Clinical characteristics and prognostic factors in COVID-19 patients aged ≥80 years

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Introduction
Since the first case was identified in Wuhan city (China) in December 2019, the novel coronavirus designated SARS-CoV-2, has caused an international outbreak of respiratory illness named coronavirus disease 2019 (COVID-19). The spectrum of COVID-19 is various, ranging from possible asymptomatic patients to severe progressive pneumonia and acute respiratory distress syndrome leading to death.1–5

After the first case of COVID-19 was diagnosed in the Lombardy region of Italy, in February, one of the largest and most serious clusters of COVID-19 in the world struck the Italian nation. Despite an aggressive effort of containment put in place, the disease continues to spread and the number of affected patients is still rising; furthermore, the case fatality rate has been very high and dominated by older patients.6

Italy presents one of the highest life expectancies in the world, which is at birth 80.3 years for men and 84.9 years for women.7 In Italy, people aged ≥65 years now represent approximately 22.6% of the population, and older adults aged ≥80 years represent 6.5% of the total population.7

The overall estimated case fatality rate of COVID-19 in Italy is 7.2%; however, the median age for all COVID-19 related death is 81 years (73–86 years), and the case fatality rate in patients aged ≥80 years is >20%.8 Nevertheless, up to now, limited data are available for COVID-19 in older patients, and no reports have focused on patients aged ≥80 years.9–11

The aim of the present study was to describe the clinical presentation of patients aged ≥80 years with coronavirus disease 2019 (COVID-19), and provide insights regarding the prognostic factors and the risk stratification in this population.

Methods

Study design
This was a single-center, retrospective, observational study carried out in an urban teaching hospital, which is a referral center for COVID-19, in central Italy. We reviewed the clinical records of all the patients aged ≥80 years consecutively admitted to our emergency department (ED) for suspected COVID-19 over a 1-month period (1–31 March 2020). COVID-19 was diagnosed based on the World Health Organization interim guidance.12 We included...
in the analysis only patients with a positive result on real-time reverse transcription polymerase chain reaction assay of nasal and pharyngeal swab specimens.

We excluded from the study cohort patients discharged from ED, and patients already on orotracheal intubation at ED arrival. For patients with more than one admission, only the latest access was included in the analysis.

### Study variables

We extracted from computerized clinical records clinical, laboratory and radiological findings at admission. We included in the analysis the following:

- Physiological parameters: age, sex, temperature, heart rate, respiratory rate, blood pressure, Glasgow Coma Scale score, oxygen supplementation and peripheral oxygen saturation (pO2). Based on physiological parameters, we calculated the National Early Warning Score for all patients.
- Symptoms at admission: fever (core temperature >37.5°C), dyspnea, cough, fatigue or other (including sore throat, headache, diarrhea, abdominal pain, dysgeusia).
- Radiographic findings: based on chest X-ray or CT scan obtained in ED, patients were categorized as normal, monolateral ground-glass opacity or interstitial involvement and bilateral pneumonia.
- Laboratory findings: hemoglobin, total white cell blood count, serum creatinine, blood urea nitrogen, alanine aminotransferase, lactate dehydrogenase, fibrinogen, prothrombin time, D-dimer, ferritin, C-reactive protein (CRP) and procalcitonin.
- Patient disease presentation in ED: categorized as mild for normal X-ray findings, severe for positive S-ray and pO2 ≥92%, and critical for positive X-ray and pO2 <92%.
- Clinical history: coronary artery disease or congestive heart failure, hypertension, diabetes, chronic obstructive pulmonary disease, severe dementia, malignancy and institution residency.

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**Table 1** Clinical and demographic characteristics of patients aged ≥80 years included in the study cohort

| Variable | All population (n = 69) | Survived (n = 46) | Died (n = 23) | P |
|----------|-------------------------|------------------|--------------|---|
| Age (years) | 84 (82–89) | 84 (81–89) | 85 (83–86) | 0.858 |
| Sex (male) | 37 (53.6%) | 25 (54.3%) | 12 (52.2%) | 0.864 |
| Heart rate (min⁻¹) | 85 (75–95) | 83 (75–92) | 87 (73–107) | 0.404 |
| Systolic BP (mmHg) | 127 (111–140) | 130 (112–140) | 122 (100–137) | 0.132 |
| Diastolic BP (mmHg) | 75 (65–89) | 78 (65–90) | 68 (60–86) | 0.183 |
| pO2 (%) | 94 (90–96) | 95 (93–96) | 89 (82–94) | 0.001 |
| Temperature (°C) | 36 (35.5–36.5) | 36 (35.5–36.5) | 36.2 (35.7–36.8) | 0.596 |
| GCS | 15 (15–15) | 15 (15–15) | 15 (15–15) | 0.202 |
| NEWS ≥3 | 41 (59.4%) | 24 (52.2%) | 17 (73.9%) | 0.083 |

### Symptoms

- Fever | 56 (81.2%) | 56 (81.2%) | 56 (81.2%) | 0.663 |
- Dyspnea | 32 (46.4%) | 13 (28.3%) | 19 (82.6%) | <0.001 |
- Cough | 29 (42.0%) | 22 (47.8%) | 7 (30.4%) | 0.168 |
- Fatigue | 8 (11.6%) | 6 (13.0%) | 2 (8.7) | 0.595 |
- Other | 11 (15.9%) | 7 (15.2%) | 5 (21.7%) | 0.500 |

### Clinical history

- CHF/CAD | 21 (30.4%) | 14 (30.4%) | 7 (30.4%) | 1.000 |
- Hypertension | 41 (59.4%) | 31 (67.4%) | 10 (43.5%) | 0.057 |
- Cerebrovascular disease | 20 (29.0%) | 11 (23.9%) | 9 (39.1%) | 0.189 |
- Diabetes | 9 (13.0%) | 7 (15.2%) | 2 (8.7%) | 0.448 |
- COPD | 7 (10.1%) | 3 (6.5%) | 4 (17.4%) | 0.159 |
- Severe dementia | 8 (11.6%) | 2 (4.3%) | 6 (26.1%) | 0.014 |
- Malignancy | 3 (4.3%) | 2 (4.3%) | 1 (4.3%) | 1.000 |
- Living in institution | 17 (24.6%) | 11 (23.9%) | 6 (26.1%) | 0.843 |

### Radiology

- Negative | 8 (11.6%) | 7 (15.2%) | 1 (4.3%) | 1.000 |
- Monolateral pneumonia | 29 (42.0%) | 20 (43.5%) | 9 (39.1%) | 0.302 |
- Bilateral pneumonia | 32 (46.4%) | 19 (41.3%) | 13 (56.5%) | 0.005 |

### Severity classification

- Mild | 14 (20.3%) | 13 (28.3%) | 1 (4.3%) | 1.000 |
- Severe | 30 (43.5%) | 22 (47.8%) | 8 (34.8%) | 0.005 |
- Critical | 25 (36.2%) | 11 (23.9%) | 14 (60.9%) | 0.005 |

### Outcome

- ICU admission | 11 (15.9%) | 4 (8.7%) | 7 (30.4%) | 0.034 |
- Survival time (days) | 26 (11–35) | 35 (32–39) | 5 (2–13) | – |
- Deaths | 23 (33.3%) | – | – | – |

P-values are shown with regard to comparison between patients who survived and died. Survival follow up was assessed at 30 days from emergency department admission. BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; ICU, intensive care unit; NEWS, National Early Warning Score; pO2, peripheral oxygen saturation.
Study end-points

The primary study end-point was the patient’s death. Survival follow-up was assessed at 30 days from admission.

Statistical analysis

Continuous variables are reported as the median (interquartile range), and are compared at univariate analysis by Mann-Whitney U-test. Categorical variables are reported as the absolute number (percentage), and are compared by the \( \chi^2 \)-test (with Fisher’s test if appropriate).

We compared the clinical and laboratory variables by a univariate Cox analysis (proportional hazards regression) for their association with survival. The post-hoc analysis was made by log-rank test. We entered significant parameters at univariate analysis into a multivariate Cox regression model to identify independent predictors of death. For a better model fitting and hazard estimation, we categorized the continuous variables into dichotomous parameters (i.e. low/high). For each variable, we obtained the optimal dividing cut-off by Youden’s index, carrying out a receiver operating characteristic (ROC) curve analysis.

### Table 2  Laboratory values of patients aged \( \geq 80 \) years in the study cohort

| Laboratory                  | Reference value | Entire population (\( n = 69 \)) | Survived (\( n = 46 \)) | Died (\( n = 23 \)) | \( P \) |
|-----------------------------|-----------------|----------------------------------|-------------------------|---------------------|-------|
| Haematology                 |                 |                                  |                         |                     |       |
| Hemoglobin (g/dL)           | 13.0–16.0       | 13.2 (11.9–14.5)                 | 13.2 (11.9–14.3)        | 13.2 (11.7–14.7)    | 0.784 |
| White cell blood count (x10^9/L) | 3.5–9.5       | 5.78 (4.55–7.67)                 | 5.78 (4.83–7.50)        | 5.93 (3.94–8.27)    | 0.636 |
| Biochemistry                |                 |                                  |                         |                     |       |
| Creatinine (mg/dL)          | 0.67–1.17       | 1.05 (0.88–1.52)                 | 1.03 (0.88–1.32)        | 1.45 (0.88–2.05)    | 0.068 |
| Blood urea nitrogen (mg/dL) | 10–23           | 22 (17–38)                       | 20 (16–31)              | 39 (20–58)          | 0.006 |
| Alanine aminotransferase (U/L) | 7–45           | 19 (14–32)                       | 18 (13–27)              | 21 (15–53)          | 0.175 |
| Lactate dehydrogenase (U/L) | <250            | 322 (269–480)                    | 305 (259–409)           | 511 (297–724)       | 0.005 |
| Blood coagulation           |                 |                                  |                         |                     |       |
| Prothrombin time (s)        | 11–13           | 11.3 (18.8–11.9)                 | 11.2 (10.9–11.9)        | 11.4 (10.8–12.6)    | 0.678 |
| Fibrinogen (mg/dL)          | 200–400         | 478 (375–551)                    | 475 (372–530)           | 497 (394–649)       | 0.225 |
| D-dimer (ng/mL)             | <500            | 1446 (916–4729)                  | 1374 (946–4824)         | 1875 (834–5090)     | 0.962 |
| Inflammatory markers        |                 |                                  |                         |                     |       |
| C-reactive protein (mg/dL)  | <5              | 88.1 (33.2–156.7)                | 62.4 (28.1–102.6)       | 145.7 (77.9–210.5)  | 0.002 |
| Procalcitonin (ng/mL)       | <0.5            | 0.11 (0.00–0.35)†                | 0.06 (0.00–0.18)†       | 0.29 (0.11–0.55)†   | 0.001 |
| Ferritin (ng/mL)            | 12–240          | 732 (493–1267)                   | 721 (413–1302)          | 806 (566–1381)      | 0.888 |

The \( P \)-value comparison is shown for differences between patients who survived and patients who died.

† A total of 14 procalcitonin values are missing: nine among patients who survived and five among patients who died.

Figure 1  Multivariate Cox regression for prognostic factors. The forest plot graphically represents hazard ratios (95% confidence interval) for peripheral oxygen saturation (pO2), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), C-reactive protein (CRP) and dementia. All parameters were assessed at emergency department admission.
characteristic (ROC) curve analysis with respect to association with death. Survival curves were estimated by the Kaplan–Meier method. We regarded a two-sided P-value ≤0.05 as significant. Data were analyzed by SPSS v25 (IBM, Chicago, IL, USA) and Medcalc 18.2 (MedCalc Software, Ostend, Belgium).

**Statement of ethics**

The study was carried out in accordance with the Declaration of Helsinki, and was approved by the local ethics committee.

**Results**

A total of 69 patients, aged 80–98 years, met the inclusion criteria and were included in the study cohort. The median age was 84 years (82–89 years is interquartile range); 37 patients (53.6%) were men. Globally, 14 patients (20.3%) presented a mild, 30 (43.5%) a severe and 25 (36.2%) a critical COVID-19 disease (Table 1). Overall, 23 patients died. Interestingly, the age and sex distribution were similar between the patients who survived and died (Table 1).

Clinical history was quite homogeneous among the patients, and the patients who survived did not present relevant differences compared with those who died. However, the patients who died presented more frequently a history of severe dementia (Table 1). As expected, the disease severity classification in ED was associated with outcome: among the patients who died, 14 (60.9%) had a critical, eight (34.8%) a severe and just one patient had a mild presentation. Disease progression was quite fast in the patients who died. The median survival time for non-survivors was 5 days (2–13 days is interquartile range).

Among physiological parameters at admission, pO2 was the only parameter significantly associated with death in the present cohort. For as laboratory values, patients who died had higher blood urea nitrogen, lactate dehydrogenase, CRP and procalcitonin levels (Table 2). By using the ROC analysis with regard to these continuous variables, we found the best cut-off values discriminating death occurrence. Values were pO2 ≤90% (AUC 0.748 [0.608–0.889], P = 0.001), blood urea nitrogen >37 mg/dL (AUC 0.680 [0.526–0.835], P = 0.023), CRP >112 mg/dL (AUC 0.717 [0.577–0.857], P = 0.006) and lactate dehydrogenase >464 U/L (AUC 0.708 [0.561–0.855]). The best discriminating value for procalcitonin was >0.19 ng/mL; however, we did not include it in the multivariate model, as we had 14 missing values.

Multivariate Cox regression analysis showed that severe dementia, pO2 ≤90 at admission and lactate dehydrogenase >464 U/L were independent risk factors for survival in these patients (Fig. 1).

**Discussion**

The present study evaluated the clinical course and risk factors for patients aged >80 years affected by COVID-19. Our data suggest that for patients aged ≥80 years, further increasing age is not a risk factor for survival, whereas a history of severe dementia, low pO2 at admission, high CRP and lactate dehydrogenase >464 U/L are risk factors for death.

Until 2002, four coronavirus were known to infect humans, and they globally accounted for 10–30% of upper respiratory tract infections in adults, with mild clinical consequences.5,13 The outbreak of SARS-CoV and MERS-CoV caused international alarm, whereas the factors associated with transmission of these human coronaviruses remain poorly understood.14,15 Similar to SARS-CoV, the SARS-CoV-2 binds to human angiotensin-converting enzyme 2 (ACE2) for cell entry.15,16 Angiotensin-converting enzyme 2 is a membrane protein expressed in the lung, heart, kidney and intestine. Angiotensin-converting enzyme 2 is largely expressed in the upper and lower respiratory tract, and this could explain both the infectivity and lethality of Sars-Cov2.15

There is clear evidence that older patients are at higher risk of death from COVID-19.1–5,17–20 Italian national data show an overall mortality rate of 12.6%.21 However, mortality steeply increases with age; for patients aged ≤50 years it is ≤1%, in the fifth decade it is 2.6%, in the sixth decade it is 9.8%, in the seventh decade it rises to 24.2% and in the eighth decade it rises to 29.0%. Interestingly, the mortality rate decreases to 24.7% in people aged ≥90 years.20 The present data, although in a limited sample, appear to confirm this tendency. We found, in the present cohort of people aged ≥80 years, that increasing age does not represent a risk factor for death. Whether this is due to a minor susceptibility of patients aged >90 years to Sars-CoV-2 infection damage, or possibly to a reduced secondary lung inflammation, should be further investigated.

As the Sars-CoV2 cell entry receptor is located mainly in the lungs, more than half of patients might develop dyspnea, and >10% might require ventilatory support.1–5,17–20 With acute hypoxia being the main determinant of disease progression and severity, the pO2 at admission is crucial for death risk stratification. The present data confirm that patients aged ≥80 years who are severely hypoxic at ED admission (pO2 <90%) have an increased risk of death. However, a pO2 ≤90% was not associated with death in the present cohort at multivariate analysis. Certainly, the reduced sample and the subsequent wide confidence interval of our hazard estimation could not provide final clues on this point. Indeed, the present patients were mainly severe and critical at admission, thus reducing the relative influence of hypoxia on our final hazard estimation.

An elevation of lactate dehydrogenase in COVID-19 patients who died was found in most of the studies currently available.22 These observations appear to be consistent with SARS, where multivariate analysis identified elevated lactate dehydrogenase as a marker associated with worse outcomes.23 However, lactate dehydrogenase is a non-specific marker, which is commonly found in critically ill patients. Nevertheless, the present data confirm that >464 U/L could be a relevant prognostic factor in patients aged ≥80 years affected by COVID-19.

The CRP level correlates to inflammation, and its concentration is not affected by age, sex and physical condition.24 CRP is a well-known index of severe pulmonary infections, and CRP levels were shown to positively correlate with lung lesions and disease severity in COVID-19.1–5,25 The present data suggest that elevated CRP could have a predictive role in oldest-old patients with COVID-19; however, because of the small sample size in the present study, an association between elevated CRP and an increased risk of death cannot be established with certainty.

A distinct aspect of the present study is the association between dementia and poor outcome. Indeed, medical assistance to COVID-19 patients could be extremely difficult for patients with dementia.26 First, the new hospital environment can lead to increased stress and behavioral problems in these patients.27 Second, hypoxia, which is a prominent clinical feature of COVID-19, could complicate the presentation of dementia and induce delirium, increasing the need for medical care, and the need for dementia support.28

The outbreak of the COVID-19 pandemic has raised great concerns for the >50 million people living with dementia worldwide.26 These people might have difficulties in remembering...
safeguard procedures, such as wearing masks, and self-quarantine measures could not apply to patients who are not self-sufficient. Finally, long-term care facilities for dementia patients are at extreme risk for COVID-19 infection. The present data suggest that severe dementia itself is an independent risk factor for survival in COVID-19 patients aged ≥80 years. Thus, as recommended by Alzheimer’s Disease International, specific support for people living with dementia and their caregivers is urgently required, worldwide.

As for any retrospective study, several limitations of the present study are worth considering. First, our sample size was small, thus limiting the power of our analysis. Furthermore, we carried out the study at a single institution, and as such, the findings might be not representative of the general population of COVID-19 patients aged ≥80 years. Finally, the study focused on patient deaths. For this reason, we cannot extrapolate relevant outcomes for this population, such as permanent need for oxygen support, loss of autonomy or the need to transfer to a residential nursing facility.

Patients aged ≥80 years are the most at risk of a poor outcome for COVID-19. Nevertheless, to date, scarce data are available about the distinctive expression of disease in this frailter part of the population. Although carried out in a small sample, the present study could give relevant clues on clinical risk factors for COVID-19 in patients aged ≥80 years. The present data suggest that the might could be not age dependent in this population. Furthermore, dementia appears to be one of the most relevant risk factors for death. Severe COVID-19, as expressed by elevated lactate dehydrogenase, elevated CRP and low oxygen saturation at admission, is associated with a rapid progression to death in these patients.

Disclosure statement

The authors declare no conflict of interest.

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