (median age 69 [IQR 55.0- 81.0], 57.5% male). 78.2% had at least one underlying comorbidity, the most frequent was hypertension (55.8%). Most frequent symptoms at presentation were fever (75.3%), cough (65.7%) and dyspnea (58.1%). 81 patients were admitted to the intensive care unit (ICU) (median age 62 [IQR 51-71], 74.1% male). 1393 patients had an outcome at the end of the study period (case fatality ratio: 21.2% (296/1,393)). The independent factors associated with fatality (OR; 95% CI): age (1.07; 1.06-1.09), male sex (2.86; 1.85-4.50), neurological disease (1.93; 1.19-3.13), chronic kidney disease (2.83; 1.40-5.71) and neoplasia (4.29; 2.40-7.67). The percentage of hospital beds occupied with COVID-19 almost doubled (702/361), with the number of patients in ICU quadrupling its capacity (32/8). Median length of stay was 9 days (IQR 6-14). **Conclusions:** This study provides clinical characteristics, complications and outcomes of COVID-19 patients admitted to a European secondary hospital. Fatal outcomes were similar to those reported by hospitals with a higher level of complexity.

STRENGTHS AND LIMITATIONS OF THIS STUDY-This is a large retrospective case series study of 1549 sequentially hospitalized patients with confirmed SARS-CoV-2.

-The study describes the response of a secondary hospital based in a region of Spain with the highest incidence of COVID-19, and how the hospital was transformed into a center entirely dedicated to COVID-19.

-A complete follow-up was made of all patients during hospital stay, although after discharge no outcome information was collected, so only in-hospital fatality could be estimated.

BACKGROUND

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in China and spread globally, causing a new infectious disease named “coronavirus disease 2019” (COVID-19) (1). By 28 May 2020, the epidemic reaches 5,593,631 confirmed cases and more than 353,334 deaths across 216 countries all over the world (2).

The first confirmed case of COVID-19 in Spain was reported from La Gomera (Canary Islands) on 31 January 2020 (3). But it was not until the last week of February 2020 when the first five cases were reported in the Community of Madrid (4).

During March and April 2020, Spain has been one of the most affected countries by the coronavirus, being one of the main outbreaks of the disease worldwide. Spain, with 237,906 cases as of 28 May 2020, is the third country in Europe with the highest number of confirmed cases after the Russian Federation and the United Kingdom (UK)

(2,5). The rate of infections in the Community of Madrid has exceeded every other region in Spain, with more than 25% of all confirmed cases in Spain and an accumulated number of 41,972 hospitalized patients and 8,691 deaths as of 28 May (5)

The Infanta Leonor University Hospital (ILUH) is a secondary level hospital with 361 beds, including 8 in the intensive care unit (ICU). It serves the population of Vallecas (305,262 individuals) (6) Our healthcare area has a disproportionate number of inhabitants per bed (845 inhabitants/hospital bed and 38,150 inhabitants/ICU bed). Vallecas is one of the COVID-19 most affected neighborhood in the city of Madrid (Spain) with 4,360 total confirmed COVID-19 cases as of 28 May 2020 (7). Therefore, the level of hospital saturation during the epidemy has been one of the greatest in Spain. As a consequence, the hospital was in March transformed into a center entirely dedicated to COVID-19 and all its professionals focused on assisting patients affected by the SARS-CoV-2 infection.

Limited information is available to describe characteristics, complications and mortality in COVID-19 overloaded secondary Spanish hospitals. The available data from Spain refer to tertiary hospitals, multi-centric studies or primary care settings (8–11).

This study describes the clinical characteristics, severity, types of treatments and overall outcomes of patients with confirmed SARS-CoV-2 infection admitted to ILUH in Madrid (Spain).

METHODS

Study design and participants:

A single-center retrospective observational study that included patients attended at ILUH with a laboratory-confirmed COVID-19 between 1 March 2020 and 28 May 2020. SARS-CoV-2 infection was confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay from nasopharyngeal swabs. Patients discharged from the emergency department and those transferred to another hospital in the first 48 hours were not included in the final analysis.

Epidemiological and demographic data, medical history, baseline comorbidities, symptoms and signs both at admission and during follow-up, laboratory findings, RT-PCR results, treatment strategy used for COVID-19, complications and survival data were obtained from patient's electronic medical records. All-cause mortality was calculated including deaths occurred both in patients pending admission (first 48 hours) and during hospitalization. ICU admission, hospitalization length of stay and ventilatory support (invasive mechanical ventilation, noninvasive mechanical ventilation or oxygen mask) were also registered. Different time intervals were calculated: lag time between symptoms onset and diagnosis, length of stay at ICU and global length of stay at the hospital.

Data were collected and managed using REDCap electronic data capture tools hosted at Ideas for Health Association. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies (12).

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

Patient and Public Involvement

There was no patient or public involvement in the development of the research design or in conducting the study.

Statistical Analysis:

A descriptive analysis of the clinical background and baseline characteristics of the patients was performed. Continuous variables are presented as median and interquartile range (IQR), after testing normal distribution. Categorical variables are expressed as number of patients and percentage. Two age-groups were defined using a cut off value of 65 (<65 and ≥65 years old) for the comparison of the clinical characteristics of the cohort. For the ICU analysis, the comparison of the characteristics between admitted and non-admitted to ICU patients were limited to patients under 65 because of the uneven opportunities for ICU admission due to the scarce availability of ICU resources.

For the mortality analysis, the case fatality ratio (CFR) was defined as number of deaths of laboratory-confirmed COVID-19 patients divided by the number of laboratory-confirmed COVID-19 cases admitted to the hospital. The outcomes were defined as death or recovered, and the clinical characteristics between these groups were compared using Chi-square test for the categorical variables and Median test for the quantitative variables.

Logistic regression analysis was carried out to ascertain the effect of sociodemographic and clinical background characteristics on mortality. Variables that showed statistical significance in the univariate analysis and clinical variables that have potential relevance on the outcome according to the current available evidence

were included in the model. Odds Ratio (OR) and 95% confidence intervals (95% CI) were calculated.

Statistical analyses were done using Stata software (version 14.0; Stata Corporation, College Station, Texas, USA).

Ethical aspects:

The Institutional Investigation and Ethics Review Board of Infanta Leonor University Hospital (CEI-ILUH) approved the study (Code ILUH R 027-20) and due to its retrospective nature, the need for informed consent from patients was waived.

RESULTS

Overall, 2,259 COVID-19 confirmed cases were attended at ILUH during the study period. The daily number of confirmed COVID-19 cases are plotted by the date of diagnosis (date of positive RT-PCR) and by the date of symptoms onset in **Figure 1.** The first positive patient in our hospital was diagnosed on 1 March 2020 and the epidemic curve peaked on 19 March when 126 PCR tested positive. From that date, the incidence declined gradually but it took over a month to have a daily number of new cases below 10**.** The percentage of ICU beds and total hospital beds occupied with COVID-19 patients are shown in **Figure 1**. On 27 March, our hospital almost doubled its bed capacity with 702 hospitalized patients. On 6 April, 32 patients were in ICU, reaching 400% of hospital ICU capacity.

Among these 2,259 patients, we analyzed 1,549 cases and excluded 710 because they were discharged from the emergency department or transferred to other hospitals in the first 48 hours. For the complications, ICU and mortality analysis, 156 patients

with an uncomplete episode were excluded because they were transferred to other hospitals during their stay or were still hospitalized by 28 May 2020 (**Figure 2**).

The median age of the 1,549 hospitalized patients was 69 (IQR 55.0-81.0) and 57.5% were male. All patients except for a three-week-old baby were adults. 55.0% had hypertension, 24.8% diabetes, 24.3% cardiovascular disease, 15.7% obesity, 13.7% chronic obstructive pulmonary disease (COPD) and 8.5% obstructive sleep apnea syndrome (OSAS). HIV infection (0.6%) and autoimmune disease (5.2%) were rare. Overall, 1,221 (78.2%) patients had at least one underlying comorbidity.

The median lag time between symptoms onset and diagnosis was 7 days (IQR: 4-9) (**Figure 1**). The commonest symptoms at presentation were fever (75.3%), cough (65.7%) and dyspnea (58.1%). Diarrhea (17.6%) and anosmia (3.6%) were less common in our case series. Fever, headache, cough, diarrhea, nausea/vomiting, anosmia, muscle or chest pain were more frequent in younger patients while cognitive deterioration was in older patients (**Table 1**).

The most frequent therapies used for treating COVID-19 were the combination hydroxychloroquine plus azithromycin (59.9%) and the combination hydroxychloroquine plus azithromycin plus lopinavir-ritonavir (18.5%). Any treatment combination including lopinavir-ritonavir was more frequently used in older patients. Tocilizumab was used in 15.5% of the patients and corticosteroids in 44.2%. (**Table 1**).

The analysis of the complications during admission showed that 14.3% of patients had acute respiratory distress syndrome with no differences between age groups, 12.0% had acute kidney failure which was more frequent in older patients (15.7% vs. 6.7%),

6.7% had a clinical thrombotic event and 0.7% had disseminated intravascular coagulation (**Table 1**).

Among patients with a complete episode at ILUH, 81 were admitted to ICU: median age 62 (IQR 51-71) and 74.1% male. Clinical characteristics are shown in **Table 2**. Among the 575 patients younger than 65 years old with a complete episode at ILUH, risk factors associated to ICU admission in the univariate analysis were: being male, obesity, hypertension, OSAS, having an increased respiratory rate, a low blood oxygen saturation level (SpO2) at admission, a high neutrophil/lymphocyte ratio, an elevated plasma INR, lactate dehydrogenase (LDH), aspartate transaminase (AST), creatinine and C-reactive protein and the presence of alveolar pulmonary infiltrates in the chest x-ray. (**Table 2**). We calculated CFR in ICU patients with a complete episode at ILUH (70 patients): global CFR was 72.9% (62.8% in the under 65 group and 88.9% in the older group).

The overall CFR in our cohort was 21.2% (296/1,393 cases). The median length of stay was 9 days (IQR 6-14). Among the 296 deaths, 48 occurred in the first 48 hours and the rest during hospitalization. These 48 patients had a higher median age compared to the global cohort (82.5 vs 69) and their median lag time from symptom onset until fatality was lower (7 days vs 13.5 days, $p<0.001$). As shown in **Table 3**, patients who died were older and more likely to be male, current smoker/ex-smoker, and had hypertension, cardiovascular disease, COPD, OSAS, diabetes mellitus, neurological disease, chronic kidney disease and neoplasia in the univariate analysis. Also, they received more frequently ventilatory support during hospitalization and showed more alveolar pulmonary infiltrates in chest x-ray than people who recovered.

In the multivariate analysis, independent factors related to death were: years of age (OR 1.07; 95% CI: 1.06-1.09), being male (OR 2.86; 95% CI: 1.85-4.50), neurological disease (OR 1.93; 95% CI: 1.19-3.13), chronic kidney disease (OR 2.83; 95% CI: 1.40-5.71) and neoplasia (OR 4.29; 95% CI: 2.40-7.67).

Among the 1,549 hospitalized patients, 65 were readmitted (4.2%): 64.6% were male and 67.7% were 65 years old or older. CFR during readmissions was 10.8% (7/65).

DISCUSSION

This study describes the COVID-19 series of a secondary level hospital in Madrid, Spain. Patients baseline characteristics are similar to the largest published series in Spain (9), although our patients were older and with a higher proportion of males compared to other tertiary Spanish hospital series (8).

We found that younger patients showed a high incidence of fever, cough, headache, muscle pain and diarrhea, whereas older patients showed a less specific clinical presentation. Other studies did not find differences in clinical presentation related to age (13). This information could be crucial for the rapid identification and isolation of the suspected cases at any healthcare level.

Our cohort showed a high incidence of acute kidney failure during hospitalization similar to other non-Spanish series (14,15) but higher than other Madrid series (8), with no association to drug administration. This could be explained for the rapid hydroelectrolytic imbalance in older patients in the context of an acute systemic viral disease. We also found a high incidence of thrombotic events (6.7%) comparable to previous reports (16), although disseminated intravascular coagulation was rare.

Lopinavir/ritonavir-based treatments were more frequently used in older patients. This finding is due to the use of this drug as standard treatment in our hospital protocol

during the first half of the outbreak, when most of the patients were older than 65. Tocilizumab, with or without corticosteroids, was used following Spanish Drug Agency recommendations in patients who developed cytokine release storm (CRS) which is believed to cause acute respiratory distress syndrome (ARDS), although corticosteroids were also used in others clinical contexts.

Our findings in the ICU analysis in patients under 65 years old were analogous to other studies (15,17,18) in terms of clinical characteristics and laboratory values. As described in the New York series (15), it seems that obesity and OSAS were related factors leading to ICU admission, even more than the presence of a previous pulmonary disease. This could suggest that patients with a baseline ventilatory compromise could entail a higher risk for ICU admission due to alveolar hypoventilation and acute-on-chronic hypercapnic respiratory failure. However, this analysis has some limitations related to scarce availability of ICU resources in our center and the number of ICU patients who were transferred to other hospitals.

The CFR in our series was 21.2%. It has probably been overestimated due to a significant proportion of patients transferred to other hospitals in the first 48 hours, who had a less severe disease. Some published series showed a lower CFR (19), although others reported a similar (8,9,15) or even higher CFR (14,20). The differences could be related to demographic factors, different hospital admission criteria, case definition and healthcare system overload level (21). It is interesting to note that the CFR found in our study is similar to other Spanish tertiary level hospitals (8), despite our sample had a higher proportion of older and male patients and our center had a lower proportion of conventional hospitalization and ICU beds availability. The CFR in our UCI is slightly lower than other studies (15).

Comparing the patients who died in the first 48 hours (48/296) with the rest of the deceased, the median age was higher and the median days from symptom onset until fatality was lower. This could reflect a steep clinical deterioration in older patients compared to younger patients. Further studies are required to support the evidence of a severe clinical phenotype of SARS-CoV-2 infection characterized by a quick progression of an acute respiratory failure with severe hypoxemia in older patients that leads to fatal outcome.

We found similarities with other series (22) about variables associated to fatality in the univariate analysis, such as hypertension, cardiovascular disease or pulmonary diseases. Nevertheless, after adjusting by sociodemographic variables and comorbidities at admission, risk factors related to death were age, male gender, neurological disease, chronic kidney disease and cancer. These findings are consistent with other studies that identify male sex and age as important predictors for mortality (23). However, this analysis has some limitations because it only focuses in hospitalized patients skewing estimates of the morbi-mortality and risk factors of COVID-19 globally (10).

The strength of this study lies on the sequential collection of patients (all COVID-19 patients admitted to hospital were included) and on the complete follow-up of all patients during their entire hospital stay. On the other hand, it also has some limitations. First, its observational and retrospective nature. Second, some variables (i.e. anosmia and history of thromboembolic event) have a relatively large number of missing values because they were not registered from the beginning of the study, due to changes in the evidence related to COVID-19 during the progression of the pandemic. Third, there is no follow-up after hospital discharge, so only in-hospital fatality can be estimated.

CONCLUSION

This study describes the epidemic progression, clinical characteristics, complications and outcomes of COVID-19 patients attended in a secondary level hospital in one of the highest COVID-19 incidence neighborhoods of Madrid, which turned into an entire COVID center and almost doubled its bed capacity. Fatal outcomes were similar to those reported by hospitals with a higher level of complexity.

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FOOTNOTES

- **Contributors:** EJ, MFV, JV, IFJ, PR and MPB conceived the study idea. EJ, MFV, JV, IFJ, PR, MPB, EAA, EIG and AL contributed to the study design. EJ, MFV, IFJ, PR, EAA, EIG, AL and EG performed the data collection. MFV and EJ performed the analysis. EJ, MFV, JV, IFJ, PR, MPB, EAA, EIG and AL drafted the first version of the manuscript. All authors critically reviewed the manuscript and approved the final version.
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LIST OF IMAGES:

Table 1. Clinical characteristics and treatment (N= 1549)

	Global n/N (%)	< 65 y.o. n/N (%)	≥ 65 y.o. n/N (%)	p-value
Male	890/1549 (57.5)	400/642 (62.3)	490/907 (54.0)	0.001
Migrant	385/1549 (24.8)	296/642 (46.1)	89/642 (13.9)	<0.001
Clinical background				
Influenza vaccine 19/20	498/1101 (45.2)	90/463 (19.4)	408/638 (63.9)	<0.001
Cardiological disease	375/1545 (24.3)	37/640 (5.8)	338/905 (37.3)	<0.001
High blood pressure	851/1548 (55.0)	185/641 (28.9)	666/907 (73.4)	<0.001
Diabetes mellitus	382/1541 (24.8)	85/636 (13.4)	297/905 (32.8)	<0.001
Tobacco smoker/ex-smoker	374/1344 (27.8)	121/555 (21.8)	253/789 (32.0)	<0.001
Obesity	240/1531 (15.7)	110/636 (17.3)	130 /895 (14.5)	0.129
COPD	211/1541 (13.7)	37/638 (5.8)	174/903 (19.3)	<0.001
Asthma	122/1545 (7.9)	51/639 (8.0)	71/906 (7.8)	0.668
OSAS	79/935 (8.4)	32/401 (8.0)	47/534 (8.8)	0.654
Cerebrovascular disease	57/125 (45.6)	12/28 (42.7)	45/97 (46.4)	0.741
Thromboembolic disease	41/939 (4.4)	10/410 (2.4)	31/529 (5.9)	0.011
Neurological disease	178/1540 (11.6)	37/637 (5.8)	141/903 (15.6)	<0.001
Chronic kidney disease	104/1543 (6.7)	16/639 (2.5)	88/904 (9.7)	<0.001
Cirrhosis	28/1540 (1.8)	13/638 (2.0)	15/902 (1.7)	0.209
Haematological/oncological cancer	103/1540 (6.7)	21/640 (3.3)	82/900 (9.1)	<0.001
HIV	9/1542 (0.6)	7/639 (1.1)	2/903 (0.2)	0.012
Autoimmune disease	47/913 (5.1)	17/393 (4.3)	30/520 (5.8)	0.328
Symptoms				
Fever	1159/1540 (75.3)	533/638 (83.5)	626/902 (69.4)	<0.001
Headache	133/1533 (8.7)	92/634 (14.5)	41/899 (4.6)	<0.001
Malaise	671/1533 (43.8)	282/637 (44.3)	389/896 (43.3)	0.928
Confused	87/1532 (5.7)	11/633 (1.7)	76/899 (8.4)	<0.001
Dyspnea	891/1533 (58.1)	362/632 (57.3)	529/901 (58.7)	0.382
Superior respiratory tract symptoms	316/1534 (20.6)	153/635 (24.1)	163/899 (18.1)	0.009
Cough	1010/1538 (65.7)	469/638 (73.5)	541/900 (60.1)	<0.001
Expectoration	194/1535 (12.6)	69/635 (10.9)	125/900 (13.9)	0.167
Hemoptysis	26/1532 (1.7)	15/633 (2.3)	11/899 (1.2)	0.207
Chest pain	134/1534 (8.7)	79/635 (12.4)	55/899 (6.1)	<0.001
Muscle pain	291/1534 (19.0)	166/635 (26.1)	125/899 (13.9)	<0.001
Abdominal pain	49/1534 (3.19)	16/635 (2.52)	33/899 (3.67)	0.280

Nausea/vomiting	178/1532 (11.6)	88/636 (13.8)	90/896 (10.0)	0.040
Diarrhea	269/1530 (17.6)	143/636 (22.5)	126/894 (14.1)	<0.001
Skin rash	8/1531 (0.5)	5/636 (0.8)	3/895 (0.3)	0.087
Anosmia	41/1153 (3.6)	29/489 (5.9)	12/664 (1.8)	<0.001
Complications during admission				
Bacterial pneumonia	43/1362 (3.2)	13/551 (2.4)	30/811 (3.7)	0.320
Sepsis	28/1372 (2.0)	16/554 (2.9)	12/818 (1.5)	0.054
Respiratory distress syndrome	195/1368 (14.2)	74/550 (13.4)	121/818 (14.8)	0.557
Pneumothorax	5/1373 (0.4)	3/556 (0.5)	2/817 (0.2)	0.488
Pleural effusion	29/1367 (2.1)	6/552 (1.1)	23/815 (2.8)	0.032
Stroke	11/1373 (0.8)	4/555 (0.7)	7/818 (0.9)	0.669
Disseminated intravascular coagulation	9/1369 (0.7)	2/554 (0.4)	7/815 (0.9)	0.360
Thrombosis	55/824 (6.7)	23/338 (6.8)	32/486 (6.6)	0.833
Acute renal failure	165/1373 (12.0)	37/556 (6.6)	128/817 (15.7)	<0.001
Treatment				
HCQ monotherapy	28/1549 (1.8)	7/642 (1.1)	21/907 (2.3)	0.075
HCQ + AZ	927/1549 (59.8)	448/642 (69.8)	479/907 (52.8)	<0.001
HCQ + LP/r	98/1549 (6.3)	32/642 (5.0)	66/907 (7.3)	<0.001
HCQ + AZ + LP/r	287/1549 (18.5)	90/642 (14.0)	197/907 (21.7)	<0.001
HCQ + LP/r + IFN-b	37/1549 (2.4)	12/642 (1.9)	25/907 (2.8)	0.260
HCQ + AZ + LP/r + IFN-b	113/1549 (7.3)	37/642 (5.8)	76/907 (8.4)	0.051
Tocilizumab	240/1549 (15.5)	144/642 (22.4)	96/907 (10.6)	<0.001
Corticosteroids	684/1549 (44.2)	264/642 (41.1)	420/907 (46.3)	<0.001

COPD: Chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; ICU: intensive care unit; HCQ: hydroxicloroquine; AZ: azithromicine; LP/r: lopinavir-ritonavir; IFN-b: interferon-beta

Table 2. Clinical laboratory and diagnosis imaging characteristics of COVID-19 patients who have been admitted in ICU. Comparison between patients under 65 years admitted to ICU vs non-admitted to ICU.

	ICU patients cohort (n=81)	<65 y.o patients (n=575)		
		Admitted to ICU (n=50)	Non-admitted to ICU (n=525)	p-value
Age[1]	62 (51-71) (N=81)	54 (48-60) (N=50)	53 (45-59) (N=525)	0.625
Male[2]	60/81 (74.1)	21/50 (42.0)	325/525 (61.9)	0.048
Migrant[2]	25/81 (30.9)	21/50 (42.0)	238/525 (45.3)	0.651
Influenza vaccine 19-20[2]	12/42 (28.6)	5/28 (17.9)	75/395 (19.0)	0.883
Clinical background				
Cardiovascular disease[2]	17/81 (21.0)	6/50 (12.0)	29/523 (5.5)	0.069
High blood pressure[2]	43/81 (53.1)	23/50 (46.0)	147/524 (28.1)	0.008
Diabetes mellitus[2]	23/81 (28.4)	10/50 (20.0)	65/519 (12.5)	0.315
Tobacco smoker/ex-smoker[2]	23/76 (30.3)	13/49 (26.5)	98/450 (21.8)	0.447
Obesity[2]	23/81 (28.4)	17/50 (34.0)	80/520 (15.4)	0.001
COPD[2]	7/81 (8.6)	4/50 (8.0)	30/521 (5.8)	0.522
Asthma[2]	5/81 (6.2)	4/50 (8.0)	43/522 (8.2)	0.117
OSAS[2]	8/39 (20.5)	8/27 (29.6)	22/332 (6.6)	<0.001
Thromboembolic disease[2]	2/40 (5.0)	2/28 (7.1)	8/338 (2.4)	0.136
Neurological disease[2]	5/80 (6.3)	2/49 (4.1)	31/521 (6.0)	0.786
Chronic kidney disease[2]	5/81 (6.2)	3/50 (6.0)	12/522 (2.3)	0.118
Liver cirrhosis[2]	1/80 (1.3)	1/50 (2.0)	11/522 (2.1)	0.117
Haematological/oncological cancer[2]	4/81 (4.9)	1/50 (2.0)	19/523 (3.6)	0.548
HIV[2]	0/81 (0.0)	0/50 (0.0)	7/522 (1.3)	0.529
Clinical and laboratory presentation				
Heart rate, beats per minute[1]	94 (83-107) (N=73)	54 (48-60) (N=50)	53 (45-59) (N=525)	0.625
Respiratory rate, breaths per minute[1]	23 (18-30) (N=44)	24 (18-30) (N=33)	18 (16-20) (N=222)	0.002
Systolic blood pressure, mmHg[1]	133 (119-142) (N=66)	128 (118-141) (N=42)	125 (114-137) (N=292)	0.591

SpO2, %[1]	88 (76-93) (N=69)	88 (66-94) (N=44)	96 (92-97) (N=454)	<0.001
SpO2<90%[2]	39/81 (48.1)	26/50 (52.0)	53/525 (10.1)	<0.001
SpO2 after oxygen administration, %[1]	95 (90-97) (N=39)	95 (90-98) (N=27)	96 (94-98) (N=91)	0.813
SpO2<90% after oxygen administration[2]	9/81 (11.1)	5/50 (10.0)	0/525 (0.0)	<0.001
Hemoglobin, g/L[1]	13.9 (11.9-15.0= (N=81)	14.1 (12.1-15.2) (N=50)	14.1 (13.1-15.1) (N=493)	0.946
Neutrophils, cells count/µL[1]	6300 (4500-9300) (N=81)	7000 (4600-8800) (N=50)	4700 (3500-6700) (N=495)	0..001
Lymphocytes, cells count/µL [1]	900 (600-1200) (N=81)	900 (700-1300) (N=50)	1100 (800-1400) (N=495)	0.252
Neutrophil/lymphocyte ratio[1]	6.64 (5.0-12.7) (N=81)	6.69 (4.8-12.3) (N=50)	4.4 (2.9-7.1) (N=495)	<0.001
Platelets, x10^9/L[1]	209 (170-267) (N=81)	205 (172-265) (N=50)	213 (171-274) (N=495)	0.777
INR[1]	1.1 (1.0-1.2) (N=81)	1.1 (1.0-1.2) (N=50)	1.1 (1.0-1.1) (N=484)	0.035
D-dimer, mg/L[1]	940 (485-2095) (N=56)	790 (470-2350) (N=35)	640 (400-1080) (N=334)	0.163
LDH, U/L[1]	408 (279-542) (N=70)	415 (279-605) (N=43)	271 (215-348) (N=430)	<0.001
ALT, U/L[1]	45 (32-67) (N=80)	50 (34-80) (N=50)	44 (30-66) (N=494)	0.075
AST, U/L[1]	59 (40-82) (N=79)	60 (43-85) (N=50)	40 (29-57) (N=485)	<0.001
Creatinine, mg/dL[1]	1.1 (0.9-1.3) (N=78)	1.1 (1.0-1.3) (N=48)	0.9 (0.7-1.1) (N=480)	<0.001
C-reactive protein, mg/L[1]	1157 (481-2054) (N=80)	1234 (678-2133) (N=49)	522 (174-1152) (N=494)	<0.001
Diagnosis imaging				
Bilateral pulmonary infiltrates[2]	61/74 (82.4)	40/46 (87.0)	388/476 (81.5)	0.359
Interstitial pulmonary infiltrates[2]	61/81 (75.3)	38/50 (76.0)	360/525 (68.6)	0.277
Alveolar pulmonary infiltrates[2]	51/81 (63.0)	33/50 (66.0)	230/525 (43.8)	0.003
Respiratory supplementation				
Oxygen therapy[2]	77/81 (95.1)	47/50 (94.0)	345/516 (66.9)	<0.001
Non-invasive ventilation[2]	38/80 (47.5)	26/49 (53.1)	25/513 (4.9)	<0.001
Invasive ventilation[2]	67/81 (82.7)	43/50 (86.0)	0/514 (0.0)	<0.001

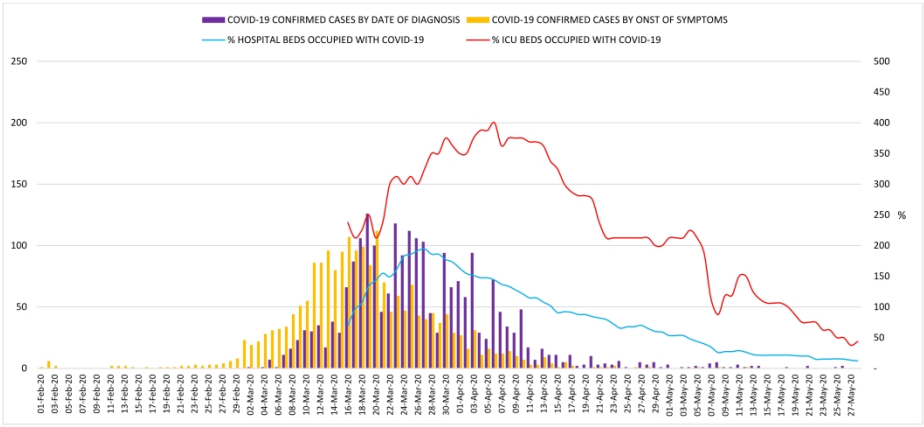
COPD: chronic obstructive pulmonary disease; OSAS: Obstructive sleep apnea syndrome; HIV: Human immunodeficiency virus; SpO2: partial oxygen saturation; LDH: Lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase
[1]continuous variable (median, IQR, N); [2]categorical variables (n/N, %)

Table 3. Clinical, laboratory and diagnosis imaging characteristics of COVID-19 patients who died or recovered.

	Death (n=296)	Recovered (n=1097)	p-value
Age[1]	82 (71.5-87) (N=246)	65 (53-78) (N=1097)	<0.001
Male[2]	208/296 (70.3)	593/1097 (54.1)	<0.001
Migrant[2]	41/296 (13.8)	296/1097 (27.0)	<0.001
Clinical background			
Influenza vaccine 19/20[2]	113/183 (61.7)	342/820 (41.7)	<0.001
Cardiovascular disease[2]	124/296 (41.9)	217/1093 (19.8)	<0.001
High blood pressure[2]	208/296 (70.3)	565/1096 (51.5)	<0.001
Diabetes mellitus[2]	90/295 (30.5)	260/1090 (23.8)	0.038
Tobacco smoker/exs-smoker[2]	111/260 (42.7)	236/950 (23.8)	<0.001
Obesity[2]	42/292 (14.4)	169/1085 (15.6)	0.169
COPD[2]	67/293 (22.9)	120/1092 (11.0)	<0.001
Asthma[2]	17/296 (5.7)	95/1093 (8.7)	0.166
OSAS[2]	20/156 (12.8)	53/687 (7.7)	0.041
Thromboembolic disease[2]	11/161 (6.8)	26/681 (3.8)	0.093
Neurological disease[2]	59/293 (20.1)	101/1091 (9.3)	<0.001
Chronic kidney disease[2]	40/295 (13.6)	58/1092 (5.3)	<0.001
Liver cirrhosis[2]	8/292 (2.7)	17/1093 (1.5)	0.352
Haematological/oncological cancer[2]	48/293 (16.4)	50/1092 (4.6)	<0.001
HIV[2]	0/295 (0.0)	8/1091 (0.7)	0.327
Clinical and laboratory presentation			
Heart rate, beats per minute[1]	88 (78-102) (N=242)	88 (78-100) (N=881)	0.856
Respiratory rate, breaths per minute[1]	21.5 (16-28) (N=116)	18 (16-20.5) (N=397)	<0.001
Systolic blood pressure, mmHg[1]	130 (111-147) (N=217)	130 (117-143) (N=683)	0.877
SpO2, %[1]	89 (82-93) (N=239)	95 (92-97) (N=945)	0.033

SpO2<90%[2]	121/203 (59.6)	152/945 (16.1)	<0.001
SpO2 after oxygen administration, %[1]	94 (90.5-97) (N=112)	96 (94-98) (N=203)	0.003
SpO2<90% after oxygen administration[2]	18/112 (16.1)	7/203 (0.1)	<0.001
Hemoglobin, g/L[1]	12.70 (11.00-14.50) (N=292)	13.70 (12.60-14.70) (N=1054)	<0.001
Neutrophils, cells count/µL[1]	6100 (4200-8550) (N=292)	4800 (3500-6800) (N=1057)	<0.001
Lymphocytes, cells count/µL [1]	800 (500-1100) (N=292)	1000 (800-1300) (N=1057)	<0.001
Neutrophil/lymphocyte ratio[1]	7.17 (4.3-12.9) (N=292)	4.67 (3.1-7.4) (N=1057)	<0.001
Platelets, x10^9/L[1]	190 (142.5-263.5) (N=292)	209 (162-273) (N=1057)	0.040
INR[1]	1.1 (1.0-1.3) (N=283)	1.1 (1.0-1.2) (N=1026)	<0.001
D-dimer, mg/L[1]	1060 (570-2560) (N=167)	750 (450-1330) (N=685)	<0.001
LDH, U/L[1]	345 (249-479) (N=235)	259 (210-331) (N=887)	<0.001
ALT, U/L[1]	31 (23-47) (N=287)	36 (25-55) (N=1050)	<0.001
AST, U/L[1]	47 (30-67) (N=284)	38 (28-55) (N=1035)	<0.001
Creatinine, mg/dL[1]	1.2 (0.9-1.7) (N=285)	0.9(0.7-1.2) (N=1032)	<0.001
C-reactive protein, mg/L[1]	105.9 (36.2-182.4) (N=291)	53.8 (18.3-111.4)	<0.001
Diagnosis imaging			
Bilateral pulmonary infiltrates[2]	218/259 (84.2)	762/960 (79.4)	0.084
Interstitial pulmonary infiltrates[2]	182/296 (61.5)	689/1097 (62.8)	0.677
Alveolar pulmonary infiltrates[2]	153/296 (51.7)	458/1097 (41.7)	0.002
Respiratory supplementation			
Oxygen therapy[2]	285/292 (97.6)	458/1075 (76.5)	0.001
Non-invasive ventilation[2]	57/289 (19.7)	64/1072 (6.0)	<0.001
Invasive ventilation[2]	46/292 (15.7)	15/1075 (1.4)	<0.001

COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; HIV: Human immunodeficiency virus; SpO2: partial oxygen saturation; LDH: Lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase
[1]continous variable (median, IQR, N); [2]categorical variable (n/N, %)



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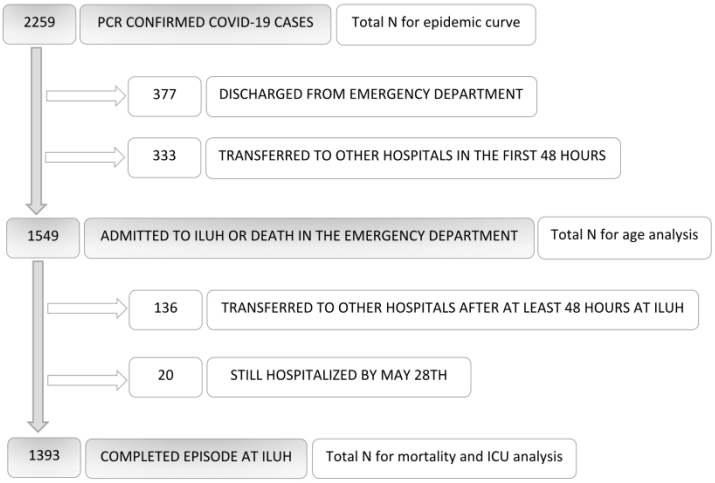

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Characteristics, Complications and Outcomes Among 2259 Patients Hospitalized with COVID-19 in a Secondary Level Hospital in Madrid, Spain

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	***Yes*** ***Pag 1-2***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	***Yes*** ***Pag 1-2***
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	***Yes*** ***Pag 3-4***
Objectives	3	State specific objectives, including any prespecified hypotheses	***Yes*** ***Pag 4***
Methods			
Study design	4	Present key elements of study design early in the paper	***Yes*** ***Pag 5***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	***Yes*** ***Pag 5***
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	***Yes*** ***Pag 5***
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	***Yes*** ***Pag 5-6***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***Yes*** ***Pag 5-6***
Bias	9	Describe any efforts to address potential sources of bias	***Yes*** ***Pag 5-6***
Study size	10	Explain how the study size was arrived at	***Yes*** ***Pag 6***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	***Yes*** ***Pag 6***

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	***Yes*** ***Pag 6***
		(*b*) Describe any methods used to examine subgroups and interactions	***Yes*** ***Pag 6***
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	***Yes*** ***Pag 7***
		(b) Give reasons for non-participation at each stage	***Yes*** ***Fig 2***
		(c) Consider use of a flow diagram	***Yes*** ***Fig 2***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	***Yes*** ***Pag 7-10*** ***Fig 1*** ***Tables 1-3***
		(b) Indicate number of participants with missing data for each variable of interest	***Yes*** ***Tables 1-3***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	***Yes*** ***Pag 9*** ***Fig 1***
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	***Yes*** ***Pag 9*** ***Table 3***
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	***Yes*** ***Pag 7-10*** ***Tables 1-3***
		(*b*) Report category boundaries when continuous variables were categorized	***Yes*** ***Pag 7-10*** ***Tables 1-3***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	***Yes*** ***Pag 9*** ***Uni/multivariate***
Discussion			
Key results	18	Summarise key results with reference to study objectives	***Yes*** ***Pag 10-12***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	***Yes*** ***Pag 10-12***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	***Yes*** ***Pag 10-12***
Generalisability	21	Discuss the generalisability (external validity) of the study results	***Yes*** ***Pag 12***

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	***Yes*** ***Pag 14***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Characteristics, Complications and Outcomes Among 1,549 Patients Hospitalized with COVID-19 in a Secondary Hospital.

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Characteristics, Complications and Outcomes Among 1,549 Patients Hospitalized with COVID-19 in a Secondary Hospital

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KEYWORDS: COVID-19, secondary-level hospital, epidemiology.

ABSTRACT

Objectives: to describe demographic, clinical, radiological and laboratory characteristics, as well as outcomes, of patients admitted for COVID-19 in a secondary hospital. **Design and setting:** Retrospective case series of sequentially hospitalized patients with confirmed SARS-CoV-2, at Infanta Leonor University Hospital (ILUH) in Madrid, Spain. **Participants:** All patients attended at ILUH testing positive to RT-PCR on nasopharyngeal swabs and diagnosed with COVID-19 between 1 March 2020 and 28 May 2020. **Results:** A total of 1,549 COVID-19 cases were included (median age 69 [IQR 55.0- 81.0], 57.5% male). 78.2% had at least one underlying comorbidity, the most frequent was hypertension (55.8%). Most frequent symptoms at presentation were fever (75.3%), cough (65.7%) and dyspnea (58.1%). 81 (5.8%) patients were admitted to the intensive care unit (ICU) (median age 62 [IQR 51-71]; 74.1% male; median length of stay 9 days [IQR 5-19]) 82.7% of them needed invasive ventilation support. 1393 patients had an outcome at the end of the study period (case fatality ratio: 21.2% (296/1,393)). The independent factors associated with fatality (OR; 95% CI): age (1.07; 1.06-1.09), male sex (2.86; 1.85-4.50), neurological disease (1.93; 1.19-3.13), chronic kidney disease (2.83; 1.40-5.71) and neoplasia (4.29; 2.40-7.67). The percentage of hospital beds occupied with COVID-19 almost doubled (702/361), with the number of patients in ICU quadrupling its capacity (32/8). Median length of stay was 9 days (IQR 6-14). **Conclusions:** This study provides clinical characteristics, complications and outcomes of COVID-19 patients admitted to a European secondary hospital. Fatal outcomes were similar to those reported by hospitals with a higher level of complexity.

STRENGTHS AND LIMITATIONS OF THIS STUDY-This is a large retrospective case series study of 1549 sequentially hospitalized patients with confirmed SARS-CoV-2.

-The study describes the response of a secondary hospital based in a region of Spain with the highest incidence of COVID-19, and how the hospital was transformed into a center entirely dedicated to COVID-19.

-A complete follow-up was made of all patients during hospital stay, although after discharge no outcome information was collected, so only in-hospital fatality could be estimated.

BACKGROUND

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in China and spread globally, causing a new infectious disease named “coronavirus disease 2019” (COVID-19) (1). By 28 May 2020, the epidemic reaches 5,593,631 confirmed cases and more than 353,334 deaths across 216 countries all over the world (2).

The first confirmed case of COVID-19 in Spain was reported from La Gomera (Canary Islands) on 31 January 2020 (3). But it was not until the last week of February 2020 when the first five cases were reported in the Community of Madrid (4).

During March and April 2020 (first COVID-19 wave in Spain and Europe), Spain had been one of the most affected countries by the coronavirus, being one of the main outbreaks of the disease worldwide. Spain, is now the second country in Europe with

the highest number of confirmed cases (after the Russian Federation) with 470.973 cases as of 1 September 2020 (2,5,6). The rate of infections in the Community of Madrid has exceeded every other region in Spain, with more than 27% of all confirmed cases in Spain and an accumulated number of 45,074 hospitalized patients and 8,662 deaths as of 1 September 2020 (5).

Hospitals of the various regional health services of Spain are categorized into different complexity levels depending on their size, technological resources and the higher or lower availability of different clinical departments, thus, in ascending order of complexity we have primary, secondary and tertiary level hospitals; tertiary hospitals often have specific clinical departments that attend patients coming from different parts of the country. The Infanta Leonor University Hospital (ILUH) is a secondary level hospital with 361 beds, including 8 in the intensive care unit (ICU). It serves the population of Vallecas (305,262 individuals) (7). Our healthcare area has a disproportionate number of beds per inhabitants: 1.07 beds per 1000 people compared to 2.15 beds per 1000 people overall within the region. Vallecas is one of the COVID-19 most affected areas in the city of Madrid (Spain) with 9,947 total confirmed COVID-19 cases as of 1 September 2020 (8). Therefore, the level of hospital saturation during the epidemy has been one of the greatest in Spain. As a consequence, the hospital was in March transformed into a center entirely dedicated to COVID-19 and all its professionals focused on assisting patients affected by the SARS-CoV-2 infection.

Limited information is available to describe characteristics, complications and mortality in COVID-19 overloaded secondary Spanish hospitals. The available data from Spain refer to tertiary hospitals, multi-centric studies or primary care settings (9–12).

This study describes the clinical characteristics, severity, types of treatments and overall outcomes of patients with confirmed SARS-CoV-2 infection admitted to ILUH in Madrid (Spain).

METHODS

Study design and participants:

A single-center retrospective observational study that included patients attended at ILUH with a laboratory-confirmed COVID-19 between 1 March 2020 and 28 May 2020. SARS-CoV-2 infection was confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay (FTD SARS-CoV-2 Assay by SIEMENS) from nasopharyngeal swabs (Deltaswab by Deltalab). Patients discharged from the emergency department and those transferred to another hospital in the first 48 hours were not included in the final analysis; although these patients were hospitalized at ILUH, they didn't stay enough time to record all the relevant clinical data due to the hospital overcapacity context. Once selected patients that met inclusion criteria, no-one was excluded.

Epidemiological and demographic data, medical history, baseline comorbidities, symptoms and signs both at admission and during follow-up, laboratory findings, RT-PCR results, treatment strategy used for COVID-19, complications and survival data were obtained from patient's electronic medical records. All-cause mortality was calculated including deaths occurred both in patients pending admission (first 48 hours) and during hospitalization. ICU admission, hospitalization length of stay and ventilatory support (invasive mechanical ventilation, noninvasive mechanical ventilation or oxygen mask) were also registered. Different time intervals were

calculated: lag time between symptoms onset and diagnosis, length of stay at ICU andoverall length of stay at the hospital.

Data were collected and managed using REDCap electronic data capture tools hosted at Ideas for Health Association. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies (13).

The STROBE statement guidelines were followed in the conduct and reporting of the study (see Supplementary files).

Patient and Public Involvement:

There was no patient or public involvement in the development of the research design or in conducting the study.

Statistical Analysis:

A descriptive analysis of the clinical background and baseline characteristics of the patients was performed. Continuous variables are presented as median and interquartile range (IQR), after testing normal distribution. Categorical variables are expressed as number of patients and percentage. Two age-groups were defined using a cut off value of 65 (<65 and ≥65 years old) for the comparison of the clinical characteristics of the cohort. For the ICU analysis, the comparison of the characteristics between admitted and non-admitted to ICU patients were limited to patients under 65 because age was one of the major criteria for a better allocation of ICU resources in a context of limited availability of them.

For the mortality analysis, the case fatality ratio (CFR) was defined as number of deaths of laboratory-confirmed COVID-19 patients divided by the number of

laboratory-confirmed COVID-19 cases admitted to the hospital. The outcomes were defined as death or recovered, and the clinical characteristics between these groups were compared using Chi-square test for the categorical variables and Median test for the quantitative variables.

Logistic regression analysis was carried out to ascertain the effect of sociodemographic and clinical background characteristics on mortality. Variables that showed statistical significance ($p<0.05$) in the univariate analysis and clinical variables that could have potential relevance on the outcome according to the current available evidence were included in the model. Odds Ratio (OR) and 95% confidence intervals (95% CI) were calculated.

Statistical analyses were done using Stata software (version 14.0; Stata Corporation, College Station, Texas, USA).

Ethical aspects:

The Institutional Investigation and Ethics Review Board of Infanta Leonor University Hospital (CEI-ILUH) approved the study (Code ILUH R 027-20) and due to its retrospective nature, the need for informed consent from patients was waived.

RESULTS

Overall, 2,259 COVID-19 confirmed cases were attended at ILUH during the study period. The daily number of confirmed COVID-19 cases are plotted by the date of diagnosis (date of positive RT-PCR) and by the date of symptoms onset in **Figure 1.** The first positive patient in our hospital was diagnosed on 1 March 2020 and the epidemic curve peaked on 19 March when 126 PCR tested positive. From that date,

the incidence declined gradually but it took over a month to have a daily number of new cases below 10**.** The percentage of ICU beds and total hospital beds occupied with COVID-19 patients are shown in **Figure 1**. On 27 March, our hospital almost doubled its bed capacity with 702 hospitalized patients. On 6 April, 32 patients were in ICU, reaching 400% of hospital ICU capacity.

Among these 2,259 patients, we analyzed 1,549 cases and excluded 710 because they were discharged from the emergency department or transferred to other hospitals in the first 48 hours. For the complications, ICU and mortality analysis, 156 patients with an uncomplete episode were excluded because they were transferred to other hospitals during their stay or were still hospitalized by 28 May 2020 (**Figure 2**)**.**

Age range of the 1,549 hospitalized patients varied from 3 weeks to 102 years old, median was 69 (IQR 55.0-81.0), and 57.5% were male. All patients except for the three-week-old baby were adults. 55.0% had hypertension, 24.8% diabetes, 24.3% cardiovascular disease, 15.7% obesity, 13.7% chronic obstructive pulmonary disease (COPD) and 8.5% obstructive sleep apnea syndrome (OSAS). HIV infection (0.6%) and autoimmune disease (5.2%) were rare. Overall, 1,221 (78.2%) patients had at least one underlying comorbidity.

The median lag time between symptoms onset and diagnosis was 7 days (IQR: 4-9) (**Figure 1**). The commonest symptoms at presentation were fever (75.3%), cough (65.7%) and dyspnea (58.1%). Diarrhea (17.6%) and anosmia (3.6%) were less common in our case series. Fever, headache, cough, diarrhea, nausea/vomiting, anosmia, muscle or chest pain were more frequent in younger patients while cognitive deterioration was in older patients (**Table 1**).

Table 1. Clinical characteristics and treatment (N= 1549)				
	Overall	< 65 y.o.	≥ 65 y.o.	
	n/N (%)	n/N (%)	n/N (%)	p-value
Male	890/1549 (57.5)	400/642 (62.3)	490/907 (54.0)	0.001
Migrant	385/1549 (24.8)	296/642 (46.1)	89/642 (13.9)	<0.001
Clinical background				
Influenza vaccine 19/20	498/1101 (45.2)	90/463 (19.4)	408/638 (63.9)	<0.001
Cardiological disease	375/1545 (24.3)	37/640 (5.8)	338/905 (37.3)	<0.001
High blood pressure	851/1548 (55.0)	185/641 (28.9)	666/907 (73.4)	<0.001
Diabetes mellitus	382/1541 (24.8)	85/636 (13.4)	297/905 (32.8)	<0.001
Tobacco smoker/ex-smoker	374/1344 (27.8)	121/555 (21.8)	253/789 (32.0)	<0.001
Obesity	240/1531 (15.7)	110/636 (17.3)	130 /895 (14.5)	0.129
COPD	211/1541 (13.7)	37/638 (5.8)	174/903 (19.3)	<0.001
Asthma	122/1545 (7.9)	51/639 (8.0)	71/906 (7.8)	0.668
OSAS	79/935 (8.4)	32/401 (8.0)	47/534 (8.8)	0.654
Cerebrovascular disease	57/125 (45.6)	12/28 (42.7)	45/97 (46.4)	0.741
Thromboembolic disease	41/939 (4.4)	10/410 (2.4)	31/529 (5.9)	0.011
Neurological disease	178/1540 (11.6)	37/637 (5.8)	141/903 (15.6)	<0.001
Chronic kidney disease	104/1543 (6.7)	16/639 (2.5)	88/904 (9.7)	<0.001
Cirrhosis	28/1540 (1.8)	13/638 (2.0)	15/902 (1.7)	0.209
Haematological/oncological cancer	103/1540 (6.7)	21/640 (3.3)	82/900 (9.1)	<0.001
HIV	9/1542 (0.6)	7/639 (1.1)	2/903 (0.2)	0.012
Autoimmune disease	47/913 (5.1)	17/393 (4.3)	30/520 (5.8)	0.328
Symptoms				
Fever	1159/1540 (75.3)	533/638 (83.5)	626/902 (69.4)	<0.001
Headache	133/1533 (8.7)	92/634 (14.5)	41/899 (4.6)	<0.001
Malaise	671/1533 (43.8)	282/637 (44.3)	389/896 (43.3)	0.928
Confused	87/1532 (5.7)	11/633 (1.7)	76/899 (8.4)	<0.001
Dyspnea	891/1533 (58.1)	362/632 (57.3)	529/901 (58.7)	0.382
Superior respiratory tract symptoms	316/1534 (20.6)	153/635 (24.1)	163/899 (18.1)	0.009
Cough	1010/1538 (65.7)	469/638 (73.5)	541/900 (60.1)	<0.001
Expectoration	194/1535 (12.6)	69/635 (10.9)	125/900 (13.9)	0.167
Hemoptysis	26/1532 (1.7)	15/633 (2.3)	11/899 (1.2)	0.207
Chest pain	134/1534 (8.7)	79/635 (12.4)	55/899 (6.1)	<0.001
Muscle pain	291/1534 (19.0)	166/635 (26.1)	125/899 (13.9)	<0.001
Abdominal pain	49/1534 (3.19)	16/635 (2.52)	33/899 (3.67)	0.280
Nausea/vomiting	178/1532 (11.6)	88/636 (13.8)	90/896 (10.0)	0.040
Diarrhea	269/1530 (17.6)	143/636 (22.5)	126/894 (14.1)	<0.001
Skin rash	8/1531 (0.5)	5/636 (0.8)	3/895 (0.3)	0.087
Anosmia	41/1153 (3.6)	29/489 (5.9)	12/664 (1.8)	<0.001
Complications during admission				
Bacterial pneumonia	43/1362 (3.2)	13/551 (2.4)	30/811 (3.7)	0.320
Sepsis	28/1372 (2.0)	16/554 (2.9)	12/818 (1.5)	0.054
Respiratory distress syndrome	195/1368 (14.2)	74/550 (13.4)	121/818 (14.8)	0.557
Pneumothorax	5/1373 (0.4)	3/556 (0.5)	2/817 (0.2)	0.488
Pleural effusion	29/1367 (2.1)	6/552 (1.1)	23/815 (2.8)	0.032

Stroke	11/1373 (0.8)	4/555 (0.7)	7/818 (0.9)	0.669
Disseminated intravascular coagulation	9/1369 (0.7)	2/554 (0.4)	7/815 (0.9)	0.360
Thrombosis	55/824 (6.7)	23/338 (6.8)	32/486 (6.6)	0.833
Acute renal failure	165/1373 (12.0)	37/556 (6.6)	128/817 (15.7)	<0.001
Treatment				
HCQ monotherapy	28/1549 (1.8)	7/642 (1.1)	21/907 (2.3)	0.075
HCQ + AZ	927/1549 (59.8)	448/642 (69.8)	479/907 (52.8)	<0.001
HCQ + LP/r	98/1549 (6.3)	32/642 (5.0)	66/907 (7.3)	<0.001
HCQ + AZ + LP/r	287/1549 (18.5)	90/642 (14.0)	197/907 (21.7)	<0.001
HCQ + LP/r + IFN-b	37/1549 (2.4)	12/642 (1.9)	25/907 (2.8)	0.260
HCQ + AZ + LP/r + IFN-b	113/1549 (7.3)	37/642 (5.8)	76/907 (8.4)	0.051
Tocilizumab	240/1549 (15.5)	144/642 (22.4)	96/907 (10.6)	<0.001
Corticosteroids	684/1549 (44.2)	264/642 (41.1)	420/907 (46.3)	<0.001

COPD: Chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; ICU: intensive care unit; HCQ: hydroxicloroquine; AZ: azithromicine; LP/r: lopinavir-ritonavir; IFN-b: interferon-beta

The most frequent therapies used for treating COVID-19 were the combination hydroxychloroquine plus azithromycin (59.9%) and the combination hydroxychloroquine plus azithromycin plus lopinavir-ritonavir (18.5%). Any treatment combination including lopinavir-ritonavir was more frequently used in older patients. Tocilizumab was used in 15.5% of the patients and corticosteroids in 44.2%. (**Table 1**).

The analysis of the complications during admission showed that 14.3% of patients had acute respiratory distress syndrome with no differences between age groups, 12.0% had acute kidney failure which was more frequent in older patients (15.7% vs. 6.7%), 6.7% had a clinical thrombotic event and 0.7% had disseminated intravascular coagulation (**Table 1**).

Among patients with a complete episode at ILUH, 81 were admitted to ICU: median age 62 (IQR 51-71); 74.1% male.; median length of stay 9 days [IQR 5-19] and 82.7% of them needed invasive ventilation support Clinical characteristics are shown in **Table**

2. Among the 575 patients younger than 65 years old with a complete episode at ILUH, risk factors associated to ICU admission in the univariate analysis were: being male, obesity, hypertension, OSAS, high respiratory rate, a low blood oxygen saturation level (SpO2) at admission, a high neutrophil/lymphocyte ratio, an elevated plasma INR, lactate dehydrogenase (LDH), aspartate transaminase (AST), creatinine and C-reactive protein and the presence of alveolar pulmonary infiltrates in the chest x-ray. (**Table 2**). We calculated CFR in ICU patients with a complete episode at ILUH (70 patients): global CFR was 72.9% (62.8% in the under 65 group and 88.9% in the older group).

Table 2. Clinical, laboratory and diagnosis imaging characteristics of COVID-19 patients who have been admitted in ICU. Comparison between patients under 65 years of age admitted to ICU vs non-admitted to ICU.

		<65 y. old patients (n=575)		
	ICU patients cohort (n=81)	**Admitted to ICU (n=50)**	**Non-admitted to ICU (n=525)**	**p-value**
Age[1]	62 (51-71) (N=81)	54 (48-60) (N=50)	53 (45-59) (N=525)	0.625
Male[2]	60/81 (74.1)	21/50 (42.0)	325/525 (61.9)	0.048
Migrant[2]	25/81 (30.9)	21/50 (42.0)	238/525 (45.3)	0.651
Influenza vaccine 19-20[2]	12/42 (28.6)	5/28 (17.9)	75/395 (19.0)	0.883
Clinical background				
Cardiovascular disease[2]	17/81 (21.0)	6/50 (12.0)	29/523 (5.5)	0.069
High blood pressure[2]	43/81 (53.1)	23/50 (46.0)	147/524 (28.1)	0.008
Diabetes mellitus[2]	23/81 (28.4)	10/50 (20.0)	65/519 (12.5)	0.315
Tobacco smoker/ex-smoker[2]	23/76 (30.3)	13/49 (26.5)	98/450 (21.8)	0.447
Obesity[2]	23/81 (28.4)	17/50 (34.0)	80/520 (15.4)	0.001
COPD[2]	7/81 (8.6)	4/50 (8.0)	30/521 (5.8)	0.522
Asthma[2]	5/81 (6.2)	4/50 (8.0)	43/522 (8.2)	0.117

OSAS[2]	8/39 (20.5)	8/27 (29.6)	22/332 (6.6)	<0.001
Thromboembolic disease[2]	2/40 (5.0)	2/28 (7.1)	8/338 (2.4)	0.136
Neurological disease[2]	5/80 (6.3)	2/49 (4.1)	31/521 (6.0)	0.786
Chronic kidney disease[2]	5/81 (6.2)	3/50 (6.0)	12/522 (2.3)	0.118
Liver cirrhosis[2]	1/80 (1.3)	1/50 (2.0)	11/522 (2.1)	0.117
Haematological/oncological cancer[2]	4/81 (4.9)	1/50 (2.0)	19/523 (3.6)	0.548
HIV[2]	0/81 (0.0)	0/50 (0.0)	7/522 (1.3)	0.529
Clinical and laboratory presentation				
Heart rate, beats per minute[1]	94 (83-107) (N=73)	54 (48-60) (N=50)	53 (45-59) (N=525)	0.625
Respiratory rate, breaths per minute[1]	23 (18-30) (N=44)	24 (18-30) (N=33)	18 (16-20) (N=222)	0.002
Systolic blood pressure, mmHg[1]	133 (119-142) (N=66)	128 (118-141) (N=42)	125 (114-137) (N=292)	0.591
SpO2, %[1]	88 (76-93) (N=69)	88 (66-94) (N=44)	96 (92-97) (N=454)	<0.001
SpO2<90%[2]	39/81 (48.1)	26/50 (52.0)	53/525 (10.1)	<0.001
SpO2 after oxygen administration, %[1]	95 (90-97) (N=39)	95 (90-98) (N=27)	96 (94-98) (N=91)	0.813
SpO2<90% after oxygen administration[2]	9/81 (11.1)	5/50 (10.0)	0/525 (0.0)	<0.001
Hemoglobin, g/L[1]	13.9 (11.9-15.0= (N=81)	14.1 (12.1-15.2) (N=50)	14.1 (13.1-15.1) (N=493)	0.946
Neutrophils, cells count/μL[1]	6300 (4500-9300) (N=81)	7000 (4600-8800) (N=50)	4700 (3500-6700) (N=495)	0..001
Lymphocytes, cells count/μL[1]	900 (600-1200) (N=81)	900 (700-1300) (N=50)	1100 (800-1400) (N=495)	0.252
Neutrophil/lymphocyte ratio[1]	6.64 (5.0-12.7) (N=81)	6.69 (4.8-12.3) (N=50)	4.4 (2.9-7.1) (N=495)	<0.001
Platelets, $x10^9$/L[1]	209 (170-267) (N=81)	205 (172-265) (N=50)	213 (171-274) (N=495)	0.777
INR[1]	1.1 (1.0-1.2) (N=81)	1.1 (1.0-1.2) (N=50)	1.1 (1.0-1.1) (N=484)	0.035
D-dimer, mg/L[1]	940 (485-2095) (N=56)	790 (470-2350) (N=35)	640 (400-1080) (N=334)	0.163
LDH, U/L[1]	408 (279-542) (N=70)	415 (279-605) (N=43)	271 (215-348) (N=430)	<0.001
ALT, U/L[1]	45 (32-67) (N=80)	50 (34-80) (N=50)	44 (30-66) (N=494)	0.075
AST, U/L[1]	59 (40-82) (N=79)	60 (43-85) (N=50)	40 (29-57) (N=485)	<0.001

Creatinine, mg/dL[1]	1.1 (0.9-1.3) (N=78)	1.1 (1.0-1.3) (N=48)	0.9 (0.7-1.1) (N=480)	<0.001
C-reactive protein, mg/L[1]	1157 (481-2054) (N=80)	1234 (678-2133) (N=49)	522 (174-1152) (N=494)	<0.001
Diagnosis imaging				
Bilateral pulmonary infiltrates[2]	61/74 (82.4)	40/46 (87.0)	388/476 (81.5)	0.359
Interstitial pulmonary infiltrates[2]	61/81 (75.3)	38/50 (76.0)	360/525 (68.6)	0.277
Alveolar pulmonary infiltrates[2]	51/81 (63.0)	33/50 (66.0)	230/525 (43.8)	0.003
Respiratory supplementation				
Oxygen therapy[2]	77/81 (95.1)	47/50 (94.0)	345/516 (66.9)	<0.001
Non-invasive ventilation[2]	38/80 (47.5)	26/49 (53.1)	25/513 (4.9)	<0.001
Invasive ventilation[2]	67/81 (82.7)	43/50 (86.0)	0/514 (0.0)	<0.001

COPD: chronic obstructive pulmonary disease; OSAS: Obstructive sleep apnea syndrome; HIV: Human immunodeficiency virus; SpO2: partial oxygen saturation; LDH: Lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase

[1]continuous variable (median, IQR, N); [2]categorical variables (n/N, %)

The overall CFR in our cohort was 21.2% (296/1,393 cases). The median length of stay was 9 days (IQR 6-14). Among the 296 deaths, 48 occurred in the first 48 hours and the rest during hospitalization. These 48 patients had a higher median age compared to the global cohort (82.5 vs 69) and their median lag time from symptom onset until fatality was lower (7 days vs 13.5 days, p<0.001). As shown in **Table 3**, patients who died were older and more likely to be male, current smoker/ex-smoker, and had hypertension, cardiovascular disease, COPD, OSAS, diabetes mellitus, neurological disease, chronic kidney disease and neoplasia in the univariate analysis. Also, they received more frequently ventilatory support during hospitalization and showed more alveolar pulmonary infiltrates in chest x-ray than people who recovered.

Table 3. Clinical, laboratory and diagnosis imaging characteristics of COVID-19 patients who died or recovered.

	Death (n=296)	**Recovered (n=1097)**	**p-value**
Age[1]	82 (71.5-87) (N=246)	65 (53-78) (N=1097)	<0.001
Male[2]	208/296 (70.3)	593/1097 (54.1)	<0.001

Migrant[2]	41/296 (13.8)	296/1097 (27.0)	<0.001
Clinical background			
Influenza vaccine 19/20[2]	113/183 (61.7)	342/820 (41.7)	<0.001
Cardiovascular disease[2]	124/296 (41.9)	217/1093 (19.8)	<0.001
High blood pressure[2]	208/296 (70.3)	565/1096 (51.5)	<0.001
Diabetes mellitus[2]	90/295 (30.5)	260/1090 (23.8)	0.038
Tobacco smoker/exs-smoker[2]	111/260 (42.7)	236/950 (23.8)	<0.001
Obesity[2]	42/292 (14.4)	169/1085 (15.6)	0.169
COPD[2]	67/293 (22.9)	120/1092 (11.0)	<0.001
Asthma[2]	17/296 (5.7)	95/1093 (8.7)	0.166
OSAS[2]	20/156 (12.8)	53/687 (7.7)	0.041
Thromboembolic disease[2]	11/161 (6.8)	26/681 (3.8)	0.093
Neurological disease[2]	59/293 (20.1)	101/1091 (9.3)	<0.001
Chronic kidney disease[2]	40/295 (13.6)	58/1092 (5.3)	<0.001
Liver cirrhosis[2]	8/292 (2.7)	17/1093 (1.5)	0.352
Haematological/oncological cancer[2]	48/293 (16.4)	50/1092 (4.6)	<0.001
HIV[2]	0/295 (0.0)	8/1091 (0.7)	0.327
Clinical and laboratory presentation			
Heart rate, beats per minute[1]	88 (78-102) (N=242)	88 (78-100) (N=881)	0.856
Respiratory rate, breaths per minute[1]	21.5 (16-28) (N=116)	18 (16-20.5) (N=397)	<0.001
Systolic blood pressure, mmHg[1]	130 (111-147) (N=217)	130 (117-143) (N=683)	0.877
SpO2, %[1]	89 (82-93) (N=239)	95 (92-97) (N=945)	0.033
SpO2<90%[2]	121/203 (59.6)	152/945 (16.1)	<0.001
SpO2 after oxygen administration, %[1]	94 (90.5-97) (N=112)	96 (94-98) (N=203)	0.003
SpO2<90% after oxygen administration[2]	18/112 (16.1)	7/203 (0.1)	<0.001
Hemoglobin, g/L[1]	12.70 (11.00-14.50) (N=292)	13.70 (12.60-14.70) (N=1054)	<0.001
Neutrophils, cells count/μL[1]	6100 (4200-8550) (N=292)	4800 (3500-6800) (N=1057)	<0.001
Lymphocytes, cells count/μL [1]	800 (500-1100) (N=292)	1000 (800-1300) (N=1057)	<0.001
Neutrophil/lymphocyte ratio[1]	7.17 (4.3-12.9) (N=292)	4.67 (3.1-7.4) (N=1057)	<0.001
Platelets, $x10^9$/L[1]	190 (142.5-263.5) (N=292)	209 (162-273) (N=1057)	0.040
INR[1]	1.1 (1.0-1.3) (N=283)	1.1 (1.0-1.2) (N=1026)	<0.001
D-dimer, mg/L[1]	1060 (570-2560) (N=167)	750 (450-1330) (N=685)	<0.001
LDH, U/L[1]	345 (249-479) (N=235)	259 (210-331) (N=887)	<0.001
ALT, U/L[1]	31 (23-47) (N=287)	36 (25-55) (N=1050)	<0.001

AST, U/L[1]	47 (30-67) (N=284)	38 (28-55) (N=1035)	<0.001
Creatinine, mg/dL[1]	1.2 (0.9-1.7) (N=285)	0.9(0.7-1.2) (N=1032)	<0.001
C-reactive protein, mg/L[1]	105.9 (36.2-182.4) (N=291)	53.8 (18.3-111.4)	<0.001
Diagnosis imaging			
Bilateral pulmonary infiltrates[2]	218/259 (84.2)	762/960 (79.4)	0.084
Interstitial pulmonary infiltrates[2]	182/296 (61.5)	689/1097 (62.8)	0.677
Alveolar pulmonary infiltrates[2]	153/296 (51.7)	458/1097 (41.7)	0.002
Respiratory supplementation			
Oxygen therapy[2]	285/292 (97.6)	458/1075 (76.5)	0.001
Non-invasive ventilation[2]	57/289 (19.7)	64/1072 (6.0)	<0.001
Invasive ventilation[2]	46/292 (15.7)	15/1075 (1.4)	<0.001
COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; HIV: Human immunodeficiency virus; SpO2: partial oxygen saturation; LDH: Lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase [1]continous variable (median, IQR, N); [2]categorical variable (n/N, %)			

In the multivariate analysis, independent factors related to death were: years of age (OR 1.07; 95% CI: 1.06-1.09), being male (OR 2.86; 95% CI: 1.85-4.50), neurological disease (OR 1.93; 95% CI: 1.19-3.13), chronic kidney disease (OR 2.83; 95% CI: 1.40-5.71) and neoplasia (OR 4.29; 95% CI: 2.40-7.67).

Among the 1,549 hospitalized patients, 65 were readmitted (4.2%): 64.6% were male and 67.7% were 65 years old or older. CFR during readmissions was 10.8% (7/65).

DISCUSSION

This study describes the COVID-19 series of a secondary level hospital in Madrid, Spain.

During the outbreak, hospital wards almost doubled their capacity (702/361), with the number of patients in ICU quadrupling its capacity (32/8). Beds were brought from other hospitals (antique not working hospitals) to turn single rooms into double rooms

and to make surge beds in large waiting room areas, which became ward beds. A cohort system (confirmed cases located together and patients with similar suspect degree too) was followed during the early stages of the epidemic in order to avoid hospital transmission. Some weeks after the beginning of the pandemic the Gym used for patient's rehabilitation, was transformed into a semi-critical unit where patients discharged from the ICU or patients needing closer monitoring or High Flow Oxygen were admitted. The ordinary activity in consultations and elective surgery was canceled, the pediatric emergencies were referred to other hospitals and all doctors attended patients with COVID-19 exclusively. All physicians and nursing staff were organized into two groups: the COVID Assistance group, led by the internal medicine department: they attended COVID-19 patients; and the COVID Non-Assistance group which gave all the administrative support: requesting laboratory tests, writing clinical reports, informing about clinical evolution to patient's relatives, etc. Regarding Critical Care beds: our hospital regular capacity comprises 8 beds for ICU, and 6 for the Surgical Critical Care. Surge critical care beds where made available in the Post Anesthesia Care Unit (6 beds) and the Outpatient Surgery Post-Anesthesia Care Unit (12 beds), to a maximum of 32 critical care beds.

Patients baseline characteristics were similar to the largest published series in Spain (10), although our patients were older and with a higher proportion of males compared to other tertiary Spanish hospital series (9).

We found that younger patients showed a high incidence of fever, cough, headache, muscle pain and diarrhea, whereas older patients showed a less specific clinical presentation. Other studies did not find differences in clinical presentation related to age (14). This information could be crucial for the rapid identification and isolation of the suspected cases at any healthcare level.

Our cohort showed a high incidence of acute kidney failure during hospitalization similar to other non-Spanish series (15,16) but higher than other Madrid series (9), with no association to drug administration. This could be explained for the rapid hydroelectrolytic imbalance in older patients in the context of an acute systemic viral disease. We also found a high incidence of thrombotic events (6.7%) comparable to previous reports (17), although disseminated intravascular coagulation was rare.

Lopinavir/ritonavir-based treatments were more frequently used in older patients. This finding is due to the use of this drug as standard treatment in our hospital protocol during the first half of the outbreak, when most of the patients were older than 65. Tocilizumab, with or without corticosteroids, was used following Spanish Drug Agency recommendations in patients who developed cytokine release storm (CRS) which is believed to cause acute respiratory distress syndrome (ARDS), although corticosteroids were also used in others clinical contexts.

During the study, criteria for ICU admission was the need for mechanical ventilation. Due to the number of ICU beds made available for the number of patients admitted to hospital, which doubled the usual hospital capacity, during the study period 22 patients were transferred to other ICUs of Madrid, to make ILUH's ICU beds available for other patients. In the same way, due to the scarce ICU bed capacity, triage of patients had to be done. The selection for ICU admission opportunity was made individually, based on each patient's comorbidities, functional capacity, age (never solely age as a criteria) and depending on the availability of critical care beds at the moment. A local guideline for patient admission on critical care unit was made, based on the consensus document released by the Spanish Society of Intensive and Critical Care (SEMICYUC) and other 17 medical societies (18). On the other hand, Non Invasive Mechanical

Ventilation or High Flow Oxygen, managed by pneumologists, was available in the ward for selected patients not admitted to ICU

Our findings in the ICU analysis in patients under 65 years old were analogous to other studies (16,19,20) in terms of clinical characteristics and laboratory values. As described in the New York series (16), it seems that obesity and OSAS were related factors leading to ICU admission, even more than the presence of a previous pulmonary disease. This could suggest that patients with a baseline ventilatory compromise could entail a higher risk for ICU admission due to alveolar hypoventilation and acute-on-chronic hypercapnic respiratory failure. However, this analysis has some limitations related to scarce availability of ICU resources in our center and the number of ICU patients who were transferred to other hospitals.

The CFR in our series was 21.2%. It has probably been overestimated due to a significant proportion of patients transferred to other hospitals in the first 48 hours, who had a less severe disease. Some published series showed a lower CFR (21), although others reported a similar (9,10,16) or even higher CFR (15,22). The differences could be related to demographic factors, different hospital admission criteria, case definition and healthcare system overload level (23). It is interesting to note that the CFR found in our study is similar to other Spanish tertiary level hospitals (9), despite our sample had a higher proportion of older and male patients and our center had a lower proportion of conventional hospitalization and ICU beds availability. The CFR in our ICU was slightly lower than other studies (16). Our CRF similar to other hospitals with greater capacity could be related to a better reorganization of spaces and resources. Some areas of the hospital were reoriented to attend COVID-19 patients like pediatric or anesthesia areas. Comparing the patients who died in the first 48 hours (48/296) with the rest of the deceased, the median age was higher and the median days from

symptom onset until fatality was lower. This could reflect a steep clinical deterioration in older patients compared to younger patients. Further studies are required to support the evidence of a severe clinical phenotype of SARS-CoV-2 infection characterized by a quick progression of an acute respiratory failure with severe hypoxemia in older patients that leads to fatal outcome.

We found similarities with other series (24) about variables associated to fatality in the univariate analysis, such as hypertension, cardiovascular disease or pulmonary diseases. Nevertheless, after adjusting by sociodemographic variables and comorbidities at admission, risk factors related to death were age, male gender, neurological disease, chronic kidney disease and cancer. These findings are consistent with other studies that identify male sex and age as important predictors for mortality (25). However, this analysis has some limitations because it only focuses in hospitalized patients skewing estimates of the morbi-mortality and risk factors of COVID-19 globally (11).

The strength of this study lies on the sequential collection of patients (all COVID-19 patients admitted to hospital were included) and on the complete follow-up of all patients during their entire hospital stay. On the other hand, it also has some limitations. First, its observational and retrospective nature. Second, some variables (i.e. anosmia and history of thromboembolic event) have a relatively large number of missing values because they were not registered from the beginning of the study, due to changes in the evidence related to COVID-19 during the progression of the pandemic. Third, there is no follow-up after hospital discharge, so only in-hospital fatality can be estimated.

We are now attending a second outbreak of COVID-19 in Madrid. Compared to the first outbreak, the speed of community transmission is lower, the case detection capacity is higher, there is more knowledge of the disease and the possible treatments and healthcare settings are better prepared. All these factors will probably have a great impact on the analysis if the study were to be repeated now. Future analysis comparing results from first and consecutive waves of COVID-19 pandemic at ILUH would be interesting to make.

CONCLUSION

This study describes the epidemic progression, clinical characteristics, complications and outcomes of COVID-19 patients attended in a secondary level hospital in one of the highest COVID-19 incidence neighborhoods of Madrid, which turned into an entire COVID-19 center and almost doubled its bed capacity, during the first wave of COVID-19 pandemic in Spain. Fatal outcomes were similar to those reported by hospitals with a higher level of complexity.

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FOOTNOTES

- **Contributors:** EJ, MFV, JV, IFJ, PR and MPB conceived the study idea. EJ, MFV, JV, IFJ, PR, MPB, EAA, EIG and AL contributed to the study design. EJ, MFV, IFJ, PR, EAA, EIG, AL and EG performed the data collection. MFV and EJ performed the analysis. EJ, MFV, JV, IFJ, PR, MPB, EAA, EIG and AL drafted the first version of the manuscript. EJ, MFV, JV, IFJ, MPB, PR, EG, EAA, EIG, AL, JT, AJTM, BGM, GPL, AAM and LM critically reviewed the manuscript and approved the final version. All authors meet the ICMJE criteria for authorship.
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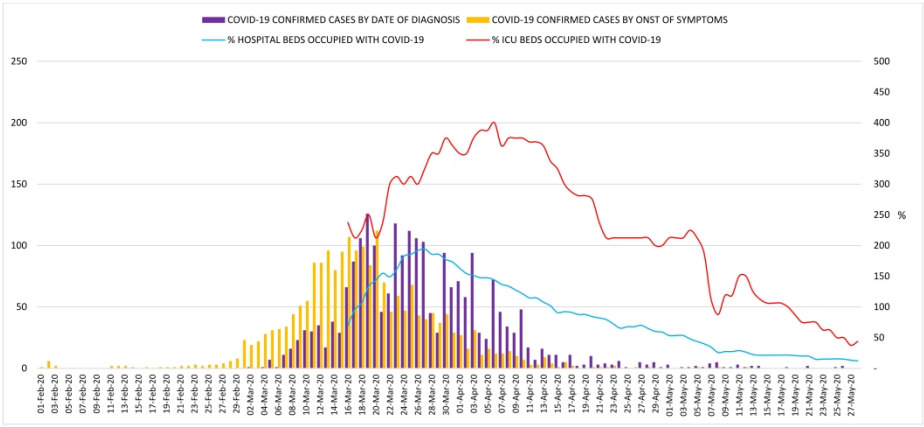

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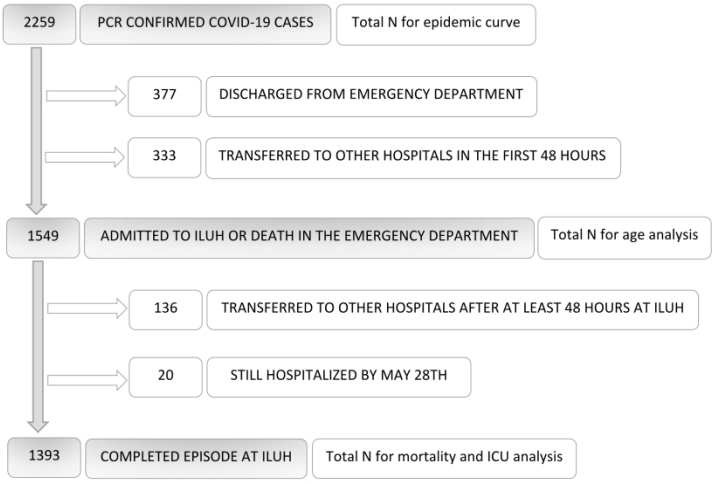

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Characteristics, Complications and Outcomes Among 2259 Patients Hospitalized with COVID-19 in a Secondary Level Hospital in Madrid, Spain

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	***Yes*** ***Pag 1-2***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	***Yes*** ***Pag 1-2***
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	***Yes*** ***Pag 3-4***
Objectives	3	State specific objectives, including any prespecified hypotheses	***Yes*** ***Pag 4***
Methods			
Study design	4	Present key elements of study design early in the paper	***Yes*** ***Pag 5***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	***Yes*** ***Pag 5***
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	***Yes*** ***Pag 5***
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	***Yes*** ***Pag 5-6***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***Yes*** ***Pag 5-6***
Bias	9	Describe any efforts to address potential sources of bias	***Yes*** ***Pag 5-6***
Study size	10	Explain how the study size was arrived at	***Yes*** ***Pag 6***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	***Yes*** ***Pag 6***

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	***Yes*** ***Pag 6***
		(*b*) Describe any methods used to examine subgroups and interactions	***Yes*** ***Pag 6***
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	***Yes*** ***Pag 7***
		(b) Give reasons for non-participation at each stage	***Yes*** ***Fig 2***
		(c) Consider use of a flow diagram	***Yes*** ***Fig 2***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	***Yes*** ***Pag 7-10*** ***Fig 1*** ***Tables 1-3***
		(b) Indicate number of participants with missing data for each variable of interest	***Yes*** ***Tables 1-3***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	***Yes*** ***Pag 9*** ***Fig 1***
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	***Yes*** ***Pag 9*** ***Table 3***
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	***Yes*** ***Pag 7-10*** ***Tables 1-3***
		(*b*) Report category boundaries when continuous variables were categorized	***Yes*** ***Pag 7-10*** ***Tables 1-3***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	***Yes*** ***Pag 9*** ***Uni/multivariate***
Discussion			
Key results	18	Summarise key results with reference to study objectives	***Yes*** ***Pag 10-12***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	***Yes*** ***Pag 10-12***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	***Yes*** ***Pag 10-12***
Generalisability	21	Discuss the generalisability (external validity) of the study results	***Yes*** ***Pag 12***

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	***Yes*** ***Pag 14***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Characteristics, Complications and Outcomes Among 1,549 Patients Hospitalized with COVID-19 in a Secondary Hospital in Madrid, Spain: a Retrospective Case Series Study

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Characteristics, Complications and Outcomes Among 1,549 Patients Hospitalized with COVID-19 in a Secondary Hospital in Madrid, Spain: a Retrospective Case Series Study

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KEYWORDS: COVID-19, secondary-level hospital, epidemiology.

ABSTRACT

Objectives: to describe demographic, clinical, radiological and laboratory characteristics, as well as outcomes, of patients admitted for COVID-19 in a secondary hospital. **Design and setting:** Retrospective case series of sequentially hospitalized patients with confirmed SARS-CoV-2, at Infanta Leonor University Hospital (ILUH) in Madrid, Spain. **Participants:** All patients attended at ILUH testing positive to RT-PCR on nasopharyngeal swabs and diagnosed with COVID-19 between 1 March 2020 and 28 May 2020. **Results:** A total of 1,549 COVID-19 cases were included (median age 69 [IQR 55.0- 81.0], 57.5% male). 78.2% had at least one underlying comorbidity, the most frequent was hypertension (55.8%). Most frequent symptoms at presentation were fever (75.3%), cough (65.7%) and dyspnea (58.1%). 81 (5.8%) patients were admitted to the intensive care unit (ICU) (median age 62 [IQR 51-71]; 74.1% male; median length of stay 9 days [IQR 5-19]) 82.7% of them needed invasive ventilation support. 1393 patients had an outcome at the end of the study period (case fatality ratio: 21.2% (296/1,393)). The independent factors associated with fatality (OR; 95% CI): age (1.07; 1.06-1.09), male sex (2.86; 1.85-4.50), neurological disease (1.93; 1.19-3.13), chronic kidney disease (2.83; 1.40-5.71) and neoplasia (4.29; 2.40-7.67). The percentage of hospital beds occupied with COVID-19 almost doubled (702/361), with the number of patients in ICU quadrupling its capacity (32/8). Median length of stay was 9 days (IQR 6-14). **Conclusions:** This study provides clinical characteristics, complications and outcomes of COVID-19 patients admitted to a European secondary hospital. Fatal outcomes were similar to those reported by hospitals with a higher level of complexity.

STRENGTHS AND LIMITATIONS OF THIS STUDY-This is a large retrospective case series study of 1549 sequentially hospitalized patients with confirmed SARS-CoV-2.

-The study describes the response of a secondary hospital based in a region of Spain with the highest incidence of COVID-19, and how the hospital was transformed into a center entirely dedicated to COVID-19.

-A complete follow-up was made of all patients during hospital stay, although after discharge no outcome information was collected, so only in-hospital fatality could be estimated.

BACKGROUND

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in China and spread globally, causing a new infectious disease named “coronavirus disease 2019” (COVID-19) (1). By 28 May 2020, the epidemic reaches 5,593,631 confirmed cases and more than 353,334 deaths across 216 countries all over the world (2).

The first confirmed case of COVID-19 in Spain was reported from La Gomera (Canary Islands) on 31 January 2020 (3). But it was not until the last week of February 2020 when the first five cases were reported in the Community of Madrid (4).

During March and April 2020 (first COVID-19 wave in Spain and Europe), Spain had been one of the most affected countries by the coronavirus, being one of the main

outbreaks of the disease worldwide. Spain, is now the second country in Europe with the highest number of confirmed cases (after the Russian Federation) with 470.973 cases as of 1 September 2020 (2,5,6). The rate of infections in the Community of Madrid has exceeded every other region in Spain, with more than 27% of all confirmed cases in Spain and an accumulated number of 45,074 hospitalized patients and 8,662 deaths as of 1 September 2020 (5).

Hospitals of the various regional health services of Spain are categorized into different complexity levels depending on their size, technological resources and the higher or lower availability of different clinical departments, thus, in ascending order of complexity we have primary, secondary and tertiary level hospitals; tertiary hospitals often have specific clinical departments that attend patients coming from different parts of the country. The Infanta Leonor University Hospital (ILUH) is a secondary level hospital with 361 beds, including 8 in the intensive care unit (ICU). It serves the population of Vallecas (305,262 individuals) (7). Our healthcare area has a disproportionate number of beds per inhabitants: 1.07 beds per 1000 people compared to 2.15 beds per 1000 people overall within the region. Vallecas is one of the COVID-19 most affected areas in the city of Madrid (Spain) with 9,947 total confirmed COVID-19 cases as of 1 September 2020 (8). Therefore, the level of hospital saturation during the epidemy has been one of the greatest in Spain. As a consequence, the hospital was in March transformed into a center entirely dedicated to COVID-19 and all its professionals focused on assisting patients affected by the SARS-CoV-2 infection.

Limited information is available to describe characteristics, complications and mortality in COVID-19 overloaded secondary Spanish hospitals. The available data from Spain refer to tertiary hospitals, multi-centric studies or primary care settings (9–12).

This study describes the clinical characteristics, severity, types of treatments and overall outcomes of patients with confirmed SARS-CoV-2 infection admitted to ILUH in Madrid (Spain).

METHODS

Study design and participants:

A single-center retrospective observational study that included patients attended at ILUH with a laboratory-confirmed COVID-19 between 1 March 2020 and 28 May 2020. SARS-CoV-2 infection was confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay (FTD SARS-CoV-2 Assay by SIEMENS) from nasopharyngeal swabs (Deltaswab by Deltalab). Patients discharged from the emergency department and those transferred to another hospital in the first 48 hours were not included in the final analysis; although these patients were hospitalized at ILUH, they didn't stay enough time to record all the relevant clinical data due to the hospital overcapacity context. Once selected patients that met inclusion criteria, no-one was excluded.

Epidemiological and demographic data, medical history, baseline comorbidities, symptoms and signs both at admission and during follow-up, laboratory findings, RT-PCR results, treatment strategy used for COVID-19, complications and survival data were obtained from patient's electronic medical records. All-cause mortality was calculated including deaths occurred both in patients pending admission (first 48 hours) and during hospitalization. ICU admission, hospitalization length of stay and ventilatory support (invasive mechanical ventilation, noninvasive mechanical ventilation or oxygen mask) were also registered. Different time intervals were

calculated: lag time between symptoms onset and diagnosis, length of stay at ICU andoverall length of stay at the hospital.

Data were collected and managed using REDCap electronic data capture tools hosted at Ideas for Health Association. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies (13).

The STROBE statement guidelines were followed in the conduct and reporting of the study (see Supplementary files).

Patient and Public Involvement:

There was no patient or public involvement in the development of the research design or in conducting the study.

Statistical Analysis:

A descriptive analysis of the clinical background and baseline characteristics of the patients was performed. Continuous variables are presented as median and interquartile range (IQR), after testing normal distribution. Categorical variables are expressed as number of patients and percentage. Two age-groups were defined using a cut off value of 65 (<65 and ≥65 years old) for the comparison of the clinical characteristics of the cohort. For the ICU analysis, the comparison of the characteristics between admitted and non-admitted to ICU patients were limited to patients under 65 because age was one of the major criteria for a better allocation of ICU resources in a context of limited availability of them.

For the mortality analysis, the case fatality ratio (CFR) was defined as number of deaths of laboratory-confirmed COVID-19 patients divided by the number of

laboratory-confirmed COVID-19 cases admitted to the hospital. The outcomes were defined as death or recovered, and the clinical characteristics between these groups were compared using Chi-square test for the categorical variables and Median test for the quantitative variables.

Logistic regression analysis was carried out to ascertain the effect of sociodemographic and clinical background characteristics on mortality. Variables that showed statistical significance ($p<0.05$) in the univariate analysis and clinical variables that could have potential relevance on the outcome according to the current available evidence were included in the model. Odds Ratio (OR) and 95% confidence intervals (95% CI) were calculated.

Statistical analyses were done using Stata software (version 14.0; Stata Corporation, College Station, Texas, USA).

Ethical aspects:

The Institutional Investigation and Ethics Review Board of Infanta Leonor University Hospital (CEI-ILUH) approved the study (Code ILUH R 027-20) and due to its retrospective nature, the need for informed consent from patients was waived.

RESULTS

Overall, 2,259 COVID-19 confirmed cases were attended at ILUH during the study period. The daily number of confirmed COVID-19 cases are plotted by the date of diagnosis (date of positive RT-PCR) and by the date of symptoms onset in **Figure 1.** The first positive patient in our hospital was diagnosed on 1 March 2020 and the epidemic curve peaked on 19 March when 126 PCR tested positive. From that date,

the incidence declined gradually but it took over a month to have a daily number of new cases below 10**.** The percentage of ICU beds and total hospital beds occupied with COVID-19 patients are shown in **Figure 1**. On 27 March, our hospital almost doubled its bed capacity with 702 hospitalized patients. On 6 April, 32 patients were in ICU, reaching 400% of hospital ICU capacity.

Among these 2,259 patients, we analyzed 1,549 cases and excluded 710 because they were discharged from the emergency department or transferred to other hospitals in the first 48 hours. For the complications, ICU and mortality analysis, 156 patients with an uncomplete episode were excluded because they were transferred to other hospitals during their stay or were still hospitalized by 28 May 2020 (**Figure 2**)**.**

Age range of the 1,549 hospitalized patients varied from 3 weeks to 102 years old, median was 69 (IQR 55.0-81.0), and 57.5% were male. All patients except for the three-week-old baby were adults. 55.0% had hypertension, 24.8% diabetes, 24.3% cardiovascular disease, 15.7% obesity, 13.7% chronic obstructive pulmonary disease (COPD) and 8.5% obstructive sleep apnea syndrome (OSAS). HIV infection (0.6%) and autoimmune disease (5.2%) were rare. Overall, 1,221 (78.2%) patients had at least one underlying comorbidity.

The median lag time between symptoms onset and diagnosis was 7 days (IQR: 4-9) (**Figure 1**). The commonest symptoms at presentation were fever (75.3%), cough (65.7%) and dyspnea (58.1%). Diarrhea (17.6%) and anosmia (3.6%) were less common in our case series. Fever, headache, cough, diarrhea, nausea/vomiting, anosmia, muscle or chest pain were more frequent in younger patients while cognitive deterioration was in older patients (**Table 1**).

Table 1. Clinical characteristics and treatment (N= 1549)				
	Overall	< 65 y.o.	≥ 65 y.o.	
	n/N (%)	n/N (%)	n/N (%)	p-value
Male	890/1549 (57.5)	400/642 (62.3)	490/907 (54.0)	0.001
Migrant	385/1549 (24.8)	296/642 (46.1)	89/642 (13.9)	<0.001
Clinical background				
Influenza vaccine 19/20	498/1101 (45.2)	90/463 (19.4)	408/638 (63.9)	<0.001
Cardiological disease	375/1545 (24.3)	37/640 (5.8)	338/905 (37.3)	<0.001
High blood pressure	851/1548 (55.0)	185/641 (28.9)	666/907 (73.4)	<0.001
Diabetes mellitus	382/1541 (24.8)	85/636 (13.4)	297/905 (32.8)	<0.001
Tobacco smoker/ex-smoker	374/1344 (27.8)	121/555 (21.8)	253/789 (32.0)	<0.001
Obesity	240/1531 (15.7)	110/636 (17.3)	130 /895 (14.5)	0.129
COPD	211/1541 (13.7)	37/638 (5.8)	174/903 (19.3)	<0.001
Asthma	122/1545 (7.9)	51/639 (8.0)	71/906 (7.8)	0.668
OSAS	79/935 (8.4)	32/401 (8.0)	47/534 (8.8)	0.654
Cerebrovascular disease	57/125 (45.6)	12/28 (42.7)	45/97 (46.4)	0.741
Thromboembolic disease	41/939 (4.4)	10/410 (2.4)	31/529 (5.9)	0.011
Neurological disease	178/1540 (11.6)	37/637 (5.8)	141/903 (15.6)	<0.001
Chronic kidney disease	104/1543 (6.7)	16/639 (2.5)	88/904 (9.7)	<0.001
Cirrhosis	28/1540 (1.8)	13/638 (2.0)	15/902 (1.7)	0.209
Haematological/oncological cancer	103/1540 (6.7)	21/640 (3.3)	82/900 (9.1)	<0.001
HIV	9/1542 (0.6)	7/639 (1.1)	2/903 (0.2)	0.012
Autoimmune disease	47/913 (5.1)	17/393 (4.3)	30/520 (5.8)	0.328
Symptoms				
Fever	1159/1540 (75.3)	533/638 (83.5)	626/902 (69.4)	<0.001
Headache	133/1533 (8.7)	92/634 (14.5)	41/899 (4.6)	<0.001
Malaise	671/1533 (43.8)	282/637 (44.3)	389/896 (43.3)	0.928
Confused	87/1532 (5.7)	11/633 (1.7)	76/899 (8.4)	<0.001
Dyspnea	891/1533 (58.1)	362/632 (57.3)	529/901 (58.7)	0.382
Superior respiratory tract symptoms	316/1534 (20.6)	153/635 (24.1)	163/899 (18.1)	0.009
Cough	1010/1538 (65.7)	469/638 (73.5)	541/900 (60.1)	<0.001
Expectoration	194/1535 (12.6)	69/635 (10.9)	125/900 (13.9)	0.167
Hemoptysis	26/1532 (1.7)	15/633 (2.3)	11/899 (1.2)	0.207
Chest pain	134/1534 (8.7)	79/635 (12.4)	55/899 (6.1)	<0.001
Muscle pain	291/1534 (19.0)	166/635 (26.1)	125/899 (13.9)	<0.001
Abdominal pain	49/1534 (3.19)	16/635 (2.52)	33/899 (3.67)	0.280
Nausea/vomiting	178/1532 (11.6)	88/636 (13.8)	90/896 (10.0)	0.040
Diarrhea	269/1530 (17.6)	143/636 (22.5)	126/894 (14.1)	<0.001
Skin rash	8/1531 (0.5)	5/636 (0.8)	3/895 (0.3)	0.087
Anosmia	41/1153 (3.6)	29/489 (5.9)	12/664 (1.8)	<0.001
Complications during admission				
Bacterial pneumonia	43/1362 (3.2)	13/551 (2.4)	30/811 (3.7)	0.320
Sepsis	28/1372 (2.0)	16/554 (2.9)	12/818 (1.5)	0.054
Respiratory distress syndrome	195/1368 (14.2)	74/550 (13.4)	121/818 (14.8)	0.557
Pneumothorax	5/1373 (0.4)	3/556 (0.5)	2/817 (0.2)	0.488
Pleural effusion	29/1367 (2.1)	6/552 (1.1)	23/815 (2.8)	0.032

Stroke	11/1373 (0.8)	4/555 (0.7)	7/818 (0.9)	0.669
Disseminated intravascular coagulation	9/1369 (0.7)	2/554 (0.4)	7/815 (0.9)	0.360
Thrombosis	55/824 (6.7)	23/338 (6.8)	32/486 (6.6)	0.833
Acute renal failure	165/1373 (12.0)	37/556 (6.6)	128/817 (15.7)	<0.001
Treatment				
HCQ monotherapy	28/1549 (1.8)	7/642 (1.1)	21/907 (2.3)	0.075
HCQ + AZ	927/1549 (59.8)	448/642 (69.8)	479/907 (52.8)	<0.001
HCQ + LP/r	98/1549 (6.3)	32/642 (5.0)	66/907 (7.3)	<0.001
HCQ + AZ + LP/r	287/1549 (18.5)	90/642 (14.0)	197/907 (21.7)	<0.001
HCQ + LP/r + IFN-b	37/1549 (2.4)	12/642 (1.9)	25/907 (2.8)	0.260
HCQ + AZ + LP/r + IFN-b	113/1549 (7.3)	37/642 (5.8)	76/907 (8.4)	0.051
Tocilizumab	240/1549 (15.5)	144/642 (22.4)	96/907 (10.6)	<0.001
Corticosteroids	684/1549 (44.2)	264/642 (41.1)	420/907 (46.3)	<0.001

COPD: Chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; ICU: intensive care unit; HCQ: hydroxicloroquine; AZ: azithromicine; LP/r: lopinavir-ritonavir; IFN-b: interferon-beta

The most frequent therapies used for treating COVID-19 were the combination hydroxychloroquine plus azithromycin (59.9%) and the combination hydroxychloroquine plus azithromycin plus lopinavir-ritonavir (18.5%). Any treatment combination including lopinavir-ritonavir was more frequently used in older patients. Tocilizumab was used in 15.5% of the patients and corticosteroids in 44.2%. (**Table 1**).

The analysis of the complications during admission showed that 14.3% of patients had acute respiratory distress syndrome with no differences between age groups, 12.0% had acute kidney failure which was more frequent in older patients (15.7% vs. 6.7%), 6.7% had a clinical thrombotic event and 0.7% had disseminated intravascular coagulation (**Table 1**).

Among patients with a complete episode at ILUH, 81 were admitted to ICU: median age 62 (IQR 51-71); 74.1% male.; median length of stay 9 days [IQR 5-19] and 82.7% of them needed invasive ventilation support Clinical characteristics are shown in **Table**

2. Among the 575 patients younger than 65 years old with a complete episode at ILUH, risk factors associated to ICU admission in the univariate analysis were: being male, obesity, hypertension, OSAS, high respiratory rate, a low blood oxygen saturation level (SpO2) at admission, a high neutrophil/lymphocyte ratio, an elevated plasma INR, lactate dehydrogenase (LDH), aspartate transaminase (AST), creatinine and C-reactive protein and the presence of alveolar pulmonary infiltrates in the chest x-ray. (**Table 2**). We calculated CFR in ICU patients with a complete episode at ILUH (70 patients): global CFR was 72.9% (62.8% in the under 65 group and 88.9% in the older group).

Table 2. Clinical, laboratory and diagnosis imaging characteristics of COVID-19 patients who have been admitted in ICU. Comparison between patients under 65 years of age admitted to ICU vs non-admitted to ICU.

		<65 y. old patients (n=575)		
	ICU patients cohort (n=81)	**Admitted to ICU (n=50)**	**Non-admitted to ICU (n=525)**	**p-value**
Age[1]	62 (51-71) (N=81)	54 (48-60) (N=50)	53 (45-59) (N=525)	0.625
Male[2]	60/81 (74.1)	21/50 (42.0)	325/525 (61.9)	0.048
Migrant[2]	25/81 (30.9)	21/50 (42.0)	238/525 (45.3)	0.651
Influenza vaccine 19-20[2]	12/42 (28.6)	5/28 (17.9)	75/395 (19.0)	0.883
Clinical background				
Cardiovascular disease[2]	17/81 (21.0)	6/50 (12.0)	29/523 (5.5)	0.069
High blood pressure[2]	43/81 (53.1)	23/50 (46.0)	147/524 (28.1)	0.008
Diabetes mellitus[2]	23/81 (28.4)	10/50 (20.0)	65/519 (12.5)	0.315
Tobacco smoker/ex-smoker[2]	23/76 (30.3)	13/49 (26.5)	98/450 (21.8)	0.447
Obesity[2]	23/81 (28.4)	17/50 (34.0)	80/520 (15.4)	0.001
COPD[2]	7/81 (8.6)	4/50 (8.0)	30/521 (5.8)	0.522
Asthma[2]	5/81 (6.2)	4/50 (8.0)	43/522 (8.2)	0.117

OSAS[2]	8/39 (20.5)	8/27 (29.6)	22/332 (6.6)	<0.001
Thromboembolic disease[2]	2/40 (5.0)	2/28 (7.1)	8/338 (2.4)	0.136
Neurological disease[2]	5/80 (6.3)	2/49 (4.1)	31/521 (6.0)	0.786
Chronic kidney disease[2]	5/81 (6.2)	3/50 (6.0)	12/522 (2.3)	0.118
Liver cirrhosis[2]	1/80 (1.3)	1/50 (2.0)	11/522 (2.1)	0.117
Haematological/oncological cancer[2]	4/81 (4.9)	1/50 (2.0)	19/523 (3.6)	0.548
HIV[2]	0/81 (0.0)	0/50 (0.0)	7/522 (1.3)	0.529
Clinical and laboratory presentation				
Heart rate, beats per minute[1]	94 (83-107) (N=73)	54 (48-60) (N=50)	53 (45-59) (N=525)	0.625
Respiratory rate, breaths per minute[1]	23 (18-30) (N=44)	24 (18-30) (N=33)	18 (16-20) (N=222)	0.002
Systolic blood pressure, mmHg[1]	133 (119-142) (N=66)	128 (118-141) (N=42)	125 (114-137) (N=292)	0.591
SpO2, %[1]	88 (76-93) (N=69)	88 (66-94) (N=44)	96 (92-97) (N=454)	<0.001
SpO2<90%[2]	39/81 (48.1)	26/50 (52.0)	53/525 (10.1)	<0.001
SpO2 after oxygen administration, %[1]	95 (90-97) (N=39)	95 (90-98) (N=27)	96 (94-98) (N=91)	0.813
SpO2<90% after oxygen administration[2]	9/81 (11.1)	5/50 (10.0)	0/525 (0.0)	<0.001
Hemoglobin, g/L[1]	13.9 (11.9-15.0= (N=81)	14.1 (12.1-15.2) (N=50)	14.1 (13.1-15.1) (N=493)	0.946
Neutrophils, cells count/μL[1]	6300 (4500-9300) (N=81)	7000 (4600-8800) (N=50)	4700 (3500-6700) (N=495)	0..001
Lymphocytes, cells count/μL[1]	900 (600-1200) (N=81)	900 (700-1300) (N=50)	1100 (800-1400) (N=495)	0.252
Neutrophil/lymphocyte ratio[1]	6.64 (5.0-12.7) (N=81)	6.69 (4.8-12.3) (N=50)	4.4 (2.9-7.1) (N=495)	<0.001
Platelets, $x10^9$/L[1]	209 (170-267) (N=81)	205 (172-265) (N=50)	213 (171-274) (N=495)	0.777
INR[1]	1.1 (1.0-1.2) (N=81)	1.1 (1.0-1.2) (N=50)	1.1 (1.0-1.1) (N=484)	0.035
D-dimer, mg/L[1]	940 (485-2095) (N=56)	790 (470-2350) (N=35)	640 (400-1080) (N=334)	0.163
LDH, U/L[1]	408 (279-542) (N=70)	415 (279-605) (N=43)	271 (215-348) (N=430)	<0.001
ALT, U/L[1]	45 (32-67) (N=80)	50 (34-80) (N=50)	44 (30-66) (N=494)	0.075
AST, U/L[1]	59 (40-82) (N=79)	60 (43-85) (N=50)	40 (29-57) (N=485)	<0.001

Creatinine, mg/dL[1]	1.1 (0.9-1.3) (N=78)	1.1 (1.0-1.3) (N=48)	0.9 (0.7-1.1) (N=480)	<0.001
C-reactive protein, mg/L[1]	1157 (481-2054) (N=80)	1234 (678-2133) (N=49)	522 (174-1152) (N=494)	<0.001
Diagnosis imaging				
Bilateral pulmonary infiltrates[2]	61/74 (82.4)	40/46 (87.0)	388/476 (81.5)	0.359
Interstitial pulmonary infiltrates[2]	61/81 (75.3)	38/50 (76.0)	360/525 (68.6)	0.277
Alveolar pulmonary infiltrates[2]	51/81 (63.0)	33/50 (66.0)	230/525 (43.8)	0.003
Respiratory supplementation				
Oxygen therapy[2]	77/81 (95.1)	47/50 (94.0)	345/516 (66.9)	<0.001
Non-invasive ventilation[2]	38/80 (47.5)	26/49 (53.1)	25/513 (4.9)	<0.001
Invasive ventilation[2]	67/81 (82.7)	43/50 (86.0)	0/514 (0.0)	<0.001

COPD: chronic obstructive pulmonary disease; OSAS: Obstructive sleep apnea syndrome; HIV: Human immunodeficiency virus; SpO2: partial oxygen saturation; LDH: Lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase

[1]continuous variable (median, IQR, N); [2]categorical variables (n/N, %)

The overall CFR in our cohort was 21.2% (296/1,393 cases). The median length of stay was 9 days (IQR 6-14). Among the 296 deaths, 48 occurred in the first 48 hours and the rest during hospitalization. These 48 patients had a higher median age compared to the global cohort (82.5 vs 69) and their median lag time from symptom onset until fatality was lower (7 days vs 13.5 days, p<0.001). As shown in **Table 3**, patients who died were older and more likely to be male, current smoker/ex-smoker, and had hypertension, cardiovascular disease, COPD, OSAS, diabetes mellitus, neurological disease, chronic kidney disease and neoplasia in the univariate analysis. Also, they received more frequently ventilatory support during hospitalization and showed more alveolar pulmonary infiltrates in chest x-ray than people who recovered.

Table 3. Clinical, laboratory and diagnosis imaging characteristics of COVID-19 patients who died or recovered.

	Death (n=296)	**Recovered (n=1097)**	**p-value**
Age[1]	82 (71.5-87) (N=246)	65 (53-78) (N=1097)	<0.001
Male[2]	208/296 (70.3)	593/1097 (54.1)	<0.001

Migrant[2]	41/296 (13.8)	296/1097 (27.0)	<0.001
Clinical background			
Influenza vaccine 19/20[2]	113/183 (61.7)	342/820 (41.7)	<0.001
Cardiovascular disease[2]	124/296 (41.9)	217/1093 (19.8)	<0.001
High blood pressure[2]	208/296 (70.3)	565/1096 (51.5)	<0.001
Diabetes mellitus[2]	90/295 (30.5)	260/1090 (23.8)	0.038
Tobacco smoker/exs-smoker[2]	111/260 (42.7)	236/950 (23.8)	<0.001
Obesity[2]	42/292 (14.4)	169/1085 (15.6)	0.169
COPD[2]	67/293 (22.9)	120/1092 (11.0)	<0.001
Asthma[2]	17/296 (5.7)	95/1093 (8.7)	0.166
OSAS[2]	20/156 (12.8)	53/687 (7.7)	0.041
Thromboembolic disease[2]	11/161 (6.8)	26/681 (3.8)	0.093
Neurological disease[2]	59/293 (20.1)	101/1091 (9.3)	<0.001
Chronic kidney disease[2]	40/295 (13.6)	58/1092 (5.3)	<0.001
Liver cirrhosis[2]	8/292 (2.7)	17/1093 (1.5)	0.352
Haematological/oncological cancer[2]	48/293 (16.4)	50/1092 (4.6)	<0.001
HIV[2]	0/295 (0.0)	8/1091 (0.7)	0.327
Clinical and laboratory presentation			
Heart rate, beats per minute[1]	88 (78-102) (N=242)	88 (78-100) (N=881)	0.856
Respiratory rate, breaths per minute[1]	21.5 (16-28) (N=116)	18 (16-20.5) (N=397)	<0.001
Systolic blood pressure, mmHg[1]	130 (111-147) (N=217)	130 (117-143) (N=683)	0.877
SpO2, %[1]	89 (82-93) (N=239)	95 (92-97) (N=945)	0.033
SpO2<90%[2]	121/203 (59.6)	152/945 (16.1)	<0.001
SpO2 after oxygen administration, %[1]	94 (90.5-97) (N=112)	96 (94-98) (N=203)	0.003
SpO2<90% after oxygen administration[2]	18/112 (16.1)	7/203 (0.1)	<0.001
Hemoglobin, g/L[1]	12.70 (11.00-14.50) (N=292)	13.70 (12.60-14.70) (N=1054)	<0.001
Neutrophils, cells count/μL[1]	6100 (4200-8550) (N=292)	4800 (3500-6800) (N=1057)	<0.001
Lymphocytes, cells count/μL [1]	800 (500-1100) (N=292)	1000 (800-1300) (N=1057)	<0.001
Neutrophil/lymphocyte ratio[1]	7.17 (4.3-12.9) (N=292)	4.67 (3.1-7.4) (N=1057)	<0.001
Platelets, $x10^9$/L[1]	190 (142.5-263.5) (N=292)	209 (162-273) (N=1057)	0.040
INR[1]	1.1 (1.0-1.3) (N=283)	1.1 (1.0-1.2) (N=1026)	<0.001
D-dimer, mg/L[1]	1060 (570-2560) (N=167)	750 (450-1330) (N=685)	<0.001
LDH, U/L[1]	345 (249-479) (N=235)	259 (210-331) (N=887)	<0.001
ALT, U/L[1]	31 (23-47) (N=287)	36 (25-55) (N=1050)	<0.001

AST, U/L[1]	47 (30-67) (N=284)	38 (28-55) (N=1035)	<0.001
Creatinine, mg/dL[1]	1.2 (0.9-1.7) (N=285)	0.9(0.7-1.2) (N=1032)	<0.001
C-reactive protein, mg/L[1]	105.9 (36.2-182.4) (N=291)	53.8 (18.3-111.4)	<0.001
Diagnosis imaging			
Bilateral pulmonary infiltrates[2]	218/259 (84.2)	762/960 (79.4)	0.084
Interstitial pulmonary infiltrates[2]	182/296 (61.5)	689/1097 (62.8)	0.677
Alveolar pulmonary infiltrates[2]	153/296 (51.7)	458/1097 (41.7)	0.002
Respiratory supplementation			
Oxygen therapy[2]	285/292 (97.6)	458/1075 (76.5)	0.001
Non-invasive ventilation[2]	57/289 (19.7)	64/1072 (6.0)	<0.001
Invasive ventilation[2]	46/292 (15.7)	15/1075 (1.4)	<0.001
COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; HIV: Human immunodeficiency virus; SpO2: partial oxygen saturation; LDH: Lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase [1]continous variable (median, IQR, N); [2]categorical variable (n/N, %)			

In the multivariate analysis, independent factors related to death were: years of age (OR 1.07; 95% CI: 1.06-1.09), being male (OR 2.86; 95% CI: 1.85-4.50), neurological disease (OR 1.93; 95% CI: 1.19-3.13), chronic kidney disease (OR 2.83; 95% CI: 1.40-5.71) and neoplasia (OR 4.29; 95% CI: 2.40-7.67).

Among the 1,549 hospitalized patients, 65 were readmitted (4.2%): 64.6% were male and 67.7% were 65 years old or older. CFR during readmissions was 10.8% (7/65).

DISCUSSION

This study describes the COVID-19 series of a secondary level hospital in Madrid, Spain.

During the outbreak, hospital wards almost doubled their capacity (702/361), with the number of patients in ICU quadrupling its capacity (32/8). Beds were brought from other hospitals (antique not working hospitals) to turn single rooms into double rooms

and to make surge beds in large waiting room areas, which became ward beds. A cohort system (confirmed cases located together and patients with similar suspect degree too) was followed during the early stages of the epidemic in order to avoid hospital transmission. Some weeks after the beginning of the pandemic the Gym used for patient's rehabilitation, was transformed into a semi-critical unit where patients discharged from the ICU or patients needing closer monitoring or High Flow Oxygen were admitted. The ordinary activity in consultations and elective surgery was canceled, the pediatric emergencies were referred to other hospitals and all doctors attended patients with COVID-19 exclusively. All physicians and nursing staff were organized into two groups: the COVID Assistance group, led by the internal medicine department: they attended COVID-19 patients; and the COVID Non-Assistance group which gave all the administrative support: requesting laboratory tests, writing clinical reports, informing about clinical evolution to patient's relatives, etc. Regarding Critical Care beds: our hospital regular capacity comprises 8 beds for ICU, and 6 for the Surgical Critical Care. Surge critical care beds where made available in the Post Anesthesia Care Unit (6 beds) and the Outpatient Surgery Post-Anesthesia Care Unit (12 beds), to a maximum of 32 critical care beds.

Patients baseline characteristics were similar to the largest published series in Spain (10), although our patients were older and with a higher proportion of males compared to other tertiary Spanish hospital series (9).

We found that younger patients showed a high incidence of fever, cough, headache, muscle pain and diarrhea, whereas older patients showed a less specific clinical presentation. Other studies did not find differences in clinical presentation related to age (14). This information could be crucial for the rapid identification and isolation of the suspected cases at any healthcare level.

Our cohort showed a high incidence of acute kidney failure during hospitalization similar to other non-Spanish series (15,16) but higher than other Madrid series (9), with no association to drug administration. This could be explained for the rapid hydroelectrolytic imbalance in older patients in the context of an acute systemic viral disease. We also found a high incidence of thrombotic events (6.7%) comparable to previous reports (17), although disseminated intravascular coagulation was rare.

Lopinavir/ritonavir-based treatments were more frequently used in older patients. This finding is due to the use of this drug as standard treatment in our hospital protocol during the first half of the outbreak, when most of the patients were older than 65. Tocilizumab, with or without corticosteroids, was used following Spanish Drug Agency recommendations in patients who developed cytokine release storm (CRS) which is believed to cause acute respiratory distress syndrome (ARDS), although corticosteroids were also used in others clinical contexts.

During the study, criteria for ICU admission was the need for mechanical ventilation. Due to the number of ICU beds made available for the number of patients admitted to hospital, which doubled the usual hospital capacity, during the study period 22 patients were transferred to other ICUs of Madrid, to make ILUH's ICU beds available for other patients. In the same way, due to the scarce ICU bed capacity, triage of patients had to be done. The selection for ICU admission opportunity was made individually, based on each patient's comorbidities, functional capacity, age (never solely age as a criteria) and depending on the availability of critical care beds at the moment. A local guideline for patient admission on critical care unit was made, based on the consensus document released by the Spanish Society of Intensive and Critical Care (SEMICYUC) and other 17 medical societies (18). On the other hand, Non Invasive Mechanical

Ventilation or High Flow Oxygen, managed by pneumologists, was available in the ward for selected patients not admitted to ICU

Our findings in the ICU analysis in patients under 65 years old were analogous to other studies (16,19,20) in terms of clinical characteristics and laboratory values. As described in the New York series (16), it seems that obesity and OSAS were related factors leading to ICU admission, even more than the presence of a previous pulmonary disease. This could suggest that patients with a baseline ventilatory compromise could entail a higher risk for ICU admission due to alveolar hypoventilation and acute-on-chronic hypercapnic respiratory failure. However, this analysis has some limitations related to scarce availability of ICU resources in our center and the number of ICU patients who were transferred to other hospitals.

The CFR in our series was 21.2%. It has probably been overestimated due to a significant proportion of patients transferred to other hospitals in the first 48 hours, who had a less severe disease. Some published series showed a lower CFR (21), although others reported a similar (9,10,16) or even higher CFR (15,22). The differences could be related to demographic factors, different hospital admission criteria, case definition and healthcare system overload level (23). It is interesting to note that the CFR found in our study is similar to other Spanish tertiary level hospitals (9), despite our sample had a higher proportion of older and male patients and our center had a lower proportion of conventional hospitalization and ICU beds availability. The CFR in our ICU was slightly lower than other studies (16). Our CRF similar to other hospitals with greater capacity could be related to a better reorganization of spaces and resources. Some areas of the hospital were reoriented to attend COVID-19 patients like pediatric or anesthesia areas. Comparing the patients who died in the first 48 hours (48/296) with the rest of the deceased, the median age was higher and the median days from

symptom onset until fatality was lower. This could reflect a steep clinical deterioration in older patients compared to younger patients. Further studies are required to support the evidence of a severe clinical phenotype of SARS-CoV-2 infection characterized by a quick progression of an acute respiratory failure with severe hypoxemia in older patients that leads to fatal outcome.

We found similarities with other series (24) about variables associated to fatality in the univariate analysis, such as hypertension, cardiovascular disease or pulmonary diseases. Nevertheless, after adjusting by sociodemographic variables and comorbidities at admission, risk factors related to death were age, male gender, neurological disease, chronic kidney disease and cancer. These findings are consistent with other studies that identify male sex and age as important predictors for mortality (25). However, this analysis has some limitations because it only focuses in hospitalized patients skewing estimates of the morbi-mortality and risk factors of COVID-19 globally (11).

The strength of this study lies on the sequential collection of patients (all COVID-19 patients admitted to hospital were included) and on the complete follow-up of all patients during their entire hospital stay. On the other hand, it also has some limitations. First, its observational and retrospective nature. Second, some variables (i.e. anosmia and history of thromboembolic event) have a relatively large number of missing values because they were not registered from the beginning of the study, due to changes in the evidence related to COVID-19 during the progression of the pandemic. Third, there is no follow-up after hospital discharge, so only in-hospital fatality can be estimated.

We are now attending a second outbreak of COVID-19 in Madrid. Compared to the first outbreak, the speed of community transmission is lower, the case detection capacity is higher, there is more knowledge of the disease and the possible treatments and healthcare settings are better prepared. All these factors will probably have a great impact on the analysis if the study were to be repeated now. Future analysis comparing results from first and consecutive waves of COVID-19 pandemic at ILUH would be interesting to make.

CONCLUSION

This study describes the epidemic progression, clinical characteristics, complications and outcomes of COVID-19 patients attended in a secondary level hospital in one of the highest COVID-19 incidence neighborhoods of Madrid, which turned into an entire COVID-19 center and almost doubled its bed capacity, during the first wave of COVID-19 pandemic in Spain. Fatal outcomes were similar to those reported by hospitals with a higher level of complexity.

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FOOTNOTES

- **Contributors:** EJ, MFV, JV, IFJ, PR and MPB conceived the study idea. EJ, MFV, JV, IFJ, PR, MPB, EAA, EIG and AL contributed to the study design. EJ, MFV, IFJ, PR, EAA, EIG, AL and EG performed the data collection. MFV and EJ performed the analysis. EJ, MFV, JV, IFJ, PR, MPB, EAA, EIG and AL drafted the first version of the manuscript. EJ, MFV, JV, IFJ, MPB, PR, EG, EAA, EIG, AL, JT, AJTM, BGM, GPL, AAM and LM critically reviewed the manuscript and approved the final version. All authors meet the ICMJE criteria for authorship.
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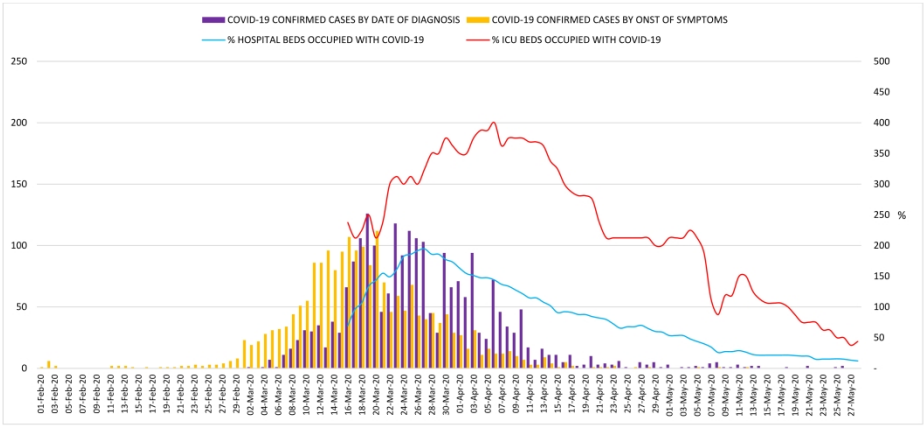

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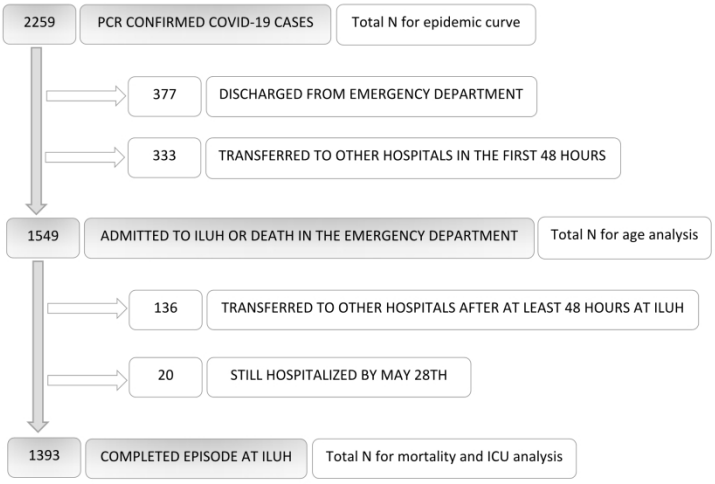

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Characteristics, Complications and Outcomes Among 2259 Patients Hospitalized with COVID-19 in a Secondary Level Hospital in Madrid, Spain

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	***Yes*** ***Pag 1-2***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	***Yes*** ***Pag 1-2***
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	***Yes*** ***Pag 3-4***
Objectives	3	State specific objectives, including any prespecified hypotheses	***Yes*** ***Pag 4***
Methods			
Study design	4	Present key elements of study design early in the paper	***Yes*** ***Pag 5***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	***Yes*** ***Pag 5***
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	***Yes*** ***Pag 5***
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	***Yes*** ***Pag 5-6***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***Yes*** ***Pag 5-6***
Bias	9	Describe any efforts to address potential sources of bias	***Yes*** ***Pag 5-6***
Study size	10	Explain how the study size was arrived at	***Yes*** ***Pag 6***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	***Yes*** ***Pag 6***

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	***Yes*** ***Pag 6***
		(*b*) Describe any methods used to examine subgroups and interactions	***Yes*** ***Pag 6***
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	***Yes*** ***Pag 7***
		(b) Give reasons for non-participation at each stage	***Yes*** ***Fig 2***
		(c) Consider use of a flow diagram	***Yes*** ***Fig 2***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	***Yes*** ***Pag 7-10*** ***Fig 1*** ***Tables 1-3***
		(b) Indicate number of participants with missing data for each variable of interest	***Yes*** ***Tables 1-3***
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	***Yes*** ***Pag 9*** ***Fig 1***
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	***Yes*** ***Pag 9*** ***Table 3***
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	***Yes*** ***Pag 7-10*** ***Tables 1-3***
		(*b*) Report category boundaries when continuous variables were categorized	***Yes*** ***Pag 7-10*** ***Tables 1-3***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	***Yes*** ***Pag 9*** ***Uni/multivariate***
Discussion			
Key results	18	Summarise key results with reference to study objectives	***Yes*** ***Pag 10-12***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	***Yes*** ***Pag 10-12***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	***Yes*** ***Pag 10-12***
Generalisability	21	Discuss the generalisability (external validity) of the study results	***Yes*** ***Pag 12***

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	***Yes*** ***Pag 14***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.