Clinical, biological and radiological features, 4-week outcomes and prognostic factors in COVID-19 elderly inpatients

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SHORT TITLE

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ABSTRACT

Objective. To describe clinical, biological, radiological presentation and W4 status in COVID-19 elderly patients.

Patients and methods. All patients ≥70 years with confirmed SARS-CoV-2 infection and hospitalized in the Infectious Diseases department of the Pitié-Salpêtrière hospital, Paris, France, from March 1st to April 15th 2020 were included. The primary outcome was death 4 weeks after hospital admission. Data on demographics, clinical features, laboratory tests, CT-scan findings, therapeutic management and complications was collected.

Results. Overall, 100 patients were analyzed, including 49 patients ≥80 years. Seventy percent had ≥2 comorbidities. Respiratory features were often severe as 48% needed oxygen support upon admission. Twenty-eight out of 43 patients (65%) with a CT-scan had a mild to severe parenchymal impairment, and 38/43 (88%) a bilateral impairment. Thirty-two patients presented a respiratory distress requiring oxygen support ≥6 liters/minute. Twenty-four deaths occurred, including 21 during hospitalization in our unit, 2 among the 8 patients transferred in ICU, and one at home after discharge from hospital, leading to a global mortality rate of 24% at W4. Age, acute renal failure and respiratory distress were associated with mortality at W4.

Conclusion. Elderly COVID-19 patients with several comorbidities and severe clinical features survived in a substantial proportion, which could argue against transferring the most fragile patients in ICU.

INTRODUCTION

COVID-19 is an infection related to the novel coronavirus SARS-CoV-2 [1]. It started spreading from Wuhan, China in December 2019, leading to a major pandemic. In early September 2020, nearly 27 million COVID-19 cases were reported worldwide, associated with 900,000 deaths [2]. In France, almost 300,500 cases and 30,500 deaths have been documented since February 2020 [3]. Elderly population bear a heavy burden, with fatality rates reaching 26% and 58% in patients aged over 70 and 80 years, respectively. Most cohort studies have found age to be the main risk factor for mortality [4–6].

On May 12th in France, people over 75 years represented 56% of inpatients, 71% of deaths having occurred during hospital stay, and only 19% of patients admitted in ICU [3]. Therefore, elderly COVID-19 patients represent a high proportion of inpatients in medical wards. Despite frequent severe respiratory forms and accumulation of risk factors, a substantial number of these patients survived the infection. However, data in this population is very limited, especially among survivors after discharge from hospital.

Herein, we aimed to describe clinical, biological and radiological presentation of COVID-19 in patients over 70 years, in the Infectious and Tropical Diseases department of the Pitié-Salpêtrière University hospital (Paris, France), as well as clinical outcome 4 weeks (W4) after admission and factors associated with mortality.

MATERIALS AND METHODS

Study design and participants

We performed a retrospective, single-center study in the Infectious and Tropical Diseases department at the Pitié-Salpêtrière University Hospital, Paris, France. We included all confirmed cases of COVID-19 over 70 years old admitted from March 1st to April 15th 2020.

Patients were considered to have a confirmed infection if testing by RT-PCR from nasopharyngeal swab and/or sputum came back positive.

Outcomes

The primary outcome was vital status (survival or death) 4 weeks after hospital admission. The secondary outcomes were length of hospital stay, occurrence of acute respiratory distress and/or other complications during clinical course, transfer to ICU, "do not resuscitate" order, use of hypnotic and opioid drugs, place of residence (at home or retirement home, subacute care ward, ICU) 4 weeks after hospital admission for survivors, and factors associated with vital status at week 4 (W4).

Procedures

We obtained data retrospectively from electronic medical records, carefully reviewed by three trained physicians. Patient data included demographics, home medications, comorbidities, initial signs and symptoms, onset of signs and symptoms, triage vitals, initial laboratory tests, value of cycle threshold (Ct) for SARS-CoV-2 RT-PCR, chest computed tomographic scan results, treatments received during hospitalization (antivirals, antibiotics, corticosteroids and oxygen support), maximum body temperature, and length of hospital stay. Charlson index was used to evaluate patients' medical state before admission [7]. NEWS-2 score was used to standardize the assessment of acute-illness severity at admission [8]. The occurrence of acute respiratory distress during clinical course was defined as the recourse to oxygen support ≥6 liters/minute to maintain blood oxygen saturation (SpO_2) ≥94%. We also collected other significant complications (acute renal injury, acute hepatitis, bacterial infection) and maximum C-reactive protein (CRP) during hospital stay.

Nasopharyngeal swab and sputum samples were collected and tested by RT-PCR with the Cobas® SARS-CoV-2 kit (Roche), as recommended by the manufacturer, after neutralization with an equal amount of Cobas lysis buffer for the SARS-CoV-2 (400/400 µL). Three categories of Ct were retained: Ct<20 (high SARS-CoV-2 viral load), 20 <Ct ≤30 (mild viral load) and Ct >30 (low viral load).

All scans were performed on a dedicated scanner (Siemens Somaton Edge) either without iodine injection or after IV of 60 mL iodinated contrast agent (Iomeprol 400 Mg I/mL, Bracco Imaging, Milan, IT) in cases of suspected pulmonary embolism. Radiologist (SB) who were blinded to clinical and biological features including RT-PCR results, reviewed all chest CT images on a PACS workstation (Carestream Health, Rochester, NY) and classified the chest CT as positive or negative for COVID-19 according to CT features previously described [9–11]. The radiologist also described main CT features (ground-glass opacity, consolidation, reticulation/thickened interlobular septa, nodules, emphysema, pleural effusion), and lesion distribution (left, right or bilateral lungs). A semi-quantitative score was assigned (0% involvement; less than 25%; 25% to less than 50%; 50% to less than 75%; 75% or greater). All images were viewed on both lung and mediastinal settings.

We reported for each patient whether a transfer to ICU had been considered during clinical course, a “do not resuscitate” order had been collectively decided, and whether hypnotic or opioid drugs were used.

Patients or family were contacted by a physician 4 weeks after admission to collect vital status and place of residence at W4.

Statistics

We analyzed the vital status 4 weeks after hospital admission using a logistic regression model. Factors investigated were: sex of patients, age, place of residence before hospital admission,

number of comorbidities, Charlson's score, time from onset of symptoms and hospital admission, NEW-2 score, Oxygen support need at admission, lymphocyte count at admission, SARS-CoV-2 RT-PCR Ct, total lesion extension, presence of bilateral lesion, duration of hospital stay and respiratory distress (requiring oxygen support ≥6 liters/minute). For all these factors, missing values were defined as "unknown". A descriptive analysis of the dependent and independent variables was performed. A univariate analysis was conducted, and all factors associated with death 4 weeks after hospital admission were entered into the multivariate model. We decided to exclude from the analysis the lost to follow-up. The vital status 4 weeks after hospital admission was also compared between patients aged 70 to 79, 80 to 89 and >90 year-old using a chi-square test. Survival curve was showed using Kaplan-Meier estimates. All analyses were performed using R studio Version 1.2.5033 (© 2009-2019 RStudio, Inc.) and a p value<0.05 was considered as significant.

Ethics

All discharged inpatients were included in the prospective COVID-PSL cohort, for the 4-week telephonic follow-up. They signed a written informed consent. This cohort was approved by the Ethics Committee Ile-De-France X (n°47-2020, NCT 04402905).

RESULTS

Demographics and medical background

Overall, 100 patients were included for analysis, including 59 men (Table 1). Median age was 79 years (IQR 74-85). Fifty-one patients were between 70 and 79 years, 37 between 80 and 89 years, and 12 over 90 years. Eighty-nine lived independently at home and 11 in retirement home before being admitted to hospital.

Fifty-six of them had a Charlson index ≥5 and 71 had at least 2 comorbidities (Table 1). The most prevalent comorbidities were high blood pressure (56%), chronic heart failure (31%), dementia (25%), diabetes (24%) and/or active cancer (21%). Eleven patients had a long-term immunosuppressive and/or corticosteroid therapy.

Clinical and biological feature at hospital admission

Median time between the onset of symptoms and hospital admission was 4 days (IQR 2-7). Seventy percent of patients were admitted to hospital before the 7th day.

All SARS-CoV-2 infections were confirmed by RT-PCR from nasopharyngeal swab and/or sputum, with a low Ct (≤20) in 21% of cases and a mild Ct (21-35) in 28% of cases.

The most prevalent symptoms reported at admission were fever (69%), cough (50%), dyspnea (36%), diarrhea (16%) and confusion (14%) (Table 1). Fifty-five patients had a NEWS-2 score ≥3 and 22% needed oxygen therapy ≥3 liters/minute upon admission.

Regarding biological parameters, 80% of patients had lymphopenia, 23% had thrombopenia, 32% had acute renal failure and 35% had hepatic cytolysis.

Thoracic CT-scan outcomes

46 CT-scans were analyzed from 43 patients (3 patients had 2 CT-scans). 39 (91%) patients were with abnormal lung changes: 91% had ground class opacities (GGO), 63% had crazy paving (GGO associated with superimposed intralobular reticulations) and 30% had condensations. 29 patients (65%) had a mild to severe parenchymal impairment, 38 patients (88%) had a bilateral impairment, and the lesions were mainly distributed in the lower lungs in 35 patients (81%) (Table 2). 6 patients had pleural effusion. 11 patients were with common accompanying diseases of which emphysema (n=9), bronchiectasis (n=1), and pleural sequelae

(n=1). Associated pulmonary oedema was detected in one patient. CT scan were injected in 42% of cases, with no pulmonary embolism detected.

Therapeutic management and clinical course during hospitalization

Sixty-five patients received antibiotics, including a beta-lactam in 97% of cases and/or a macrolide in 98% of cases (Table 3). Thirty percent of patients received hydroxychloroquine for a median duration of 9 days (IQR 2-10). No cardiac side effects were observed in patients treated by hydroxychloroquine. Seven percent of patients received short-term corticosteroid therapy (2-5 days).

Thirty-two patients presented a clinical deterioration with respiratory distress requiring oxygen support ≥6 liters/minute. Respiratory distress occurred after a median time of 10 days (IQR 4-13 after the onset of symptoms. Among these 32 patients, 8 (25%) were transferred to ICU (Figure 1). All were <80 years. For the 24 others, a "do not resuscitate" order was decided. Hypnotic and opioid drugs were used in 17 of them.

Mortality rate and place of residence at W4

Overall, 24 deaths occurred from hospital admission to W4, including 21 deaths during hospitalization in our unit, 2 deaths in ICU and one death at home after discharge from hospital, leading to a global mortality rate of 24% at W4 (Figure 2a). The mortality rate in 70-79, 80-89 and >90 year-old patients was 10/47 (21%), 10/36 (28%) and 4/11 (36%), respectively. The duration of hospital stay was significantly shorter in deceased patients than in discharged patients (7.1 vs. 11.1 days, OR 0.70, 95%CI 0.47-0.88, p=0.017). Among deceased patients, death occurred 9 days (IQR 13-16) in median after the onset of symptoms.

Overall, among surviving patients, 46/67 (69%) had returned home or to their institution and 21/67 (31%) were still hospitalized in a subacute care ward.

Factors associated to death at W4

The older the age was, the greater was the risk of dying (OR 1.15, 95%CI 1.05-1.27, p=0.005); in other words, 10 more years equated to 15% more risk of dying due to COVID-19.

The occurrence of a respiratory distress was also associated with death (OR 6.53, 95%CI 1.20-45.6, p=0.038). Interestingly, 13 patients survived despite acute respiratory distress, without mechanical ventilation and having received sustained oxygen support (6, 9 and 15 liters/minute for 4, 3 and 6 patients, respectively).

Except age and respiratory distress, only acute renal failure at admission was strongly associated with mortality at W4 (OR 73.8, 95%CI 5.7-3721.2, p=0.006).

DISCUSSION

In our study, patients aged ≥65 years with COVID-19 presented severe clinical course and frequently required respiratory support. The high mortality rate (24%) is consistent with similar findings in other countries such as China, Korea or USA [12–14]. In a recent cohort conducted in French acute care geriatric wards, this mortality rate was higher (31%), probably due to higher median age (86 vs. 79 years in our population) and poorer general health conditions (29% lived in institution vs. 11% in our population) [15].

Although our population was characterized by a high frequency of severe comorbidities and included several very old patients (half of them were ≥80 years), 76% of patients survived during their hospital stay. Moreover, 70% of our patients were admitted at hospital before D7, i.e. before the theorical degradation of the clinical condition. This survival rate is all the more interesting as some patients presented a temporary critical condition (n=13) and few were transferred to ICU (n=8).

Viral pneumonia is one of the most frequent complications of COVID-19, requiring oxygen therapy and endo-tracheal intubation for the most severe forms [16]. Intensive care unit (ICU) stays are often extended for several weeks and burdened with high mortality rates, especially among older patients [17,18] In many centers, access to ICU for patients over 70 years was strongly restricted, due to the poor prognosis [19]. In our study, no ICU transfer was decided for patients ≥80 years. Indeed, reported mortality rates in ICU in this population up to now are 40 to 80%, although more robust data on short-and long-term outcomes is needed [17,20]. Oxygen support was performed by nasal canula, simple mask, or non-rebreathing mask. We did not have the possibility to use very high flow oxygen therapy (Optiflow system) or non-invasive ventilation, that could be an alternative to endo-tracheal intubation with enhancing the survival.

In order to assess delayed mortality in elderly patients with COVID-19, we systematically contacted discharged patients or their families 4 weeks after their admission in our department. Before analysis, we expected a non-negligible mortality at discharge due to sequalae of the disease and loss of autonomy, but we were able to authenticate the death after discharge in only one patient, that could suggest a satisfactory recovery after the disease. However, a significant proportion of our patients were still hospitalized in subacute care wards, despite full pre-admission autonomy, suggesting a slow return to health baseline. And we could not formally exclude the death of the 8 lost to follow-up patients.

As in previous cohorts, the most frequent symptoms associated with SARS-CoV-2 infection were fever, cough and dyspnea [17,21]. However, digestive disorders and confusion as isolated symptoms were not rare (16% and 14%, respectively, in our population), highlighting the special attention that clinicians should have in elderly patients [22].

Radiological presentations were in adequation with clinical presentations, with frequent severe parenchymal impairment. Previous works showed that pulmonary lesions are more extensive

and more often bilateral in elderly patients, in comparison with younger patients [23,24]. Surprisingly, no pulmonary embolism was detected, while venous thromboembolic disease could reach 20% during COVID-19 course in hospitalized patients [25]. The number of patients receiving an anticoagulant treatment before the infection (23%) could partially explain this result.

Antibiotics were widely used, and certainly over-used, due to lack of knowledge in the beginning of the pandemic outbreak. We treated patients using MERS-CoV-2 management as model [26]. That being said, no antibiotics side effect were reported (no allergic reactions, no *Clostridioides difficile* colitis, no catheter infections). On the other hand, almost half of patients received hydroxychloroquine. Data, including ours, has now shown lack of positive impact of this antiparasitic on the SARS-CoV-2 infection [27,28] but was not yet available when managing our patients. There was no significant difference on mortality between patients having received or not hydroxychloroquine in our population of elderly patients. Some patients received corticosteroids, according to the clinician's judgment, in case of aggravation and/or arguments for inflammatory evolution of the disease. The impact of corticosteroids on the COVID-19 course is currently debated, but recent data tends to show their positive effect in the COVID-19 management [29].

Several comorbidities such as cardiovascular and lung diseases, diabetes, dementia or cancer, all which increase with age [30]. We investigated whether clinical and biological characteristics were associated with death. In our population, the age and the occurrence of respiratory distress were significantly associated with mortality at W4, that match the prognostic factors found in other studies [6,15,31,32]. The acute renal failure at hospital admission was also associated with mortality. Other works have shown that renal impairment was observed in severe forms of COVID-19, and was an independent factor associated with mortality [33,34]. Several other factors such as comorbidities, severe initial clinical presentation (reflected by the NEWS-2

score) or biological abnormalities have been reported to be poor prognostic factors [6,15,31,32], but not in our population. We assume that the characteristics of our patient sample were too homogeneous to detect significant differences according to the final outcome. Indeed, all patients were hospitalized in the same medicine department, almost all had a significant number of comorbidities as medical background, and almost all faced severe SARS-CoV-2 infection.

This study has several limitations. First, it was a retrospective study with a relatively small number of patients and some unavailable biological data, limiting the field of our analysis with possible confounding. Second, our study subjects consisted of hospitalized patients. Thus, those deemed sufficiently fit for home isolation were not included, which could explain the high mortality and severity observed. Therefore, our results are not generalizable to mild cases. Finally, we did not have standardized geriatric scales (i.e. ADL, IALD) to accurately assess the overall progress of our elderly patients.

In conclusion, although being the most vulnerable population to COVID-19, a high proportion of elderly patients with several comorbidities and severe respiratory feature survived the infection without mechanical ventilation. In view of the extremely poor prognosis of elderly patients in ICU, our findings argue for maximum and optimized care in medical departments for this population.

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TRANSPARENCY DECLARATION

No authors have any conflicts of interest to declare.

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363

FIGURE 1. Study flow chart and W4 outcomes.

FIGURE 2. Survival curve of study patients.

Table 1. Patient's characteristics at study entry (n=100).

Demographics	
Gender, n (%)	
Male	59/100 (59)
Female	41/100 (41)
Age, years, median (IQR)	79 (74-85)
Age range, n (%)	
70-79 years	51/100 (51)
80-89 years	37/100 (37)
≥90 years	12/100 (12)
Place of residence before hospital admission, n (%)	
Home	87/100 (87)
Retirement home	13/100 (13)
Comorbidities	
Diabetes, n (%)	24/100 (24)
Hypertension, n (%)	56/100 (56)
Chronic heart failure, n (%)	31/100 (31)
Cancer, n (%)	21/100 (21)
Dementia, n (%)	25/100 (25)
Auto-immune disorder, n (%)	10/100 (10)
Immunosuppression (HIV or transplant) , n (%)	4/100 (4)

COPD or asthma, n (%)	16/100 (16)
Chronic kidney disease, n (%)	13/100 (13)
Obesity (BMI ≥30 kg/m^2)	6/100 (6)
Current smoking, n (%)	6/100 (6)
Number of comorbidities, n (%)	
0-1	29/100 (29)
2-3	47/100 (47)
≥4	24/100 (24)
Charlson's score, n (%)	
0-4	34/100 (34)
≥5	66/100 (66)
Treatments	
ACE inhibitor, n (%)	14/100 (14)
ARB treatment, n (%)	9/100 (9)
Other antihypertensive treatment, n (%)	57/100 (57)
Oral antidiabetic agent, n (%)	13/100 (13)
Insulin, n (%)	12/100 (12)
Corticosteroid, n (%)	7/100 (7)
Immunosuppressive therapy, n (%)	5/100 (5)
Statin, n (%)	28/100 (28)
Anticoagulant, n (%)	23/100 (23)
Antiplatelet agent, n (%)	21/100 (21)
Proton pump inhibitor, n (%)	29/100 (29)

Psychotropic treatment, n (%)	36/100 (36)
Bronchodilator, n (%)	12/100 (12)
Symptoms	
Fever, n (%)	69/100 (69)
Cough and sputum, n (%)	50/100 (50)
Chest tightness, difficulty breathing, n (%)	36/100 (36)
Headache, n (%)	8/100 (8)
Diarrhea, n (%)	16/100 (16)
Loss of smell and/or taste, n (%)	5/100 (5)
Confusion, n (%)	14/100 (14)
Hospital admission	
Time from onset of symptoms, days, median (IQR)	4 (2-7)
NEW-2 score, n (%)	
0-2	45/100 (45)
≥3	55/100 (55)
Oxygen support need, n (%)	
No	52/100 (52)
1-2 L/min	26/100 (26)
≥3 L/min	22/100 (22)
Biological parameters	
Hemoglobin (g/L), median (IQR)	12.5 (11.75-13)
Anemia, n (%)	12/95 (13)

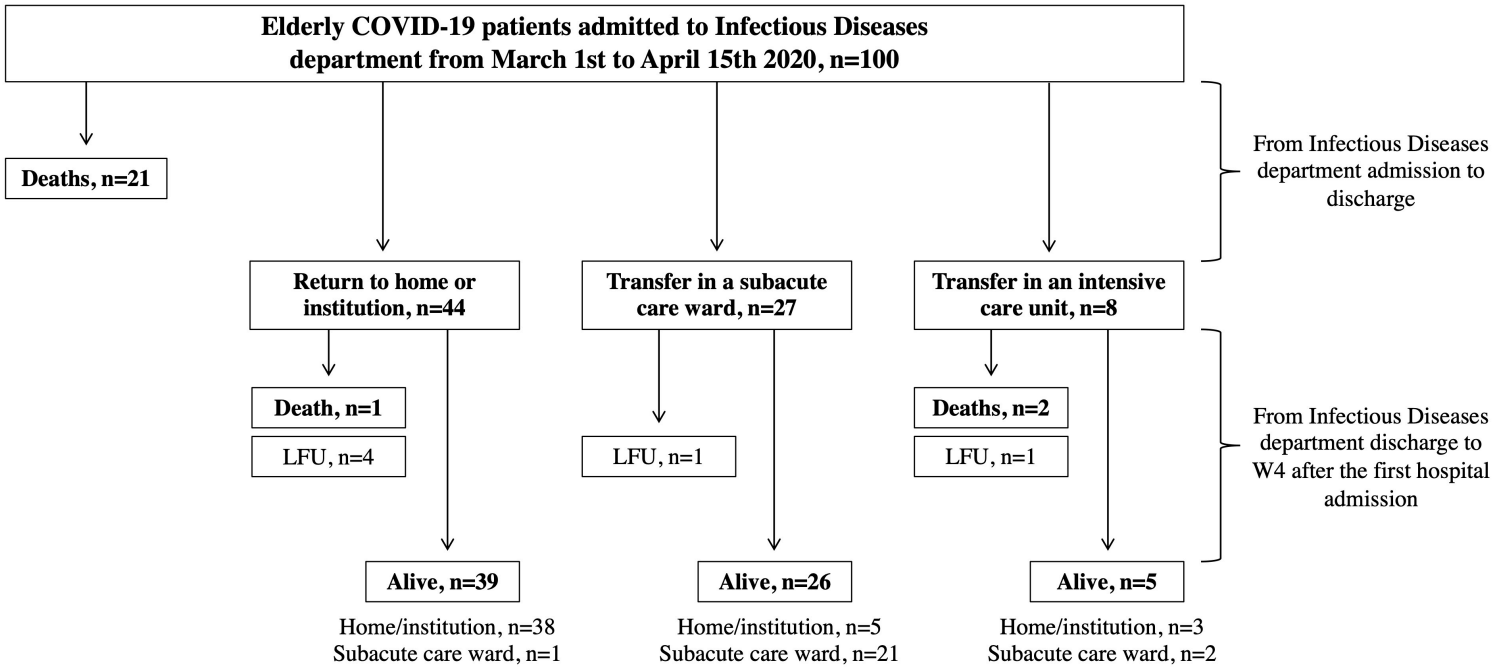
Platelets (x10^9/L), median (IQR)	188 (151.5-245)
Thrombopenia, n (%)	22/95 (23)
Total white blood cell count (x10^9/L), median (IQR)	4.81 (2.63-6.50)
Lymphocyte count (x10^9/L), median (IQR)	86 (60 – 122)
Lymphopenia, n (%)	72/90 (80)
Neutrophil count (x10^9/L), median (IQR)	349 (205 – 496)
Serum ALAT (U/L), median (IQR)	26 (20 -35)
Hepatic cytolysis, n (%)	25/72 (35)
Serum creatinine (µmol/L), median (IQR)	85 (71-106)
Acute renal failure, n (%)	30/93 (32)
SARS-CoV-2 RT-PCR	
Ct <20	15/72 (21)
20 <Ct ≤30	37/72 (51)
Ct >30	20/72 (28)

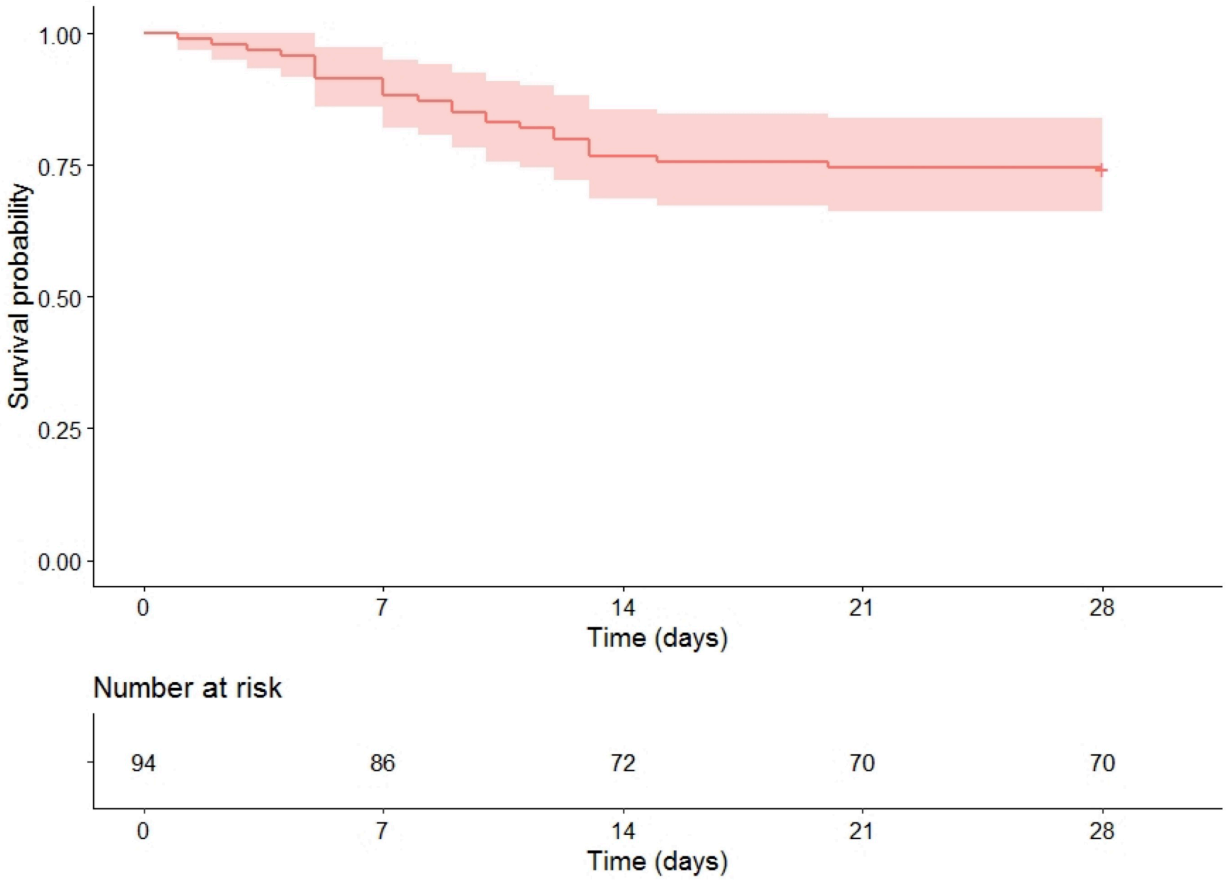
Table 2. Pulmonary CT-scan outcomes (n=43).

Normal CT	4/43 (9)
Ground glass lesion extension, n (%)	
0%	4/43 (9)
1-25%	19/43 (45)
26-50%	16/43 (37)
51-75%	4/43 (9)
Crazy paving	27/43 (63)
Condensation lesion extension, n (%)	
0%	30/43 (70)
1-25%	11/43 (25)
26-50%	2/43 (5)
51-75%	0/43 (0)
Total lesion extension, n (%)	
0%	4/43 (9)
1-25%	11/43 (26)
26-50%	21/43 (49)
51-75%	7/43 (16)
Bilateral lesion, n (%)	38/43 (88)
Inferior lung involvement	35/43 (81)
Pulmonary embolism, n (%)	0/43 (0)

Table 3. Therapeutic management during hospitalization (n=100).

Antibiotics, n (%)	
Beta-lactam	64/100 (64)
Macrolide	12/100 (12)
Other	1/100 (1)
Antiviral and/or immunomodulator treatments, n (%)	
Hydroxychloroquine	29/100 (29)
Corticosteroid	7/100 (7)
Azithromycin	1/100 (1)
Tocilizumab	1/100 (1)
Lopinavir/ritonavir	1/100 (1)
Respiratory distress requiring oxygen support ≥6 liters/minute, n (%)	32/100 (32)


Elderly COVID-19 patients admitted to Infectious Diseases department from March 1st to April 15th 2020, n=100
Deaths, n=21
Return to home or institution, n=44
Transfer in a subacute care ward, n=27
Transfer in an intensive care unit, n=8
From Infectious Diseases department admission to discharge
Death, n=1
LFU, n=4
LFU, n=1
Deaths, n=2
LFU, n=1
From Infectious Diseases department discharge to W4 after the first hospital admission
Alive, n=39
Alive, n=26
Alive, n=5
Home/institution, n=38
Subacute care ward, n=1
Home/institution, n=5
Subacute care ward, n=21
Home/institution, n=3
Subacute care ward, n=2


1.00
0.75
0.50
0.25
0.00
Survival probability
0
7
14
21
28
Time (days)
Number at risk
94
86
72
70
70
0
7
14
21
28
Time (days)