Clinical characteristics and outcomes of 1,331 patients with COVID-19: HM Spanish Cohort

Background. Spain is one of the European countries most affected by the COVID-19 pandemic. Epidemiologic studies are warranted to improve the disease understanding, evaluate the care procedure and prepare for futures waves. The aim of the study was to describe epidemiologic characteristics associated with hospitalized patients with COVID-19.

Methods. This real-world, observational, multicenter and retrospective study screened all consecutive patients admitted to 8 Spanish private hospitals. Inclusion criteria: hospitalized adults (age≥18 years old) with clinically and radiologically findings compatible with COVID-19 disease from March 1st to April 5th, 2020. Exclusion criteria: patients presenting negative PCR for SARS-CoV-2 during the first 7 days from hospital admission, transfer to a hospital not belonging to the HM consortium, lack of data and discharge against medical advice in emergency departments.

Results. One thousand and three hundred thirty-one COVID-19 patients (medium age 66.9 years old; males n= 841, medium length of hospital stayed 8 days, non-survivors n= 233) were analyzed. One hundred and fifteen were admitted to intensive care unit (medium length of stay 16 days, invasive mechanical ventilation n= 95, septic shock n= 37 and renal replacement therapy n= 17). Age, male gender, leukocytes, platelets, oxygen saturation, chronic therapy with steroids and treatment with hydroxychloroquine/azithromycin were independent factors associated with mortality. The proportion of patients that survive and received tocilizumab and steroids were lesser and higher respectively than those that die, but their association was not significant.

Conclusions. Overall crude mortality rate was 17.5%, rising up to 36.5% in the subgroup of patients that were admitted to the intensive care unit. Seven factors impact in hospital mortality. No immunomodulatory intervention were associated with in-hospital mortality.

Keywords: SARS-CoV-2; COVID-19; pandemic; epidemiology

Características clínicas y evolutivas de 1.331 pacientes hospitalizados con COVID-19: Cohorte española HM

Introducción. España es uno de los países europeos más afectados por la pandemia de COVID-19. Conocer las características epidemiológicas y evolutivas permitirá mejorar la comprensión de la enfermedad, evaluar el procedimiento de atención y prepararse para las olas futuras. El objetivo del estudio fue describir las características epidemiológicas asociadas a los pacientes hospitalizados por COVID-19.
MATERIAL AND METHODS

Diseño observacional, multicéntrico y retrospectivo del mundo real realizado en 8 hospitales privados de España. Criterios de inclusión: adultos hospitalizados (edad ≥ 18 años) con hallazgos clínicos y radiológicos compatibles con enfermedad COVID-19 entre el 1 de marzo al 5 de abril de 2020. Criterios de exclusión: PCR negativa para SARS-CoV-2 durante los primeros 7 días de ingreso hospitalario, traslado a un hospital no perteneciente al consorcio HM, falta de datos y alta contra consejo médico en urgencias.

Resultados. Se analizaron 1.331 pacientes con COVID-19 (edad media 66,9 años; varones n = 841, estancia media hospitalaria 8 días, no supervivientes n = 233). Ciento quince ingresaron en la unidad de cuidados intensivos (estancia media 16 días, ventilación mecánica invasiva n = 95, choque séptico n = 37 y terapia renal sustitutiva n = 17). La edad, el sexo masculino, los leucocitos, las plaquetas, la saturación de oxígeno, la terapia crónica con esteroides y el tratamiento con hidroxicloroquina / azitromicina fueron factores independientes asociados con la mortalidad.

Conclusiones. La tasa de mortalidad bruta global fue del 17,5%, elevándose hasta el 36,5% en el subgrupo de pacientes que ingresaron en la unidad de cuidados intensivos. Siete factores impactan en la mortalidad hospitalaria.

Palabras clave: SARS-CoV-2; COVID-19; pandemia; epidemiología

INTRODUCTION

Last December, the World Health Organization (WHO) received information on a group of pneumonia cases of unknown etiology that were admitted to Hospitals in Wuhan city, China [1]. The pathogen causing this pneumonia was identified as a novel enveloped RNA virus in the family Coronaviridae, named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) due to its phylogenetic similarity to the previously described SARS-CoV. The clinical presentation associated with SARS-CoV-2 has been named COVID-19. After the initial outbreak in China, the virus spread around the world and was declared a pandemic on March 11th.

Since the first case of COVID-19 reported on January 31st, the dramatic growth of cases makes Spain one of the most affected countries worldwide [2]. Recently, a nationwide epidemiological report including COVID-19 hospitalized patients from the outbreak’s beginning in Spain was published by Berenguer et al. [3]. This study described the COVID-19 situation at very early stages, reporting only about the first stage of the Spanish outbreak. Other Spanish studies have included low number of patients or specific populations. Thus, the aims of this study were to describe the epidemiological and clinical characteristics of a wide cohort of hospitalized patients with COVID-19 and to identify clinical and laboratory predictors of in-hospital mortality.

MATERIAL AND METHODS

This real-world, observational, multicenter and retrospective study screened all consecutive patients admitted to the following Spanish hospitals: HM Sanchinarro University Hospital (Madrid), HM Torrelodones University Hospital (Madrid), HM Montepríncipe University Hospital (Madrid), HM Puerta del Sur University Hospital (Madrid), HM Madrid University Hospital (Madrid), HM Valles (Alcalá de Henares), HM Regla (Leon) and HM Nuevo-Belen (Galicia). All hospitals belong to HM Hospital Group, a private consortium of general and high complexity hospitals.

Inclusion criteria. Hospitalized adults (age ≥ 18 years) with clinically and radiologically findings compatible with COVID-19 disease from March 1st to April 5th, 2020. For patients who were discharged and subsequently readmitted, only the first episode was considered.

Cases were classified as confirmed or suspected. The former, was considered when a positive SARS-CoV-2 Real Time-Polymerase chain reaction (RT-PCR) result was obtained. The latter, was considered when the RT-PCR was not performed. The decision to include the latter subgroup of patients was based on two reasons: (a) on March 25th, 2020, the Spanish Health Secretary recommended not to confirm the COVID-19 when the clinical and radiological presentation was typical and (b), at bedside, these patients were considered and treated as COVID-19.

Exclusion criteria. Patients that presented negative PCR during the first 7 days from hospital admission (this criterion was adopted assuming that the only available evidence was against the SARS-CoV2 diagnosis), transfer to a hospital not belonging to the HM consortium, lack of data and discharge against medical advice at emergency departments.

HM Hospital Group has a unique and centralized Electronic Health Record system denominated HOSMA. All patients, independently of the hospital in which they had been consulted, were registered with a unique identification number. For assistance purposes, at the beginning of the outbreak, HOSMA record was adapted with the aim to allow doctors participating in the patient’s assistance (e.g. emergentist, internist, intensivist, etc.) to explicitly register patients with probable or confirmed COVID-19.

Clinical presentation, presence of comorbidities, signs and laboratory findings, admission to intensive care unit (ICU), major complications (requirement of mechanical ventilation, tracheotomy, renal replace therapy, septic shock and hospital death) and pharmacological treatments were retrieved. Follow up was performed until hospital discharge.

Regarding the antiviral therapy, it was always prescribed and administered during the first 24 hours from emergency consultation. Although they were prescribed according to the physician criteria, all treatments were standardized (more than one treatment could be prescribed simultaneously) and included: hydroxychloroquine (400mg BID the first day and then 200mg BID) plus azithromycin (500mg QID) for 5 to 10 days and lopinavir/ritonavir 200/50 BID for 5 to 10 days.

Regarding adjuvant medications, they were also pre-
scribed according to the physician criteria but were not stand-
dardized and the time when were administered varied widely.
Thus, for the purpose of this study, some adjustments had to be
performed:

- Tocilizumab. The accumulative dose of tocilizumab was
calculated as the sum of milligram that each patient re-
duced during their hospitalization. Then, it was stratified in:
no received, low (0 mg – 600 mg), intermediate (601
mg – 1,000 mg) and high (>1,000 mg) dose.

- Steroid. Firstly, daily dose of steroids was transformed in
to equivalent methylprednisolone dose according to
equations reported in https://www.rccc.eu/ppc/calculado-
ras/corticoides.htm (accessed on July 15, 2020). Then, all
daily methylprednisolone equivalent doses that each pa-
tient received were added (accumulative equivalent dose
of methylprednisolone). Subsequently, the accumulative
equivalent dose of methylprednisolone was divided by
the number of days that the patient had received steroids
(mean methylprednisolone equivalent dose). Finally, the
mean methylprednisolone equivalent dose was stratified as:
no steroids, low (1 mg/day – 50 mg/day), intermediate
(51 mg/day – 100 mg/day) and high (>100 mg/day) dose.

- Methylprednisolone bolus. It was defined as a daily dose
equivalent methylprednisolone ≥ 150mg.

- Other interventions: vitamin C, colchicine, polyvalent im-
munoglobulins, cytostatic and montelukast were consid-
red dichotomous (received vs not received).

Tocilizumab and steroids cut-off were defined arbitrarily
and before starting the statistical analysis. A posteriori, with
the aim to assess the effect of the time evolution, each in-
tervention was stratified in early (<3 days) or late (≥3 days)
regarding the day of hospital admission in which it were pre-
scribed.

The study was approved by the by the Ethics Committee
of HM Group. Written informed consent was waived in light
of the urgent need to collect data and absence of intervention.

Statistical analysis. Continuous variables are presented
as median and range interquartile (RIQ). Categorical variables
as absolute frequency and percentage. Variables with more
than 30% of missing values have not been considered. Mu-
tivariable Cox regression analyses was performed to identify
factors associated to in-hospital death. The variable effect was
expressed as the hazard ratio (HR) and 95% CI. A two-sided
p<0.05 was considered statistically significant.

Statistical analysis was performed with R package. The
Strengthening the Reporting of Observational Studies in Ep-
Idemiology (STROBE) recommendations and their check list
were used to increase the accurate and transparency of the
study.

RESULTS

During the study period, 2,015 patients were assisted at
HM Hospitales Group with a clinical suspicion of COVID-19.
From these, 1,956 were hospitalized and 1,331 were analyz-
ed (reasons of exclusion: negative SARS-Cov2 PCR n=425,
no COVID19 diagnosis n=112, translate to a no HM Hospital-
es center n=49, pediatric n= 39). Minor differences between
suspected (n=457) and confirmed (n=874) COVID-19 infection
were identified (supplementary table 1).

The peak of daily hospital admissions was on March 18th
(91 patients). Then it started to stabilize until the peak of hos-
pitalized patients (March 30, 610 patients) (figure 1).

The clinical and epidemiological characteristics of the
population are shown in table 1. Gender distribution was not
equal, with a predominance of males (n 841; 63.1%). The me-
dian age was 66.9 years [RIQ 55.7; 76.8]. Almost 4 of 10 pa-
tients lack co-morbidities. The median of days from the symp-
toms initiation to hospital admission was 7 [RIQ 3.0; 9.0]. The
three most frequent symptoms were fever (n= 1,110, 83.4%),
dry cough (n=905; 68.0%) and dyspnea (n= 936; 70.3%). No-\tably, D dimer and protein C reactive were elevated in more
than 75% of the patients.

Regarding anti-COVID-19 treatment (table 2, figure 2),
most of the patients received hydroxychloroquine/ azithro-
mycin (n= 1,197; 89.9%) and/or lopinavir/ritonavir (n= 956;
71.8%). With respect anti-inflammatory/immunomodulatory
treatments (table 2, figure 2), the most frequent pharma-
ological interventions were the use of steroids (n =623; 46.8%)
and tocilizumab (n= 321; 21,1%). Within the group of steroids,
amost 40% received at least one bolus. Other pharmacological
interventions (statins, cytostatic, colchicine, polyvalent immu-
noglobulins, montelukast, ascorbic acid) were prescribed in less
than 11% of the population (table 2).

Regarding severe complications, 115 (8.6%) patients
were admitted to intensive care unit (ICU). Forty-two of them
(37.5%) died. The main findings of ICU-cohort of patients can
be appreciated in table 3.

Two hundred thirty-three patient died during the study
period (17.5%). The univariate analysis between dead and
survivors’ patients are shown in table 1.In multivariate analy-
ysis, independent factors associated to in-hospital mortality
included older age (HR 1.081 [IC95%1.064; 1.099]; p<0.001),
gender (HR 1.417 [IC95% 1.004; 2.000]; p= 0.047),
higher leukocytes count (HR 1.072 [IC95%1.036; 1.109];
p< 0.001), lower platelets count (HR 0.996 [IC95% 0.994; 0.998];
p< 0.001), lower oxygen saturation (HR 0.957 [IC95% 0.941;
0.974]; p< 0.001), previous chronic therapy with steroids
(HR 3.082 [IC95% 1.436; 6.612]; p= 0.004) and no treatment
with hydroxychloroquine/azithromycin (HR 0.303 [IC95%
0.200; 0.460]; p < 0.001) (table 4). Despite early prescription
of Lopinavir/Ritonavir and Steroids were associated to an in-
creased survivor rate in the survival analysis (supplementary
figure 1), their positive effect disappeared when were included
in the COX-regression model.

DISCUSSION

The present study, evaluating features and outcomes of a
| General features                      | All patients (n=1,331) | Death (n=233) | Alive (n=1,098) | p value |
|--------------------------------------|------------------------|---------------|----------------|---------|
| PCR confirmed*                       | 874 (65.7)             | 168 (72.1)    | 706 (64.3)     | 0.028   |
| Male*                                | 841 (63.1)             | 166 (71.2)    | 675 (61.4)     | 0.006   |
| Age [years]**                        | 66.9 [55.7; 76.8]      | 79.2 [73.0; 85.5] | 64.0 [53.7; 73.5] | <0.001 |
| Age stratified (years)*              |                        |               |                |         |
| <40                                  | 72 (5.4)               | 0 (0)         | 72 (6.6)       |         |
| 40-60                                | 362 (27.2)             | 8 (3.4)       | 354 (32.2)     |         |
| 61-80                                | 661 (49.7)             | 122 (52.3)    | 539 (49.1)     |         |
| >80                                  | 236 (17.3)             | 103 (44.2)    | 133 (12.1)     | <0.001  |
| Length of hospital stayed (days)**   | 8.00 [6.00; 13.0]      | 8.00 [4.00; 13.0] | 8.00 [6.00; 13.0] | 0.024   |
| ICU admission*                       | 115 (8.6)              | 42 (18.0)     | 73 (6.8)       | <0.001  |

### Sign and symptoms at emergency department

| Onset of symptoms to hospital admission (d) | 7.00 [3.00; 9.00] | 4.00 [3.00; 7.00] | 7.00 [4.00; 10.0] | <0.001 |
|--------------------------------------------|-------------------|------------------|------------------|---------|
| Headache*                                  | 16 (1.2)          | 3 (1.3)          | 13 (1.2)         | 0.751   |
| Anosmia*                                   | 14 (1.1)          | 2 (0.9)          | 12 (1.1)         | 1.000   |
| Dyspnea*                                   | 936 (70.3)        | 168 (72.1)       | 768 (69.9)       | 0.565   |
| Cough *                                    |                   |                  |                  |         |
| No                                         | 344 (25.8)        | 74 (31.8)        | 270 (24.6)       |         |
| Cough + red sputum                         | 5 (0.4)           | 0 (0.0)          | 5 (0.5)          |         |
| Cough + greenish sputum                    | 8 (0.6)           | 3 (1.3)          | 5 (0.5)          |         |
| Cough + colourless sputum                  | 69 (5.2)          | 14 (6.0)         | 55 (5.0)         |         |
| Dry cough                                  | 905 (68.0)        | 142 (60.9)       | 763 (69.4)       | 0.049   |
| Fever*                                     | 1110 (83.4)       | 184 (79.0)       | 926 (84.3)       | 0.057   |
| Nausea*                                    | 68 (5.1)          | 8 (3.4)          | 60 (5.5)         | 0.265   |
| Diarrhea*                                  | 141 (10.6)        | 13 (5.6)         | 128 (11.7)       | 0.009   |
| Systolic blood pressure (mmHg)**           | 130 [117; 144]    | 132 [114; 147]   | 130 [118; 144]   | 0.939   |
| Diastolic blood pressure (mmHg)**          | 76.0 [67.0; 84.0] | 73.0 [63.5; 79.0] | 76.0 [69.0; 84.0] | <0.001 |
| Heart rate (bpm)**                         | 90.0 [80.0; 102.0] | 90.0 [80.0; 102.0] | 90.0 [80.0; 102.0] | 0.970   |
| Temperature [ºC]**                         | 36.7 [36.3; 37.4] | 36.8 [36.3; 37.4] | 36.7 [36.3; 37.4] | 0.703   |
| Oxygen saturation (%)**                    | 94.0 [90.0; 96.0] | 90.0 [82.0; 94.0] | 94.0 [91.0; 96.0] | <0.001 |

### Comorbidities

| Number of comorbidities | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|-------------------------|---|---|---|---|---|---|---|---|
|                         | 528 (39.7) | 374 (28.1) | 250 (18.7) | 121 (9.1) | 40 (3.0) | 10 (0.8) | 7 (0.5) | 1 (0.1) |
|                         | 47 (20.2)  | 71 (30.5)  | 54 (21.2)  | 39 (16.7) | 11 (4.7) | 6 (2.6)  | 4 (0.4)  | 1 (0.1)  |
|                         | 481 (43.8) | 303 (27.6) | 196 (17.8) | 82 (7.5)  | 29 (2.8) | 4 (0.4)  | 3 (0.3)  | 0 (0.0)  |
|                         |            |            |            |            |            |            |            | <0.001   |
large cohort of hospitalized COVID-19 patients, highlights several interesting clinical points about the first pandemic wave in Spain.

First, despite the dramatic increasing initial flow of hospital admissions for COVID-19 in the first 3 weeks of the outbreak with 6 times more in the third week (peak of the pandemic) compared to the first week of the outbreak (figure 1), more than 80% of the patients survived.

Second, less than 9% of hospitalized patients were admitted to ICU. Critically ill patients had much higher mortality (close to 40%) and complications such as invasive mechanical ventilation and septic shock, with longer stay at ICU and under mechanical ventilation than previous report from non-COVID19 patients[4]. In this setting, several factors were independently associated to mortality: older age, male gender, previous chronic use of systemic steroids, high leukocytes count [at emergency], low platelets count [at emergency], low oxygen saturation [at emergency] and early treatment with hydroxychloroquine/azithromycin. All anti-inflammatory/immunomodulate interventions have a neutral effect. Mortality rate in hospitalized COVID19 patients has been described with a wide range, from 13.6% [5] to 28.0% [3]. Our rate (17.5%) is intermediate and similar to other reports from Spain [6], others countries [7] and an international meta-analysis that included 58 studies with 122,191 patients [8]. Indeed, the mortality rate from those that were admitted to ICU was also very similar to international reports [9]. We have identified

| Comorbidities | All patients (n= 1,331) | Death (n= 233) | Alive (n= 1,098) | p value |
|---------------|-------------------------|----------------|-----------------|---------|
| Malignancy *  | 56 (4.2)                | 21 (9.0)       | 35 (3.2)        | <0.001  |
| Diabetes*     | 167 (12.5)              | 47 (20.2)      | 120 (10.9)      | <0.001  |
| Immunosupression* | 8 (0.6)            | 1 (0.4)        | 7 (0.6)         | 1.000   |
| HIV/AIDS *    | 1 (0.1)                 | 0 (0.0)        | 1 (0.1)         | 1.000   |
| Thyroid disease* | 99 (7.4)            | 22 (9.4)       | 77 (7.0)        | 0.252   |
| Dislipemia*   | 274 (20.6)              | 57 (24.5)      | 217 (19.8)      | 0.128   |
| Smoking*      | 54 (4.1)                | 10 (4.3)       | 44 (4.1)        | 0.986   |
| Chronic obstructive pulmonary disease* | 63 (4.7) | 26 (11.2) | 37 (3.4) | <0.001 |
| Asthma*       | 52 (3.9)                | 8 (3.4)        | 44 (4.0)        | 0.822   |
| Neurologic disease* (Stroke, TIA or dementia) | 52 (3.9) | 29 (12.4) | 23 (2.1) | <0.001 |
| High blood pressure (mmHg)** | 500 (37.6) | 126 (54.1) | 374 (34.1) | <0.001 |
| Acute coronary disease* | 93 (7.0) | 30 (12.9) | 63 (5.7) | <0.001 |
| Alcohol abuse* | 25 (1.9)               | 6 (2.6)        | 19 (1.7)        | 0.422   |
| Chronic kidney disease* | 39 (2.9) | 14 (6.0) | 25 (2.3) | 0.004 |
| Chronic liver disease* | 14 (1.0) | 4 (1.7) | 10 (0.9) | 0.285 |

**Table 1**

Univariate analysis (cont).

| Chronic Medication | All patients (n= 1,331) | Death (n= 233) | Alive (n= 1,098) | p value |
|-------------------|-------------------------|----------------|-----------------|---------|
| Statins*          | 233 (17.5)              | 49 (21.0)      | 184 (16.8)      | 0.143   |
| Anticoagulants*   | 82 (6.2)                | 30 (12.9)      | 52 (4.7)        | <0.001  |
| Antiagregants*    | 123 (9.2)               | 35 (15.0)      | 88 (8.0)        | 0.001   |
| IEC/ARAII*        | 328 (24.6)              | 70 (30.0)      | 258 (23.5)      | 0.043   |
| Beta blockers*    | 150 (11.3)              | 43 (18.5)      | 107 (9.7)       | <0.001  |
| Diuretics*        | 103 (7.7)               | 37 (15.9)      | 66 (6.0)        | <0.001  |
| Thyroid replacement hormones* | 96 (7.2) | 20 (8.6) | 76 (6.9) | 0.452 |
| Oral steroids*    | 21 (1.6)                | 10 (4.3)       | 11 (1.0)        | 0.001   |
| Inhaled steroids* | 48 (3.6)                | 12 (5.2)       | 36 (3.3)        | 0.231   |
| Inhaled b2 agonist* | 33 (2.5)               | 6 (2.6)        | 27 (2.5)        | 1.000   |
| Inhaled antimuscarinic* | 30 (2.3) | 9 (3.9) | 21 (1.9) | 0.114 |

* n (%). **p<0.05 [p25; 075]. ICU: intensive care unit
seven factors independently associated with the mortality. Five of them (age, gender, leukocytes, platelets and oxygen saturation) have been reported and widely analyzed in other studies [3, 10, 11]. Thus, we will focus the discussion in the others two factors: previous chronic use of systemic steroid and treatment with hydroxychloroquine/azithromycin.

Our study reported that chronic use of steroid is associated to increased risk of hospital mortality. The evidence to support this association is scarce. However, we speculate that could be explained, at least, by two factors. Firstly, it has been described that chronic steroid therapy increases the risk of developing infections, including those produced by virus [12]. Secondly, it could be possible that steroid being a confounding factor and the real risk factor could be the disease that requires the steroids. In favor of this proposal is the fact that several chronical diseases that commonly require steroids (e.g. asthma, COPD, malignancies, etc.) were overrepresented in the subgroup of died patient. On the other hand, until the recent evidence reported by well-designed RCTs[13, 14] and meta-analysis[15], the effect of steroid administered during hospital stay had been widely debated with observatory studies in favor[16, 17], against [18, 19] and neutral [20]. Our study did not find an association, neither with steroid at different doses nor with boluses. Although this result is online with some previously mentioned, we have to be very cautiously at their interpretation as several studies, with more evidence hierarchy, support their prescription at low doses, for a limited period of time and in patient with moderate and severe disease [13-15]. Additionally, pharmacological effects of steroids depend on the daily dose and the treatment length, and it is problematic to measure the concept of "chronic use" of corticosteroids in every patient’s medical history, due to this therapeutic heterogeneity. At the beginning of the pandemic a small study proposed that hydroxychloroquine/azithromycin could be an effective therapy for improving the viral clearance [21]. Then, their prescription off-label increased abruptly which explain that 80% of our patients received this treatment. In this setting, several observational studies, like in our cohort, have reported that this combination could improve the outcome in COVID19 patients. However, several RCTs and meta-analysis have suggested the futility of this intervention [22, 23]. Regarding the tocilizumab, we did not find a significant association between it and hospital mortality, which is online with several RCTs. Indeed, the preliminary report of the Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (EMPACTA) mentioned that 28-day mortality was not affected by this IL-6 receptor blocker. It is obvious that interpreting the evidence to support the COVID-19 treatments is a real challenge since there is an evident disagreement between observational and RCT studies [24]. This controversy should not be a surprise as it have happened with several intervention in the past and may be explained by several reasons; probably the three most relevant are the assignment bias typically associated to observatory studies, the better control of confounding and the more homogenous population in RCT compared to observational studies [24]. Every clinician should always remind that evidence from RCTs is considered the gold standard for establishing causality, giving the best assurance that the association between exposure and outcome is not related to confounding. However, observational studies can provide accurate evidence from real world data [25].

Regarding the clinical presentation at emergency department, the three most frequent symptoms in our study were fever, cough, and dyspnea, which is in line with other reports [7, 26]. Although COVID19 is usually associated to respiratory symptoms, it is important to point out that more than 10% of
## Laboratory findings at emergency department

|                      | All patients (n=1,331) | Death (n=233) | Alive (n=1,098) | p value |
|----------------------|------------------------|---------------|-----------------|---------|
| Hemoglobin (g/dL) ** | 14.1 [13.1;15.2]       | 13.8 [12.3;15.2] | 14.2 [13.1;15.2] | 0.002   |
| White Blood cell (count x10⁹/L) ** | 6.33 [4.91;8.51]       | 7.15 [5.18;10.1] | 6.21 [4.85;8.23] | <0.001  |
| Neutrophil (count x10⁹/L) ** | 4.69 [3.33;6.81]       | 5.76 [3.77;8.45] | 4.58 [3.28;6.41] | <0.001  |
| Lymphocyte (count x10⁹/L) ** | 1.00 [0.71;1.35]       | 0.77 [0.52;1.19] | 1.02 [0.76;1.39] | <0.001  |
| Monocyte (count x10⁹/L) ** | 0.45 [0.32;0.63]       | 0.47 [0.30;0.68] | 0.44 [0.32;0.63] | 0.980   |
| Basophils (count x10⁹/L) ** | 0.01 [0.01;0.02]       | 0.01 [0.01;0.01] | 0.01 [0.01;0.02] | 0.714   |
| Eosinophil (count x10⁹/L) ** | 0.00 [0.00;0.02]       | 0.00 [0.00;0.02] | 0.00 [0.00;0.02] | 0.444   |
| Platelet (count x10⁹/L) ** | 192 [154;245]          | 174 [139;225]   | 196 [156;249]   | <0.001  |
| Glucose (mg/dl) ** | 116 [104;136]          | 126 [110;155]   | 114 [103;133]   | <0.001  |
| Protrombine activity (%) ** | 76.0 [68.0;85.0]       | 73.0 [61.8;82.0] | 78.0 [69.0;86.0] | <0.001  |
| Activated partial thromboplastin time (s) ** | 32.2 [30.0;34.8] | 32.5 [29.7;35.7] | 32.1 [30.0;34.5] | 0.215 |
| Total bilirubine (mg/dl) ** | 0.46 [0.34;0.62]       | 0.51 [0.35;0.76] | 0.45 [0.34;0.60] | 0.052   |
| Aspartate aminotransferase (U/L) ** | 36.0 [26.0;55.8]       | 39.8 [27.1;62.0] | 35.0 [25.3;53.3] | 0.005   |
| Alanine aminotransferase (U/L) ** | 116 [104;136]          | 126 [110;155]   | 114 [103;133]   | <0.001  |
| International normalized ratio ** | 1.19 [1.11;1.30]       | 1.23 [1.15;1.38] | 1.19 [1.11;1.28] | <0.001  |
| D dimer (mg/L) ** | 724 [144;1178]         | 1173 [1173;1205]| 658 [144;1060]  | <0.001  |
| Lactate dehydrogenase (U/L) ** | 554 [430;714]          | 680 [506;959]   | 537 [421;674]   | <0.001  |
| Sodium (mmol/L) ** | 136 [134;139]          | 136 [134;139]   | 136 [134;139]   | 0.218   |
| Potassium (mmol/L) ** | 4.17 [3.87;4.50]       | 4.27 [3.85;4.73] | 4.16 [3.66;4.47] | 0.002   |
| C reactive protein (mg/dL) ** | 32.7 [25.0;45.8]       | 47.0 [36.8;71.5] | 30.2 [24.0;41.0] | <0.001  |

### Pharmacological treatments during hospitalization

| Treatment                  | All patients (n=1,331) | Death (n=233) | Alive (n=1,098) | p value |
|---------------------------|------------------------|---------------|-----------------|---------|
| Tocilizumab*              | 321 (24.1)             | 76 (32.6)     | 245 (22.3)      | <0.001  |
| Tocilizumab**             |                        |               |                 |         |
| No                        | 1010 (75.9)            | 157 (67.4)    | 853 (77.7)      |         |
| 0-599mg                   | 80 (6.0)               | 21 (9.0)      | 59 (5.4)        |         |
| 600-999mg                 | 213 (16.0)             | 42 (18.0)     | 171 (15.6)      |         |
| ≥1000mg                   | 28 (2.1)               | 13 (5.6)      | 15 (1.3)        | <0.001  |
| Steroids*                 | 623 (46.8)             | 153 (11.5)    | 470 (35.3)      | <0.001  |
| Steroids**                |                        |               |                 |         |
| No                        | 708 (53.2)             | 80 (34.3)     | 628 (57.2)      |         |
| 0-49 mg/day               | 144 (10.8)             | 27 (11.6)     | 117 (10.6)      |         |
| 50-99 mg/day              | 231 (17.3)             | 44 (18.9)     | 187 (17.0)      |         |
| ≥100 mg/day               | 248 (18.6)             | 82 (35.2)     | 168 (15.1)      | <0.001  |
| Steroids bolus            | 249 (18.7)             | 75 (32.2)     | 174 (15.8)      | <0.001  |
| Lopinavir/ritonavir*      | 1197 (89.9)            | 180 (77.2)    | 1017 (92.8)     | <0.001  |
| Cystostatic               | 956 (71.8)             | 147 (63.1)    | 809 (73.6)      |         |
| Colchicine*               | 38 (2.8)               | 5 (2.1)       | 33 (3.0)        | 0.618   |
| Polyclonal immunoglobulines* | 13 (1.0)              | 8 (3.4)       | 5 (0.4)         | <0.001  |
| Montelukast*              | 78 (5.9)               | 11 (4.7)      | 67 (6.1)        | 0.508   |
| Ascorbic acid*            | 30 (2.3)               | 13 (5.6)      | 17 (1.5)        | <0.001  |
| HMG-CoA*                  | 144 (10.8)             | 36 (15.4)     | 108 (9.8)       | 0.017   |

*Accumulative dose; †Mean methylprednisolone equivalent dose per day of treatment HMG-CoA: 3-hidroxi-3-metil-glutaril-CoA reductase
*dichotomous variable and n (%). **p<0.05 [p25; 075].
our cohort presented diarrhea (sometimes as initial and even only symptom) which could difficult the diagnosis if the physician is not aware about this fact. Likewise, this frequent symptom is over-represented in the subgroup of survivors patients which may reflect any effect on the virus infection pathophysiology and transmissibility.

The number of days with symptoms at hospital admission was greater in the surviving group with respect died patients. We speculate that it could be explained by a faster evolution in more aggressive infection cases. Further studies should clarify this issue.

Almost 9% of hospitalized patients developed severe clinical deterioration and had to be admitted to the ICU, with almost double mortality rate with respect non-ICU patients. Likewise, this subgroup of patients has features different from non-COVID19 patients [27]. For example, the ICU stayed and...
Table 3  Univariate analysis of patients admitted to the intensive care unit

|                      | All patients (n= 115) | Death (n=42) | Alive (n=73) | p-value  |
|----------------------|-----------------------|--------------|--------------|----------|
| Days at ICU**        | 16.0 [9.00; 31.0]     | 12.0 [7.25; 30.5] | 20.0 [10.0; 31.0] | 0.106    |
| Days from hospital to ICU admission** | 3.00 [1.00; 4.50] | 3.00 [2.00; 6.00] | 3.00 [1.00; 4.00] | 0.079    |
| Invasive mechanical ventilation | 95 (82.6) | 36 (85.7) | 59 (80.8) | 0.681    |
| Days of invasive mechanical ventilation** | 16.5 [9.00;27.8] | 14.0 [8.50; 28.0] | 18.0 [9.00; 27.5] | 0.584    |
| Tracheotomy*         | 55 (56.1)            | 17 (47.2)    | 38 (61.3)    | 0.254    |
| Days from ICU admission to tracheostomy** | 14.0 [12.0;17.0] | 15.0 [12.0; 16.0] | 14.0 [12.0; 17.0] | 0.666    |
| Septic shock*        | 37 (32.2)            | 23 (54.8)    | 14 (19.2)    | <0.001   |
| Renal replace therapy* | 17 (14.8)       | 9 (21.4)     | 8 (11.0)     | 0.211    |

* n (%). **p50 [p25; 075]. ICU: intensive care unit

Table 4  Cox model for hospital mortality

|                      | Hazard ratio (IC95%) | p value  |
|----------------------|----------------------|----------|
| Age (years)          | 1.081 (1.064; 1.099) | <0.001   |
| Male                 | 1.417 (1.004; 2.000) | 0.047    |
| Systemic steroids (chronic medication) | 3.082 (1.436; 6.612) | 0.004    |
| Leukocytes at emergency (count x10⁹) | 1.072 (1.036; 1.109) | <0.001   |
| Platelets at emergency (count x10⁹/L) | 0.996 (0.994; 0.998) | <0.001   |
| Oxygen saturation at emergency (%) | 0.957 (0.941; 0.974) | <0.001   |
| Hydroxychloroquine/azithromycin | 0.303 (0.200; 0.460) | <0.001   |

Our study has several limitations. First, it is retrospective study. However, its impact should be limited as all information was registered prospectively in a centralized and unique database. Indeed, all physicians were trained to register COVID-19 patients at the moment they were assisting them. Secondly, we could not consider some potentially relevant clinical, laboratory and imagen variables (e.g. respiratory frequency, interleukin 6 levels, thorax x-ray, etc.), although the lack of these parameters does not invalid results we are reporting. Thirdly, for analyzing steroids and tocilizumab we had to perform some equivalences that may interfere with the accuracy of the final result. Fourthly, we had to face a new infection whose treatment was unknown and changing; indeed, the same patients could receive more than one intervention, simultaneously or consecutively. Fifth, probably the most important limitation: our study is descriptive, so it suffers from indication bias and lacks of a comparator, which limits the conclusions. This is particularly evident in the case of antimalarial medications and steroids, which protective effect has been questioned by several RCTs.

On the other hand, this study has several strengths. Firstly, it includes a large sample size of consecutively patients which accurately reflect the reality of the first outbreak in Spain. Indeed, we have followed up all patients until their hospital discharge. This fact is not common in several recognized observational studies [3, 7, 30]. Secondly, the fact that all hospitals belong to the same group and share all the information and clinical practices allow us to reduce the traditional variability seen in most multicenter studies.

As a summary, here we report a mortality rate of 17.5% in a large cohort of hospitalized patients in the first Spanish pandemic wave. This value rises up to 36.2% in the patients...
admitted to ICU admission. We have identified seven factors associated to in-hospital mortality, with the observation that hydroxychloroquine could be an effective treatment, associated with lower mortality. This finding should be considered with caution as several RCTs have questioned its utility.

**FUNDING**

None to declare

**CONFLICT OF INTEREST**

all authors declare no conflict of interest

**REFERENCES**

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33. DOI: 10.1056/NEJMoa2001017

2. Tarraso Castillo J, Posadas Blazquez TJ, Lahosa Cordoba C, Signes-Costa J. COVID-19: New disease, new manifestations. Arch Bronconeumol. 2020;56(12):825–6. DOI: 10.1016/j.arbres.2020.07.007

3. Berenguer J, Ryan P, Rodriguez-Bano J, Jarrin I, Carratala J, Pachon J, et al. Characteristics and predictors of death among 4,035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect. 2020. DOI: 10.1016/j.cmi.2020.07.024

4. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA. 2002;287(3):345-55. DOI: 10.1001/jama.287.3.345

5. Gil-Rodrigo A, Miro O, Pinera P, Burillo-Putze G, Jimenez S, Martin A, et al. Analysis of clinical characteristics and outcomes in patients with COVID-19 based on a series of 1000 patients treated in Spanish emergency departments. Emergencias. 2020;32(4):233-41.

6. Iftimie S, Lopez-Azcona AF, Vicente-Miralles M, Descarrega-Reina R, Hernandez-Agullera A, Riu F, et al. Risk factors associated with mortality in hospitalized patients with SARS-CoV-2 infection. A prospective, longitudinal, unicenter study in Reus, Spain. PLoS One. 2020;15(9):e0234452. DOI: 10.1371/journal.pone.0234452

7. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052-9. DOI: 10.1001/jama.2020.6775

8. Noor FM, Islam MM. Prevalence and Associated Risk Factors of Mortality Among COVID-19 Patients: A Meta-Analysis. J Community Health. 2020. DOI: 10.1007/s10900-020-00920-x

9. Zhou S, Yang Y, Zhang X, Li Z, Liu X, Hu C, et al. Clinical Course of 195 Critically Ill COVID-19 Patients: A Retrospective Multicenter Study. Shock. 2020;54(5):644-51. DOI: 10.1097/SHK.0000000000001629

10. Hajifathalian K, Sharaia RZ, Kumar S, Krisko T, Skaf D, Ang B, et al. Development and external validation of a prediction risk model for short-term mortality among hospitalized U.S. COVID-19 patients: A proposal for the COVID-AID risk tool. PLoS One. 2020;15(9):e0239536. DOI: 10.1371/journal.pone.0239536

11. Posso M, Comas M, Roman M, Domingo L, Louro J, Gonzalez C, et al. Comorbidities and Mortality in Patients With COVID-19 Aged 60 Years and Older in a University Hospital in Spain. Arch Bronconeumol. 2020;56(11):576-8. DOI: 10.1016/j.arbres.2020.06.012

12. Youssef J, Novosad SA, Winthrop KL. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am. 2016;42(1):157-76. DOI: 10.1016/j.rdc.2015.08.004

13. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020. DOI: 10.1056/NEJMoa201436

14. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEx Randomized Clinical Trial. JAMA. 2020;324(13):1307-16. DOI: 10.1001/jama.2020.17021

15. Group WHORE-AFC-TW, Sterne JAC, Comas M, Roman M, Domingo L, Louro J, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-41. DOI: 10.1001/jama.2020.17023

16. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. Clin Infect Dis. 2020. DOI: 10.1093/cid/ciaa601

17. Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, Sancho-Lopez A, Mills-Sanchez P, Centeno-Soto GA, et al. A Retrospective Controlled Cohort Study of the Impact of Glucocorticoid Treatment in SARS-CoV-2 Infection Mortality. Antimicrob Agents Chemother. 2020;64(9). DOI: 10.1128/AAC.01168-20

18. Chen X, Zhu B, Hong W, Zeng J, He X, Chen J, et al. Associations of clinical characteristics and treatment regimens with the duration of viral RNA shedding in patients with COVID-19. Int J Infect Dis. 2020;88:352-60. DOI: 10.1016/j.ijid.2020.06.091

19. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone B, Codda G, et al. Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest. 2020;50(10):e13319. DOI: 10.1111/eci.13319

20. Zheng C, Wang J, Guo H, Lu Z, Ma Y, Zhu Y, et al. Risk-adapted Treatment Strategy For COVID-19 Patients. Int J Infect Dis. 2020;94:74-7. DOI: 10.1016/j.ijid.2020.03.047

21. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(5):525-34. DOI: 10.1016/j.ijantimicag.2020.05.094

22. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone E, Codda G, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(5):525-34. DOI: 10.1016/j.ijantimicag.2020.05.094

23. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Ave- zum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2018914

24. Kashour Z, Riaz M, Garabati MA, AlDosary O, Tylajeh H, Gerber D, et al. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis. J Antimicrob Chem-
other. 2020. DOI: 10.1093/jac/dkaa403
24. Sancho M, Muniz J, Cardinal Fernandez PA. Tocilizumab in COVID-19 patients. Med Clin (Barc) - accepted. 2020.
25. Tlayjeh H, Mhish OH, Enani MA, Alruwaili A, Tlayjeh R, Thalib L, et al. Association of corticosteroids use and outcomes in COVID-19 patients: A systematic review and meta-analysis. J Infect Public Health. 2020;13(11):1652-63. DOI: 10.1016/j.jiph.2020.09.008
26. Zhu J, Zhong Z, Ji P, Li H, Li B, Pang J, et al. Clinicopathological characteristics of 8,697 patients with COVID-19 in China: a meta-analysis. Fam Med Community Health. 2020;8(1). DOI: 10.1136/ fmc-2020-000406
27. Richards-Belle A, Orzechowska I, Gould DW, Thomas K, Doidge JC, Mouncey PR, et al. COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. Intensive Care Med. 2020;46(11):2035-47. DOI: 10.1007/s00134-020-06267-0
28. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. DOI: 10.1016/S0140-6736(20)30183-5
29. Martin Delgado MC, Aviles-Jurado FX, Alvarez Escudero J, Aldecoa Alvarez-Santuyano C, de Haro Lopez C, Diaz de Cerio Canduela P, et al. [Consensus document of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC), the Spanish Society of Otorhinolaryngology and Head and Neck Surgery (SEORL-CCC) and the Spanish Society of Anesthesiology and Resuscitation (SEDAR) on tracheotomy in patients with COVID-19 infection]. Med Intensiva. 2020;44(8):493-9. DOI: 10.1016/j.medin.2020.05.002
30. Barrasa H, Rello J, Tejada S, Martin A, Balziskueta G, Vinuesa C, et al. SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria. Anaesth Crit Care Pain Med. 2020. DOI: 10.1016/j.accpm.2020.04.001