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Identification of early predictors of clinical outcomes of COVID-19 outbreak in an Italian single center using a machine-learning approach

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*See Appendix 1

Abstract. – OBJECTIVE: SARS-CoV-2 disease (COVID-19) has become a pandemic disease, determining a public health emergency. The use of artificial intelligence in identifying easily available biomarkers capable of predicting the risk for severe disease may be helpful in guiding clinical decisions. The aim of the study was to investigate the ability of interleukin (IL)-6, troponin I, and D-dimer to identify patients with COVID-19 at risk for intensive care unit (ICU)-admission and death by using a machine-learning predictive model.

PATIENTS AND METHODS: Data on demographic characteristics, underlying comorbidities, symptoms, physical and radiological findings, and laboratory tests have been retrospectively collected from electronic medical records of patients admitted to Policlinico A. Gemelli Foundation from March 1, 2020, to September 15, 2020, by using artificial intelligence techniques.

RESULTS: From an initial cohort of 425 patients, 146 met the inclusion criteria and were enrolled in the study. The in-hospital mortality rate was 15%, and the ICU admission rate was 41%. Patients who died had higher troponin I (*p*-value<0.01) and IL-6 values (*p*-value=0.04), compared to those who survived. Patients admitted to ICU had higher levels of troponin I (*p*-value<0.01) and IL-6 (*p*-value<0.01), compared to those not admitted to ICU. Threshold values to predict in-hospital mortality and ICU admission have been identified. IL-6 levels higher than 15.133 ng/L have been associated with a 22.91% risk of in-hospital mortality, and IL-6 levels higher than 25.65 ng/L have been associated with a 56.16% risk of ICU admission. Troponin I levels higher than 12 ng/L have been associated with a 26.76% risk of in-hospital mortality and troponin I levels higher than 12 ng/L have been associated with a 52.11% risk of ICU admission.

CONCLUSIONS: Levels of IL-6 and troponin I are associated with poor COVID-19 outcomes. Cut-off values capable of predicting in-hospital mortality and ICU admission have been identified. Building a predictive model using a machine-learning approach may be helpful in supporting clinical decisions in a more precise and personalized way.

Key Words:
SARS-CoV-2, COVID-19, Cytokine, IL-6, Cardiac injury, Troponin I.

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Abbreviations

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); SARS-CoV-2 disease (COVID-19); intensive care unit (ICU); interleukin (IL); computed tomography (CT); International Classification of Diseases (ICD); interquartile range (IQR); area under the curve (AUC); receiver operating characteristic (ROC); odds ratio (OR); acute respiratory distress syndrome (ARDS); angiotensin-converting enzyme 2 (ACE-2), serine protease transmembrane serine protease 2 (TMPRSS2); glucagon-like peptide-1 (GLP-1).

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped non-segmented positive sense RNA virus first isolated in January, 2020[1]. It belongs to the family of Coronaviruses, and it was responsible for 6,881,955 deaths and 676,609,955 confirmed cases of infection worldwide on March 10th, 2023[2], raising public health concerns in the last three years. Although SARS-CoV-2 disease (COVID-19) could be characterized by mild symptoms, some patients develop a severe and critical disease with a high mortality risk[3-5]. More severe cases of COVID-19 show a multisystemic involvement with infective complications, thromboembolic disturbances, and myocardial, kidney and liver injury[6-10]. Predictors of COVID-19 severity and serological indicators that can be used for risk assessment and guidance in treatment decisions have been identified[1,6,7,11-15]. In particular, increased levels of cytokines, D-dimer and cardiac damage biomarkers have been associated with the risk of intensive care unit (ICU) admission, mechanical ventilation and mortality during the first pandemic wave[16-18]. Given the spread of COVID-19 and its impact on health resource allocation, identifying predictive models with machine-learning methods may support clinicians in clinical decision-making.

The aim of this work was to implement prediction models of disease severity, investigating the ability of interleukin (IL)-6, troponin I and D-dimer to predict COVID-19 in-hospital mortality and ICU admission in an Italian cohort of COVID-19 patients, during the first pandemic wave.

Patients and Methods

Consecutive COVID-19 patients admitted at Policlinico A. Gemelli Hospital from March 1st, 2020, to September 15th, 2020, have been included in the study. All hospitalized patients over 18 years of age, with at least one nasopharyngeal and oropharyngeal swab positive for SARS-CoV-2, a chest computed tomography (CT)-scan suggestive of SARS-CoV-2-related pneumonia, a diagnosis of COVID-19 at the discharge from the hospital and with the determination of IL-6, troponin I, D-dimer, serum levels were enrolled in the study. Patient consent was waived due to organizational issues.

Levels of IL-6 were considered elevated if higher than 4.4 ng/L. Levels of troponin I were considered elevated if higher than 57 ng/L. Levels of D-dimer were considered elevated if higher than 500 ng/ml. Data on demographic characteristics, underlying comorbidities, symptoms, physical and radiological findings, and laboratory tests have been automatically extracted from electronic medical records by analyzing structured and unstructured data. In particular, the unstructured data have been extracted using artificial intelligence techniques based on text mining, developing an ontology-based Data Mart, using the Gemelli Generator Infrastructure[19,20]. Comorbidities have been defined according to the International Classification of Diseases (ICD)-11 codes. The outcomes of the analysis were in-hospital mortality and ICU admission.

Statistical Analysis

A descriptive analysis was carried out using median and interquartile range (IQR) for numerical variables and percentages for categorical variables. The distributions of the baseline characteristics of the population stratified with respect to the various outcomes were analyzed using the Chi-square or Fisher's test for categorical variables and the non-parametric Mann-Whitney Wilcoxon test for numerical variables.

An ad-hoc dashboard was then developed to analyze further any numerical values referencing blood analysis results and identify interesting cut-offs by binning the relevant values. The dashboard was developed in Python 3.8 by using the Plotly Dash framework together with Pandas and Sklearn. The user simply needed to select a single variable from a drop-down list in the user interface and the dashboard backend then ran a specifically tailored algorithm that discretized the selected continuous variable into a series of equal-sized buckets, dropped one of the buckets

(at the user's choice) to create a reference category and later transformed the buckets into dummy variables to be then used in a univariate logistical regression. A more detailed overview of the parameters available to the user is shown in Figure 1. The regression results were then further processed iteratively by analyzing the significance of each bin and then reducing the number of bins by 1, in cases that resulted in high coefficient *p*-values (with the *p*-value cut-off set to 0.05) showing non-significant separation between the buckets. This resulted in a reduction of the number of generated bins until all bins returned significant *p*-values in the logistical regression. These generated bins were then saved as cut-offs for the specific variables under analysis. The coefficients of the final regression for each variable were then converted into percentages describing the variation of outcome probability of each bin compared to the baseline values and presented to the user in conjunction with descriptive statistics on the outcome probability of the overall population, as shown in the example interface depicted it in Figure 2, to allow a quick visual comparison. Any variables presenting significant risk variations were chosen as possible candidates for further analysis.

Numerical variables discretized (following the methodology above) and statistically correlated with the outcomes were selected to fit a multivariate logistic regression model. Model performance was estimated by measuring the area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

Statistical analysis was performed with R version 3.6 (The R Foundation for Statistical Com-

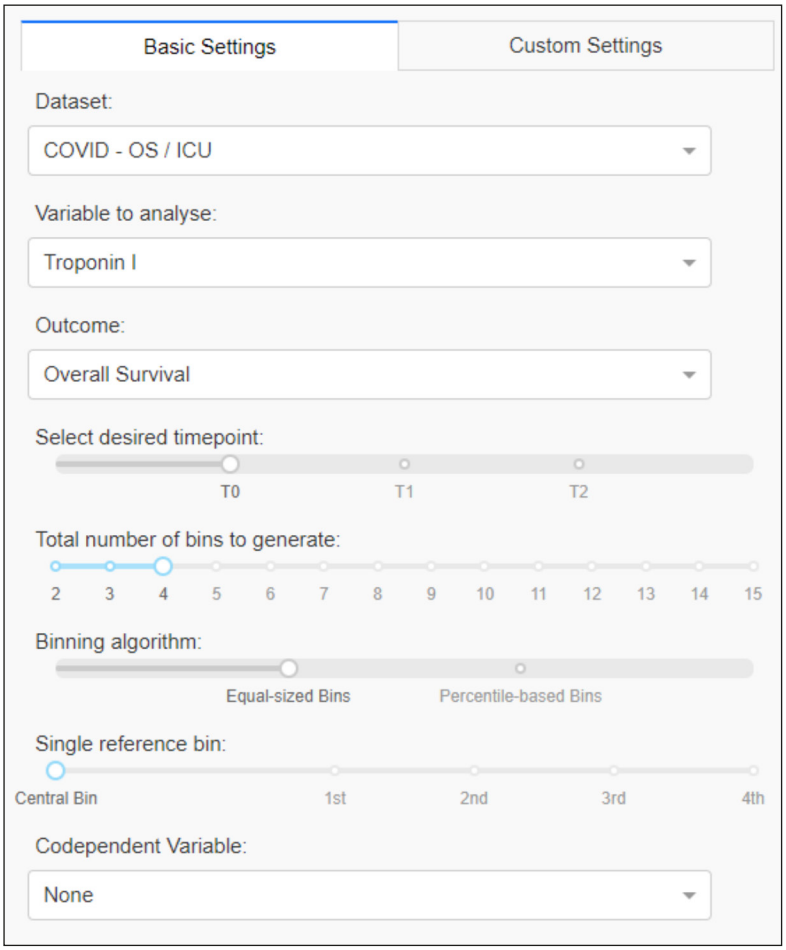


Figure 1. The figure shows the available parameters to the user. The user can select the variable to analyze, the desired outcome, the desired time point, the total number of bins to generate through the discretization algorithm, the reference bin to use during the analysis, and any eventual codependent variables to take into account.

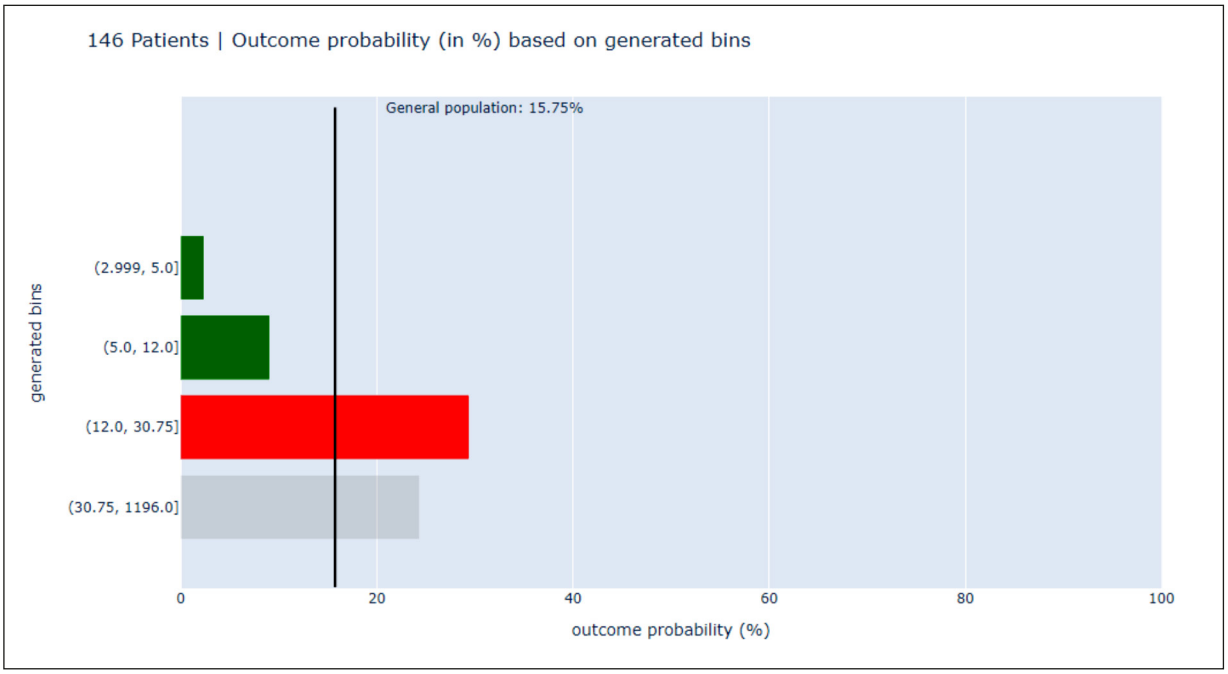


Figure 2. Example of data presented to the user. In this case, with an output of four bins selected, the algorithm shows a significant difference between bin 1, bin 2, and bin 3, while no significant difference between bin 3 and bin 4 could be found. In this case the suggested cutoff value is 12.0 and a suggestion to possibly merge bin 1 and 2 and merge bin 3 and 4. The green color stands for a lower risk in respect to the overall population, the red color stands for an increased risk compared to the overall population, gray highlights hey high p-value and the vertical black bar shows the risk probability for the overall population.

puting, Vienna, Austria) and data were stored in SAS Viya V.03.05 and accessed through R with SWAT library version 1.5.0.

Results

Overall, 146 out of 425 patients met the initial inclusion criteria and had all the selected biomarker values available. The in-hospital mortality rate was 15%, and the ICU admission rate was 41%. The mean age of the population was 69 years, and most of the patients were men. The most representative comorbidities were hypertension, myocardial infarction, cancer and diabetes. 117 (81%) patients presented fever at admission, while 54 (37%) had a cough and 86 (59%) had dyspnea. Mean IL-6, troponin I and D-dimer levels were respectively 21.5 ng/L, 12 ng/L and 1031 ng/ml. A general description of the characteristics of the cohort is shown in Table I. Compared to the patients who survived, patients who did not survive were older, had lower lymphocyte count (p=0.07), and had higher levels of IL-6 (p-value=0.04) and troponin I (p-value<0.01) (Table II). Compared to patients not admitted to the ICU, those who were admitted had lower lymphocyte count (p-value<0.01), higher levels of C-reactive protein (p-value<0.01), higher levels of IL-6 (p-value<0.01) and higher levels of troponin I (p-value<0.01) (Table III).

In-Hospital Mortality

The analysis with the dashboard showed clear indications that the binning process produced significant results in generating cut-off values for two of the three variables: IL-6, troponin I and D-dimer, as shown in Figure 3. In the case of IL-6, a clear cut-off point has been found on 15.13 ng/L, showing a risk probability of 4.08% for the first bin (2.499 ng/L-15.133 ng/L) and 22.91% for the second bin (15.133 ng/L-52.7 ng/L), in contrast to the general probability of 15.75%. A similar difference has been seen in troponin I; the first bin with a cut-off of 12.0 ng/L has shown a risk probability of 5.33% (2.999 ng/L-12 ng/L), while the second bin has shown a risk probability of 26.76% (12 ng/L-1196 ng/L), in contrast to a general probability of 15.75%. As for the last variable, D-dimer, no significant cut-off has been detected.

The IL-6 with a cut-off of 15.13 ng/L and the troponin I with a cut-off of 12 ng/L were used to fit the multivariate logistic regression model. The estimated coefficients, odds ratio (OR) and *p*-values are shown in Table IV. The AUC value of the ROC curve is 0.74.

Admission to the Intensive Care Unit

The analysis with the dashboard showed clear indications that the binning process produced significant results in generating cut-off values for two of three variables: IL-6, troponin I and D-dimer, as shown in Figure 4. In the case of IL-6, a clear cut-off point has been found on 25.65 ng/L, showing a risk probability of 26.02% for the first bin (2.499 ng/L-25.65 ng/L) and 56.16% for the second bin (25.65 ng/L-5501 ng/L), in contrast to the general probability of 41.10%. A similar difference has been seen in troponin I; the first bin with a cut-off of 12.0 ng/L has shown a risk probability of 30.66% (2.999 ng/L-12 ng/L), while the second bin has shown a risk probability of 52.11% (12 ng/L-1196 ng/L) in contrast to a general probability of 41.10%. As for the last variable, D-dimer, no significant cut-off has been detected.

The results of the multivariate logistic regression model for ICU admission prediction are shown in Table V. The corresponding value of the AUC of the ROC curve is 0.70.

Discussion

Given the spread of COVID-19 with its huge health, social, and economic implications, different works[1,11,13,21] have focused their attention on finding biomarkers useful to predict disease outcomes and support clinical decisions.

Table I. A general description of the entire cohort.

Clinical characteristics		Patients (N=146)
Demographics	Age, median (IQR)	69 (55-79)
	Male, n (%)	285 (67%)
Laboratory analysis	IL-6, ng/L, median (IQR)	21.5 (9.3-74)
	D-dimer, ng/mL, median (IQR)	1,031 (462-1,812)
	Troponin I serum levels, ng/L, median (IQR)	12 (5-31)
	White blood cell count, $\times 10^9$/L, median (IQR)	6.8 (4.9-8.8)
	Lymphocyte count, $\times 10^9$/L, median (IQR)	1.1 (0.8-1.7)
	Hemoglobin level, g/dL, median (IQR)	14 (12-15)
	Platelets, $\times 10^9$/L, median (IQR)	202 (166-261)
	Creatinine level, mg/dL, median (IQR)	0.9 (0.7-1.1)
	C-reactive protein level, mg/L, median (IQR)	55 (20-129)
	Urea nitrogen, mg/dL, median (IQR)	5.3 (3.9-6.4)
	Albumin, g/L, median (IQR)	34 (30-38)
Comorbidities	Any, n (%)	109 (75%)
	Diabetes, n (%)	29 (20%)
	Hypertension, n (%)	65 (45%)
	Lung pathology, n (%)	20 (14%)
	Heart failure, n (%)	9 (6%)
	Tumor, n (%)	31 (21%)
	Cerebrovascular disease, n (%)	2 (1.4%)
	Current or former smoker, n (%)	6 (4%)
	Arteriopathy, n (%)	2 (1.4%)
	HIV, n (%)	2 (1.4%)
	Myocardial infarction, n (%)	30 (21%)
	Autoimmune Disease, n (%)	5 (3%)
	Hepatic ulcer, n (%)	2 (1.4%)
	Neurological impairment, n (%)	4 (3%)
Symptoms	Any, n (%)	127 (87.5%)
	Cough, n (%)	54 (37%)
	Dyspnea, n (%)	86 (59%)
	Fever, n (%)	117 (81%)
	Nausea, n (%)	1 (0.68%)
	Diarrhea, n (%)	17 (12%)

Starting from the clinical characteristics of COVID-19, markers of inflammation, myocardial damage and coagulation have been correlated with COVID-19 severity[1,11,13,14].

Differences in treatments between the multiple waves of infections of SARS-CoV-2, however, have changed the characteristics of the disease. In fact, a less intense cytokine response was shown[22] in the second wave of COVID-19, compared with the first.

Our study was conducted during the first wave of COVID-19. With a machine-learning approach, we have shown that levels of IL-6 and troponin I at-hospital admission were associated with COVID-19 severity. In particular, threshold values of IL-6 and troponin I, able to predict ICU admission and mortality, have been identified.

COVID-19 is characterized by a broad spectrum of symptoms, including fever, cough, dyspnea, sore throat, anosmia, ageusia, myalgia, headache, nausea or vomiting and diarrhea. In line with previous evidence[1,23,24], the most representative symptoms at hospital admission of our cohort were fever, cough and dyspnea; moreover, most of the population was composed of men[1,25-28]. COVID-19 could manifest as a mild or severe disease, developing interstitial pneumonia, severe acute respiratory distress syndrome (ARDS) and multiorgan failure, requiring ICU admission with a high risk of death[29]. We have shown that 41% of the population required ICU admission and that the mortality rate of our cohort was 15%. Given the differences in sample size and methods used, our data, however, could not be assimilated to other studies[1,21,25-28], which observed a mortality rate going from 15% to 67% in hospitalized patients.

From 60% to 90% of the hospitalized population described in the literature presented comorbidities, that impacted COVID-19 outcomes[29]. In line with previous studies[1,30,31], hypertension, history of myocardial infarction, cancer, diabetes and lung diseases are the most representative underlying pathologies at hospital admission of our cohort. We did not, however, observe differences in comorbidities related to COVID-19 severity.

Pathogenesis of COVID-19 can be divided into two distinct phases. The first phase is characterized by virus entry into cells and proliferation. As for SARS-CoV-2, it has been demonstrated[32,33] that SARS-CoV-2 enters the cells through its spike glycoproteins by binding the angiotensin-converting enzyme 2 (ACE-2) receptor. Spike glycoproteins are composed of two subunits: S1 and S2. After the binding of S1 to ACE-2 receptor, S2 is cleaved by host cells proteases, including the serine protease transmembrane serine protease 2 (TMPRSS2), and facilitates SARS-CoV-2 fusion into the host cells[33]. ACE-2 receptors are ubiquitous. In fact, they are expressed by upper airway epithelial cells, alveolar epithelial cells, endothelial cells, myocardial tissue, kidney, liver and gastrointestinal tract and neuronal cells[17,29,34,35]. This, therefore, reflects the respiratory and extrapulmonary SARS-CoV-2 involvement[17,29,34,35]. The virus proliferation in pulmonary parenchyma causes activation of the innate immunity response[17,36]. The innate immunity response favors a cytokines cascade, that contributes to respiratory failure, until ARDS, and, in case of an abnormal response, multiorgan failure[17,36]. In particular, inflammatory cytokines production results in lung injury. It increases, in fact, pulmonary vascular permeability, enhances alveolar cell apoptosis and inflammatory cell recruitment and activates a fibrosis process in response to hypoxia[17]. The second phase of infection begins with the activation of adaptative immunity response and activation of CD4+ and CD8+ T cells, with the release of other inflammatory molecules, which enhance parenchymal lung injury[17].

Both innate and adaptative immunity response contribute to the systemic involvement of COVID-19. Moreover, the excessive inflammatory response plays a pivotal role in determining the severity of COVID-19. Elevation in levels of certain cytokines has been correlated to poor outcomes[1,37]. In particular, levels of IL-6, a mediator of humoral immune pathway, have been associated with the risk of a critical disease[38-40]. Our work has confirmed these results. Specifically, we have found a cut-off value of IL-6 able to predict COVID-19 severity. IL-6 values greater than 15.133 ng/L predicted a 22.91% risk of mortality, and levels higher than 25.65 ng/L predicted a 56.16% risk of ICU admission. These data are in line with previous works[38,41,42]. Herlod et al[38] have demonstrated that levels of IL-6 represented the best predictor of future respiratory failure, showing that IL-6 levels greater than 35 pg/mL correlated with the risk for respiratory failure[38]. Similarly, another study by Galván-Román et al[41] has shown that IL-6 levels higher than 30 pg/mL predicted the risk of mechanical ventilation. Interestingly, the early administration of an IL-6 inhibitor, in particular tocilizumab, was associated with improvement in respiratory function in these patients, while those with low levels of IL-6 treated with tocilizumab have shown a high mortality[41]. Despite the conclusion of the COVACTA

Table II. Clinical characteristics of patients who survived compared with patients who did not survive.

Clinical characteristics		Died (N=23)	Survived (N=122)	*p*-value
Demographics	Age, median (IQR)	79 (71-82)	64 (54-76)	<0.01
	Male, n (%)	15 (65%)	89 (73%)	0.6
Laboratory analysis	IL-6, ng/L, median (IQR)	44 (22-84)	21 (9-72)	0.04
	D-dimer, ng/mL, median (IQR)	1,319 (617-3,516)	978 (421-1,740)	0.2
	Troponin I serum levels, ng/L, median (IQR)	27 (13-49)	9 (4-29)	<0.01
	White blood cell count, $\times 10^9$/L, median (IQR)	7.4 (5-8.7)	6.7 (5-9)	0.9
	Lymphocyte count, $\times 10^9$/L, median (IQR)	0.9 (0.8-1.8)	1.3 (0.8-1.8)	0.07
	Hemoglobin level, g/dL, median (IQR)	13 (11-14)	14 (12.6-15)	0.06
	Platelets, $\times 10^9$/L, median (IQR)	153 (126-200)	211 (174-262)	<0.01
	Creatinine level, mg/dL, median (IQR)	0.8 (0.7-1.3)	0.9 (0.8-1.1)	0.4
	C-reactive protein level, mg/L, median (IQR)	56 (38-129)	54 (20-128)	0.8
	Urea nitrogen, mg/dL, median (IQR)	6 (4-6)	5 (4-6)	0.1
	Albumin, g/L, median (IQR)	32 (27-36)	35 (30-39)	0.03
Comorbidities	Any, n (%)	17 (77%)	92 (75%)	1
	Diabetes, n (%)	4 (18%)	25 (20%)	0.9
	Hypertension, n (%)	9 (41%)	56 (46%)	0.7
	Lung pathology, n (%)	4 (18%)	16 (13%)	0.8
	Heart failure, n (%)	1 (4.5%)	8 (6%)	1
	Tumor, n (%)	4 (18%)	27 (22%)	0.8
	Cerebrovascular disease, n (%)	1 (4.5%)	1 (1%)	0.7
	Current or former smoker, n (%)	1 (4.5%)	5 (4%)	1
	Arteriopathy, n (%)	1 (4.5%)	1 (1%)	0.7
	HIV, n (%)	1 (4.5%)	1 (1%)	0.7
	Myocardial infarction, n (%)	7 (32%)	23 (19%)	0.3
	Autoimmune Disease, n (%)	1 (4.5%)	4 (3%)	1
	Hepatic ulcer, n (%)	0	2 (1.6%)	1
	Neurological impairment, n (%)	2 (9%)	2 (1.6%)	0.2
Symptoms	Any, n (%)	19 (86%)	108 (88%)	0.6
	Cough, n (%)	6 (27%)	48 (39%)	0.3
	Dyspnea, n (%)	15 (68%)	71 (58%)	0.7
	Fever, n (%)	15 (68%)	102 (84%)	0.07
	Nausea, n (%)	0	1 (1%)	1
	Diarrhea, n (%)	0	17 (14%)	0.12

trial[43], where it has been shown that tocilizumab did not result in better clinical status or lower mortality in hospitalized COVID-19 patients, a meta-analysis[44] has demonstrated that IL-6 inhibitors reduced all-cause mortality rate. As noted in an editorial by Rubin et al[45], the different results regarding the treatment of COVID-19 with IL-6 inhibitors could be due to differences in the pathogenesis of COVID-19 among those who present a severe disease at the early stage and those who present a severe disease at the late stage[45]. Identifying a threshold value of IL-6 predictive for poor outcomes may help to identify a set of patients where the use of tocilizumab could be useful to improve a COVID-19 prognosis. Further studies, however, are needed to address this issue.

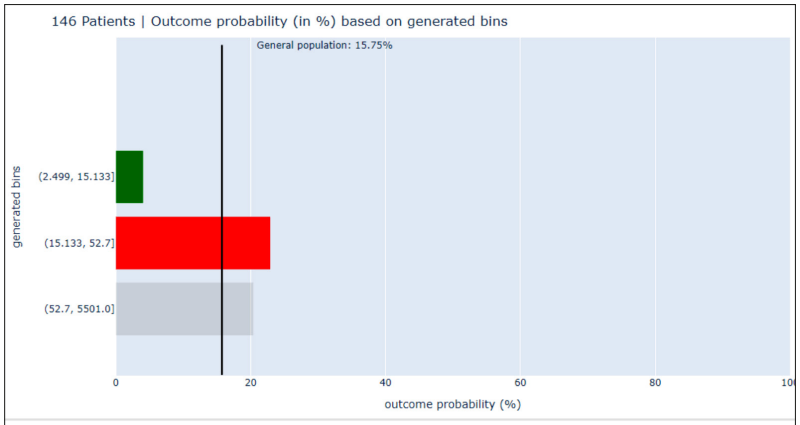
In addition to the role of IL-6, our study has identified a correlation between values of troponin I and poor prognosis. In particular, we have shown that values of troponin I higher than 12 ng/L were associated with a 26.76% risk of mortality, while levels higher than 12 ng/L were associated with a 52.11% risk of ICU admission. The threshold of 12 ng/L is below the reference value to identify heart damage; however, our results are similar to those of Qin et al[46]. In fact, in their retrospective study on 3,219 COVID-19 patients, they established cut-offs of troponin I values much lower than the normal values to determine cardiac injury. They also showed that elevation in troponin I levels coincided with elevation in neutrophil and C-reactive protein but preceded the elevation of IL-6[46]. Cardiac injury is common among COVID-19 hospitalized patients. A study by Smilowitz et al[11] has shown that cardiac damage interested 16.8% of COVID-19 patients[11].

Table III. Clinical characteristics of patients not admitted to ICU compared with patients admitted to ICU.

Clinical characteristics		Died (N=23)	Survived (N=122)	*p*-value
Demographics	Age, median (IQR)	69 (57-78)	68 (52-81)	0.9
	Male, n (%)	43	61	0.9
Laboratory analysis	IL-6, ng/L, median (IQR)	72 (19-229)	18 (8-108)	<0.01
	D-dimer, ng/mL, median (IQR)	1,319 (503-2,242)	901 (462-1,732)	0.2
	Troponin I serum levels, ng/L, median (IQR)	17 (7-40)	9 (4-29)	<0.01
	White blood cell count, $\times 10^9$/L, median (IQR)	7 (5-9)	6 (5-9)	0.2
	Lymphocyte count, $\times 10^9$/L, median (IQR)	0.9 (0.7-1.4)	1.3 (0.8-1.8)	<0.01
	Hemoglobin level, g/dL, median (IQR)	14 (12-15)	14 (12-15)	0.4
	Platelets, $\times 10^9$/L, median (IQR)	205 (173-262)	201 (161-260)	0.6
	Creatinine level, mg/dL, median (IQR)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.9
	C-reactive protein level, mg/L, median (IQR)	96 (38-155)	41 (13-108)	<0.01
	Urea nitrogen, mg/dL, median (IQR)	5 (4-6)	5 (4-6)	0.3
	Albumin, g/L, median (IQR)	33 (29-37)	35 (30-39)	0.08
Comorbidities	Any, n (%)	45 (76%)	64 (74%)	0.9
	Diabetes, n (%)	12 (20%)	17 (20%)	1
	Hypertension, n (%)	27 (46%)	38 44%)	0.9
	Lung pathology, n (%)	7 (12%)	13 (15%)	0.7
	Heart failure, n (%)	2 (3%)	7 (8%)	0.4
	Tumor, n (%)	10 (17%)	21 (24%)	0.4
	Cerebrovascular disease, n (%)	0	2 (2%)	0.6
	Current or former smoker, n (%)	1 (2%)	5 (6%)	0.4
	Arteriopathy, n (%)	1 (2%)	1 (1%)	1
	HIV, n (%)	1 (2%)	1 (1%)	1
	Myocardial infarction, n (%)	16 (27%)	14 (16%)	0.1
	Autoimmune Disease, n (%)	2 (3%)	3 (3%)	1
	Hepatic ulcer, n (%)	1 (2%)	1 (1%)	1
	Neurological impairment, n (%)	2 (3%)	2 (2%)	1
Symptoms	Any, n (%)	51 (86%)	76 (88%)	0.9
	Cough, n (%)	24 (41%)	30 (35%)	0.6
	Dyspnea, n (%)	40 (68%)	46 (53%)	0.1
	Fever, n (%)	44 (74%)	73 (85%)	0.2
	Nausea, n (%)	1 (2%)	0	1
	Diarrhea, n (%)	7 (12%)	10 (12%)	1

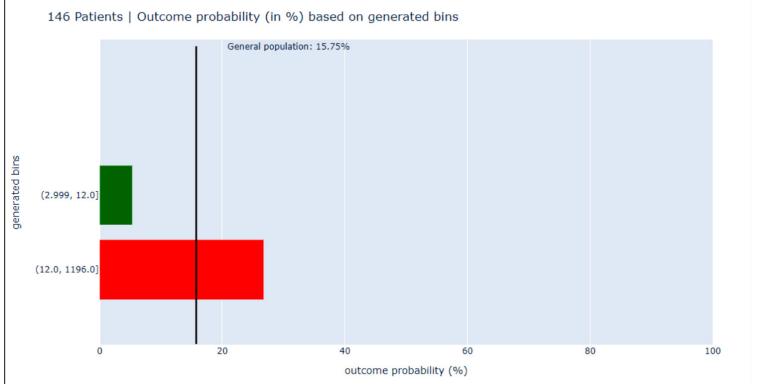
Moreover, a report by Wang et al[25] has shown that 22.2% of patients admitted to ICU had cardiac injury[25]. Elevation in troponin I levels has been associated with noninvasive and invasive ventilation[7] and a major risk of death[6,7]. Furthermore, it has been shown that heart injury in COVID-19 patients could manifest as acute myocardial infarction, cardiac arrest and arrhythmias[6,47-50]. The mechanisms of SARS-CoV-2 cardiac damage are different[17]. The first descriptions[26,51,52] of cardiomyopathies and myocarditis related to COVID-19 have led to speculation regarding the direct role of SARS-CoV-2 on the heart. No viral particles, however, have been identified in myocardial biopsies of COVID-19 patients[53]. Moreover, a study by Metkus et al[54], that compared cardiac injury in patients with ARDS COVID-19-related and ARDS non-COVID-19-related, has found that myocardial damage in severe COVID-19 is an epiphenomenon of older age, baseline comorbidities and multisystem organ injury, corroborating the hypothesis that cardiac disturbances are the result of an indirect action of SARS-CoV-2 infection[54]. In an interesting review by Abudalo et al[55], the role of glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment of COVID-19 has been described. In fact, in addition to their metabolic effects, GLP-1 receptor agonists also have anti-inflammatory and antioxidant effects, which show promise in the treatment of cardiovascular diseases. As previously mentioned, COVID-19 is characterized by an abnormal inflammatory response, and patients with diabetes and cardiovascular comorbidities are at higher risk of death. Therefore, GLP-1 receptor agonists may effectively improve the prognosis of COVID-19 patients with underlying comorbidities[55].

In particular, in COVID-19 patients, a relationship between inflammatory biomarkers and cardiac damage has been demonstrated[56]. It is



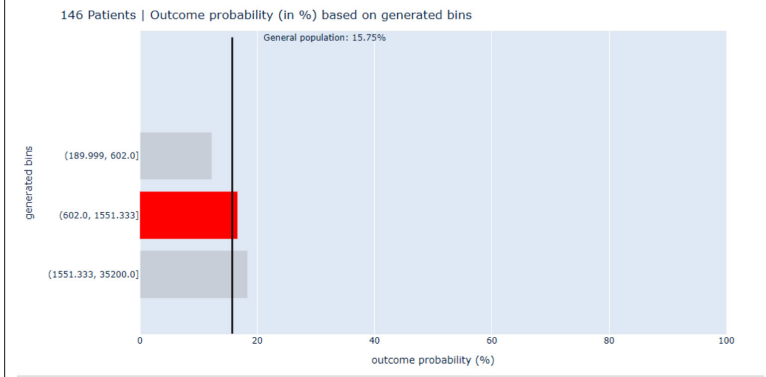
Bins	Patients in bin	% of total	Coefficients	P>|z|	Odds Ratios	Probabilities	Baseline Adjusted Coefficients	B.A. Odds Ratios	B.A. Probabilities
(2.499, 15.133]	49	33.562	-1.944	0.015	0.143	0.125	-3.157	0.043	4.082
(15.133, 52.7]	48	32.877	-1.213	0	0.297	0.229	-1.213	0.297	22.917
(52.7, 5501.0]	49	33.562	-0.148	0.764	0.862	0.463	-1.361	0.256	20.408

a)



Bins	Patients in bin	% of total	Coefficients	P>|z|	Odds Ratios	Probabilities	Baseline Adjusted Coefficients	B.A. Odds Ratios	B.A. Probabilities
(2.999, 12.0]	75	51.37	-1.87	0.001	0.154	0.134	-2.876	0.056	5.333
(12.0, 1196.0]	71	48.63	-1.007	0	0.365	0.268	-1.007	0.365	26.761

b)



Bins	Patients in bin	% of total	Coefficients	P>|z|	Odds Ratios	Probabilities	Baseline Adjusted Coefficients	B.A. Odds Ratios	B.A. Probabilities
(189.999, 602.0]	49	33.562	-0.36	0.537	0.698	0.411	-1.969	0.14	12.245
(602.0, 1551.333]	48	32.877	-1.609	0	0.2	0.167	-1.609	0.2	16.667
(1551.333, 35200.0]	49	33.562	0.118	0.826	1.125	0.529	-1.492	0.225	18.367

c)

Figure 3. Dashboard visualization of IL-6, troponin I and D-Dimer (**a**), (**b**) and (**c**), respectively, with overall in-hospital mortality as the selected outcome. Each variable is represented through the risk-projection graph and the corresponding descriptive table. **a**, IL-6 analysis: 146 available patients divided into 3 distinct bins. The separation between bin 1 and 2 is statistically significant, while bin 3 does not result in a statistically significant separation. The chosen cut-off is 15.13. The risk probability of bin 1 is 4.0%, while the risk probability of bin 2 is 22.9% (with the risk probability of the non-significant bin 3 at 20.4%). **b**, Troponin I analysis: 146 available patients divided into 2 distinct bins. The separation between bins 1 and 2 is statistically significant. The chosen cut-off is 12.0. The risk probability of bin 1 is 5.3%, while the risk probability of bin 2 is 26.7%. **c**, D-Dimer analysis: 146 available patients divided into 3 distinct bins. The separation between bins 1, 2 and 3 does not result in statistical significance. No cut-off has been chosen.

Bins	Patients in bin	% of total	Coefficients	P>|z|	Odds Ratios	Probabilities	Baseline Adjusted Coefficients	B.A. Odds Ratios	B.A. Probabilities
(2.499, 25.65]	73	50	-1.045	0	0.352	0.26	-1.045	0.352	26.027
(25.65, 5501.0]	73	50	1.292	0	3.641	0.785	0.248	1.281	56.164

Bins	Patients in bin	% of total	Coefficients	P>|z|	Odds Ratios	Probabilities	Baseline Adjusted Coefficients	B.A. Odds Ratios	B.A. Probabilities
(2.999, 12.0]	75	51.37	-0.816	0.001	0.442	0.307	-0.816	0.442	30.667
(12.0, 1196.0]	71	48.63	0.9	0.009	2.46	0.711	0.085	1.088	52.113

Figure 4. Dashboard visualization of IL-6 and troponin I (**a**) and (**b**) respectively, with transfer to ICU as the selected outcome. Each variable is represented through the risk-projection graph and the corresponding descriptive table. **a**, IL-6 analysis: 146 available patients divided into 2 distinct bins. The separation between bin 1 and 2 is statistically significant. The chosen cut-off is 25.65. The risk probability of bin 1 is 26.0%, while the risk probability of bin 2 is 56.1%. **b**, Troponin I analysis: 146 available patients divided into 2 distinct bins. The separation between bin 1 and 2 is statistically significant. The chosen cut-off is 12.0. The risk probability of bin 1 is 30.6%, while the risk probability of bin 2 is 52.1%.

Table IV. The multivariate logistic regression model for in-hospital mortality.

Variable	Coefficient	Odds ratio	*p*-value
Intercept	-3.83	0.02	<0.01
IL-6_15.13	1.43	4.2	0.05
Troponin_12	1.6	4.8	<0.01

Table V. The multivariate logistic regression model for in-hospital mortality.

Variable	Coefficient	Odds ratio	*p*-value
Intercept	-1.37	0.25	<0.01
IL-6_25.65	1.2	3.3	<0.01
Troponin_12	0.7	2.1	0.03

known that inflammatory response is correlated to endothelial dysfunction[57-59] and atherosclerosis progression[60]. A histopathologic report by Nicolai et al[61] has shown the presence of inflammatory microvascular thrombi composed of neutrophil extracellular traps associated with platelets and fibrin in the lung, kidney, and heart[61]. This evidence suggests that coagulation disturbances due to an inflammatory state can determine cardiac damage. A correlation between hypercoagulation and cardiac injury has been described[14]. Moreover, a synchronous alteration in D-dimer levels along with the progression of cardiac injury has been demonstrated[14]. Although D-dimer values were a good predictor of COVID-19[62], our study failed to show a correlation between D-dimer and COVID-19. Specifically, it lacked in identifying a cut-off value to predict COVID-19 prognosis. Interestingly, a study by Zhang et al[18] has found that patients with a fourfold elevation in D-dimer levels had a more severe form of COVID-19, identifying a cut-off of 2,000 ng/ml to predict mortality[18]. As shown in Table I, D-dimer values identified in our population at hospital admission ranged from 462 ng/ml to 1,812 ng/ml. This may justify not finding a correlation between D-dimer and COVID-19 poor outcome, suggesting even greater sensitivity of IL-6 and troponin I in predicting COVID-19 severity.

Due to the retrospective design of the study, a limitation of the study is that selection bias could not be ruled out; moreover, no validation cohort was available. However, we have just shown how our results are consistent with previous literature on the first wave of COVID-19.

Although our work is based on a small sample and analyzes data regarding the first period of the pandemic, its strength lies in the use of artificial intelligence techniques, based on data mining and text mining. Specifically, the development of a prognostic predictive model of disease outcomes, based on machine-learning methods, may be applied to different scenarios and may be useful to analyze big data and trends in different diseases. In fact, just like the COVID-19 pandemic and its various waves, the use of a flexible and fast data analysis tool can help clinical decision-making and may be helpful in developing new personalized treatment strategies.

Conclusions

In COVID-19 patients hospitalized at an Italian center during the first wave of the pandemic, IL-6 and troponin I were identified as good predictors for COVID-19 outcomes, by an analysis conducted using artificial intelligence techniques.

Machine-learning methods can help to understand the pathological mechanisms of diseases and may be useful to develop different and new therapeutic interventions. It, therefore, allows personalized treatment approaches. In our research setting, a predictive model of COVID-19 severity based on readily available biomarkers, such as IL-6 and troponin I, could help physicians to identify high-risk patient subsets with poor prognosis and conduct more aggressive and personalized treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contributions
Conceptualization, M.M.R. and F.B.; methodology, M.M.R, F.B., C.M.; formal analysis, C.M. and N.D.C.; resources, C.C, M.S. and M.M.; data curation, A.F.; writing-original draft preparation, M.M.R.; writing-review and editing, M.M.R., F.B., A.F., M.A.N., E.N. and A.L.C., supervision, G.P., M.M., A.G., A.F. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy (protocol code 4186; date of approval: May 27th, 2021).

Informed Consent
Not applicable.

Availability of Data and Materials
The datasets generated and analyzed during the current study are not publicly available as the data also forms part of an ongoing study but are available from the corresponding author upon reasonable request.

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