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Analysis of prognostic factors in COVID-19 hospitalized patients: an Italian single-center case-control study

A. CONCISTRÈ[1,3], L. PETRAMALA[2], C.L. PUGLIANO[1], M. CELI[1], F. VINCI[1], E. ASSANTO[1], I. BARCHETTA[1], E.P. PERRONE[1], S. RELLA[1], F. IANNAZZO[1], A. ANGHELONI[1], L. CORAGGIO[1], F. DI RIENZO[1], D. MAGGI[1], F. CIRCOSTA[3], G. GALARDO[4], M. MUSCARITOLI[1,2], C. LETIZIA[1,3]

[1]Internal Medicine COVID-19 Unit, Policlinico "Umberto I" University Hospital, Rome, Italy
[2]Department of Translational and Precision Medicine, "Sapienza" University of Rome, Rome, Italy
[3]Department of Clinical, Internal Medicine, Anesthesiology and Cardiovascular Sciences, "Sapienza" University of Rome, Rome, Italy
[4]Emergency Medicine Unit, Department of Emergency-Acceptance, Critical Areas and Trauma, Policlinico "Umberto I", Rome, Italy

A. Concistrè and L. Petramala have contributed equally to this work and share first authorship

Abstract. – OBJECTIVE: COVID-19 clinical presentation ranges from asymptomatic infection to an inflammatory cytokine storm with multi-organ failure and fatal outcomes. The identification of high-risk patients for severe disease is crucial to plan an early treatment and intensive follow-up. We aimed to investigate negative prognostic factors in a group of patients hospitalized for COVID-19.

PATIENTS AND METHODS: 181 patients (90 men and 91 women, mean age 66.56 ± 13.53 years) were enrolled. Each patient received a work-up including medical history, clinical examination, arterial blood gas analysis, laboratory blood tests, feasible ventilatory support required during hospital stay, intensive care setting required, duration of illness and length of hospital stay (>or<25 days). For the assessment of the severity of COVID-19, three main indicators were considered: 1) the intensive care unit (ICU) admission 2) the hospitalization length >25 days; 3) the need of non-invasive ventilation (NIV).

RESULTS: The independent risk factor associated with the ICU admission were lactic dehydrogenase elevation (p=0.046), C reactive protein elevation (p=0.014) at hospital admission and direct oral anticoagulant home therapy (p=0.048); for hospital length >25 days: early corticosteroid therapy (p=0.035); for NIV treatment: ferritin elevation at hospital admission (p=0.006).

CONCLUSIONS: The presence of the above factors may be useful to identify patients at high risk of developing a severe COVID-19 that need an early treatment and intensive follow-up.

Key Words:
COVID-19, SARS-CoV-2, Prediction, Lactic Dehydrogenase, Prognosis, ICU, Hospitalization, NIV, C Reactive Protein, Corticosteroid therapy, Prognosis, Hospitalization.

Introduction

Infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its related disease (COVID-19) have become an urgent public health problem due to the increasing number of affected patients worldwide and it is straining healthcare providers and researchers, dealing with unprecedented unknowns[1].

COVID-19 clinical presentation ranges from asymptomatic infection to interstitial pneumonia, respiratory failure, and acute respiratory distress syndrome (ARDS). Moreover, the disease can worsen further, with an evolution towards inflammatory cytokine storm with multi-organ failure and fatal outcomes[2]. The heterogeneity of the clinical course of COVID-19 makes the management of affected patients very difficult. Therefore, in addition to the search for effective therapies and vaccines, a crucial role is played by prognostic factors that may be used in decision-making related to the care of patients with COVID-19. Although multiple prognostic factors have been pro-

Corresponding Author: Claudio Letizia, MD; e-mail: claudio.letizia@uniroma1.it

posed and some of them have been accepted by the scientific community, the predictive value of most of these potential prognostic factors has not been robustly evaluated and remains uncertain.

According to data from a large observational database that collects patients from Asia, Europe, and the United States, the female gender seems to be a protective factor related to lower in-hospital mortality. Also, men are at greater risk of being admitted to an intensive care unit (ICU) than women[3]. This could be explained by the higher percentage of smokers and the higher prevalence of cardiovascular disease in men compared to women. In addition to the different lifestyle habits, the greater risk for ICU admission in men when compared to women with COVID-19 may be related to some gender differences (including enzymatic, metabolic, endocrine, and immune activity), and a different response to drugs[4]. Furthermore, androgens modulate cellular expression of ACE2 and regulate the transmembrane serine protease-2 that allows the interaction between SARS-CoV-2 and ACE2 and the viral RNA entry into the host cell[5].

Age has also been reported as an important factor affecting COVID-19 outcome. Older subjects (beyond the sixth decade of life) are more frequently hospitalized in intensive care unit and have a higher rate of mortality. The higher susceptibility to infections in older people appears to be related to their immunosenescence and a greater number of comorbidities[6-8].

Furthermore, both Italian and Chinese epidemiological data confirm that the risk of complications and mortality in COVID-19 is closely linked to the number of underlying comorbidities, such as hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic coronary disease, heart failure (HF), obesity, chronic renal failure (CRF), history of tumors[6,9]. Diabetes and other comorbidities such as hypertension are associated with the activation of the renin-angiotensin system (SRA) and an increase in ACE2, through which SARS-CoV-2 binds to and penetrates host cells. On the other hand, the correlation between clinical performance and the intake of ACE inhibitors and angiotensin receptor blockers (ARBs) was denied[3,7].

Hyperglycemia, insulin resistance, and chronic activation of inflammatory pathways would be the cause of a reduced immune response, a greater susceptibility to infections and a more severe clinical evolution in obese patients[10]. Several abnormalities in haematological, biochemical, inflammatory, and immune patterns have also been identified responsible for influencing the course of the disease. For example, elevation of C reactive protein (CRP), lactic dehydrogenase (LDH), D-Dimer and lymphopenia, are common laboratory changes seen in COVID-19. Systemic inflammation and host immune response play an important role in this disease: the decrease in the lymphocyte count observed in COVID-19 patients is associated with excessive inflammation and uncontrolled immune activation resulting in organ or tissue injury[11]. Thus, the inflammatory parameters could be prognostic biomarkers for predicting the prognosis of severe COVID-19.

Although several studies[3,6,7,9] on predisposing factors for severe disease are present in the literature, they are often discordant. Nevertheless, the unmet need for novel parameters to optimize risk stratification remains. The aim of this study was to analyze the clinical and laboratory characteristics of a group of patients hospitalized for COVID-19 in an Italian Single Center, in order to identify useful prognostic predictors for severe disease.

Patients and Methods

We analyzed the clinical data of 181 patients (90 men and 91 women, mean age 66.56 ± 13.53 years), hospitalized in our COVID-19 Internal Medicine Unit, (Policlinico Umberto I Hospital, Rome, Italy), from December 2020 to June 2021. The examined patients were admitted to the Emergency Department (ED) and subsequently confirmed as cases of COVID-19 using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens, and they were diagnosed with COVID-19 pneumonia using high-resolution computed tomography (HRCT). After that, they came to our ward where we clinically followed them throughout their hospital stay until the discharge. Data were extracted from the paper and electronic clinical documentation and inserted in a SPSS version 24 format database (IBM Corp., Armonk, NY, USA). The identity of each patient was made anonymous, and all data was used in compliance with the Declaration of Helsinki. The following data were included in the database: sex, age, nutritional status, previous comorbidities (arterial hypertension, DM, dyslipidemia, chronic heart diseases, chronic respiratory diseases, thyroid diseases, autoimmune diseases, NAFLD),

home therapy, days between the onset of symptoms and the hospital admission, the diagnostic work-up of the ED including vital signs [systolic and diastolic blood pressure (BP), heart rate (HR) and respiratory rate (RR), body temperature (TC)], an arterial blood gas analysis (whenever possible performed on room air), laboratory blood tests (blood count with leukocyte formula, parameters of glucose metabolism, parameters of liver and kidney function, pancreatic enzymes, total proteins, albuminemia, inflammatory indexes and coagulation pattern), most intensive form of ventilatory support required during the hospital stay (IMV, NIV, oxygen support), most intensive setting of care required during the hospital stay [(semi-intensive respiratory unit (ICUs)], the duration of the illness (starting from the onset of symptoms) and the duration of hospital stay (> or <25 days). For further assessment of the severity of COVID-19, three additional separate indicators were considered: 1) need for transfer to ICU at any time during hospital stay; 2) total duration of hospitalization > 25 days; 3) need for NIV at any time during the hospital stay, 4) in-hospital death. All methods were performed in accordance with relevant guidelines and regulations. All patients gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using dedicated statistical software SPSS version 24 (IBM Corp., Armonk, NY, USA,). The distribution of the variables was determined by the Kolmogorov-Smirnov test and the non-Gaussian variables were transformed and/or analyzed with non-parametric methods. Quantitative variables with normal distribution were reported as mean±SD. ANOVA test, Student's *t*-test, or Mann Whitney test for independent samples were used for the comparison of quantitative variables, as appropriate. Paired-sample *t*-test or Wilcoxon's test was used for paired-sample comparisons. Categorical variables are reported as frequency and/or percentage and were compared with Chi-square tests. Multivariate and binomial logistic regression analysis was used to identify independent predictors of ICU admission, NIV use, and length of hospital stay> 25 days. We compared the predictive performance of CRP and LDH as continuous variables using the receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC) to discriminate the diagnostic performance for ICU admission in the population studied. All analyses were considered significant for a p-value level <0.05.

Results

The baseline characteristics, the laboratory findings at the admission to the ED,and the clinical data during hospitalization of COVID-19 total cohort are shown in Table I. The 181 patients included in the study were analyzed for four clinical outcome parameters: ICU admission, total length of hospitalization> 25 days, and use of NIV.

Admission to ICU

The patient population was divided into two groups: ordinary hospitalization, 134 patients (63 M / 71 F) and ICU admission, 47 patients (27 M/20 F).

The comparison between ICU and non-ICU patients is summarized in Table II and Table III.

Comparing patients of the ICU group with patients of the non-ICU group, we found the first group were more frequently in antihypertensive therapy (ordinary hospitalization 44.8%, hospitalization in ICU 80%, $p = 0.049$) and in Direct Oral Anticoagulants therapy DOAC (ordinary hospitalization 10.3%, intensive care hospitalization 40%, $p = 0.035$). Patients who went in ICU were also more frequently admitted to the ED with fever (ordinary hospitalization 48.3%, intensive care hospitalization 90%, $p = 0.021$), and they more frequently needed O2 supportive therapy (ordinary hospitalization 24%, ICU hospitalization 60%, $p = 0.038$) and antibiotic therapy at admission (hospitalization ordinary 31%, hospitalization in intensive care 80%, $p = 0.007$) compared to patients of the non-ICU group. In multivariate analysis, the antihypertensive therapy (OR = 4.923, $p = 0.068$), fever (OR = 9.643, $p = 0.043$), the O2 support therapy (OR = 4.714, $p = 0.046$), the antibiotic therapy (OR = 8.889, $p = 0.014$) and the DOAC therapy (OR = 5.778, $p = 0.048$) were confirmed as risk factors for ICU admission.

Furthermore, patients of the ICU group had lower P/F ratio (ordinary hospitalization 399.61 ± 71.33, ICU hospitalization 365.60 ± 144.30, $p = 0.036$), and higher LDH (ordinary hospitalization 164.17 ± 75 U/l, ICU hospitalization 347.14 ± 130.2 U/l, $p = 0.039$) , AST (ordinary hospitalization 27.36 ± 21.04 U/l, ICU hospitalization 45.63 ± 20.15 U/l, $p = 0.047$), CRP (ordinary hospitalization 5.62 ± 9.46 md/dl, ICU hospitalization 15.92

Table I. Baseline characteristics of 181 COVID-19 hospitalized patients. Demographic characteristics, vital signs, arterial blood gas analysis and laboratory parameters, comorbidities, home drug therapy, COVID-19 symptoms, chest CT examination, ED admission therapy, and use of assisted ventilation.

Variables	Mean
Age (years)	66.56±13.53
SBP (mmHg)	131.59±23.07
DBP (mmHg)	75.05±12.34
HR (bpm)	85.87±17.22
Anamnestic data	**%**
Male sex	48.7
Overweight patients	20.5
Obese patients	7.7
Medical history of arterial hypertension	59
Medical history of diabetes mellitus	20.5
Medical history of dyslipidemia	28.2
Medical history of chronic heart disease	33.3
Medical history of chronic respiratory disease	10.3
Medical history of thyroid disease	17.9
Medical history of autoimmune disease	10.3
Medical history of NAFLD	2.6
Drug treatment	
Home antihypertensive drug therapy	53.8
Home metformin drug therapy	12.8
Syntoms	%
Asthenia	25.6
Dyspnea	38.5
Fever	59
Ageusia	2.6
Anosmia	2.6
Cough	46.2
Pharyngodynia	10.3
Therapy administered	**%**
O_2 supportive therapy	33.3
Cortisone drug therapy	56.4
Antiviral drug therapy	10.3
Antibiotic drug therapy	43.6
DOAC drug therapy	17.9
Antiplatelet drug therapy	20.5
Heparin drug therapy	30.8
Hospitalization	
Mean±SD	
ER-Symptom Latency (days)	4.9±5.08
COVID-19 disease duration (days)	30.31±13.94
Total days of hospitalization	30.56±16.44
Days in the ICU	2.33±4.88
Emogasanalisys parameters	**Mean±SD**
PH	7.48±0.07
PCO_2 (mmHg)	33.5±5.61
PO_2 (mmHg)	84.85±20
P/F ratio (mmHg)	390.66±94.91
FiO_2 (%)	22.47±6.55
SO_2 (%)	96.56±3.37

Table contineud

Table I. ***(Continued)*****.** Baseline characteristics of 181 COVID-19 hospitalized patients. Demographic characteristics, vital signs, arterial blood gas analysis and laboratory parameters, comorbidities, home drug therapy, COVID-19 symptoms, chest CT examination, ED admission therapy, and use of assisted ventilation.

Variables	Mean
Laboratory parameters	**Mean±SD**
Haemoglobin (g/dl)	13.18±2.24
WBC (x10^9/L)	7.65±3.87
Neutrophils (x10^9/L)	5.76±3.66
Lymphocytes (x10^9/L)	1.22±0.96
PLT (x10^9/L)	214±69.9
Creatinine (mg/dl)	1.04±0.49
LDH (U/l)	282.9±94.62
AST (U/l)	31.79±22
ALT (U/l)	30.06±27.02
GGT (U/l)	51.35±57.76
Amylase (U/l)	71.11±31.84
Lipase (U/l)	26.71±13.29
Total bilirubin (mg/dl)	0.55±0.33
Dir bilirubin (mg/dl)	0.19±0.10
Glucose (mg/dl)	126.09±41.75
CRP (mg/dL)	8.33±14.93
Ferritin (ng/ml)	793.16±845.33
DDimer (ng/ml)	991.78±979.82
Fibrinogen (mg/dl)	484.31±107.03
INR	1.15±0.85
Total protein (g/dl)	6.48±1.04
Albumin (g/dl)	5.03±6
	%
Mild lymphopenia (<1,000/µl)	10.3
Moderate lymphopenia (<800/µl)	35.9
Severe lymphopenia (<400/µl)	51.3
	%
CT with GGO	25.6
NIV	39
ETI	2.6

(NAFLD=Non-Alcoholic Fatty Liver Disease) (DOAC=Direct Oral AntiCoagulants) (PCO_2=Partial Pressure of Carbon Dioxide) (PO_2= Partial Oxygen Pressure) (FiO_2=Inhaled Fraction of Oxygen) (SO_2=Oxygen Saturation) (SBP=Systolic Blood Pressure) (DBP=Diastolic Blood Pressure) (HR=Heart Ratio) (WBC=White Blood Cells) (PLT=Platelets) (LDH=Lactate Dehydrogenase) (AST=Aspartate Aminotransferase) (ALT=Alanine Aminotransferase) (GGT=Gamma Glutamyl Transferase) (CRP=C Reactive Protein) (INR=International Normalized Ratio) (ICU=Intensive Care Unit) (NIV=Non-Invasive assisted Ventilation) (ETI = Endotracheal Intubation) (GGO=Ground Glass Opacity).

± 26.69 mg/dl, p = 0.022) and ferritin (ordinary hospitalization 577.57 ± 757.76 ng/ml, admission to ICU 1452.8 ± 781.83 ng/ml, p = 0.038) levels than patients of the non-ICU group.

In multivariate analysis (Table IV), only the LDH increase (p = 0.046), the CRP increase (p = 0.014) and the DOAC therapy (p = 0.048) remained statistically significant.

The prognostic performance of CRP and LDH for ICU admission were also compared using the ROC curve (Figure 1). The optimal prognostic threshold value was 4 mg/dl for PCR (sensitivity 85.7%, specificity 37.5%) and 293U/l for LDH (sensitivity 71.4%, specificity 33.3%).

Total Length of Hospitalization

The cohort of patients was divided according to the length of hospitalization: hospitalization < 25 days, 69 patients (41M/28F) and hospitalization > 25 days, 112 patients (49M/63F).

The comparison between hospitalization >25 days group and hospitalization <25 days groups is summarized in Table V and Table VI.

The group of patients with hospitalization > 25 days had more frequently started the corticosteroid therapy at the onset of symptoms (hospitalization < 25 days 33.3%, hospitalization > 25 days 70.8%, p = 0.022) with an Odds Ratio (OR = 4.857, p = 0.026).

Table II. General characteristics, comorbidities, symptoms, therapy and baseline radiological imaging of the non-ICU patient group and the ICU patient group.

	Univariate analysis			Multivariate analysis	
	Ordinary hospitalization (n. 134)	Admission to the ICU (n. 47)	*p*-value	Odds ratio (IC 95%)	*p*-value
Age (years)	66.1±14.4	67.9±11.22	0.342		
Male sex (%)	41.4%	70%	0.118		
Female sex (%)	58.5%	30%	0.118		
Overweight patients (%)	13.8%	40%	0.195		
Obese patients (%)	10.3%	0	0.195		
Home antihypertensive drug therapy (%)	44.8%	80%	**0.049**	**4.923 (0.887-27.31)**	0.068
Medical history of arterial hypertension (%)	55.2%	70%	0.411		
Medical history of diabetes mellitus (%)	27.6%	0	0.062		
Home metformin drug therapy (%)	17.2%	0	0.160		
Medical history of dyslipidemia (%)	27.6%	30%	0.884		
Medical history of chronic heart disease (%)	27.6%	50%	0.195		
Medical history of chronic respiratory disease (%)	10.3%	10%	0.975		
Medical history of thyroid disease (%)	24.1%	0	0.086		
Medical history of autoimmune disease (%)	13.8%	0	0.215		
Medical history of NAFLD (%)	3.4%	0	0.552		
Asthenia (%)	27.6%	20%	0.636		
Dyspnea (%)	34.5%	50%	0.384		
Fever (%)	48.3%	90%	**0.021**	**9.643 (1.079-86.21)**	**0.043**
Ageusia (%)	3.4%	0	0.552		
Anosmia (%)	3.4%	0	0.552		
Cough (%)	48.3%	40%	0.651		
Pharyngodynia (%)	10.3%	10%	0.975		
O_2 supportive therapy (%)	24.1%	60%	0.038	**4.714 (1.026-21.65)**	**0.046**
Cortisone drug therapy (%)	51.7%	70%	0.315		
Antiviral drug therapy (%)	6.9%	20%	0.239		
Antibiotic drug therapy (%)	31%	80%	**0.007**	**8.889 (1.564-50.53)**	**0.014**
DOAC therapy (%)	10.3%	40%	**0.035**	**5.778 (1.014-32.93)**	**0.048**
Antiplatelet drug therapy (%)	17.2%	30%	0.389		
Heparin drug therapy (%)	37.9%	10%	0.099		
Mild lymphopenia (<1000/µl) (%)	6.9%	20%	0.510		
Moderate lymphopenia (<800/µl) (%)	37.9%	30%	0.510		
Severe lymphopenia (<400/µl) (%)	51.7%	50%	0.510		
Negative CT for GGO (%)	17.2%	0	0.124		
CT with GGO (%)	82.7%	10%	0.101		
CT with GGO <20% (%)	65.5%	60%	0.124		
CT with GGO >20% (%)	13.8%	40%	0.124		

(ICU=Intensive Care Unit) (NAFLD=Non-Alcoholic Fatty Liver Disease) (DOAC=Direct Oral AntiCoagulants) (GGO=Ground Glass Opacity).

Furthermore, the elevation of the D-Dimer (hospitalization <25 days 593.92 ± 382.55 ng/ml, hospitalization > 25 days 1230.5 ± 1149.65 ng/ml, $p = 0.009$), was correlated with a longer length of hospital stay.

In multivariate analysis (Table VII), the D-Dimer lost the statistical significance ($p = 0.169$), while early corticosteroid therapy remained significant ($p = 0.035$).

NIV Treatment

The last analyzed parameter related to the clinical outcome was the use of non-invasive mechanical ventilation (NIV). The patient population was divided into two groups: non-NIV group, 111 patients (46M/65F) and NIV group, 70 patients (44M / 26F).

The comparison between the NIV group and the non-NIV group is summarized in Table VIII and Table IX.

Comparing the two groups, the NIV group required more frequently O_2 supportive therapy at admission in ED (patients underwent NIV 10%, patients did not undergo NIV 58%, $p = 0.002$); with an Odds Ratio (OR = 2.857, $p = 0.032$).

Furthermore, patients in the NIV group had lower SO2 levels (patients did not undergo NIV

Table III. General, hematochemical and arterial blood gas analysis data of the non-ICU patient group and the ICU patient group.

Variable	Univariate analysis		
	Ordinary hospitalization (n. 134)	Admission to the ICU (n. 47)	*p*-value
Symptom-PS latency (days)	4.38±2.46	6.4±3.56	0.103
P/F ratio	399.61±71.33	365.60±144.30	0.036
SBP (mmHg)	132.41±25.5	129.2±14.37	0.254
DBP (mmHg)	75.07±13.6	75±8.16	0.565
HR (bpm)	85.34±18.62	87.4±12.99	0.182
Hb (g/dl)	12.71±2.19	14.48±1.93	0.678
WBC (x10^9/L)	7.92±4.14	6.9±3.04	0.553
Neutrophils (x10^9/L)	5.89±3.98	5.39±2.72	0.482
Lymphocytes (x10^9/L)	1.33±1.07	0.92±0.42	0.266
PLT (x10^9/L)	219.93±72.9	194.4±61	0.472
Creatinine (mg / dl)	1.05±0.55	1.01±0.25	0.154
LDH (U/l)	164.17±75	347.14±130.2	0.039
AST (U/l)	27.36±21.04	45.63±20.15	0.047
ALT (U/l)	28.23±30.49	35.33±12.5	0.223
GGT (U/l)	44.79±60.12	69.14±50.53	0.895
Total bilirubin (mg/dl)	0.56±0.36	0.5±0.26	0.563
Dir bilirubin (mg/dl)	0.21±0.11	0.15±0.05	0.378
Glucose (mg/dl)	127.23±46.3	122.9±26.77	0.157
CRP (mg/dl)	5.62±9.46	15.92±26.69	0.022
Ferritin (ng/ml)	577.57±757.76	1452.8±781.83	0.038
DDimer (ng/ml)	1071.48±1099.59	788.1±574.64	0.122
Fibrinogen (mg/dl)	493.78±72.84	460.11±169.94	0.780
INR	1.19±0.98	1.05±0.14	0.406
Albumin (g/dl)	5.4±6.98	3.97±0.44	0.276

(ICU=Intensive Care Unit) (SBP=Systolic Blood Pressure) (DBP=Diastolic Blood Pressure) (HR=Heart Ratio) (WBC= White Blood Cells) (PLT=Platelets) (LDH=Lactate Dehydrogenase) (AST=Aspartate Aminotransferase) (ALT=Alanine Aminotransferase) (GGT=Gamma Glutamyl Transferase) (CRP=C Reactive Protein) (INR=International Normalized Ratio).

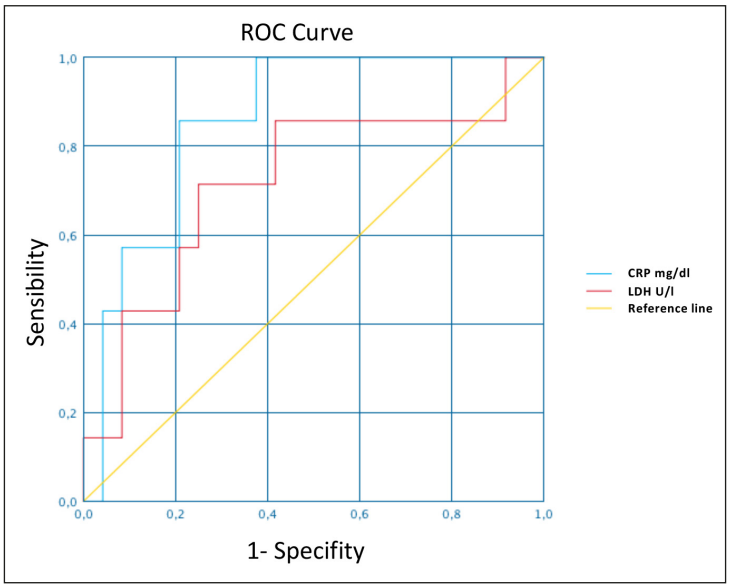

Figure 1. The ROC curve analysis compares the prognostic performance of CRP (AUC = 0.857; p <0.001) and LDH (AUC = 0.72; p <0.001) for ICU admission. Optimal threshold value for CRP 4 mg/dl (sensitivity 85.7%, specificity 37.5%); optimal threshold value for LDH 293 U/l (sensitivity 71.4%, specificity 33.3%). (ICU = intensive care unit) (LDH = lactate dehydrogenase) (CRP = C reactive protein).

Table IV. Multivariate analysis. Dependent variable: ICU admission R^2: 0.585, R^2 adjusted: 0.427, p=0.008.

	Multivariate analysis			
Variable	**Standardized Beta**	**95% IC Lower limit**	**95% IC Upper limit**	***p*-value**
LDH (U/l)	0.292	0.000	0.003	0.046
CRP (mg/dl)	0.407	0.007	0.057	0.014
AST (U/l)	-0.160	-0.011	0.005	0.327
Fever	0.128	-0.166	0.383	0.334
Antibiotic drug therapy	0.183	-0.139	0.449	0.171
DOAC therapy	0.318	0.004	0.67	0.048

(ICU=Intensive Care Unit) (LDH=Lactate Dehydrogenase) (CRP=C Reactive Protein) (AST=Aspartate Aminotransferase) (DOAC=Direct Oral AntiCoagulants).

Table V. General characteristics, comorbidities, symptoms, therapy, and baseline radiological imaging of the patient group with hospitalization> 25 days and the group of patients with hospitalization <25 days.

	Univariate analysis			Multivariate analysis	
Variable	**Hospitalization <25 days (n. 69)**	**Hospitalization > 25 days (n. 112)**	***p*-value**	**Odds ratio (IC 95%)**	***p*-value**
Age (years)	66.8±14.28	66.4±13.35	0.629		
Male sex (%)	60%	41.7%	0.265		
Female sex (%)	40%	58.3%	0.265		
Overweight patients (%)	26.7%	16.7%	0.630		
Obese patients (%)	6.7%	8.3	0.849		
Home antihypertensive drug therapy (%)	53.3%	54.2%	0.959		
Medical history of arterial hypertension (%)	66.7%	54.2%	0.440		
Medical history of diabetes mellitus (%)	26.7%	16.7%	0.452		
Home metformin drug therapy (%)	20%	8.3%	0.289		
Medical history of dyslipidemia (%)	33.3%	25%	0.547		
Medical history of chronic heart disease (%)	40%	29.2%	0.485		
Medical history of chronic respiratory disease (%)	6.7%	12.5%	0.559		
Medical history of thyroid disease (%)	13.3%	20.8%	0.553		
Medical history of autoimmune disease (%)	0	16.7%	0.095		
Medical history of NAFLD (%)	0	4.2%	0.423		
Asthenia (%)	13.3%	33.3%	0.164		
Dyspnea (%)	26.7%	45.8%	0.231		
Fever (%)	53.3%	62.5%	0.571		
Ageusia (%)	6.7%	0	0.200		
Anosmia (%)	6.7%	0	0.200		
Cough (%)	40%	50%	0.542		
Pharyngodynia (%)	13.3%	8.3%	0.617		
O_2 supportive therapy (%)	20%	41.7%	0.163		
Cortisone drug therapy (%)	33.3%	70.8%	**0.022**	**4.857 (1.212-19.464)**	**0.026**
Antiviral drug therapy (%)	6.7%	12.5%	0.559		
Antibiotic drug therapy (%)	33.3%	50%	0.307		
DOAC therapy (%)	13.3%	20.8%	0.553		
Antiplatelet drug therapy (%)	20%	20.8%	0.950		
Heparin drug therapy (%)	26.7%	33.3%	0.661		
Mild lymphopenia (<1000/µl) (%)	13.3%	8.3%	0.873		
Moderate lymphopenia (<800/µl) (%)	33.3%	37.5%	0.873		
Severe lymphopenia (<400/µl) (%)	53.3%	50%	0.873		
Negative CT for GGO (%)	26.7%	4.2%	0.094		
CT with GGO (%)	66.7%	95.8%	**0.049**	6.9 (0.637-74.6)	0.112
CT with GGO <20% (%)	53.3%	70.8%	0.094		
CT with GGO >20% (%)	13.3%	25%	0.094		
Multicomorbidity = 2 (%)	53.3%	50%	0.839		
Multicomorbidity = 3 (/%)	40%	29.2%	0.485		

(NAFLD=Non-Alcoholic Fatty Liver Disease) (DOAC=Direct Oral AntiCoagulants) (GGO=Ground Glass Opacity).

97.7 ± 1.32 %, patients underwent NIV 95.42 ± 4.34 %, p = 0.006), and lymphopenia (patients did not undergo NIV 1.45 ± 1.27 µl, patients undergo NIV = 0.99 ± 0.41 µl, p = 0.046), higher AST (patients did not undergo NIV 20.53 ± 8.37 U/l, patients underwent NIV 43.75 ± 25.73 U/l, p = 0.007), ALT (patients did not undergo NIV 20.1 ± 10.24 U/l, patients underwent NIV 43.33 ± 36.07 U/l, p = 0.006), GGT (patients did not undergo NIV 23.14 ± 13.38 U/l, patients receiving NIV 84.25 ± 71.96 U/l, p = <0.001) values, ferritin elevation (patients did not undergo NIV 267.6 ± 311.24 ng/ml, patients underwent NIV 1377.11 ± 877.46 ng/ml, p = <0.001), and INR values above normal (patients did not undergo NIV 1 ± 0.14, patients underwent NIV 1.36 ± 1.29, p = 0.044).

However, only ferritin was confirmed as statistically significant in the multivariate analysis (p = 0.006) (Table X).

Discussion

In this single-center case-control study, we illustrated the baseline characteristics, the clinical data, and the outcomes expressed in terms of hos-

Table VI. General, haematochemical and arterial blood gas analysis data of the group of patients with hospitalization >25 days and of the group of patients with hospitalization <25 days.

	Univariate analysis		
Variable	Hospitalization <25 days (n. 69)	Hospitalization > 25 days (n. 112)	p-value
PH	7.48±0.08	7.47±0.06	0.347
PCO_2 (mmHg)	33.33±4.97	33.6	0.361
PO_2 (mmHg)	85.47±18.29	84.44±31.43	0.304
P/F ratio (mmHg)	398.33±81.46	385.65±104.22	0.182
FiO_2 (%)	21.47±1.8	23.13±8.3	0.124
SO_2 (%)	97.43±1.69	95.99±4.05	0.066
SBP (mmHg)	129.33±20.95	133±24.58	0.983
DBP (mmHg)	74±11.21	75.71±13.18	0.949
HR (bpm)	90.73±23.6	82.83±11.22	0.095
Hb (g/dl)	13.03±2.3	13.28±2.25	0.814
WBC (x10^9/L)	7.48±4.94	7.76±3.1	0.545
Neutrophils (x10^9/L)	5.75±4.56	5.77±3.05	0.807
Lymphocytes (x10^9/L)	1.06±0.52	1.33±1.16	0.197
PLT (x10^9/L)	217.67±68.1	211.61±72.48	0.741
Creatinine (mg/dl)	1.01±0.48	1.06±0.5	0.914
LDH (U/l)	266.18±88.46	292.10±98.82	0.980
AST (U/l)	31±27.75	32.24±18.73	0.903
ALT (U/l)	28.85±24.28	32.55±28.78	0.790
GGT (U/l)	38.27±56.11	60.93±58.96	0.459
Amylase (U/l)	77.67±37.89	58±8.9	0.048
Lipase (U/l)	35.5±9.81	15±5	0.293
Total bilirubin (mg/dl)	0.41±0.2	0.71±0.4	0.067
Dir bilirubin (mg/dl)	0.13±0.05	0.26±0.10	0.150
Glucose (mg/dl)	127.76±47.69	125.65±38.51	0.285
CRP (mg/dl)	7.25±12.47	9.03±16.57	0.988
Ferritin (ng/ml)	680±944.46	845.38±831.17	0.716
DDimer (ng/ml)	593.92±382.55	1230.5±1149.65	0.009
Fibrinogen (mg/dl)	479.08±98.42	487.45±114.25	0.787
INR	1.33±1.36	1.04±0.15	0.034
Total protein (g/dl)	6.95±0.78	6.17±1.220.473	
Albumin (g/dl)	3.91±0.34	5.6±7.36	0.178
ER-Symptom Latency (days)	3.67±4.67	5.67±5.27	0.678

(PCO_2 = CO_2 Partial Pressure) (PO_2 = O_2 Partial Pressure) (FiO_2 = Inhaled Fraction of Oxygen) (SO_2 = Oxygen Saturation) (SBP=Systolic Blood Pressure) (DBP=Diastolic Blood Pressure) (HR=Heart Ratio) (WBC= White Blood Cells) (PLT=Platelets) (LDH=Lactate Dehydrogenase) (AST=Aspartate Aminotransferase) (ALT=Alanine Aminotransferase) (GGT=Gamma Glutamyl Transferase) (CRP=C Reactive Protein) (INR=International Normalized Ratio).

Table VII. Multivariate analysis. Dependent variable: hospitalization> 25 days R^2: 0.384, R^2 adjusted: 0.147, p <0.001.

Variable	Multivariate analysis			
	Standardized Beta	95% IC Lower limit > 25 days	95% IC Upper limit	*p*-value
Early cortisone drug therapy	0.343	0.025	0.645	**0.035**
D-dimer (ng/ml)	0.584	0.000	0.002	0.169
CT with GGO	0.186	-0.132	0.442	0.279

(GGO=Ground Glass Opacity).

Table VIII. General characteristics, comorbidities, symptoms, therapy and baseline radiological imaging of the patient group receiving NIV and of the patient group not-receiving NIV.

Variable	Univariate analysis			Multivariate analysis	
	Patients not receiving NIV (n. 111)	Patients receiving NIV (n. 70)	*p*-value	Odds ratio (IC 95%)	*p*-value
Age (years)	65.25±15.8	67.95±10.9	0.206		
Male sex (%)	40%	57.9%	0.264		
Female sex (%)	60%	42.1%	0.264		
Overweight patients (%)	15%	26.3%	0.810		
Obese patients (%)	10%	5.3%	0.579		
Home antihypertensive drug therapy (%)	40%	68.4%	0.075		
Medical history of arterial hypertension (%)	50%	68.4%	0.242		
Medical history of diabetes mellitus (%)	15%	26.3%	0.382		
Home metformin drug therapy (%)	10%	15.8%	0.589		
Medical history of dyslipidemia (%)	35%	21%	0.333		
Medical history of chronic heart disease (%)	35%	31.6%	0.821		
Medical history of chronic respiratory disease (%)	15%	5.3%	0.316		
Medical history of thyroid disease (%)	15%	21%	0.622		
Medical history of autoimmune disease (%)	15%	5.3%	0.316		
Medical history of NAFLD (%)	5%	0	0.323		
Asthenia (%)	25%	26.3%	0.925		
Dyspnea (%)	40%	36.8%	0.839		
Fever (%)	50%	68.4%	0.242		
Ageusia (%)	5%	0	0.323		
Anosmia (%)	5%	0	0.323		
Cough (%)	45%	47.4%	0.882		
Pharyngodynia (%)	10%	10.5%	0.957		
O_2 supportive therapy (%)	10%	57.9%	**0.002**	**2.857 (0.636-12.844)**	**0.032**
Cortisone drug therapy (%)	45%	68.4%	0.140		
Antiviral drug therapy (%)	5%	15.8%	0.267		
Antibiotic drug therapy (%)	30%	57.9%	0.079		
DOAC therapy (%)	10%	26.3%	0.184		
Antiplatelet drug therapy (%)	20%	21%	0.935		
Heparin drug therapy (%)	25%	36.8%	0.423		
Mild lymphopenia (<1000/µl) (%)	10%	10.5%	0.784		
Moderate lymphopenia (<800/µl) (%)	40%	31.6%	0.784		
Severe lymphopenia (<400/µl) (%)	45%	57.9%	0.784		
Negative CT for GGO (%)	20%	5.3%	0.147		
CT with GGO (%)	75%	94.7%	0.122		
CT with GGO <20% (%)	65%	63.2%	0.147		
CT with GGO >20% (%)	10%	31.6%	0.147		
Multicomorbidity = 2 (%)	55%	47.4%	0.634		
Multicomorbidity = 3 (%)	35%	31.6%	0.821		

(NIV = Non-Invasive Mechanical Ventilation) (NAFLD=Non-Alcoholic Fatty Liver Disease) (DOAC=Direct Oral AntiCoagulants) (GGO=Ground Glass Opacity).

Table IX. General, haematochemical and arterial blood gas analysis data of the patient group receiving NIV and of the patient group not-receiving NIV.

Variable	Univariate analysis		
	Patients not receiving NIV (n. 70)	Patients receiving NIV (n. 70)	*p*-value
PH	7.47±0.06	7.49±0.07	0.940
PCO_2 (mmHg)	34.79±5.06	32.19±5.97	0.423
PO_2 (mmHg)	87.89±16.12	81.8±23.29	0.069
P/F ratio (mmHg)	411.68±73.09	369.63±110.64	0.112
SO_2 (%)	97.7±1.32	95.42±4.34	0.006
SBP (mmHg)	134.58±14.32	134.58±14.32	0.095
DBP (mmHg)	74.25±16.16	75.89±6.64	0.096
HR (bpm)	97.7±1.32	83.95±12.86	0.688
Hb (g/dl)	12.58±2.11	13.78±2.27	0.530
WBC ($x10^9$/L)	7.57±4.56	7.73±3.16	0.642
Neutrophils ($x10^9$/L)	5.42±4.22	6.1±3.09	0.935
Lymphocytes ($x10^9$/L)	1.45±1.27	0.99±0.41	0.046
PLT ($x10^9$/L)	215.53±82.77	212.47±56.46	0.096
Creatinine (mg/dl)	1±0.51	1.09±0.47	0.873
LDH (U/l)	241.81±60.59	326.73±106.13	0.095
AST (U/l)	20.53±8.37	43.75±25.73	0.007
ALT (U/l)	20.1±10.24	43.33±36.07	0.006
GGT (U/l)	23.14±13.38	84.25±71.96	<0.001
Amylase (U/l)	69.67±30.92	74±40.6	0.634
Lipase (U/l)	21.6±12.22	39.5±2.12	0.323
Total bilirubin (mg/dl)	0.66±0.38	0.37±0.09	0.210
Dir bilirubin (mg/dl)	0.23±0.14	0.16±0.05	0.067
Glucose (mg/dl)	119.22±46.69	133.72±35.21	0.423
CRP (mg/dl)	6.53±11	10.32±18.5	0.455
Ferritin (ng/ml)	267.6±311.24	1377.11±877.46	<0.001
DDimer (ng/ml)	1171.59±1195.86	788±638.5	0.093
Fibrinogen (mg/dl)	484.88±88.13	483.75±126.12	0.844
INR	1±0.14	1.36±1.29	0.044
Albumin (g/dl)	5.95±8.05	3.89±0.37	0.088
COVID-19 disease duration (days)	25.4±12.82	35.47±13.48	0.620
Total days of hospitalization	25.3±14.54	36.11±16.85	0.688
ER-Symptom Latency (days)	3.85±4.76	6±5.3	0.925

(NIV=Non-Invasive Mechanical Ventilation) (PCO_2 = CO_2 Partial Pressure) (PO_2 = O_2 Partial Pressure) (FiO2 = Inhaled Fraction of Oxygen) (SO2 = Oxygen Saturation) (SBP=Systolic Blood Pressure) (DBP=Diastolic Blood Pressure) (HR=Heart Ratio) (WBC= White Blood Cells) (PLT=Platelets) (LDH=Lactate Dehydrogenase) (AST=Aspartate Aminotransferase) (ALT=Alanine Aminotransferase) (GGT=Gamma Glutamyl Transferase) (CRP=C Reactive Protein) (INR=International Normalized Ratio).

pitalization in ICU, hospital stay > 25 days and NIV treatment of a cohort of patients diagnosed with SARS-CoV-2 related pneumonia hospitalized in a COVID-19 Internal Medicine Unit. Our study aimed to contribute to the search for the negative prognostic factors related to worse outcome in hospitalized COVID-19 patients.

First, although many studies on the subject[5-7], such as the one conducted by the SARS-RAS research group of the Italian Society of Hypertension, have identified comorbidities (especially DM, COPD and CRF) as the main factors responsible for the poor prognosis in COVID-19 patients[6], in our study there were no differences regarding comorbidities in the patient groups studied. Obesity, which Busetto et al[10] identified as the major determinant of the mechanical ventilation use and ICU admission in patients with elevated BMI, did not affect the outcome of our patients.

Nevertheless, antihypertensive therapy and the oral anticoagulant DOAC therapy, both expressions of underling cardiovascular disease, seem to play a different role in developing COVID-19 outcomes. The results of the univariate analysis showed higher percentage of patients treated with antihypertensive and DOAC therapy in the group of ICU admitted patients. However, once the confounding factors were eliminated, statistical sig-

Table X. Multivariate analysis. Dependent variable: NIV R^2: 0.776, R^2 adjusted: 0.603, p <0.001.

	Multivariate analysis			
Variable	Standardized Beta	95% IC Lower limit > 25 days	95% IC Upper limit	*p*-value
SpO_2 (%)	-0.175	-0.175	0.096	0.514
AST (U/l)	-0.540	-0.033	0.012	0.315
ALT (U/l)	-0.313	-0.027	0.018	0.670
GGT (U/l)	0.105	-0.014	0.016	0.905
Ferritin (ng/ml)	1.290	0.000	0.002	0.006
INR	0.202	-2.357	4.097	0.113
Lymphocytes (x10^9/L)	-0.295	-0.662	0.240	0.544

(SpO_2=O_2 Peripheral Saturation) (AST=Aspartate Aminotransferase) (ALT=Alanine Aminotransferase) (GGT=Gamma Glutamyl Transferase) (INR=International Normalized Ratio).

nificance was confirmed exclusively for DOAC therapy. Therefore, in light of the above, antihypertensive therapy wouldn't represent a predictor of ICU admission, although it may be associated with a higher relative risk; while patients treated with DOAC would present a 5-times greater risk of ICU admission during COVID-19 disease. This result would not only indicate that patients with chronic heart disease have a worse course of COVID-19 disease, but it also confirms the results of the study by Schiavone et al[12], which correlated the use of DOAC with an increase in the use of NIV and a higher mortality in hospitalized COVID-19 patients.

Many abnormalities in hematological, biochemical, inflammatory, and immune patterns have been identified as causes of a worse course of COVID-19 disease[13,14]. Lymphopenia appears to be the major factor associated with COVID-19 patient outcome, not only because of a worse disease course and increased ICU admission, but also for causing greater mortality in affected patients. The association between lymphopenia, severe clinical course and high mortality seems to remain significant even after the adjustment of possible confounding factors and it appears to be independent of its severity degree (mild, moderate, or severe)[15,16]. In our study, the initial results that correlated lymphopenia with the use of NIV, were not confirmed in the multivariate analysis. This would suggest the presence of other concomitant factors in determining the severity of the disease and would exclude this parameter as an independent prognostic factor.

Regarding the biochemical markers, patients with elevated serum levels of CRP, D-dimer and LDH would appear to be related in several studies[17-19] to a worse clinical course, an increased development of complications and a higher mortality than patients with normal values, regardless of comorbidities, age, and sex. However, it is unclear whether these parameters may be used as independent factors for a worse prognosis; for example, Li et al[11] showed that CRP would not appear to be related with worse outcome when it increases on its own. The role of D-dimer would also seem unclear during clinical monitoring according to Ponti et al[20], so it may not be directly related to disease severity. Inflammatory markers also proved to be potential prognostic markers in our study. In particular, CRP and LDH were significantly increased in the univariate and multivariate analysis in the group of patients admitted to the ICU. D-Dimer values, which were higher in the group of patients with a hospital stay> 25 days in the univariate analysis, did not show statistical significance in the multivariate analysis. Therefore, this parameter could not be reliable when measured alone.

The correlation between the inflammatory and coagulation pathways is known, and it is also present in the specific case of COVID-19 disease, since hypercoagulability and thrombophilia occur in parallel with the worsening of inflammation mediated by SARS-CoV-2[2,21,22]. Indeed, Long et al[23] highlighted how the INR values would be increased in subjects with COVID-19 and poor prognosis in relation to various inflammatory parameters (CRP, ferritin and others), compared to patients with a positive prognosis. The same scientific work[23] argued that in patients with severe disease and poor prognosis, the INR values are always higher than in patients with equally severe disease but positive outcome, even if they fall within a normal range (INR <1.3). In our study, the results for the INR parameter seem contra-

dictory; although it was increased in the group of patients using NIV, at the same time most of the subjects with hospitalization> 25 days had normal values. Therefore, the high INR, while representing a potential predictor for the use of NIV, seems at the same time associated with a shorter length of hospitalization. Patients with high INR were likely to have a greater systemic involvement of the inflammatory and coagulation pathways, which would explain the risk of NIV. On the other hand, patients with a shorter hospital stay would carry an antithrombotic coagulation profile that would reduce the thrombotic complications of COVID-19 disease, compared to patients with a normal INR. However, INR cannot be considered an independent prognostic factor, since for both variables (hospitalization> 25 days and use of NIV) it does not maintain statistical significance in multivariate analysis.

Another important inflammatory marker in COVID-19 is ferritin. Ferritin is reported as a marker of the disease course[17], due to the finding of its elevated values in patients with a severe disease. Furthermore, elevated ferritin appears to be related to higher mortality in hospitalized patients[13,17]. Nevertheless, the correlation of ferritin levels with the risk of ICU admission is less clear. In the meta-analysis by Cheng et al[24], in fact, it emerged that an elevated ferritinemia would be significant in the prediction of ICU hospitalization only in patients with pre-existing comorbidities (particularly, in people with diabetes mellitus). In our statistical analysis, a greater percentage of patients with high ferritin values emerged in the group that was treated with NIV during hospitalization. This result was confirmed in multivariate analyses. Furthermore, in univariate analysis an elevated ferritinemia seemed to be related to ICU admission, however, these results lost statistical significance in multivariate analysis. Ferritin would therefore not be a reliable parameter for predicting ICU admission, but it could play a role as an independent risk factor for the use of NIV during COVID-19 disease.

Other biomarkers associated with a worse outcome in COVID-19 patients would appear to be liver and kidney function enzymes, pancreatic enzymes, procalcitonin, but their role is still unclear[25,26]. In our scientific work, a greater correlation emerged at first between the increase in liver function enzymes, hospitalization in the ICU, and the use of NIV; however, none of these results were confirmed in multivariate analysis. Moreover, it is not clear whether the COVID-19 hepatotoxicity represented a form of viral hepatitis (with direct hepatic involvement), a consequence of systemic inflammation or, finally, a secondary effect of medical therapy (antiviral, antibiotic, and corticosteroid therapy)[27].

Regarding the drug treatment in hospital management of COVID-19 patients, a review by Singh et al[28] showed that, in mild and moderate pneumonia, corticosteroid therapy would not seem to bring any benefit, while it would be associated with a mortality reduction in patients supported with mechanical ventilation and with a severe lung involvement. Wang et al[29] confirmed how the use of corticosteroids in patients supported with O2 therapy would reduce the length of hospitalization and the ICU admission by improving oxygenation. Wu et al[30] on the other hand, highlighted how patients with ARDS treated with steroids would have a higher index of lung disease severity, although, at the same time, mortality is reduced. This phenomenon can be explained by the fact that, while playing an immunomodulatory and suppressing role of the systemic cytokine cascade, the immunosuppressive action of this class of drugs could also worsen the course of the disease and increase the risk of secondary infections. In our study, the group with hospitalization > 25 days included patients who had started corticosteroid therapy at the onset of COVID-19 symptoms. Therefore, the use of corticosteroids in the management of COVID-19 patients should be cautious and avoided at least in the early stages of the disease.

Limitations

Our study has some limitations. First, it is a single-center study, with a small number of patients; moreover, the clinical timing of disease evolution was different in the examined subjects. At the same time, our study represents one of the few observational Italian studies on COVID-19.

Conclusions

The presence of the LDH, CRP and ferritin elevation ad hospital admission, home therapy with DOAC and the early steroid therapy at symptoms onset, may be useful to identify patients at high risk of developing a severe COVID-19 that need an early treatment and intensive follow-up. Further studies including a larger number of patients are needed to confirm our data.

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Informed Consent
All subjects gave their informed consent for inclusion before they participated in the study.

Ethics Statement
The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Sapienza University of Rome.

Authors' Contributions
AC wrote the main manuscript text, tables, and figures. MC, FV, EA, IB, EPP, SR, FI, AA, LC, FDR and DM provided the resources. CLP and AC conducted the investigation. CLP and FC worked on data curation. AC, LP and CL worked on the conceptualization of the study. LP, GG, MM and CL provided the supervision.

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ORCID ID
Antonio Concistrè: 0000-0001-5952-1853;
Luigi Petramala: 0000-0003-4463-4956;
Claudio Letizia:0000-0003-4397-0624.

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