# BMJ Open

# Clinical and imaging characteristics of patients with COVID-19 predicting hospital readmission after emergency department discharge: a single-centre cohort study in Italy

Maria Giulia Galli,[1] Olivera Djuric,[2,3] Giulia Besutti,[4,5] Marta Ottone [ID] ,[2] Lucia Amidei,[1] Lee Bitton,[1] Carlotta Bonilauri,[1] Luca Boracchia,[1] Sergio Campanale,[1] Vittoria Curcio,[1] Davide Maria Francesco Lucchesi,[1] Cesare Salvatore Mulas,[1] Francesca Santi,[1] Anna Maria Ferrari,[1] Paolo Giorgi Rossi [ID] ,[2] Francesco Luppi,[1] On behalf of the Reggio Emilia COVID-19 Working Group

## ABSTRACT

**Objective** We aimed at identifying baseline predictive factors for emergency department (ED) readmission, with hospitalisation/death, in patients with COVID-19 previously discharged from the ED. We also developed a disease progression velocity index.

**Design and setting** Retrospective cohort study of prospectively collected data. The charts of consecutive patients with COVID-19 discharged from the Reggio Emilia (Italy) ED (2 March 2 to 31 March 2020) were retrospectively examined. Clinical, laboratory and CT findings at first ED admission were tested as predictive factors using multivariable logistic models. We divided CT extension by days from symptom onset to build a synthetic velocity index.

**Participants** 450 patients discharged from the ED with diagnosis of COVID-19.

**Main outcome measure** ED readmission within 14 days, followed by hospitalisation/death.

**Results** Of the discharged patients, 84 (18.7%) were readmitted to the ED, 61 (13.6%) were hospitalised and 10 (2.2%) died. Age (OR=1.05; 95% CI 1.03 to 1.08), Charlson Comorbidity Index 3 versus 0 (OR=11.61; 95% CI 1.76 to 76.58), days from symptom onset (OR for 1-day increase=0.81; 95% CI 0.73 to 0.90) and CT extension (OR for 1% increase=1.03; 95% CI 1.01 to 1.06) were associated in a multivariable model for readmission with hospitalisation/death. A 2-day lag velocity index was a strong predictor (OR for unit increase=1.21, 95% CI 1.08 to 1.36); the model including this index resulted in less information loss.

**Conclusions** A velocity index combining CT extension and days from symptom onset predicts disease progression in patients with COVID-19. For example, a 20% CT extension 3 days after symptom onset has the same risk as does 50% after 10 days.

## BACKGROUND

Emergency admissions are a critical point in the management of the SARS-CoV-2

### Strengths and limitations of this study

► This study proposes a disease progression velocity index based on CT scan-derived parenchymal involvement and time from symptom onset.
► The velocity of disease progression can orient patient management by correctly identifying those at higher risk of readmission to emergency department who may require hospitalisation.
► The main limitation of this study is that we could not validate the performance of our model on a validation set.

pandemic, especially during the peak of an epidemic wave. Many countries have experienced two waves in 2020, with a lower case fatality rate in the second wave compared with that in March 2020, probably due to better testing capabilities and diagnosis of less severe cases.[1,2] Although the critical care bed occupancy crisis is expected to slow down, COVID-19 hospital admissions periodically increase, thus continuing to be a challenge both for healthcare workers and public health officials.[3]

Emergency departments (EDs) play a crucial role in deciding which visits require hospital treatment and which do not, thus preventing unnecessary hospital admissions in a landscape of reduced resources and increasing demands for inpatient care during the COVID-19 pandemic. In fact, shortly after the beginning of the pandemic and the implementation of public health measures to reduce transmission of the virus, the use

of healthcare services for elective and emergency conditions decreased, while hospital admissions from the ED increased.[4 5]

During the first wave in Spain, it has been estimated that among all the people with COVID-19, 14.8% required hospitalisation,[6] but actually in Italy, in the same phase, the vast majority of cases were diagnosed at ED and most of them were hospitalised.[7] The unpredictable nature of the disease and its insufficiently known natural history make it difficult for emergency staff to tell which people will need to be admitted to the hospital. Although estimated median time from symptom onset to the time patients experience dyspnoea is 5–8 days, acute respiratory distress syndrome is 8–12 days and intensive care unit (ICU) admission is 9.5–12 days, some patients with COVID-19 rapidly deteriorate about 1 week after symptom onset[8] or shortly after being discharged from the ED.[9] Many studies aimed at building models to predict the prognosis and the need for critical care[10] and some specifically starting from a set of information available at ED admission,[11 12] little is known about the probability of readmission in patients initially discharged after the first ED admission.[9] Some studies have shown that patients with a rapid worsening of symptoms and a short time between symptom onset and seeking care had the worst outcomes.[13–15]

The aim of this study was to investigate the rate of COVID-19-related readmission to the ED and its determinants in a cohort of consecutive patients with COVID-19 presenting to the provincial ED hub of Reggio Emilia, Italy, and discharged during the first epidemic peak in the Reggio Emilia province. In particular, we wanted to estimate whether a measure of the velocity of disease progression at ED admission could orient patient management by correctly identifying those at higher risk of readmission to ED who would require hospitalisation.

## METHODS
### Setting
The province of Reggio Emilia, in northern Italy, has a population of 531 751 inhabitants. The first case of SARS-COv-2 in Reggio Emilia was diagnosed on 27 February 2020; the cumulative incidence of cases during the first wave of the pandemic (March to April 2020) was about 0.9%. In October, the province began experiencing a second wave of the pandemic, with cumulative incidence reaching 1.8%. The first wave was characterised by a very high fatality rate (up to 18% in the first month),[13] and testing was limited only to symptomatic individuals, who often presented with severe symptoms.

There are six hospitals in this province, with an ED service at the main hospital in the city of Reggio Emilia, as well as at four of the five smaller health district hospitals. There is no private ED service. The annual ED admission rate in 2019 was 354.2 per 1000 inhabitants.

### Management of COVID-19 at the ED
With COVID-19, the organisation of the Reggio Emilia ED Service has changed; there are now two distinct physical areas so as to separate patients with fever and/or epidemiological criteria for SARS-CoV2 infection from all other patients. A pretriage facility outside the ED has been set up where patients' history is taken, especially regarding epidemiological data and COVID-19-related symptoms.

During the first wave of the pandemic, the local diagnostic protocol for patients with suspected COVID-19 pneumonia included nasopharyngeal and oropharyngeal swabs for reverse transcription PCR (RT-PCR), blood tests, chest ultrasound and radiological assessment (chest X-rays and a CT scan in cases of suggestive X-ray findings or negative X-ray but highly suggestive clinical features).

Given the paucity of information on COVID-19 available in early March 2020, a multidisciplinary team (pulmonologists, infectious diseases specialists, intensive care specialists and emergency physicians) defined a six-class classification based on patient features, vital signs, medical history, symptoms, blood test results and instrumental findings to manage patients presenting to the ED (table 1).

### Study design and selection of participants
A retrospective cohort study was conducted on prospectively collected data. We included all consecutive patients aged >18 years who presented to the provincial ED hub of Reggio Emilia between 2 March and 31 March 2020, who were positive for SARS-CoV-2 on RT-PCR before or during ED admission and who were discharged for home treatment after initial evaluation. No exclusion criteria were adopted.

### Putative determinants and definitions
We included in initial analyses all the variables that were available as standard parameters routinely collected for all patients and some additional information specifically introduced in ED protocols for COVID-19 suspected cases as of March 2020. Evaluated covariates included patient characteristics and presence of comorbidities, calculated separately, as well as the Charlson Comorbidity Index, which provides an overall measure of an individual patient's complexity.[16] We categorised the index in four classes: 0 (no presence of relevant comorbidity), 1, 2 and ≥3. Variables which reflect clinical criteria relevant for ED discharge included presence of fever and duration of symptoms, lab test results (arterial blood gas tests, biochemical profile) and imaging (chest CT scan).

### Blood tests and RT-PCR
C reactive protein (CRP) and lactate dehydrogenase levels, white cell count, lymphocyte, neutrophil and platelet counts as well as arterial blood gas analysis data, all measured at ED presentation, were collected. The tests were carried out in the Reggio Emilia Hospital Clinical Laboratories with routine automated methods.

**Table 1** Phenotype classification adopted for patients presenting to ED in March and April 2020, in Reggio Emilia, Italy

| Phenotype | Clinical characteristics | Suggested management |
|---|---|---|
| Phenotype 1 | Patients with fever, with or without respiratory symptoms and with $SpO_2 > 95\%$ in room air with no pathological findings on chest ultrasound (US) or X-rays. Patients were discharged after nasopharyngeal and oropharyngeal swabs and after performing a negative walking test, defined as such in the absence of significant desaturation (>3 points from baseline $SpO_2$) after walking 50 m. | Referral to the preventive medicine and public health department for follow-up and advised to home quarantine (until swab test results) and symptomatic therapy. |
| Phenotype 2a | Patients aged<70 years with no relevant medical history, with fever, with or without respiratory symptoms, with $SpO_2 > 95\%$ in room air and respiratory rate<25 breaths per minute, with radiological evidence of pneumonia. Patients were discharged after nasopharyngeal and oropharyngeal swabs and after performing a negative walking test. | Referral to preventive medicine and public health department for follow-up and advised to home quarantine (until swab test results) and start therapy with hydroxychloroquine orally. In some selected cases, antibiotics or antivirals were prescribed after consulting with the infectious diseases specialist. |
| Phenotype 2b | Patients aged>70 years with relevant medical history (ie, diabetes, hypertension, obesity, cardiovascular diseases, chronic obstructive pulmonary disease - COPD, etc) with fever, with or without respiratory symptoms, with respiratory rate<25 breaths per minute and with radiological evidence of pneumonia. | Admission to hospital wards dedicated to COVID-19 management, after positive nasopharyngeal and oropharyngeal swab. In some selected cases, patients were discharged home and referred to the preventive medicine and public health department for follow-up. They were advised to home isolation and start therapy with hydroxychloroquine and antivirals per os, plus antibiotics if needed. |
| Phenotype 3 | Any patient with radiological findings of pneumonia and respiratory failure (with $pO_2 < 60$) responsive to conventional $O_2$ therapy. | Admission to hospital wards dedicated to COVID-19 management, after positive nasopharyngeal and oropharyngeal swab. |
| Phenotype 4 | Any patient with radiological findings of complicated pneumonia and respiratory failure without acute respiratory distress syndrome (ARDS). | These patients started non-invasive ventilation in the ED and were admitted to subintensive units or directly to the intensive care unit dedicated to COVID-19 management, after positive nasopharyngeal and oropharyngeal swab. |
| Phenotype 5 | Any patient with radiological findings of complicated pneumonia and respiratory failure or with ARDS. | |

ED, emergency department.

To diagnose SARS-CoV-2 infection, a commercial one-step RT-PCR (GeneFinder) COVID-19 Plus Real Amp Kit was used, and RT-PCR assay was performed on an Applied Biosystems 7500 Sequence Detection System.

### Data sources

Data, including date of symptom onset, diagnosis, hospitalisation and death, were retrieved from the COVID-19 Surveillance Registry, coordinated by the National Institute of Health and implemented in each local health authority. The surveillance is fed by several sources: Reggio Emilia Department of Public Health's epidemiological investigations, contact tracing and symptom surveillance for people in self-isolation, laboratory reports, ED and hospital electronic records and death certificates. The system was developed to manage each individual case. In the Reggio Emilia province, the surveillance system is linked to a dedicated software collecting data on patients tested for SARS-CoV-2 and for positive cases, data on disease outcome. Thus, the software permits the management of surveillance activities on all cases; it produces a report containing all the relevant information (test results, ED admission, hospitalisation, in-hospital death) available in the data warehouse; to this, the public health officials add information on the epidemiological investigation, contract tracing and symptom surveillance for those in self-isolation.

Registry data were linked with hospital discharge databases to collect information on comorbidities from all hospital admissions occurring up to 31 January 2020, that is, before the start of the SARS-CoV-2 pandemic in Italy.

The ED database contains information on all ED visits in the Reggio Emilia province, including the level of urgency and the modality of discharge.[17]

The local health authority's laboratory information system database contains the laboratory results of all tests carried out in the province's public health network, coded using an internal classification.

### Radiological data

CT scans were performed using one of the three scanners (128-slice Somatom Definition Edge, Siemens Healthineers; 64-slice Ingenuity, Philips Healthcare; 16-slice GE Brightspeed, GE Healthcare) without contrast media

injection, with the patient in the supine position, during end-inspiration. Scanning parameters were tube voltage 120 KV, automatic tube current modulation, collimation width 0.625 or 1.25 mm, acquisition slice thickness 2.5 mm and interval 1.25 mm. Images were reconstructed with a high-resolution algorithm at slice thickness 1.0/1.25 mm. From the verbal and structured CT reports, the extension of pulmonary lesions estimated by using a visual scoring system resulted in a percentage of total lung parenchyma which had any pathological changes likely due to COVID-19.

## Outcome measures

The main outcome was readmission to the ED within 14 days from the first admission, followed by hospitalisation (within 72 hours from ED admission) lasting at least 48 hours (to exclude brief observation stays in the ED) or by death. We also considered any second ED visit occurring within 14 days from the first admission. All patients were followed up to 45 days from symptom onset or two negative RT-PCRs, whichever occurred first.

## Data analyses

Continuous variables are reported as median and IQR and categorical variables as proportions. Logistic regression models were used to estimate ORs with 95% CI for the second ED visit and hospitalisation/death, unadjusted and adjusted for age and sex. We built a synthetic indicator of the velocity of disease progression at ED admission, that is, the ratio of CT involvement and days from symptom onset to first ED admission. We used CT scan to measure disease extension, which is the most stable index of disease progression among the available data, and we can assume that, between symptom onset and ED presentation, it will not regress. We set a minimum value of 1 day from symptom onset, and we considered velocity indices with different lag times from 1 to 6 days, plus ln (1-day lag) approximating 1–1.1, to avoid losing observations at 1 day from symptom onset (ie, with denominator equal to 0).

Sex and age were selected prior to analysis, while the other potential covariates were based on the association found in the age-adjusted and sex-adjusted regression analyses. Then, the candidate variables were included in a multivariable logistic model and those with p<0.1 were used for the final set of variables used to compare models with different velocity indices, that is, combinations of CT involvement and days from symptom onset. The comparison of model performances was done by log likelihood, Akaike information criterion (AIC), p value for Z-test for velocity index and receiver operating characteristic curves from logistic model. We presented the final models using logistic models with cross-validated area under the curve, to compare the performance of the models for readmission followed by hospitalisation or death. On the same original sample, we fitted a logit model and used tenfolds cross-validation to obtain a bias-corrected estimate of predictive accuracy. This technique averages the AUCs corresponding to each fold and applies the bootstrap procedure to the cross-validated AUC. We used Stata V.16.1 IC (Stata Corporation, College Station, Texas, USA) software package.

Aggregated data for the main model are available on an open source repository.[18]

## Patient and public involvement

Patients and the public were not directly involved in the study design or implementation.

## RESULTS

### Characteristics of study subjects

Of the 959 patients admitted to the ED with a diagnosis of COVID-19 in the period 2–31 March 2020, 450 (47%) patients discharged to self-isolation and treatment were included in the analysis (figure 1). Of the discharged patients, 84 returned to the ED because their COVID-19 symptoms had worsened, resulting in an ED readmission rate of 18.7% (median time for the ED readmission was 4 days). Of these 84 patients, 61 (13.6%) were hospitalised and 10 (2.2%) died.

Both those readmitted to the ED and those hospitalised or who died after readmission to the ED were older and presented to the ED earlier after symptom onset. They had lower values of $pCO_2$ and higher values of PCR, procalcitonin (PCT) and creatine than did non-readmitted patients. Readmitted patients and those who were hospitalised/died more frequently had three or more comorbidities and higher CT disease extension (table 2). Online supplemental table 1 shows the comorbidities in patients with COVID-19 presenting to the ED. Finally, readmitted and hospitalised/deceased patients had a shorter median time between symptom onset and ED presentation.

### Characteristics associated with ED readmission and hospitalisation

Age-adjusted and sex-adjusted analyses showed that the probability of an ED readmission requiring hospitalisation was associated with a shorter time between symptom onset and ED admission, the presence of three or more comorbidities and creatine (table 3). Both univariable and multivariable regression analyses were used to examine the association between covariates and the risk of readmission to the ED (online supplemental table 2).

We also tested the association between different indices that could indicate the velocity of disease progression before the first ED admission by combining the CT scan-derived proportion of lung parenchymal involvement and the time elapsed between disease onset and CT at the ED admission. The easiest way to combine these two measures to obtain a velocity was to divide the CT involvement observed by the time needed to reach it. To avoid values that were too high or infinite in patients reporting symptom onset as the
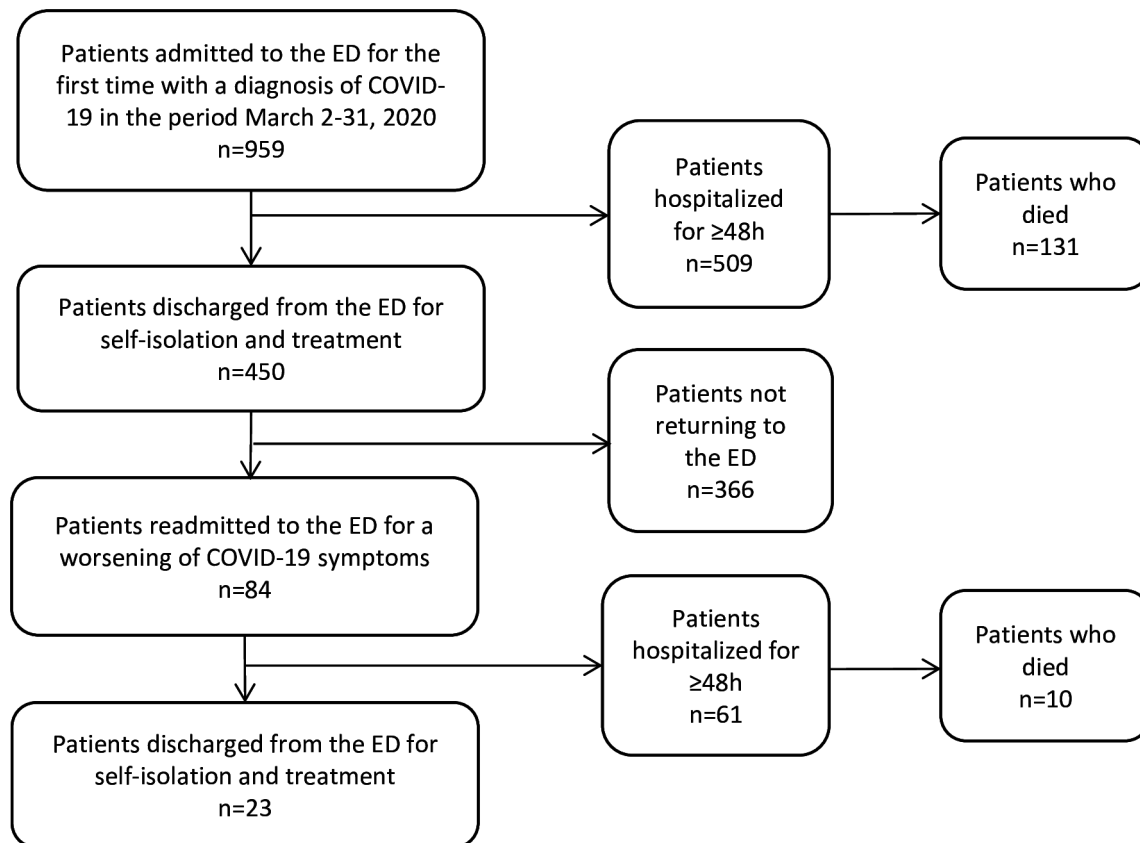
**Figure 1** Flowchart representing patient enrolment and main outcomes (readmission and hospitalisation). ED, emergency department.

same day as or the day before ED admission, we added a lag time representing the amount of time during which the disease had progressed before symptom onset. We set this lag time as 1–6 days (see Methods); we also tested a logarithmic transformation of 1-day lag.

Finally, we built multivariable models to predict readmissions requiring hospitalisation. Age, Charlson Comorbidity Index, CT involvement and time from symptom onset were entered in the model according to the selection criteria adopted, and we maintained sex in all models as an a priori choice (table 4). We compared the model built using the two components independently (CT involvement and time from symptom onset) and a model built using the composite variable 'velocity index' with different lags (online supplemental table 3). The indices from 2-day to 4-day lag showed similar and better values in the parameters used for the performance of the models. AUC had little influence on the lag choice; we gave more importance to AIC and we chose the index with a 2-day lag. It showed strong association and the best parameters in terms of model fitting compared to other lags, and it also proved to be more parsimonious than the model with the number of days from symptom onset and CT scan results included as independent variables.

Figure 2 shows the increased risk in patients with rapid disease progression, that is, in those showing lung damage a few days after symptom onset. For example, based on the multivariable model of readmissions followed by hospitalisation or death, we show the average predicted probabilities with the 2-day lag velocity index fixed at values 2 and 5. Here, the three areas of the graph defined by the two iso-risk curves identify patients with <11%, 11%–16% and >16% risk of readmission to the ED followed by death or hospitalisation. On average, a patient with 20% CT parenchymal involvement 3 days after symptom onset and a patient with 50% involvement after 10 days had the same risk of being readmitted and hospitalised or of dying.

## DISCUSSION

This study was conducted during the first wave of the SARS-CoV-2 pandemic, when the overall case fatality rate was about 18%[13] and the in-hospital mortality rate was about 27%.[7] About one-fourth of the RT-PCR-confirmed COVID-19 cases were discharged home after the initial ED evaluation; of these, only 14% were hospitalised or died after re-presenting to the ED.

The main determinants of readmission in our study were time between symptom onset and ED

**Table 2** Baseline characteristics of patients with COVID-19 who presented to the ED

| | Missing | All patients | Readmission Median (IQR) | Readmission with hospitalisation/death Median (IQR) |
|---|---|---|---|---|
| Variables | | 450 | 84 (18.7) | 61 (13.6) |
| Age (years) | | 55 (47–64) | 61 (51–72) | 63 (52–74) |
| Female sex, n (%) | | 211 (46.9%) | 37 (17.5%) | 25 (11.9%) |
| Days from symptom onset | | 7 (5–10) | 7 (3–8) | 5 (2–7) |
| CT disease extension | 14 | | | |
| <20% | | 152 (34.9%) | 26 (17.1%) | 22 (14.5%) |
| 20%–39% | | 229 (52.5%) | 37 (16.2%) | 24 (10.5%) |
| 40%–59% | | 48 (11.0%) | 13 (27.1%) | 10 (20.8%) |
| ≥60% | | 7 (1.6%) | 3 (42.9%) | 2 (28.6%) |
| $pCO_2$ | 76 | 36.1 (33.0–38.7) | 35.0 (32.4–37.3) | 34.5 (31.6–37.0) |
| $pO_2$ | 74 | 78.7 (72.0–88.1) | 78.5 (73.3–84.9) | 78.0 (73.0–82.2) |
| White cell count (x $10^9$ /L) | 7 | 5.0 (4.1–6.1) | 4.7 (4.0–6.6) | 4.8 (4.1–6.8) |
| Neutrophils | 42 | 67.5 (61.2–74.0) | 68.2 (63.3–75.1) | 70.8 (65.7–78.2) |
| Lymphocytes | 42 | 23.7 (17.8–29.7) | 21.0 (15.6–29.0) | 20.8 (14.9–28.0) |
| C reactive protein | 7 | 2.4 (1.0–4.6) | 2.8 (1.5–4.2) | 3.0 (1.6–5.1) |
| Procalcitonin | 26 | 0.07 (0.05–0.12) | 0.09 (0.06–0.14) | 0.09 (0.07–0.15) |
| Creatine | 7 | 0.86 (0.74–0.99) | 0.91 (0.77–1109) | 0.92 (0.78–1.13) |
| Lactate dehydrogenase | 58 | 480 (412–569) | 486 (396–553) | 486 (413–561) |
| Bilirubin | 33 | 0.6 (0.5–0.7) | 0.6 (0.4–0.7) | 0.6 (0.4–0.8) |
| Charlson Comorbidity Index | | | | |
| 0 | | 406 (90.2%) | 68 (16.8%) | 48 (11.8%) |
| 1 | | 22 (4.9%) | 6 (27.3%) | 4 (18.2%) |
| 2 | | 15 (3.3%) | 5 (33.3%) | 4 (26.7%) |
| 3 | | 7 (1.6%) | 5 (71.4%) | 5 (71.4%) |

Continuous variables are presented as median (IQR), and categorical variables are presented as frequencies (%).
ED, emergency department.

presentation, proportion of lung parenchyma involved as assessed on CT and the presence of comorbidities. Combining CT scan-derived parenchymal involvement and time from symptom onset, we observed that the velocity of disease progression may have been the real underlying clinical concept, explaining most of the predictive information contained in the two variables.

CT percentage of lung involvement has been extensively described as a prognostic factor for short-term prognosis in patients with COVID-19,[19–22] but it has not yet been explored as a predictor of readmission after discharge from the ED. Different scoring systems proposed in the literature are mostly based on the combined effects of the extent of pulmonary involvement and specific attenuation patterns (ie, normal, ground-glass and consolidation)[21 22] but do not consider the time from symptom onset as an important factor in outcome prediction.[13–15] Using CT scan-derived parenchymal involvement and time from symptom onset in a composite index to describe disease progression before ED admission in our study

is consistent with previous evidence that CT lung changes appear early in the course of the disease, possibly in the asymptomatic phase as well,[23] and that in studies with serial CT scans, CT scores increased faster in severe patients than in non-severe ones.[24]

The results of our study are also in line with a single study that evaluated the outcome of hospital readmission in patients with COVID-19 following ED discharge.[9] The authors observed a slightly lower rate (8.2%) of readmission in their study, but after a shorter follow-up, that is, within 7 days after ED discharge. The factors associated with readmission were the same as we observed: abnormal chest radiograph and comorbidities (hypertension and obesity, fever and hypoxia).

**Limitations**

The main limitation of this study is that we used the CT scan results to predict the outcome and also to define the velocity of disease progression, but now CT scan is

**Table 3** Logistic regression models for readmission with hospitalisation/death

| Variables | Readmission with hospitalisation/death | | | |
|---|---|---|---|---|
| | Crude | | Multivariable | |
| | OR | 95% CI | OR | 95% CI |
| Age (years) | 1.061 | 1.038 to 1.084 | – | |
| Sex | | | | |
|    Female | 1 | | – | |
|    Male | 1.319 | 0.763 to 2.282 | | |
| CT disease extension | 1.012 | 0.990 to 1.034 | 1.013 | 0.990 to 1.036 |
| Days since symptom onset | 0.787 | 0.716 to 0.864 | 0.817 | 0.743 to 0.898 |
| Velocity index 2-day lag | 1.245 | 1.117 to 1.387 | 1.206 | 1.078 to 1.349 |
| $pCO_2$ | 0.962 | 0.899 to 1.029 | 0.959 | 0.899 to 1.022 |
| $pO_2$ | 0.976 | 0.951 to 1.003 | 0.993 | 0.966 to 1.020 |
| White cell count | 1.100 | 0.951 to 1.272 | 1.093 | 0.939 to 1.271 |
| Neutrophils | 1.021 | 0.990 to 1.053 | 1.006 | 0.974 to 1.038 |
| Lymphocytes | 0.959 | 0.927 to 0.993 | 0.975 | 0.940 to 1.011 |
| C reactive protein | 1.078 | 1.008 to 1.154 | 1.057 | 0.983 to 1.136 |
| Procalcitonin | 0.958 | 0.632 to 1.453 | 0.918 | 0.511 to 1.649 |
| Creatine | 4.259 | 1.612 to 11.250 | 2.722 | 1.011 to 7.326 |
| Lactate dehydrogenase | 1.000 | 0.997 to 1.002 | 1.000 | 0.997 to 1.002 |
| Bilirubin | 0.783 | 0.349 to 1.755 | 0.598 | 0.221 to 1.615 |
| Charlson Comorbidity Index | | | | |
|    0 | 1 | | 1 | |
|    1 | 1.657 | 0.538 to 5.103 | 0.797 | 0.237 to 2.685 |
|    2 | 2.712 | 0.831 to 8.856 | 2.083 | 0.594 to 7.307 |
|    3 | 18.646 | 3.520 to 98.780 | 12.738 | 2.200 to 73.746 |

Logistic regression models for readmission followed by hospitalisation or death, adjusted for sex and age.

not a recommended test for patients presenting with COVID-19-related symptoms at the ED.[25 26]

We could not validate the performance of our model on a validation set: we built the model, including the choice of the best lag time for the velocity index, using the same patients for whom we estimated the ORs. Therefore, overfitting is certainly an issue in our model, which deals with methods of internal validation (cross-validation) for prediction models to generate a more realistic estimate of predictive performance when the number of observations is not very large.[27] Furthermore, the sample size was limited by the period of observation and we could not increase this period because of protocol changes. Nevertheless, the number of ED visits, the events and the strength of association observed in the models, in terms of pseudo $R^2$, were sufficient to estimate the number of parameters included.[28]

In our subset of patients identified as having a good prognosis, some of the most important prognostic factors of COVID-19 prognosis, such as sex,[29] oxygen saturation,[9 29] CRP[29 30] and even age,[29 31] had, instead, a surprisingly limited impact on outcome. This is most likely the effect of the criteria used to decide between hospitalisation and discharge. In fact, all patients with low oxygen saturation were referred to hospitalisation (the threshold was below 90%, but an evaluation of all other clinical characteristics was always taken into account), as were patients with >60% parenchymal involvement at CT scan and patients aged>80 years. Other clinical characteristics also influenced the decision of whether to hospitalise immediately, particularly the presence of COPD and diabetes. The consequence of this selection is that for some variables (eg, oxygen saturation), we had very small range of variation. We can therefore suppose that the threshold used was not close enough to critical values, as a certain association with the outcome should have otherwise been observed.

Moreover, our sole purpose in investigating discharged patients was to see how often an ED discharge led to a readmission just a few days later. We have no idea, instead, how many of the people who were hospitalised at the first ED presentation could in fact have been safely discharged. Furthermore, we cannot consider all the readmissions within 2 weeks

**Table 4** Multivariable logistic models for readmission followed by hospitalisation or death

| | Readmission followed by hospitalisation or death | | | |
| | Model with days from onset and CT disease extension as independent variables | | Model with the synthetic velocity index (2-day lag) | |
| Variables | OR | 95% CI | OR | 95% CI |
|---|---|---|---|---|
| Age (years) | 1.050 | 1.025 to 1.076 | 1.052 | 1.027 to 1.078 |
| Sex | | | | |
|   Female | 1 | | 1 | |
|   Male | 1.594 | 0.851 to 2.988 | 1.555 | 0.838 to 2.883 |
| Days from symptom onset | 0.812 | 0.733 to 0.899 | – | |
| CT disease extension | 1.031 | 1.005 to 1.057 | – | |
| Velocity index | – | | 1.208 | 1.076 to 1.356 |
| Charlson Comorbidity Index | | | | |
|   0 | 1 | | 1 | |
|   1 | 0.763 | 0.192 to 3.028 | 0.783 | 0.203 to 3.023 |
|   2 | 2.216 | 0.558 to 8.794 | 2.413 | 0.651 to 8.942 |
|   3 | 11.61 | 1.76 to 76.58 | 13.68 | 2.14 to 87.64 |
| Log likelihood | −141.422 | | −146.861 | |
| AIC | 298.845 | | 307.721 | |
| cvAUC (BBC 95% CI) | 0.754 | (0.694 to 0.840) | 0.751 | (0.636 to 0.788) |

Multivariable logistic models for readmission followed by hospitalisation or death.

AIC, Akaike information criterion; BBC 95% CI, bootstrap corrected 95% CI; cvAUC, cross-validated area under the curve.

from the first ED visit a failure in decision-making: some readmissions occurred more than 7 days after the first ED visit, and self-isolation might have been appropriate for that initial phase of the disease.

## Implications for practice

We show that time from symptom onset and lung parenchyma involvement were the main determinants of ED readmission. This suggests that, compared with the other known prognostic factors used to decide on hospitalisation, these two were probably not sufficiently considered:
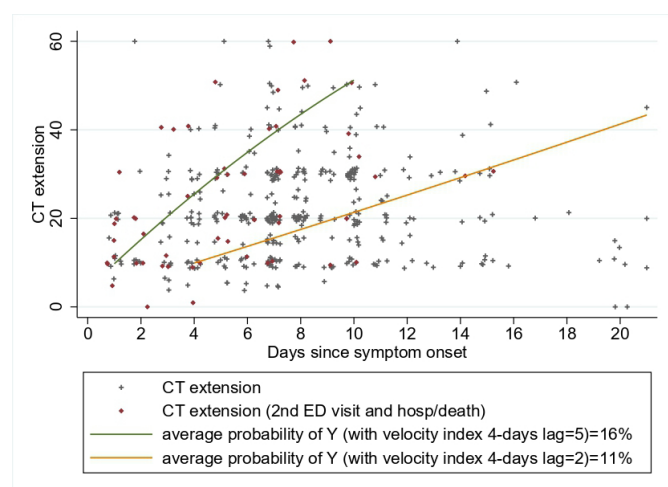


**Figure 2** Distribution of events (readmissions followed by hospitalisation or death) over time since symptom onset and CT disease extension.

the threshold of 60% of parenchymal involvement may have been too high, compared with the 90% threshold used for $O_2$ saturation.

Furthermore, we show that these two variables together provide relevant information about the velocity of disease progression prior to ED admission and that this velocity is a strong predictor of readmission. This means that, on average, a middle-aged patient with good oxygen saturation and no important comorbidities, with 20% parenchymal involvement on the second day after symptom onset, has the same probability of symptoms worsening, leading to hospitalisation, as does a patient with 50% parenchymal involvement 7 days after symptom onset.

It is important to confirm whether an indicator of the velocity of disease progression can be defined using other biomarkers of lung damage, detectable on more commonly used imaging examinations such as chest X-ray or ultrasound.

In conclusion, CT lung involvement and time from symptom onset are the main determinants of hospital readmission in patients discharged after an ED admission. Combining the two variables to obtain a velocity of disease progression produces a predictor that is stronger than is each of the two variables singly.

**Author affiliations**
[1]Emergency Department, Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy
[2]Epidemiology Unit, Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

[3]Section of Public Health, Department of Biomedical, Metabolic and Neural Sciences, Center for Environmental, Nutritional and Genetic Epidemiology (CREAGEN), University of Modena and Reggio Emilia, Modena, Emilia-Romagna, Italy
[4]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Emilia-Romagna, Italy
[5]Radiology Unit, Department of Diagnostic Imaging and Laboratory Medicine, Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy

**ORCID iDs**
Marta Ottone http://orcid.org/0000-0003-1302-0329
Paolo Giorgi Rossi http://orcid.org/0000-0001-9703-2460

## REFERENCES

1 Fan G, Yang Z, Lin Q. Decreased case fatality rate of COVID-19 in the second wave: a study in 53 countries or regions. *Transbound Emerg Dis* 2020:1–3.
2 Griffin S. Covid-19: second wave death rate is doubling fortnightly but is lower and slower than in March. *BMJ* 2020;371:m4092.
3 Heneghan C, Oke J. COVID-19: admissions to hospital – update, 2020. Available: https://www.cebm.net/covid-19/covid-19-uk-hospital-admissions/
4 Jeffery MM, D'Onofrio G, Paek H, et al. Trends in emergency department visits and hospital admissions in health care systems in 5 states in the first months of the COVID-19 pandemic in the US. *JAMA Intern Med* 2020;180:1328–33.
5 National Health Service. A&E Attendances and Emergency Admissions 2020-21, 2020. Available: https://www.england.nhs.uk/statistics/statistical-work-areas/ae-waiting-times-and-activity/ae-attendances-and-emergency-admissions-2020-21/
6 Prieto-Alhambra D, Balló E, Coma E, et al. Filling the gaps in the characterization of the clinical management of COVID-19: 30-day hospital admission and fatality rates in a cohort of 118 150 cases diagnosed in outpatient settings in Spain. *Int J Epidemiol* 2021;49:1930–9.
7 Ferroni E, Giorgi Rossi P, Spila Alegiani S, et al. Survival of hospitalized COVID-19 patients in northern Italy: a population-based cohort study by the ITA-COVID-19 network. *Clin Epidemiol* 2020;12:1337–46.
8 CDC. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19), 2021. Available: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
9 Kilaru AS, Lee K, Snider CK, et al. Return hospital admissions among 1419 COVID-19 patients discharged from five U.S. emergency departments. *Acad Emerg Med* 2020;27:1039–42.
10 Wynants L, Van Calster B, Collins GS. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ* 2021;372:n236.
11 Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369:m1966.
12 Liang W, Liang H, Ou L, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med* 2020;180:1081–9.
13 Giorgi Rossi P, Broccoli S, et al, Emilia-Romagna COVID-19 working group. Case fatality rate in patients with COVID-19 infection and its relationship with length of follow up. *J Clin Virol* 2020;128:104415.
14 EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES. Shorter time from symptom onset to hospitalization is associated with worse outcome in patients with COVID-19, 2020. Available: https://eurekalert.org/pub_releases/2020-09/esoc-stf092520.php
15 Rodríguez-Molinero A, Gálvez-Barrón C, Miñarro A, et al. Association between COVID-19 prognosis and disease presentation, comorbidities and chronic treatment of hospitalized patients. *PLoS One* 2020;15:e0239571.
16 Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
17 Ballotari P, D'Angelo S, Bonvicini L, et al. Effects of immigrant status on emergency room (ER) utilisation by children under age one: a population-based study in the province of Reggio Emilia (Italy). *BMC Health Serv Res* 2013;13:458.
18 Ottone M. Characteristics of COVID-19 patients predicting Hospital readmission after ED discharge, 2022. Zenodo. Available: https://doi.org/10.5281/zenodo.5675150
19 Ruch Y, Kaeuffer C, Ohana M, et al. CT lung lesions as predictors of early death or ICU admission in COVID-19 patients. *Clin Microbiol Infect* 2020;26:1417.e5–1417.e8.
20 Feng Z, Yu Q, Yao S, et al. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. *Nat Commun* 2020;11:4968.
21 Francone M, Iafrate F, Masci GM, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. *Eur Radiol* 2020;30:6808–17.
22 Colombi D, Bodini FC, Petrini M, et al. Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. *Radiology* 2020;296:E86–96.
23 Parry AH, Wani AH, Yaseen M, et al. Clinicoradiological course in coronavirus disease-19 (COVID-19) patients who are asymptomatic at admission. *BJR Open* 2020;2:20200033.

24  Dai M, Liu X, Zhu X, *et al*. Temporal changes of CT findings between non-severe and severe cases of COVID-19 pneumonia: a multi-center, retrospective, longitudinal study. *Int J Med Sci* 2020;17:2653–62.

25  Rubin GD, Ryerson CJ, Haramati LB, *et al*. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. *Chest* 2020;158:106–16.

26  Revel M-P, Parkar AP, Prosch H, *et al*. COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020;30:4903–9.

27  LeDell E, Petersen M, van der Laan M. Computationally efficient confidence intervals for cross-validated area under the ROC curve estimates. *Electron J Stat* 2015;9:1583–607.

28  Riley RD, Ensor J, Snell KIE, *et al*. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;368:m441.

29  Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, *et al*. Predictors of in-hospital COVID-19 mortality: a comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions. *PLoS One* 2020;15:e0241742.

30  Bastug A, Bodur H, Erdogan S, *et al*. Clinical and laboratory features of COVID-19: predictors of severe prognosis. *Int Immunopharmacol* 2020;88:106950.

31  Figliozzi S, Masci PG, Ahmadi N, *et al*. Predictors of adverse prognosis in COVID-19: a systematic review and meta-analysis. *Eur J Clin Invest* 2020;50:e13362.