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Cause-specific death in hospitalized individuals infected with SARS-CoV-2: more than just acute respiratory failure or thromboembolic events

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Abstract

Infection with SARS-CoV-2 is becoming the leading cause of death in most countries during the 2020 pandemic. The objective of this study is to assess the association between COVID-19 and cause-specific death. The design is retrospective cohort study. We included data from inpatients diagnosed with COVID-19 between March 18 and April 21, 2020, who died during their hospital stay. Demographic, clinical and management data were collected. Causes of death were ascertained by review of medical records. The sample included 128 individuals. The median age was 84 (IQR 75–89), 57% were men. In 109 patients, the death was caused by SARS-CoV-2 infection, whereas in 19 (14.8%, 95 CI 10–22%), the infection acted only as a precipitating factor to decompensate other pathologies. This second group of patients was older (88y vs 82, $p < 0.001$). In age-adjusted analysis, they had a greater likelihood of heart failure (OR 3.61 95% CI 1.15–11.32), dependency in activities of daily living (OR 12.07 95% CI 1.40–103.86), frailty (OR 8.73 95% CI 1.37–55.46). The presence of X-ray infiltrates

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was uncommon (OR 0.07, 95% CI 0.02–0.25). A higher percentage of patient deaths from causes unrelated to COVID-19 complications occurred during the two first weeks of the pandemic. Fifteen percent of patients with COVID-19 infection died from decompensation of other pathologies and the cause of death was unrelated to COVID-19 severe complications. Most of these patients had more comorbidities and were frail and elderly. These findings can partially explain the excess mortality in older people.

Graphic abstract
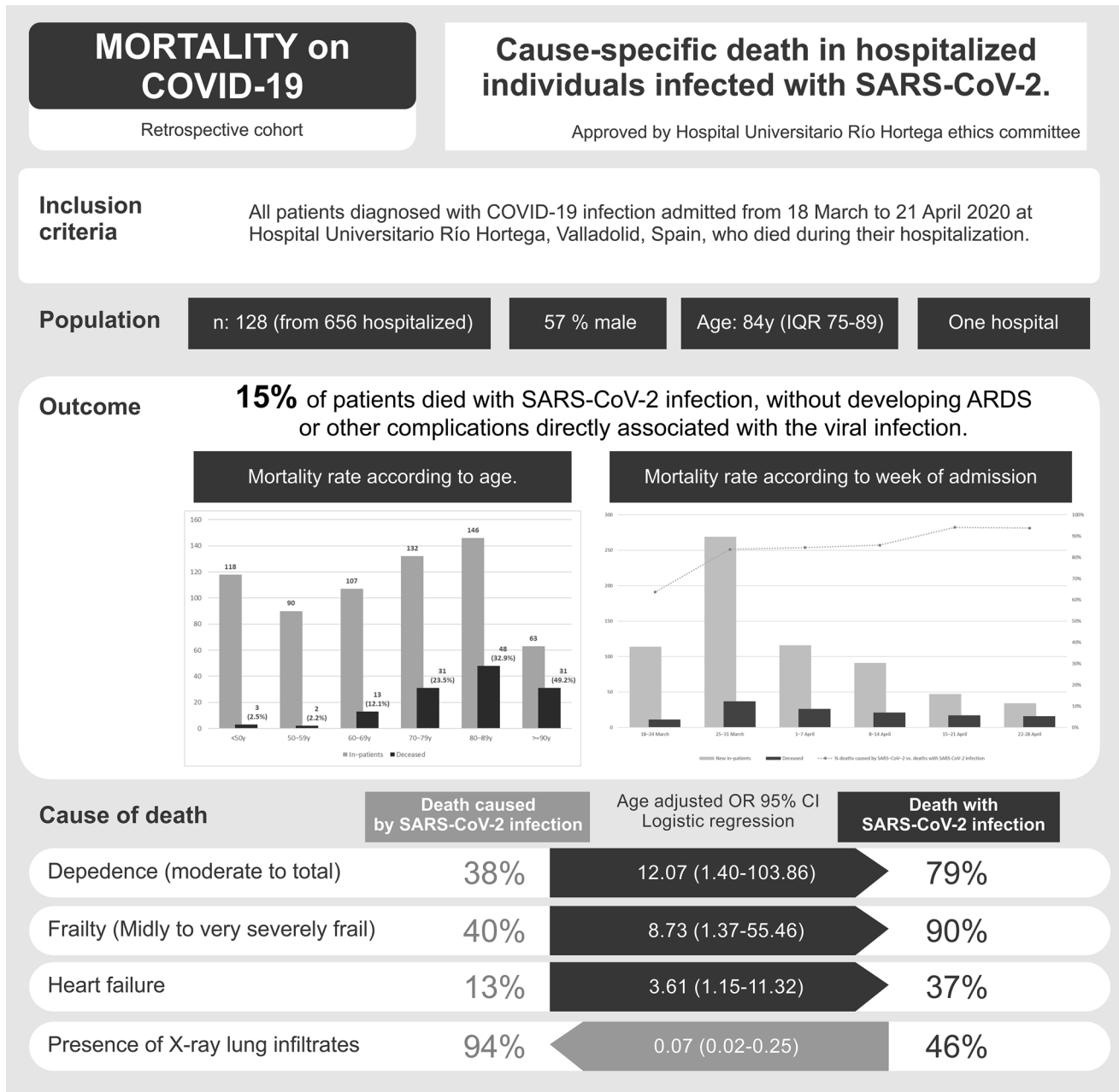
Introduction

The first case of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in China in December 2019. Since then, increasing numbers of deaths have been related to SARS-CoV-2. The case fatality rate across countries and territories varies from less than 1% to over 10% [1]. These rates should be interpreted with caution, given the many variations and the number of factors influencing the rate [2, 3].

Many risk factors are associated with death in COVID-19 infection, with old age a common factor [4]. Case fatality rates ranged from 1.3% in patients < 70 years old to 8.0% in those 70–79 years old and 14.8% in patients aged > 80 years in a large Chinese series [5]. This is also true for critical cases, with a case fatality rate of 15% in patients ≤ 63 years old admitted to intensive care units vs 36% in patients > 63 years [6]. Underlying health conditions such as respiratory disease [odds ratio (OR) 2.46, 95% confidence interval (CI) 1.76–3.44], cardiovascular diseases (OR 3.42, 95% CI 1.88–6.22) and hypertension (OR 2.36, 95% CI 1.46 to 3,83) have also been associated with increased death risk [7], as have been obesity, smoking and male sex [8, 9].

The main complications associated with SARS-CoV-2 infection and death are acute respiratory distress syndrome (ARDS), disseminate intravascular coagulation and sepsis [10]. An excessive immune response causing a cytokine storm is involved in many cases where the disease progresses rapidly [11]. These acute complications due to the infection itself could explain the death rate in young people but leave open the question of the extremely high mortality in older people, especially in very old or frail people. This excess mortality in the oldest patients could partly explain the differences in death rates between countries and regions, with higher mortality in countries such as Spain and Italy, which have some of the highest life expectancies worldwide [12].

This retrospective cohort describes the cause of death in patients infected with SARS-CoV-2 in a single hospital. We aimed to differentiate the percentage of deaths directly associated with the infection and its complications (lung injury or thromboembolic events) and those where the illness acted as a trigger to decompensate previous comorbid conditions, with this decompensation being the cause of death.

Material and methods

Study population

This is a retrospective cohort study of all patients diagnosed with COVID-19 infection who were admitted at Hospital Universitario Río Hortega Valladolid, Spain, from 18 March to 21 April 2020 and died during their hospitalization. The hospital ethics committee approved this study. Due to the nature of the retrospective chart review, waived the need for informed consent from individual patients.

Patients were included if they were diagnosed with confirmed COVID-19 and died during the study period. Patients were diagnosed according to World Health Organization guidance [13]. Laboratory confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs or a positive serology test.

Data collection

A trained team of internal medicine physicians and specialist registrars reviewed and collected epidemiological, clinical and outcome data from electronic medical records. Patient confidentiality was protected by deidentification.

Every patient's medical record was independently assessed by one of the researchers (MCS, MGM, PCM, IAJ, MRH, LHG, DVP, MCG, and MGF). The researchers were blinded to the outcome of interest during data collection. The assessment of the cause of death was done after they had gathered all the clinical information. When the cause of death was unclear, the medical record was assessed by a second researcher. Differences in opinion were resolved by discussion and consensus or by consulting one of the senior authors (LCG) if needed. Six patients' cause of death should be assessed by a second researcher. All the patients whose cause of death was assessed as not caused directly by SARS-CoV-2 infection were double checked for the senior author. Three patients initially assigned to the death with SARS-CoV-2 infection group were finally switched to the death caused by SARS-CoV2 infection group after careful assessment of laboratory and imagen data.

Study outcomes and definitions

The primary outcome was the definition of the cause of death of the patients. As the secondary outcome, we assessed the development of ARDS, hyperinflammation response, sepsis or thromboembolic events.

Acute respiratory distress syndrome (ARDS) was identified according to the Berlin Definition [14]. All the following criteria were required:

1. *Onset* respiratory symptoms must begin within 1 week of a known clinical insult, or the patient must have new or worsening symptoms during the past week.
2. *Chest imaging* bilateral opacities must be present on a chest radiograph or computed tomographic (CT) scan. These opacities must not be fully explained by pleural

effusions, lobar collapse, lung collapse or pulmonary nodules.

3. *Origin of pulmonary infiltrates* the patient's respiratory failure must not be fully explained by cardiac failure or fluid overload. ARDS can be diagnosed once cardiogenic pulmonary oedema and alternative causes of acute hypoxemic respiratory failure have been excluded.

4. *Oxygenation impairment*: a moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2), or the ratio of oxygen saturation to FiO_2 (SaO_2/FiO_2) when PaO_2 is not available. The severity of the hypoxemia defines the severity of ARDS:

   a. mild: PaO_2/FiO_2 200–300 mmHg or SaO_2/FiO_2 237–317 mmHg;
   b. moderate: PaO_2/FiO_2 100–200 mmHg or SaO_2/FiO_2 155–237 mmHg;
   c. severe: $PaO_2/FiO_2 \leq 100$ mmHg or $SaO_2/FiO_2 < 155$ mmHg.

Hyperinflammation response we considered a hyperinflammatory response present in the context of moderate to severe COVID-19 infection with a lymphocyte count of $< 1000 \times 10^9$/mL, and one of the following laboratory parameters:

1. serum ferritin > 1000 ng/mL;
2. C-reactive protein > 150 mg/L;
3. D-dimer > 800 µg/L;
4. Interleukin 6 > 20 pg/mL.

Cause-specific death in individuals infected with SARS-CoV-2 we defined clinical criteria for assessing COVID-related causes of death. It was not possible to support the diagnosis of death by necropsies, as they were not available. Patients were divided in two groups according their cause of death.

Deaths caused by SARS-CoV-2 infection we considered that death was directly caused by SARS-CoV-2 infection complications when the patient developed

1. ARDS or hyperinflammation response that led to their death;
2. acute respiratory failure leading to death without meeting ARDS and hyperinflammation response criteria, and severe lung injury likely due to COVID-19 on X-ray or CT;
3. acute respiratory failure or thrombotic events in the context of pulmonary embolism or other forms of venous thromboembolism that led to death;
4. septic shock due to SARS-CoV-2 that led to their death.

Death with SARS-CoV-2 infection we considered that COVID-19 infection was a precipitating factor to decompensate other chronic or acute pathologies and death was unrelated to severe complications of SARS-CoV-2 infection when

1. The patient developed acute respiratory failure caused by cardiogenic pulmonary oedema or other alternative causes of acute hypoxemic respiratory failure unrelated to COVID-19 that led to death. There were no lung injuries on X-ray or CT likely caused by COVID-19, or they were mild (only interstitial infiltrates of peripheral distribution, with neither alveolar infiltrates, nor consolidation, affecting less than 50% of lung in X-ray or CT scan: equivalent to Brixia score < 4 [15]).
2. The patient developed multiorgan failure associated with frailty that led to death. Septic shock was excluded. There were no lung injuries on X-ray or CT likely caused by COVID-19, or they were mild to moderate (interstitial or interstitial and alveolar infiltrates with interstitial predominance, affecting less than 50% of lung in X-ray or CT scan; equivalent to Brixia score < 7).
3. The patient's death was from any confirmed cause unrelated to COVID-19 complications, including septic shock due to another microorganism.

Patients' grade of frailty was defined according Clinical Frailty Scale [16]. The grade of dependency was assessed using Barthel Index for activities of daily living [17].

Statistical analysis

The sample size was equal to the number of patients who died during the study period. Descriptive analysis of the continuous variables is expressed as the median and interquartile range (IQR). Categorical variables are presented as the number of patients (%) with 95% CI.

Differences in distributions of patient characteristics by outcome subgroup were reported using differences with 95% CIs. Categorical data were compared using the Chi square test or the Fisher exact test when needed. For crosstabs larger than 2×2 of 3 ordinal variables (age, performance in activities of daily living and clinical frailty scale), we used the linear-by-linear association test to assess for trends. Continuous data were compared using Student's *t* test or the Mann–Whitney rank sum test with non-parametric variables. ORs adjusted by age are presented with 95% CIs for all the variables associated with the cause of death in univariate analysis. Adjustment by age was done using logistic regression.

All tests were two sided with statistical significance set at $p < 0.05$. All analyses were performed with SPSS, version 21.0 (IBM SPSS).

Results

A total of 734 patients referred to our hospital were diagnosed as infected with SARS-CoV-2 during the study period. Of these, 656 (89%, 95% CI 87–91%) patients were admitted to hospital (median age 71 years, IQR 56–85; 52% were male). Seventy-eight patients were discharged on the same day directly from the emergency room because they had mild disease without pneumonia. One hundred and twenty-eight hospitalized patients died (19.5%, 95% CI 17–23%). The distributions of inpatients and the mortality rate according to age group are detailed in Fig. 1. At the time of writing, all the patients admitted during the study period had died or had been discharged from hospital.

The median age of the patients who died was 84 years (IQR 75–89), and 57% were male. Basal characteristics, comorbidities and chronic treatment are detailed in Table 1. In 19 patients (14.8%, 95% CI 10–22%), the main cause of death was attributed to the decompensation of acute or chronic pathologies where COVID-19 infection acted as a precipitating factor. These patients were older, with more long-term conditions and higher Charlson comorbidity scores, and more frequently had heart failure, dementia or cerebrovascular disease. They had a higher grade of dependency and frailty.

The most reported symptoms are detailed in Table 2. Patients who died of COVID-19 complications were more frequently feverish or had fever or cough at admission. Dyspnoea was the most common symptom in both groups. Nearly half of the patients who died without COVID-19 complications had normal X-rays.

The COVID-19 complications and the cause of death are detailed in Table 3. Nearly four in five patients who died with complications associated with SARS-CoV-2 infection developed ARDS or hyperinflammation.

The variables associated with the cause of death are shown in Table 4. OR are age adjusted. The confidence intervals are wide due to small sample size. They should be interpreted with caution.

During the first weeks, with more pressure on the hospital from the admission of new patients with COVID-19, there was a higher ratio of deaths with SARS-CoV-2 infection vs. deaths caused by SARS-CoV-2 infection (Fig. 2). The number of new hospital admissions and the total number of deaths for week are also shown.

Discussion

In this cohort study, we have reported the clinical characteristics of patients with COVID-19 admitted to a hospital who died during hospitalization. We analysed the cause of
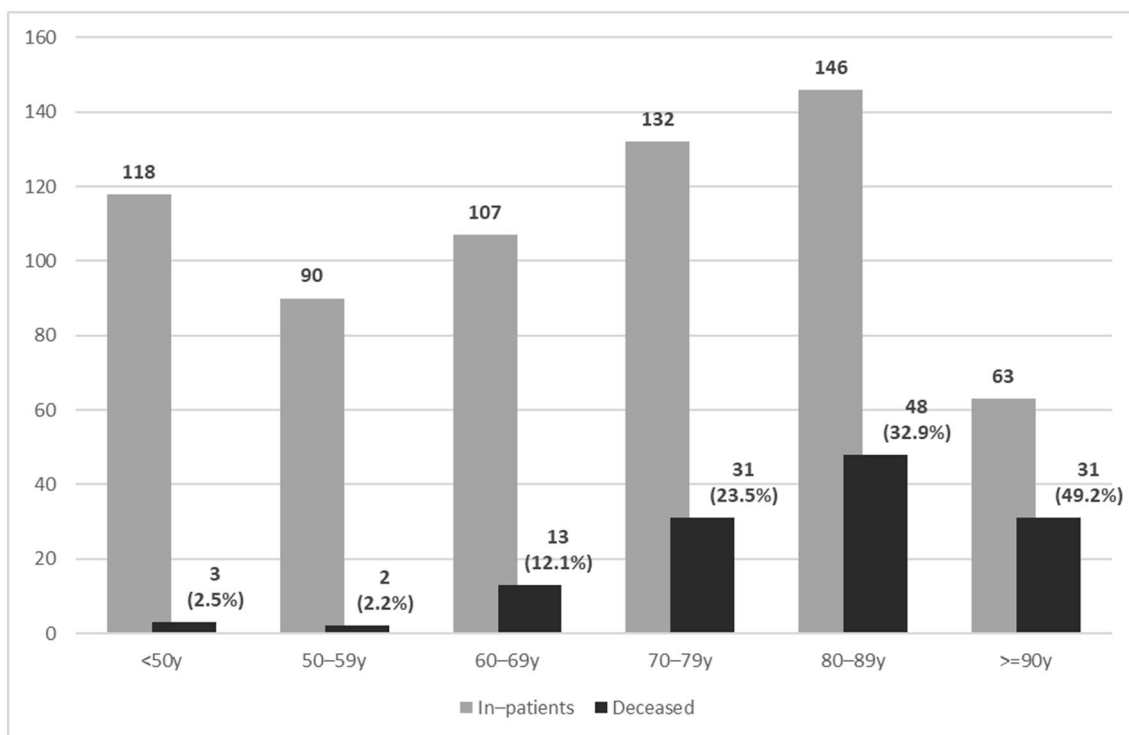

Fig. 1 Number of inpatients and mortality rate according to age

Table 1 Basal characteristics

Characteristics	Total (n = 128)	Deaths caused by SARS-CoV-2 infection (n = 109)	Death with SARS-CoV-2 infection (n = 19)	p
Age, median (IQR), years	84 (75–89)	82 (74–89)	88 (84–91)	**< 0.001**
< 50	3 (2%)	3 (3%)	0 (0%)	**0.006**
50–59	2 (2%)	2 (2%)	0 (0%)	
60–69	13 (12%)	13 (10%)	0 (0%)	
70–79	31 (24%)	30 (28%)	1 (5%)	
80–89	48 (38%)	37 (34%)	11 (58%)	
≥ 90	31 (24%)	24 (22%)	7 (37%)	
Males	73 (57%)	67 (62%)	6 (32%)	0.015
Place of residence				
Home	67 (52%)	64 (58%)	4 (21%)	0.003
Nursing home	61 (48%)	46 (42%)	15 (79%)	
Comorbidities				
Hypertension	91 (71%)	74 (68%)	17 (90%)	0.055
Dyslipidaemia	48 (38%)	42 (39%)	6 (32%)	0.563
Myocardial infarction	17 (13%)	15 (14%)	2 (11%)	0.701
Heart failure	21 (16%)	14 (13%)	7 (37%)	**0.017**
Cerebrovascular disease	15 (12%)	10 (9%)	5 (26%)	**0.048**
Dementia	35 (27%)	26 (24%)	9 (47%)	**0.034**
COPD	9 (7%)	8 (7%)	1 (5%)	0.744
Asthma	6 (5%)	5 (5%)	1 (5%)	0.898
SAHS	9 (7%)	7 (6%)	2 (11%)	0.621
Interstitial lung disease	1 (1%)	1 (1%)	0 (0%)	0.675
Connective tissue disease	1 (1%)	0 (0%)	1 (5%)	0.148
Peptic ulcer disease	12 (12%)	10 (12%)	2 (13%)	0.667
Diabetes mellitus				
Uncomplicated	36 (28%)	31 (28%)	5 (26%)	0.849
End organ damage	4 (3%)	3 (3%)	1 (5%)	0.479
Chronic liver disease				
Mild	5 (4%)	5 (5%)	0 (0%)	0.341
Moderate or severe	2 (2%)	2 (2%)	0 (0%)	0.552
Chronic kidney disease	20 (16%)	17 (16%)	3 (16%)	0.983
Solid tumour				
Localized	17 (13%)	16 (15%)	1 (5%)	0.465
Metastatic	2 (2%)	2 (2%)	0 (0%)	0.552
Leukaemia or lymphoma	5 (4%)	4 (4%)	1 (5%)	0.558
Current or past smoker	30 (23%)	27 (25%)	3 (16%)	0.579
Number of long-term conditions, median (IQR)	3 (2–5)	3 (2–4)	3 (2–6)	0.078
Charlson comorbidity index, median (IQR)	5 (3–6)	4 (3–6)	6 (4–7)	**0.004**
Performance in activities of daily living				
Independent	59 (46%)	58 (53%)	1 (5%)	
Slight dependency	21 (16%)	18 (17%)	3 (16%)	**< 0.001**
Moderate dependency	19 (15%)	13 (12%)	6 (32%)	
Severe dependency	13 (10%)	12 (11%)	1 (5%)	
Total dependency	16 (13%)	8 (7%)	8 (42%)	
Clinical Frailty Scale [16]				
Very fit	2 (2%)	2 (2%)	0 (0%)	
Well	21 (16%)	21 (19%)	0 (0%)	
Managing well	16 (13%)	15 (14%)	1 (5%)	**< 0.001**
Vulnerable	29 (23%)	28 (26%)	1 (5%)	

Table 1 (continued)

Characteristics	Total ($n = 128$)	Deaths caused by SARS-CoV-2 infection ($n = 109$)	Death with SARS-CoV-2 infection ($n = 19$)	p
Mildly frail	21 (16%)	17 (16%)	4 (21%)	
Moderately frail	12 (9%)	9 (8%)	3 (16%)	
Severely frail	9 (7%)	5 (5%)	4 (21%)	
Very severely frail	18 (14%)	12 (11%)	6 (32%)	
Chronic treatment				
ACEs	34 (27%)	24 (22%)	10 (53%)	**0.005**
ARBs	30 (23%)	24 (22%)	6 (32%)	0.3850.372
Statins	38 (30%)	34 (31%)	4 (21%)	
Metformin	23 (18%)	18 (17%)	5 (26%)	0.334
IDPP-4	18 (14%)	17 (16%)	1 (5%)	0.308
Insulin	12 (9%)	12 (11%)	0 (0%)	0.211
Inhaled corticosteroids	11 (9%)	10 (9%)	1 (5%)	0.575
Oral corticosteroids	4 (4%)	4 (4%)	0 (0%)	0.396
Immunomodulators	4 (4%)	4 (4%)	0 (0%)	0.396

Bold indicate p values that achieve statistical significance ($p < 0.05$)

Deaths caused by SARS-CoV-2 infection: patients whose death was caused directly by SARS-CoV-2 infection. Death with SARS-CoV-2 infection: patients where SARS-CoV-2 acted as a precipitating factor to decompensate other chronic or acute pathologies that were the main cause of death

ACEs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *COPD* chronic obstructive pulmonary disease, *RT-PCR* reverse transcription polymerase chain reaction, *SAHS* sleep apnoea–hypopnea syndrome

death to differentiate patients whose death was directly associated with development of COVID-19 complications (such is ARDS or pulmonary embolism) from infected patients who died of causes unrelated to any of these complications. Nearly 20% of patients died because of complications unrelated to COVID-19 infection. Most of these were old and frail patients, with only mild COVID-19 according to laboratory and X-ray findings. To the best of our knowledge, this is the first study analysing the cause of death of patients with COVID-19 to differentiate patients who died without developing COVID-19 complications.

The case fatality rate in patients with COVID-19 varies enormously across studies, from only 1.4% in the initial studies of the general population [3] to 21.9% in cohort studies of hospitalized patients with confirmed COVID-19 pneumonia [18] and more than 26% in patients admitted to intensive care units [6]. The mortality rates have been re-estimated [2]. The 15.2% rate of our study agrees with the expected mortality of 15.2% outside of China.

In all the literature, older people have a higher risk of death. However, the median age of 63 years in the first series in China [3] is far from our median age of 85 years. The marked aging of the population in our area and the greater life expectancy in Spain compared to China explain these differences. The older age of these COVID-19 victims brings the question of whether they have died prematurely [19]. For most young victims, there is no debate about the years of life lost but about their life quality. For older people, this is

also true, as more than 80% of patients in our series died of causes directly related to COVID-19 and could have lived longer without the infection.

As might be expected, age, comorbidities, frailty and dependency were associated with other causes of death unrelated to COVID-19 complications. The ongoing acute severe conditions, infections [20] or adverse events associated with prescribed drugs [21] could have played a role in these patients' deaths. Heart failure was the only comorbidity that emerged in the age adjusted regression analysis. Heart failure and dementia are two of the leading causes of death in older adults in Spain [22].

Differences existed in the drugs prescribed to the two groups. Lopinavir and ritonavir, tocilizumab, interferon and corticosteroids were practically not prescribed to the COVID-19 patients who died of unrelated causes. This is easy to explain, as these patients had only mild or no lung injury from SARS-CoV-2.

One of the most interesting associations ($p = 0.042$) was between death with SARS-CoV-2 infection and the time of hospital admission (Fig. 2). Unsurprisingly, most cases of unrelated cause of death occurred during the first 2 weeks of the epidemic in our area, when the hospital was in the process of organizing new healthcare procedures for COVID-19 patients and when the number of new admitted patients almost exceeded the hospital capacity (12 of 16 hospital wards were transformed into COVID-19 wards in only 2 weeks). The isolation in rooms of patients with

Table 2 Initial clinical, radiological and laboratory parameters and specific COVID-19 treatment

Characteristics	Total ($n=128$)	Deaths caused by SARS-CoV-2 infection ($n=109$)	Death with SARS-CoV-2 infection ($n=19$)	p
Days from illness onset to hospital admission, median (IQR), days	5 (2–7)	5 (2–7)	4 (2–7)	0.944
Signs and symptoms at diagnosis				
Shortness of breath	103 (81%)	86 (79%)	17 (90%)	0.363
Fever	89 (70%)	80 (73%)	9 (47%)	**0.023**
Cough	54 (42%)	50 (46%)	4 (21%)	**0.043**
Diarrhoea or vomiting	12 (9%)	12 (11%)	0 (0%)	0.211
Abdominal pain	7 (6%)	7 (6%)	0 (0%)	0.593
Anosmia or ageusia	22 (20%)	20 (20%)	2 (11%)	0.404
Asthenia	17 (13%)	14 (13%)	3 (16%)	0.718
Arthromyalgia	3 (2%)	3 (3%)	0 (0%)	0.464
Sore throat	3 (2%)	3 (3%)	0 (0%)	0.464
Headache	15 (12%)	12 (11%)	3 (16%)	0.550
X-ray/CT scan findings				
Normal	16 (13%)	6 (6%)	10 (54%)	**< 0.001**
Unilateral infiltrates	21 (16%)	16 (15%)	5 (26%)	
Bilateral infiltrates	91 (71%)	87 (80%)	4 (21%)	
Diagnosis				
RT-PCR positive	123 (96%)	106 (97%)	17 (90%)	0.123
Ig test positive	4 (3%)	2 (2%)	2 (10%)	
Presumptive diagnosis	1 (1%)	1 (1%)	0 (0%)	
Laboratory parameters, median (IQR)				
SaFi	390 (164–432)	390 (289–433)	390 (252–428)	0.928
PaFi	233 (177–290)	233 (169–295)	233 (195–257)	0.820
White blood cells, $\times 10^9$/mL	6700 (4325–10,450)	6500 (4300–10,100)	7900 (5200–12,100)	0.202
Lymphocytes, $\times 10^9$/mL	700 (500–1000)	700 (500–900)	1000 (500–1300)	0.074
Platelets, $\times 10^9$/mL	173 (122–228)	171 (115–227)	196 (130–230)	0.587
Haemoglobin, g/dL	130 (118–143)	130 (116–142)	131 (123–144)	0.254
D-dimer, mg/mL	673 (440–1686)	651 (422–1524)	889 (556–3359)	0.088
CRP, mg/L	120 (74–223)	121 (75–211)	104 (62–232)	0.754
Serum ferritin, ng/mL	591 (350–1440)	596 (359–1553)	489 (330–931)	0.321
Creatinine, mg/dL	1.22 (0.85–1.89)	1.23 (0.85–1.68)	1.19 (0.81–2.12)	0.665
Sodium	136 (132–140)	135 (131–140)	137 (136–143)	0.071
ALT, U/l	24 (17.37)	24 (16–35)	20 (18–49)	0.728
AST, U/l	44 (32–65)	44 (30–66)	48 (33–58)	0.494
LDH, U/l	429 (330–527)	433 (327–530)	406 (343–508)	0.881
Emergency room (ER) diagnosis				
SARS-CoV-2 was suspected in ER	123 (95%)	104 (95%)	19 (100%)	0.341
Lung injury was diagnoses in ER	88 (69%)	82 (75%)	6 (32%)	< 0.001
Treatments during study period				
Antibiotic agent	122 (95%)	105 (96%)	17 (90%)	0.391
Azithromycin	107 (84%)	91 (84%)	16 (84%)	0.356
Lopinavir and ritonavir	63 (49%)	61 (56%)	2 (11%)	**< 0.001**
Hydroxychloroquine	105 (82%)	90 (83%)	15 (80%)	0.747
Interferon	14 (11%)	14 (13%)	0 (0%)	0.128
Tocilizumab	4 (3%)	4 (4%)	0 (0%)	1.000
Corticosteroids	34 (26%)	33 (30%)	1 (5%)	0.238
Anticoagulants				
LMWH prophylaxis	84 (66%)	71 (65%)	13 (58%)	0.752

Table 2 (continued)

Characteristics	Total (n = 128)	Deaths caused by SARS-CoV-2 infection (n = 109)	Death with SARS-CoV-2 infection (n = 19)	p
LMWH extended prophylaxis	6 (5%)	6 (6%)	0 (0%)	
LMWH therapy	16 (13%)	13 (13%)	2 (11%)	
Oral anticoagulants	2 (2%)	2 (2%)	0 (0%)	
No anticoagulants	20 (16%)	16 (15%)	4 (21%)	
Respiratory support				
High-flow oxygen	2 (1%)	2 (1%)	0 (0%)	0.552
Non-invasive ventilation	12 (9%)	12 (11%)	0 (0%)	0.211
Invasive mechanical ventilation	26 (20%)	26 (24%)	0 (0%)	**0.013**
ECMO	2 (2%)	2 (2%)	0 (0%)	0.552
DNR order	20 (16%)	12 (11%)	8 (42%)	**0.002**

Bold indicate p values that achieve statistical significance ($p < 0.05$)

Deaths caused by SARS-CoV-2 infection: patients whose death was caused directly by SARS-CoV-2 infection. Death with SARS-CoV-2 infection: Patients where SARS-CoV-2 acted as a precipitating factor to decompensate other chronic or acute pathologies that were the main cause of death.

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *DNR* Do not resuscitate, *ECMO* extracorporeal membrane oxygenation, *LDH* lactate dehydrogenase, *LMWH* low molecular weight heparin, *PaFi* arterial partial pressure of oxygen/fraction of inspired oxygen, *SaFi* pulse oximetric saturation/fraction of inspired oxygen

dependency for activities of daily living, the low number of ward rounds compared with non-epidemic periods, the ban on relatives or friends accompanying the patients in their rooms, and the overload of hospitals and staff due to the high number of patients admitted every day may have played a negative role in the care of the patients admitted with COVID-19 infection. This negative effect was certainly magnified in frail patients, where the hospital care is sometimes much more important than the drugs intravenous fluids administered [23]. The way we should manage acute complications related to the disease should be different than the way we manage acute decompensation of comorbid conditions in patients with an acute viral infection with no severe disease. For many older patients with no severe COVID-19 disease, the health care, including stimulation, feeding or physical activity encouragement, as well as the management of their comorbidities, was the cornerstone of their treatment, more than the use of antivirals or immunomodulators. Several factors may be involved in the excess mortality of older people. The overload of the health system and consequent failure of hospital care standards and the need to increase isolation measures could have played a role in raising this mortality rate in patients with special care needs during admission.

Our study has several limitations. First, the causal contribution of SARS-CoV-2 infection to related deaths is a major question. It is difficult to differentiate between deaths with SARS-CoV-2 infection and deaths caused by SARS-CoV-2 infection due to the impossibility of performing necropsies. This forces interpreting our findings with caution, as exploratory and descriptive. Second, the study was conducted at a single-centre hospital with a limited sample size. Third, the study only included patients admitted to the hospital. Patients who died in their nursing homes were not included, which may lead to underestimating the real proportion of patients who died without developing COVID-19 complications. Fourth, some cases had incomplete clinical records and laboratory testing (supplementary material). To minimize the impact of missing data, we have incorporated all the electronic databases and scanned handwritten documents. Fifth, we found do not resuscitate orders (DNR) to allow natural death placed in patients with the highest grades of frailty and dependence. We do not know what the influence of DNR orders may had on the evolution of the disease and whether they could play a role in earlier deaths, just before severe symptoms of SARS-CoV-2 infection could develop. In sensitive analysis OR for dependence (OR 14.87, IC 95% 1.83–120.88) and frailty (OR 9.58, IC 95% 1.953–47.01) were statistically significant after being adjusted for the presence of DNR orders. We believe that one of the strengths of our study derives from the inclusion of all the patients who died during the study period.

Conclusion

Older and frail patients are at greater risk of death when infected by SARS-CoV-2. Although most deaths were associated with complications due to the own infection, a proportion of patients died from the decompensation of other acute or chronic pathologies. This partially explains the high fatality rate in the oldest groups of the population.

Table 3 COVID-19 complications

Characteristics	Total (n = 128)	Deaths caused by SARS-CoV-2 infection (n = 109)	Death with SARS-CoV-2 infection (n = 19)	p
Days in hospital until death, median (IQR), days	6 (3–10)	7 (3–13)	5 (1–9)	**0.035**
ARDS	93 (77%)	93 (85%)	0 (0%)	**< 0.001**
Hyperinflammation	93 (77%)	86 (79%)	7 (37%)	**< 0.001**
Septic shock	12 (9%)	11 (10%)	1 (5%)	0.505
Pulmonary embolism	3 (2%)	3 (3%)	0 (0%)	0.464
Place of death				
Hospital ward	102 (80%)	83 (76%)	19 (100%)	
Intensive care unit	26 (20%)	26 (24%)	0 (0%)	**0.013**
Main cause of death				
ARDS or severe lung injury (> 50% lung involvement in X-ray) caused by COVID	104 (81%)	104 (95%)	0 (0%)	**< 0.001**
Pulmonary thromboembolism	2 (2%)	2 (2%)	0 (0%)	
Sepsis shock due to COVID	3 (2%)	3 (3%)	0 (0%)	
Sepsis caused by bacterial infection without lung injury	3 (3%)	0 (0%)	3 (16%)	
Wasting associated with age	10 (8%)	0 (0%)	10 (53%)	
Heart failure without acute cardiac injury	2 (2%)	0 (0%)	2 (11%)	
Kidney failure without lung injury or shock	2 (2%)	0 (0%)	2 (11%)	
Bronchoaspiration	1 (1%)	0 (0%)	1 (5%)	
Gastrointestinal bleeding	1 (1%)	0 (9%)	1 (5%)	
Week of death				
18–24 March	11 (9%)	7 (6%)	4 (21%)	**0.042**
25–31 March	37 (29%)	31 (28%)	6 (32%)	
1–7 April	26 (20%)	22 (20%)	4 (21%)	
8–14 April	21 (16%)	18 (17%)	3 (16%)	
15–21 April	17 (13%)	16 (15%)	1 (5%)	
> 21 April	16 (13%)	15 (14%)	1 (5%)	

Bold indicate p values that achieve statistical significance (p < 0.05)

Deaths caused by SARS-CoV-2 infection: patients whose death was caused directly by SARS-CoV-2 infection. Death with SARS-CoV-2 infection: patients where SARS-CoV-2 acted as a precipitating factor to decompensate other chronic or acute pathologies that were the main cause of death
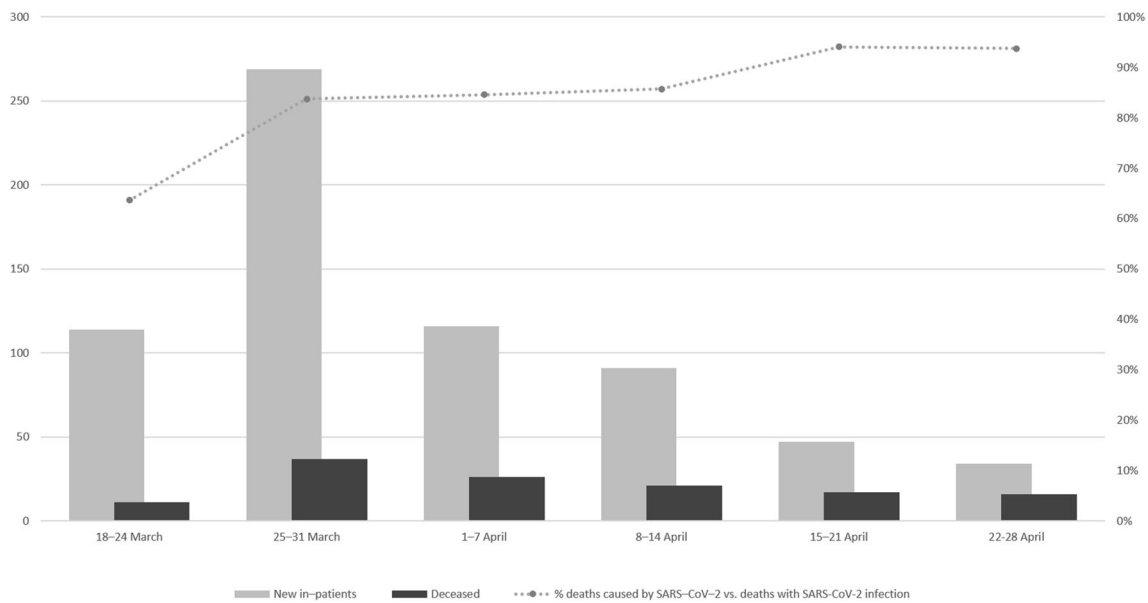
ARDS acute respiratory distress syndrome

Table 4 Age adjusted odds ratios of the variables significantly associated with death with SARS-CoV-2 infection vs. death caused by SARS-CoV-2 infection

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	p
Heart failure	3.96 (1.33–11.75)	3.61 (1.15–11.32)	**0.028**
Cerebrovascular disease	3.54 (1.05–11.86)	2.46 (0.677–8.55)	0.175
Dementia	2.87 (1.05–7.83)	2.15 (0.76–6.10)	0.150
Dependence on activities of daily living	20.47 (2.64–158.78)	12.07 (1.40–103.86)	**0.023**
Frailty	13.05 (2.87–59-34)	8.73 (1.37–55.46)	**0.022**
Fever or feverish at admission	0.33 (0.12–0.88)	0.45 (0.16–1.28)	0.134
Cough	0.32 (0.09–1.01)	0.51 (0.15–1.74)	0.282
Presence of X-ray infiltrates	0.05 (0.02–0.20)	0.07 (0.02–0.25)	**< 0.001**

Bold indicate p values that achieve statistical significance (p < 0.05)

CI confidence interval, *ns* statistically not significant, *OR* odds ratio

Fig. 2 Evolution of the proportion of deaths caused directly by SARS-CoV-2 infection

Compliance with ethical standards

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