

ORIGINAL PAPER

Infectious diseases

Time to hospitalisation, CT pulmonary involvement and in-hospital death in COVID-19 patients in an Emergency Medicine Unit

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Abstract

Background: Patients with coronavirus disease 2019 (COVID-19) are often treated at home given the limited healthcare resources. Many patients may have sudden clinical worsening and may be already compromised at hospitalisation. We investigated the burden of lung involvement according to the time to hospitalisation.

Methods: In this observational cohort study, 55 consecutive COVID-19-related pneumonia patients were admitted to the Emergency Medicine Unit. Groups of lung involvement at computed tomography were classified as follows: 0 (<5%), 1 (5%-25%), 2 (26%-50%), 3 (51%-75%) and 4 (>75%). We also investigated in-hospital death and the predictive value of Yan-XGBoost model and PREDI-CO scores for death.

Results: The median age was 74 years and 34 were men. Time to admission increased from 2 days in group 0 to 8.5-9 days in groups 3 and 4. A progressive increase in LDH, CRP and D-dimer was found across groups, while a decrease of lymphocytes paO_2/FiO_2 ratio and SpO_2 was found. Ten (18.2%) patients died during the in-hospital staying. Patients who died were older, with a trend to lower lymphocytes, a higher D-dimer, creatine phosphokinase and troponin T. The Yan-XGBoost model did not accurately predict in-hospital death with an AUC of 0.57 (95% confidence interval [CI] 0.37-0.76), which improved after the addition of the lung involvement groups (AUC 0.68, 95%CI 0.45-0.90). Conversely, a good predictive value was found for the original PREDI-CO score with an AUC of 0.76 (95% CI 0.58-0.93) which remained similar after the addition of the lung involvement (AUC 0.76, 95% CI 0.57-0.94).

Conclusion: We found that delayed hospital admission is associated with higher lung involvement. Hence, our data suggest that patients at risk for more severe disease, such as those with high LDH, CRP and D-dimer, should be promptly referred to hospital care.

Luca Marino and Marianna Suppa contributed equally to this study.

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1 | INTRODUCTION

The present pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease (COVID-19) has put many severe issues to all the world health systems. Currently, the vaccination programme is moving the first steps all over the world, but it is quite clear that the burden on hospitals and health organisations will be still significant in the next months even if a great expectation is placed on the immunisation of a large part of the population.

A significant number of infected people is asymptomatic, with a percentage varying from 40% to 70%, depending on the particular analysis considered.^{1,2}

The clinical scenario of the symptomatic infections spans from paucisymptomatic conditions, sometimes classified as mild disease,³ to a severe or critical disease according to clinical and laboratory data. The latter includes patients with interstitial lung disease and pneumonia or patients with venous and arterial thrombotic complications.^{4,5}

The average incubation for clinical manifestation for the main symptoms is around 3-5 days,⁶⁻⁸ and the most common symptoms are dry cough, myalgias and headache. Additional features include rhinorrhea, gastro-intestinal symptoms, smell and/or taste alterations, and conjunctivitis is also reported in some cases.⁹⁻¹¹ In the most serious infections, the pulmonary involvement carries dyspnoea and fever. Since the initial mild symptoms, the disease can proceed to a more severe condition in a temporal window of 7-12 days,^{12,13} and in these cases, the admission to hospital is almost always necessary. Characteristics associated with the severity of SARS-CoV-2 infection may allow early identification and management of patients with poor outcomes; these include clinical factors such as cerebrovascular and cardiovascular disease, chronic obstructive pulmonary disease, diabetes, hypertension, smoking and male sex and laboratory findings such as increased procalcitonin, increased D-dimer and thrombocytopenia.¹⁴⁻¹⁷

The management of the hospitalised patients is based on clinical, laboratory and imaging data. In particular, chest computed tomography (CT) is one of the fundamental exams for the successive therapeutic course.¹⁸

The typical pattern at the chest CT is represented by bilateral interstitial involvement sometimes with consolidative abnormalities. Additional features found in some patients are septal thickening superposes on the ground glass opacification (crazy pattern), bronchiectasis, pleural effusion,¹⁹ pericardial effusion and lymphadenopathy. The lung involvement is almost always bilateral, with the prevalence of peripheral distribution and focused at the lower lobes of the lungs, at least in the less severe conditions.

Correlation between clinical features and radiological severity score was proved for chest X-ray²⁰ and chest CT^{18,20} and, even if none of the two techniques cannot be adopted as a unique diagnostic tool, they proved to be helpful to stratify the prognostic risk and to improve the management of the patient.

However, it is unclear whether time to hospitalisation is associated with an increased burden of symptoms and lung involvement.

This is an important issue considering that in the middle of what has been named the "second wave" of the pandemic disease the

What's known

- Many patients are treated at home for COVID-19 given the limited healthcare resources
- Patients with COVID-19 may worsen suddenly
- The impact of time to admission on COVID-19 severity is unknown

What's new

- Time to admission was associated with worse lung involvement
- Lung involvement was associated with in-hospital mortality
- Yan-XGBoost model predictivity improved after the addition of lung score
- PREDI-CO score showed a good predictive value

issue of the overcrowded hospital has become crucial and, in many cases, physicians are trying to treat patients at home as much as possible unless increasing respiratory failure.

The aim of the study was to analyse the possible relationship between the clinical/radiological lung conditions and the time delay between the onset of symptoms related to COVID-19 and the time of admission to the Emergency Department. We also tested the predictive value of two scores namely Yan-XGBoost model²¹ and PREDI-CO score²² for in-hospital mortality.

2 | METHODS

We carried out a retrospective analysis on 55 patients, affected by COVID-19-related pneumonia, admitted to the Emergency Department of Umberto I University Hospital in Rome from 1 October to 30 November 2020.

All the patients were diagnosed with COVID-19 after two positive polymerase chain reaction tests on nasopharyngeal swab specimen. Patients underwent a routine laboratory screening including, among others, complete blood count (CBC), lactate dehydrogenase (LDH), C-reactive protein (CPR), ferritin, D-dimer, troponin T, prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine phosphokinase (CPK), electrolytes, renal acute injury and liver enzymes. An arterial blood gas analysis without oxygen supply was also executed and the corresponding PaO₂/FiO₂ ratio evaluated.

2.1 | Lung involvement evaluation

At the Emergency Department, a chest CT was performed for all patients and estimation of lung involvement was established on the basis of the analysis of each of the five lung lobes to evaluate a

semi-quantitative score of disease severity. More details about this procedure have been published elsewhere.^{18,23} An experienced radiologist finally gave a global estimation of the overall lung involvement and patients were divided into five groups according to the following percentage of lung involvement: group 0 (<5% involvement), group 1 (5%-25% involvement), group 2 (26%-50% involvement), group 3 (51%-75% involvement) and group 4 (>75% involvement). One point for each group of lung involvement was then added to the clinical risk scores to see if it improved their predictive value.

2.2 | Clinical risk scores calculation

The PREDI-CO score was calculated according to Bartoletti et al²² including the following items: age >70 years, obesity, fever at hospitalisation (body temperature >38°C), respiratory rate >22 breaths/minute, lymphocytes <900 cells/mm³, creatinine >1 mg/dL, C-reactive protein (CRP) >10 mg/dL and lactate dehydrogenase (LDH) >350 UI/L. Each item scored 1 point, except for the CPR that scored 2 points.

The XGBoost based model proposed by Yan et al (Yan-XGBoost model)²¹ includes three biomarkers such as LDH ≥ 365 U/L, lymphocyte >14.%, and high-sensitivity CRP ≥ 41.2 mg/dL. Each item scores 1 point.

2.3 | Statistical analysis

Continuous variables are reported as median and interquartile range. Median values between two groups were compared by the Mann-Whitney U test, while comparison among the four groups of lung involvement was performed by the Kruskal-Wallis test. Categorical variables were reported as count and percentage and compared by Pearson chi-squared test. A first descriptive analysis of clinical characteristics of patients was performed according to lung involvement. We also analysed clinical and biochemical differences between survivor and non-survivor patients.

Finally, we built the receiver operating characteristic (ROC) curve to test the predictive value against in-hospital mortality before and after the addition of the lung involvement score as previously described (from 0 to 4 points). Area under the curve (AUC) values were calculated.

The statistical significance was set at a *P* value <.005. All the analyses were performed using the IBM software SPSS 25.0.

3 | RESULTS

The clinical and radiological features are reported in Table 1. The median age of patients was 74 years 34 were men. We first analysed the clinical characteristics of patients according to the lung involvement severity (Table 1). Patients in group 0-1 (low pulmonary involvement) were younger than other groups. Patients with severe

lung disease (group 4) showed the highest proportion of diabetes and chronic obstructive pulmonary disease. A progressive increase in LDH, CRP and D-dimer was found from group 0 to 4. Conversely, the lymphocytes $\text{PaO}_2/\text{FiO}_2$ ratio and SpO_2 progressively decreased (Table 1).

Time to admission increased from 2 days in group 0 to 8.5-9 days in groups 3 and 4 (Table 1).

3.1 | In-hospital outcomes

Ten (18.2%) patients died during the in-hospital staying. Patients who died were older, with a trend to lower lymphocytes, a higher D-dimer, creatine phosphokinase, and troponin T (Table 2).

The two groups of patients did not present a significant difference in term of median time admission, but a significantly higher lung involvement was found in non-survivors patients.

We also tested the predictive value of clinical risk scores in our group of patients.

We found that the Yan-XGBoost model did not accurately predict in-hospital death with an AUC of 0.57 (95%CI 0.37-0.76) (Figure 1), which significantly improved after the addition of the lung score (AUC 0.68, 95%CI 0.45-0.90). Conversely, a good predictive value was found for the original PREDI-CO score with an AUC of 0.76 (95%CI 0.58-0.93) which remained similar after the addition of the lung involvement score (AUC 0.76, 95%CI 0.57-0.94).

4 | DISCUSSION

In this study, performed in the Emergency Medicine Unit, we found that delayed time to admission was significantly associated with a more severe lung involvement, which was associated with higher in-hospital death. We also found that the addition of lung involvement to a pre-existing score increased its predictive value.

Patients with worse lung involvement were more likely to have increased LDH, CRP, D-dimer and lower lymphocytes, $\text{PaO}_2/\text{FiO}_2$ ratio and SpO_2 . Our results are in keeping with a previous report showing that CT scores of lung involvement were correlated with CRP and LDH serum levels.²⁴ In particular, in the study by Francone et al the CT score was significantly correlated with CRP ($P < .0001$, $r = 0.6204$) and D-dimer ($P < .0001$, $r = 0.6625$) levels.¹⁸

These biomarkers may be useful to identify outpatients with a higher risk of severe lung disease. A new finding of the study is that the time to hospital admission increased progressively across lung involvement severity groups.

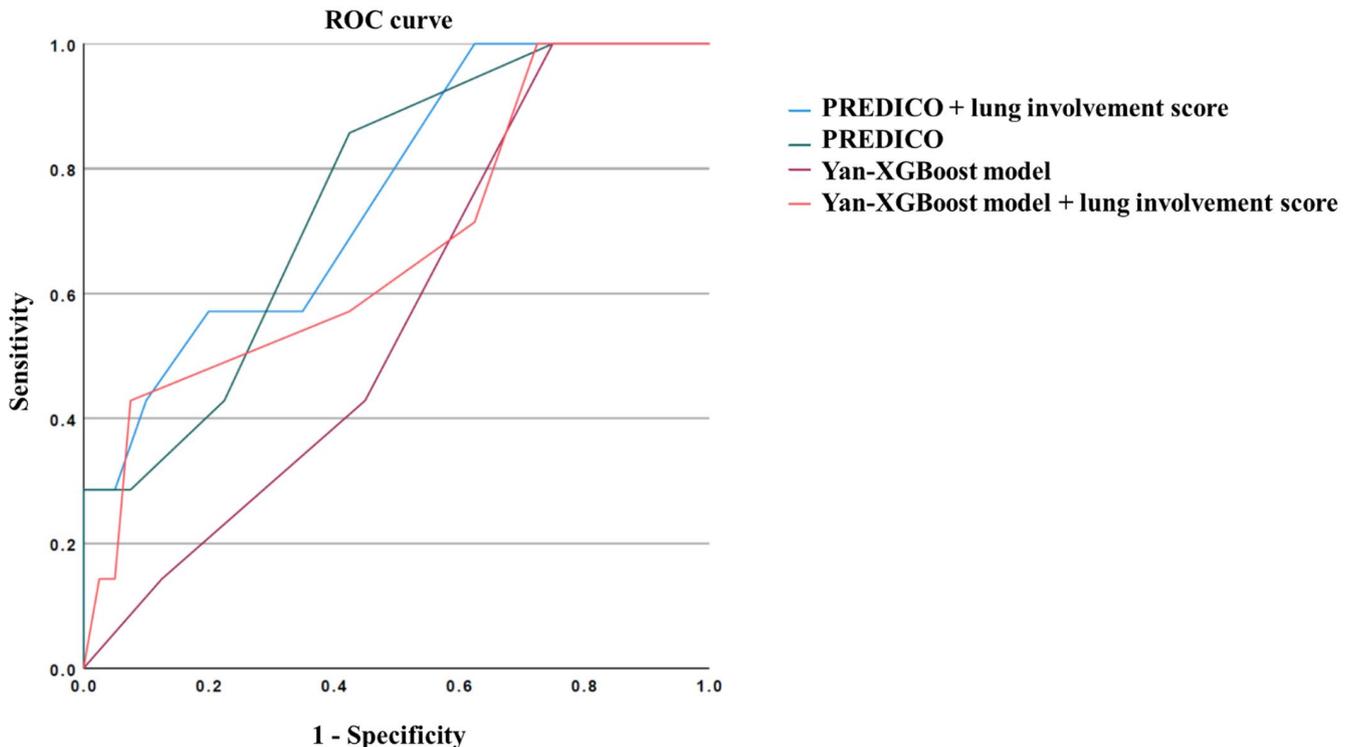
During the in-hospital staying, 18% of patients died. This case-fatality rate is similar to the reported in other studies conducted in Italy.²⁵ In our study, we found that lung involvement degree was higher in non-survivor patients. In the last months, several clinical scores were developed to assess the severity of the disease and to predict patient evolution to critical illness or death.²⁶ The proposed scores are quite heterogeneous in terms of predictors which span from demographic

TABLE 1 Characteristics of patients according to lung involvement

Lung involvement groups							
	Group 0	Group 1	Group 2	Group 3	Group 4		
	<5%	5%-25%	26%-50%	51%-75%	>75%		
Variables (normal values range)	(n = 7)	(n = 17)	(n = 17)	(n = 10)	(n = 4)	P value (among groups)	P value (group 4 vs 0)
Pulmonary involvement (%)	2 (0-5)	15.6 (10-20)	40.6 (36.25-48.75)	65 (60-70)	80 (75-85)	<.001	<.001
Age (years)	64(46.5-73.5)	69(54.7-84.53)	75(63.2-83.0)	81(59.0-90.0)	84.5(61.0-88.5)	.396	.400
Men (%)	60	56	56	89	50	.260	.240
Time to admission (days)	2 (1.5-5)	4 (2-4)	6 (4.25-9.75)	9 (5.5-11)	8.5 (7-10)	.002	.007
Hypertension (%)	33.3	50	56	55	50	.160	.250
Diabetes (%)	8	31.2	12.5	33	50	.300	.310
Chronic obstructive pulmonary disease (%)	0	18.7	18.7	0	50	.230	.500
LDH (135-225 units/L)	228 (189-252)	240 (196-387)	326 (299-376)	353 (284-461)	578 (433-856)	.055	.010
Lymphocytes ($1-3.2 \times 10^9/L$)	0.85 (0.64-1.44)	0.95 (0.71-1.37)	0.79 (0.56-1.01)	0.96 (0.58-1.23)	0.54 (0.36-0.73)	.060	.060
C-reactive protein (<0.5 mg/dL)	0.48 (0.05-1.87)	4 (1.1-11.9)	6.6 (2.6-12.8)	9 (3.6-13.9)	23 (13-33.5)	.015	.004
PaO ₂ /FiO ₂ ratio (>400)	500 (425-516)	350 (304-400)	305 (208-353)	314 (206-369)	193 (154-234)	.003	.001
SpO ₂ (%)	98 (96.5-99)	97 (95-98.7)	95 (92-97)	95 (93.5-97)	86(80-92)	.033	.013
Ferritin (30-400 ng/mL)	298 (183-315)	380 (48-843)	447 (283-784)	1000 (187-1822)	-	.220	.250
D-dimer (<500 ng/mL)	308 (170-502)	631 (255-1452)	652 (550-2480)	802 (474-1939)	1456 (964-1966)	.070	.045
Creatinine (0.1-1.2 mg/dL)	1 (0.9-6.25)	0.9 (0.7-1.8)	0.9 (0.8-1.07)	1.05 (0.9-1.1)	0.9 (0.7-1.1)	.380	.035
Creatin phosphokinase (40-300 UI/L)	63.2 (54-178)	85 (43-188)	54 (37-186)	172 (102-384)	142 (71-220)	.120	.110
Troponin T (<0.0014 µg/L)	0.058 (0.012-0.587)	0.015 (0.008-0.031)	0.012 (0.009-0.023)	0.028 (0.018-0.037)	0.015 (0.01-0.02)	.120	.400
Yan-XGBoost model	0.6 (0-1.1)	1.2 (0.1-2.2)	1.56 (0.8-2.3)	1.44 (0.45-2.46)	3	.044	.060
Yan-XGBoost model + lung involvement	1.6 (1-2)	3 (2-4)	4.5 (4-5)	6 (4.5-6)	8	<.001	<.001
PREDI-CO score	2.6 (2.1-3.2)	3.33 (2.2-5.1)	3.8 (2.8-5)	4.1 (2.3-5.6)	6 (4.6-7.4)	.056	.070
PREDI-CO + lung involvement	3.6 (3-4)	5.3 (5-7)	6.5 (6-8)	8 (6.25-9.75)	10 (8.5-11)	<.001	<.001

TABLE 2 Demographic, clinical and radiological features of the patients studied according to in-hospital outcome

	All patients (n = 55)	Alive (n = 45)	Dead (n = 10)	P value
Age (years)	74 (60-83)	66 (53-80)	86.5 (81.7-90.25)	<.001
Gender (male %)	61	60	70	.250
Time to admission (days)	5 (3-7)	5 (3-8)	5 (2.75-7)	.120
Hypertension (%)	52.7	51.1	60	.300
Diabetes (%)	23	22.2	30	.140
Chronic obstructive pulmonary disease (%)	18.2	15.6	30	.300
<i>Laboratory findings</i>				
LDH (135-225 units/L)	302 (231-400)	302 (236-374)	309 (202-467)	.451
Lymphocytes ($1-3.2 \times 10^9/L$)	0.9 (0.6-1.2)	0.95 (0.6-1.21)	0.77 (0.53- 1.19)	.081
C-reactive protein (<0.5 mg/dL)	5.46 (2.1-12)	4.5 (2-12)	7.6 (3.2-11)	.201
PaO ₂ /FiO ₂ ratio (>400)	321 (236-378)	324 (262-376)	262 (154-381)	.109
SpO ₂ (%)	96 (93-98)	96 (93-98)	96 (90-98.2)	.832
Ferritin (30-400 ng/mL)	435 (216-943)	441 (242-926)	333 (195-1000)	.912
D-dimer (<500 ng/mL)	640 (430-1630)	623 (350-1498)	825 (530-1970)	.032
Creatinine (0.1-1.2 mg/dL)	0.9 (0.8-1.13)	0.9 (0.8-1.1)	1.1 (0.9-1.45)	.081
Creatin Phosphokinase (40-300 UI/L)	86 (50.5-188)	76 (48-173)	164 (74-312)	.045
Troponin T (<0.0014 µg/L)	0.018 (0.01-0.03)	0.015 (0.009-0.028)	0.026 (0.019-0.068)	.038
Pulmonary involvement (%)	32.5 (11.2-50)	30 (10-48.7)	60 (25-73.75)	.023
<i>Risk scores</i>				
Yan-XGBoost model	1.5 (1-2)	1 (0-2)	1.8 (1-2.3)	.130
PREDI-CO score	3.5 (3-4.5)	3.3 (2-4)	5 (4-7)	.006
Yan-XGBoost model + lung involvement score	4 (3-5)	4 (2-5)	5.5 (3.25-6)	.031
PREDI-CO + lung involvement score	6 (5-8)	6 (5-8)	8 (6-11)	.014

**FIGURE 1** ROC curves with and without the addition of lung involvement groups

to laboratory and/or radiological features. However, some of them are complex and with some variables which are difficult to be obtained especially in an emergency setting. In our study, we decided to test two scores which include simple clinical and laboratory variables.

In particular, Yan et al proposed an easy mortality prediction model based on the three biomarkers LDH, CRP and the lymphocytes percentage, while Bartoletti et al²² introduced also obesity and fever as items. The low clinical predictivity ability of the Yan-XGBoost model found in our study is similar to that reported in another clinical study including 411 patients with COVID-19 showing an AUC for the mortality endpoint of 0.58.²⁷

Despite the COVID-19-related interstitial pneumonia may be difficult to be distinguished from other viral interstitial infectious diseases, much emphasis has been recently put on the prognostic value of imaging data, especially from chest CT,^{28,29} which showed a high sensitivity for the diagnosis of COVID-19.³⁰ In our study, CT features were evaluated at admission, but there is a growing body of evidence suggesting that chest CT findings may change over a mean time of 10 days from symptoms onset.²³ In particular, in the late phase of the disease, a higher rate of consolidation and signs of fibrosis have been detected.¹⁸

We found that the addition of CT data to the biomarker-based score improved its clinical value, suggesting that laboratory alone cannot be enough to correctly stratify the risk of death in patients with COVID-19 related pneumonia.

Limitations of the study. The present contribution is limited by the small sample size that could affect the statistical significance, but, from these preliminary results, we can conclude that time delay between COVID-19 symptoms onset and hospital admission can actually affect the disease progression, especially for the evolution of the lung damage. This issue is particularly significant for older patients who proved to be the most dramatically affected by the pandemic.

In conclusion, our study suggests that delayed time to hospitalisation is associated with a worse lung involvement evaluated by CT. Our results challenge the actual advice of health systems of many countries to delay hospital admission for non-severe cases, in order to ease the hospitals burden that struggles to manage the continuously increasing rate of infected people. Our opinion is that people with clinical and laboratory features suggestive of significant lung involvement (ie, high LDH, CRP and D-dimer) should not wait to be referred to the hospital.

DISCLOSURES

The authors declare no conflict of interest.

ETHICAL STATEMENT

In keeping with statements by the Italian Regulatory Authorities (<https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552>), anonymised data were retrospectively collected from medical and electronic databases in the context of an audit. Patients were not directly involved in any phase of the study. A waiver of informed consent from study participants is applied for

retrospective studies. This study was conducted in compliance with the declaration of Helsinki.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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