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Gemelli decision tree Algorithm to Predict the need for home monitoring or hospitalization of confirmed and unconfirmed COVID-19 patients (GAP-Covid19): preliminary results from a retrospective cohort study

G. VETRUGNO[1,2], P. LAURENTI[3,4], F. FRANCESCHI[5], F. FOTI[1], F. D'AMBROSIO[4], M. CICCONI[1], D.I. LA MILIA[3], M. DI PUMPO[4], E. CARINI[4], D. PASCUCCI[3,4], S. BOCCIA[3,4], R. PASTORINO[3], G. DAMIANI[3,4], F. DE-GIORGIO[2], A. OLIVA[2], N. NICOLOTTI[6], A. CAMBIERI[6], R. GHISELLINI[1], R. MURRI[7], G. SABATELLI[8], M. MUSOLINO[9], A. GASBARRINI[10]; GEMELLI-AGAINST-COVID GROUP*

[1]Risk Management Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[2]Section of Legal Medicine, Department of Health Surveillance and Bioethics, Università Cattolica del Sacro Cuore, Rome, Italy
[3]Department of Woman and Child Health and Public Health – Public Health Area, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[4]Section of Hygiene, University Department of Health Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy
[5]Department of Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Università Cattolica del Sacro Cuore, Rome, Italy
[6]Medical Management, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[7]Institute of Infectious Diseases, Fondazione Policlinico Universitario A. Gemelli IRCCS, Universitá Cattolica del Sacro Cuore, Rome, Italy
[8]Latium Regional Clinical Risk Management Unit, Rome, Italy
[9]Rieti Healthcare Department, Rieti, Italy
[10]Internal Medicine, Gastroenterology and Hepatology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Institute of Special Medical Pathology and Medical Semeiotics, Università Cattolica del Sacro Cuore, Rome, Italy

G. Vetrugno and P. Laurenti contributed equally to this work

Abstract. – OBJECTIVE: To develop a deep learning-based decision tree for the primary care setting, to stratify adult patients with confirmed and unconfirmed coronavirus disease 2019 (COVID-19), and to predict the need for hospitalization or home monitoring.

PATIENTS AND METHODS: We performed a retrospective cohort study on data from patients admitted to a COVID hospital in Rome, Italy, between 5 March 2020 and 5 June 2020. A confirmed case was defined as a patient with a positive nasopharyngeal RT-PCR test result, while an unconfirmed case had negative results on repeated swabs. Patients' medical history and clinical, laboratory and radiological findings were collected, and the dataset was used to train a predictive model for COVID-19 severity.

RESULTS: Data of 198 patients were included in the study. Twenty-eight (14.14%) had mild disease, 62 (31.31%) had moderate disease, 64 (32.32%) had severe disease, and 44 (22.22%) had critical disease. The G^2 value assessed the contribution of each collected value to decision tree building. On this basis, SpO2 (%) with a cut point at 92 was chosen for the optimal first split. Therefore, the decision tree was built using values maximizing G^2 and LogWorth. After the tree was built, the correspondence between inputs and outcomes was validated.

CONCLUSIONS: We developed a machine learning-based tool that is easy to understand and apply. It provides good discrimination in stratifying confirmed and unconfirmed COVID-19 patients with different prognoses in every con-

Corresponding Author: Federica Foti, MD; e-mail: fotifederica89@gmail.com

text. Our tool might allow general practitioners visiting patients at home to decide whether the patient needs to be hospitalized.

Key Words:
COVID-19, SARS-CoV-2, General practitioners, Primary health care, Machine learning, Community-based care.

***Gemelli-Against-Covid Group, Rome, Italy**
V. Abbate, N. Acampora, G. Addolorato, F. Agostini, M.E. Ainora, K. Akacha, E. Amato, F. Andreani, G. Andriollo, M.G. Annetta, B.E. Annicchiarico, M. Antonelli, G. Antonucci, G.M. Anzellotti, A. Armuzzi, F. Baldi, I. Barattucci, C. Barillaro, F. Barone, R.D.A. Bellantone, A. Bellieni, G. Bello, A. Benicchi, F. Benvenuto, L. Berardini, F. Berloco, R. Bernabei, A. Bianchi, D.G. Biasucci, L.M. Biasucci, S. Bibbò, A. Bini, A. Bisanti, F. Biscetti, M.G. Bocci, N. Bonadia, F. Bongiovanni, A. Borghetti, G. Bosco, S. Bosello, V. Bove, G. Bramato, V. Brandi, T. Bruni, C. Bruno, D. Bruno, M.C. Bungaro, A. Buonomo, L. Burzo, A. Calabrese, M.R. Calvello, C. Cambise, G. Cammà, M. Candelli, G. Canistro, A. Cantanale, G. Capalbo, L. Capaldi, E. Capone, E. Capristo, L. Carbone, S. Cardone, S. Carelli, A. Carfì, A. Carnicelli, C. Caruso, F.A. Casciaro, L. Catalano, P. Cattani, R. Cauda, A.L. Cecchini, L. Cerrito, M. Cesarano, A. Chiarito, R. Cianci, S. Cicchinelli, A. Ciccullo, M. Cicetti, F. Ciciarello, A. Cingolani, M.C. Cipriani, M.L. Consalvo, G. Coppola, G.M. Corbo, A. Corsello, F. Costante, M. Costanzi, M. Covino, D. Crupi, S.L. Cutuli, S. D'Addio, A. D'Alessandro, M.E. D'Alfonso, E. D'Angelo, F. D'Aversa, F. Damiano, G.M. De Berardinis, T. De Cunzo, D.K. De Gaetano, G. De Luca, G. De Matteis, G. De Pascale, P. De Santis, M. De Siena, F. De Vito, V. Del Gatto, P. Del Giacomo, F. Del Zompo, A.M. Dell'Anna, D. Della Polla, L. Di Gialleonardo, S. Di Giambenedetto, R. Di Luca, L. Di Maurizio, M. Di Muro, A. Dusina, D. Eleuteri, A. Esperide, D. Fachechi, D. Faliero, C. Falsiroli, M. Fantoni, A. Fedele, D. Feliciani, C. Ferrante, G. Ferrone, R. Festa, M.C. Fiore, A. Flex, E. Forte, A. Francesconi, L. Franza, B. Funaro, M. Fuorlo, D. Fusco, M. Gabrielli, E. Gaetani, C. Galletta, A. Gallo, G. Gambassi, M. Garcovich, I. Gasparrini, S. Gelli, A. Giampietro, L. Gigante, G. Giuliano, G. Giuliano, B. Giupponi, E. Gremese, D.L. Grieco, M. Guerrera, V. Guglielmi, C. Guidone, A. Gullì, A. Iaconelli, A. Iafrati, G. Ianiro, A. Iaquinta, M. Impagnatiello, R. Inchingolo, E. Intini, R. Iorio, I.M. Izzi, T. Jovanovic, C. Kadhim, R. La Macchia, F. Landi, G. Landi, R. Landi, R. Landolfi, M. Leo, P.M. Leone, L. Levantesi, A. Liguori, R. Liperoti, M.M. Lizzio, M.R. Lo Monaco, P. Locantore, F. Lombardi, G. Lombardi, L. Lopetuso, V. Loria, A.R. Losito, B.P.L. Mothanje, F. Macagno, N. Macerola, G. Maggi, G. Maiuro, F. Mancarella, F. Mangiola, A. Manno, D. Marchesini, G.M. Maresca, G. Marrone, I. Martis, A.M. Martone, E. Marzetti, C. Mattana, M.V. Matteo, R. Maviglia, A. Mazzarella, C. Memoli, L. Miele, A. Migneco, I. Mignini, A. Milani, D. Milardi, M. Montalto, G. Montemurro, F. Monti, L. Montini, T.C. Morena, V. Mora, C. Morretta, D. Moschese, C.A. Murace, M. Murdolo, M. Napoli, E. Nardella, G. Natalello, D. Natalini, S.M. Navarra, A. Nesci, A. Nicoletti, R. Nicoletti, T.F. Nicoletti, R. Nicolò, E.C. Nista, E. Nuzzo, M. Oggiano, V. Ojetti, F. Cosimo Pagano, G. Paiano, C. Pais, F. Pallavicini, A. Palombo, F. Paolillo, A. Papa, D. Papanice, L.G. Papparella, M. Paratore, G. Parrinello, G. Pasciuto, P. Pasculli, G. Pecorini, S. Perniola, E. Pero, L. Petricca, M. Petrucci, C. Picarelli, A. Piccioni, A. Piccolo, E. Piervincenzi, G. Pignataro, R. Pignataro, G. Pintaudi, L. Pisapia, M. Pizzoferrato, F. Pizzolante, R. Pola, C. Policola, M. Pompili, F. Pontecorvi, V. Pontecorvi, F.R. Ponziani, V. Popolla, E. Porceddu, A. Porfidia, L.M. Porro, A. Potenza, F. Pozzana, G. Privitera, D. Pugliese, G. Pulcini, S. Racco, F. Raffaelli, V. Ramunno, G.L. Rapaccini, L. Richeldi, E. Rinninella, S. Rocchi, B. Romanò, S. Romano, F. Rosa, L. Rossi, R. Rossi, E. Rossini, E. Rota, F. Rovedi, C. Rubino, G. Rumi, A. Russo, L. Sabia, A. Salerno, M. Sali, S. Salini, L. Salvatore, D. Samori, C. Sandroni, M. Sanguinetti, R. Santangelo, L. Santarelli, P. Santini, D. Santolamazza, A. Santoliquido, F. Santopaolo, M.C. Santoro, F. Sardeo, C. Sarnari, A. Saviano, L. Saviano, F. Scaldaferri, R. Scarascia, T. Schepis, F. Schiavello, G. Scoppettuolo, D. Sedda, F. Sessa, L. Sestito, C. Settanni, M. Siciliano, V. Siciliano, R. Sicuranza, B. Simeoni, J. Simonetti, A. Smargiassi, P.M. Soave, C. Sonnino, D. Staiti, C. Stella, L. Stella, E. Stival, E. Taddei, R. Talerico, E. Tamburello, E. Tamburrini, E.S. Tanzarella, E. Tarascio, C. Tarli, A. Tersali, P. Tilli, J. Timpano, E. Torelli, F. Torrini, M. Tosato, A. Tosoni, L. Tricoli, M. Tritto, M. Tumbarello, A.M. Tummolo, M.S. Vallecoccia, F. Valletta, F. Varone, F. Vassalli, G. Ventura, L. Verardi, L. Vetrone, E. Visconti, F. Visconti, A. Viviani, R. Zaccaria, C. Zaccone, C. Zanza, L. Zelano, L. Zileri Dal Verme, G. Zuccalà.

Introduction

Machine learning techniques find patterns to allow prediction from raw data and are increasingly used in medicine because of their high accuracy. Decisional trees provide a science-based tool that is particularly appropriate to apply the principles of personalized medicine, as previously highlighted[1], and can be immediately applied for clinical decision-making.

Machine learning was previously applied during the coronavirus disease 19 (COVID-19) emergency to detect vaccines/medicines and to predict respiratory failure in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) patients[1-3]. However, to our knowledge, no study has investigated the need for hospitalization of COVID-19 patients.

Since the beginning of the pandemic, several publications have shown clinical and laboratory features associated with COVID-19 severity[4,5], which are categorized as mild, moderate, severe and critical.

Starting from these definitions, we assumed that mild and moderate types could be monitored and treated at home, while severe and critical types require mechanical ventilation, close follow-up and, therefore, hospitalization.

The aim of our study was to stratify COVID-19 patients through a machine-learning technique to accurately and efficiently decide between home monitoring and hospitalization in a primary care setting before Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test results of nasal and pharyngeal swab specimens are available.

Patients and Methods

For our retrospective cohort study, we analysed data of confirmed and unconfirmed COVID-19 patients[6] admitted to COVID-19 wards of the Fondazione Policlinico A. Gemelli IRCCS, which is a tertiary care university hospital in Rome, Italy, between 5 March 2020 and 5 June 2020. At this aim, we extracted demographic data, clinical symptoms, comorbidities, laboratory and radiological findings (i.e., chest X-rays of the first 24 hours after admission) from medical records.

All patients admitted to the Emergency Department (ED) complaining of fever or other acute respiratory symptoms, such as dyspnoea during the study period were considered for recruitment. Before admission to a hospital ward, all patients had undergone nasal and oropharyngeal swabs for the detection of one or more SARS-CoV-2-specific nucleic acid targets according to the protocol established by the WHO[7]. Patients with negative samples were retested after 48-72 h. The inclusion criteria were fever and/or respiratory symptoms, regardless of RT-PCR results and chest X-ray pattern, and age ≥18 years old. Pregnancy was an exclusion criterion. The Ethics Committee approved this research (Prot. ID 3775).

Fever was defined as axillary temperature equal to or higher than 37.5°C at the time of ED admission or a recent referred episode. The presence of immunodeficiency was defined as primitive or secondary due to treatment for cancer. Chest X-ray showing any alteration attributable to phlogosis, or in which phlogosis could not be explained with the presence of other conditions, was considered positive.

A confirmed COVID-19 case was based on positive RT-PCR results on nasopharyngeal swabs[8], and an unconfirmed case was based on RT-PCR negative results for 2 days or longer (i.e., when the last swab sample was obtained)[6].

Every patient was categorized as mild, moderate, severe or critical according to illness severity[9]. Patients with mild disease were defined as symptomatic patients without evidence of viral pneumonia or hypoxia. Moderate disease patients were defined as patients with clinical signs of mild pneumonia, including SpO_2 <90% on room air. Patients with severe disease were defined as patients with clinical signs of pneumonia (such as dyspnoea) plus one of the following symptoms: respiratory rate >30 breaths/min, severe respiratory distress, SpO_2 < 90% on room air or partial pressure of arterial oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300 mmHg. Critically diseased patients were defined as patients with acute respiratory distress syndrome (ARDS), multiple organ failure, sepsis or septic shock.

Statistical Analysis

In our study, decision tree analysis[10,11] was performed to predict the relationship between the values of certain variables, called the predictors (or factors), and their response values (the "target"). A splitting algorithm recursively chooses a predictor. If the predictor is numeric, a threshold is chosen, and each patient is either assigned in the subset "value of the variable < threshold" or in the subset "value of the variable ≥ threshold". If the predictor is categorical, a threshold, which is a partition of the values of the predictor, is used. The splitting pair – variable and threshold/partition – are chosen to maximize the explained variability for target values, which can be obtained by splitting parent sets into more homogeneous subsets. Each subset obtained corresponds to a particular "rule" (which summarizes all the splitting criteria and leads to that subset). Each rule also gives the calculated probability for each value of the target value.

By means of this analysis, a predictive model for outcome observations (mild, moderate, severe and critical) could be obtained from the observation of the input variables considered.

In the present analysis, factors were either continuous or categorical. The outcome variable represents the target for our model. Since it is a categorical variable, the decision tree can be considered a "classification tree". The tree is obtained by splitting in a recursive process the original data (the "root").

The initial condition is represented in Figure 1, where all the cases considered are represented as dots partitioned according to their outcome value.

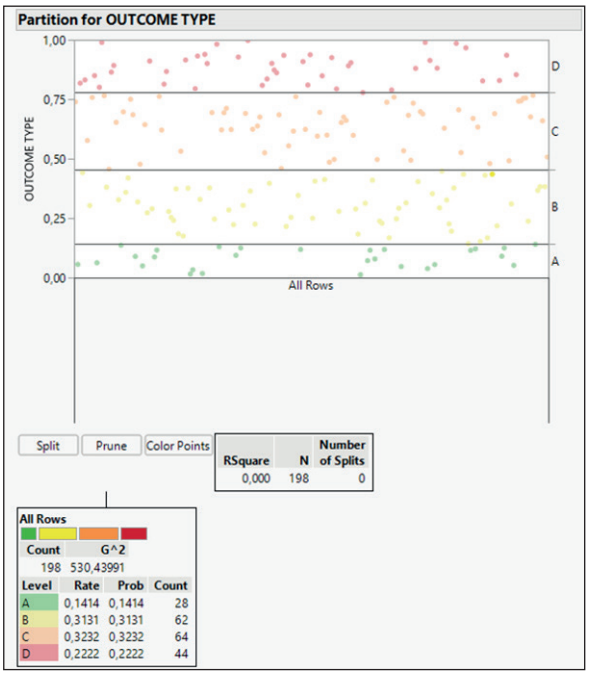

Figure 1. All the cases are represented as dots partitioned according to their outcome value. Outcome level "A" (green) represents outcome = mild; level "B" (yellow) has outcome = moderate; level "C" (orange) represents outcome = severe; level D (red) has outcome = critical.

Since no classification split is applied (number of splits = 0), RSquare is 0. The term "rate" stands for the proportion of observations for each target level. The term "Prob" is the predicted probability initially given by the rate value.

The G^2 value (likelihood ratio chi-square) is proportional to the entropy associated with the classification level. Entropy measures randomness, and its value is maximum when no split is applied. If only a level for the target value is present at a certain level in splitting, $G^2 = 0$ (perfect fit, no value in trying to split further, so entropy = 0).

When the first split is required, all the variables are characterized by JMP® software, used in the analysis, to identify the most effective split from the predictive point of view. To obtain the optimal splitting, the splitting variable must be chosen together with the most suitable "cut point". The optimal pair (variable, cut point) is identified as the one that maximizes the LogWorth indicator[12]. Usually, the G^2 value for the optimal variable results is maximized since it represents the decrement in total entropic value G^2 obtained through splitting.

Results

During the study period, 1583 patients were admitted to the ED, of whom 198 hospitalized patients were finally included to build our decision tree. The majority were male (127; 64.1%), with a mean age of 68.73 (25-103) years. Half of them (n=99, 50%) were positive for SARS-CoV-2 after a nasopharyngeal RT-PCR test, and half were negative even after repeated testing.

At presentation, 175 (88.3%) patients had fever, 113 (57.0%) dyspnoea, 91 (45.9%) dry cough, 32 (16.2%) gastrointestinal symptoms, 28 (14.1%) asthenia, and 17 (8.6%) respiratory symptoms.

Comorbidities were distributed as follows: 100 (50.5%) patients had hypertension, 65 (32.8%) cardio-cerebrovascular disease, 37 (18.6%) chronic obstructive pulmonary disease (COPD), 37 (18.6%) diabetes, 31 (15.6%) malignant neoplasm, 23 (11.6%) chronic kidney disease, 14 (7.0%) immunosuppression and 10 (5.0%) chronic liver disease. Twenty-three (11.6%) patients were current smokers or had a history of smoking. Laboratory characteristics are shown in Table I.

One hundred forty-eight (74.7%) patients had a chest X-ray suggestive of a phlogistic pattern. Regarding SARS-CoV-2 severity, 28 (n=14.14%) patients had mild disease, 62 (31.31%) had moderate disease, 64 (32.32%) had severe disease, and 44 (22.22%) had critical disease (Figure 2).

The contribution to the decision tree building was calculated for each value, as shown in Figure 3. Some of the collected values, such as age and sex, were excluded. The best splitting variable for the first split was SpO2%, with a cut point = 92. The first split is represented in Figure 4 and 5. SpO_2 (%) with a cut point at 92 was chosen for the optimal first split since both G^2 and LogWorth were maximized. For each candidate, the G^2 value represents the overall entropy reduction attainable, as shown in the next figure considering the sum of G^2 values for the split sets ("left" and "right"):

$G^2_{candidate} = G^2_{parent} - (G^2_{left} + G^2_{right})$. By iterating this procedure, the trees in Figures 6A-F were obtained. After the tree was built, the correspondence between inputs and outcomes was validated, as shown in Figure 7. Table II shows the confusion matrix with entry values concentrated around the main diagonal because, by definition, B and C outcomes or A and B outcomes are closer to each other than B and D or A and D. However, in the chosen tree algorithms, no proximity criterion is applied and instead it represents

Table I. Laboratory characteristics of the 198 patients during the first 24 h after admission (some laboratory values are missing).

Factor	Min value	Mean value	Max value
Creatine kinase	15	177.0	3615
Creatinine	0.41	1.405	15.72
CRP-C-reactive protein	0.5	97.83	513.7
Ferritin	19	452.4	1775
Hemoglobin	7	13.13	19.5
IL-6 (interleukin)	1.8	54.02	465.3
INR	0.91	1.206	8.06
LDH-Lactate Dehydrogenase	92	367.6	1618
Lymphocytes	0.18	1.477	36.23
Lymphocytes %	1.1	16.22	87.4
Procalcitonin	0.05	1.702	75
Platelets	47	249.3	994
Potassium	3	4.262	7.6
Sodium	123	138.3	156
SpO_2 (%)	6	91.74	100
Total bilirubin	0.2	0.8724	7.8
Alanine aminotransferase alt (GPT)	5	37.11	609

a result. Moreover, in the data model, the outcome variable (the target) is considered a categorical variable and not a numerical or ordinal variable, for which a proximity criterion could be suggested.

Discussion

We aimed to develop a tool for the primary care setting to allow community-based general practitioners to decide whether a patient needs to be hospitalized. The selected time interval of the study (between 5 March 2020 and 5 June 2020) allowed us to compare the ED of the hospital during the lockdown period with primary care in the current period.

Patients with mild or moderate disease were discharged without receiving mechanical ventilation or were admitted to intensive care units (ICUs). Patients with critical disease usually need intensive support and occasionally have a fatal outcome. Patients with severe disease have a clinical history that was difficult to monitor at home.

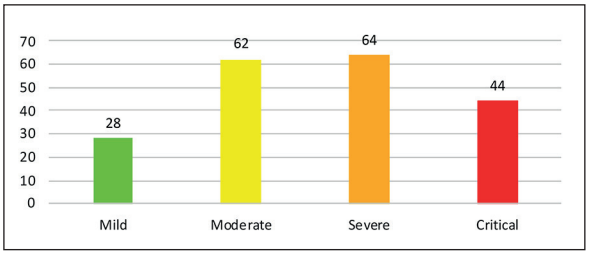

Figure 2. Outcome distribution.

We built a decisional tree model in which relationships between clinical-instrumental predictors and outcomes became stronger, and their prediction ability was converted into a decision-making tool. Colours were used with the aim of mimicking risk scales: when the tree was coloured green or yellow, the patients did not require hospitalization.

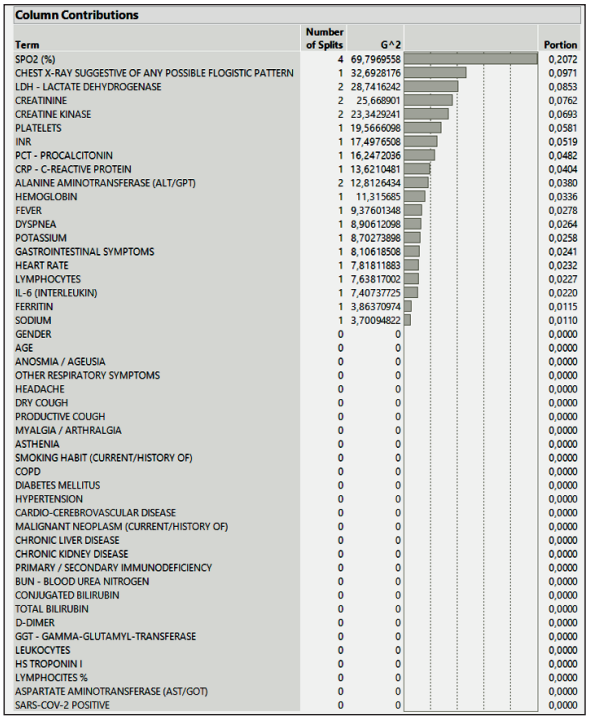

Figure 3. Contribution of each candidate assessed by G^2 value.

Candidates

Term	Candidate G^2		LogWorth	Cut Point
GENDER	3,35396158		0,468262453	F
AGE	14,20783534		1,244780209	60
ANOSMIA / AGEUSIA	6,16772991		0,984100122	0
FEVER	9,68830079		1,669377818	0
SPO2 (%)	43,31128142	*	8,909234075	92
HEART RATE	8,95759749		0,359179177	98
OTHER RESPIRATORY SYMPTOMS	4,36607898		0,648684351	0
HEADACHE	3,32279203		0,462832210	0
DRY COUGH	4,13273043		0,606453339	0
PRODUCTIVE COUGH	4,34029501		0,644001530	0
DYSPNEA	6,78412715		1,101789951	0
GASTROINTESTINAL SYMPTOMS	0,93438960		0,087713169	0
MYALGIA / ARTHRALGIA	1,16792129		0,118782051	0
ASTHENIA	0,19062505		0,009178114	0
SMOKING HABIT (CURRENT/HISTORY OF)	7,44112007		0,799678735	,0
COPD	4,86224694		0,378206196	,0
DIABETES MELLITUS	0,69337132		0,058110109	0
HYPERTENSION	6,44394601		1,036686654	0
CARDIO-CEREBROVASCULAR DISEASE	8,03772518		1,344492378	0
MALIGNANT NEOPLASM (CURRENT/HISTORY OF)	2,79313957		0,124777223	,0
CHRONIC LIVER DISEASE	5,56660405		0,484230812	0
CHRONIC KIDNEY DISEASE	1,38874754		0,024635858	0
PRIMARY / SECONDARY IMMUNODEFICIENCY	5,33707541		0,448803705	0
CHEST X-RAY SUGGESTIVE OF ANY POSSIBLE FLOGISTIC PATTERN	38,39391689		7,983129131	0
BUN - BLOOD UREA NITROGEN	15,60705031		1,545450352	15
CONJUGATED BILIRUBIN	8,19651663		0,609907922	0,4
TOTAL BILIRUBIN	8,76678839		0,444124655	0,3
CREATINE KINASE	28,53999633		4,402589082	280
CREATININE	11,64932661		0,594259988	1,27
D-DIMER	8,45489932		0,309869440	392
HEMOGLOBIN	12,27064517		0,822733143	13,3
FERRITIN	3,59957348		0,015470990	265
GGT - GAMMA-GLUTAMYL-TRANSFERASE	10,40169883		0,799308989	19
LEUKOCYTES	9,33240806		0,170652054	3,21
HS TROPONIN I	11,63828230		0,902806790	86
IL-6 (INTERLEUKIN)	8,65685602		0,401965828	22,7
INR	10,09353706		0,549289455	1,02
LDH - LACTATE DEHYDROGENASE	33,56641748		5,755115804	245
LYMPHOCYTES	13,98696927		0,952656409	1,34
LYMPHOCITES %	17,51839175		1,538907139	22,1
PLATELETS	7,92738328		0,108872428	205
POTASSIUM	7,83613275		0,301397944	6,4
PCT - PROCALCITONIN	20,91212965		2,745984535	0,14
CRP - C-REACTIVE PROTEIN	28,29733538		4,115633361	72,5
SODIUM	13,28160618		1,171266816	148
ALANINE AMINOTRANSFERASE (ALT/GPT)	13,37188080		1,034079801	18
ASPARTATE AMINOTRANSFERASE (AST/GOT)	11,92543252		0,909304144	22
SARS-COV-2 POSITIVE	4,83459527		0,734433751	0

Figure 4. G^2, LogWorth and cut point are shown for each candidate.

This model is different from others already published because of patient extraction (COVID-19 negativity at RT-PCR test was not considered an exclusion criterion, as is usual in previous studies). Moreover, the model is easy to understand and apply, allowing rapid evaluation in every context, considering that general practitioners need to stratify patients before results are available.

During the first wave of the pandemic, general practitioners were overwhelmed due to the lack of adequate personal protective equipment[13]. Currently, they should regain their function as playmakers in the management of suspected cases of COVID-19 in the primary care setting[14,15] with the aim of reducing unnecessary hospital admissions and containing the risk of ED and ICU overcrowding. In fact, when lockdown measures were adopted at the beginning, the exponential growth of COVID-19 patients was taken over by the hospital network, which required resource redistribution and reorganization of some care chains in COVID-19 units. Questions have been raised regarding whether the saturation of health services is an inevitable consequence of the pandemic[16]. Some authors[17] have emphasized the role of hygienic and behavioral measures, such as mask wearing, physical distancing and hand hygiene, to limit the spread of COVID-19 and support the health system in modulating offerings. Others[18] have stressed the importance of contact tracing as a strategy to eliminate the virus, disseminating diagnostic tests to isolate cases in a timely manner. However, these solutions may not be sufficient if not combined with other solutions that aim to relieve the pressure on hospitals given that the lack or delay of non-COVID patient treatment may have short- and medium-term effects on their survival[19,20]. For this purpose, new strategies to optimize home-based COVID-19 patient management were designed, including end-of-life support for patients unlikely to benefit from intensive care[21]. In this regard, several models predicting the need for ICU assistance or mortality

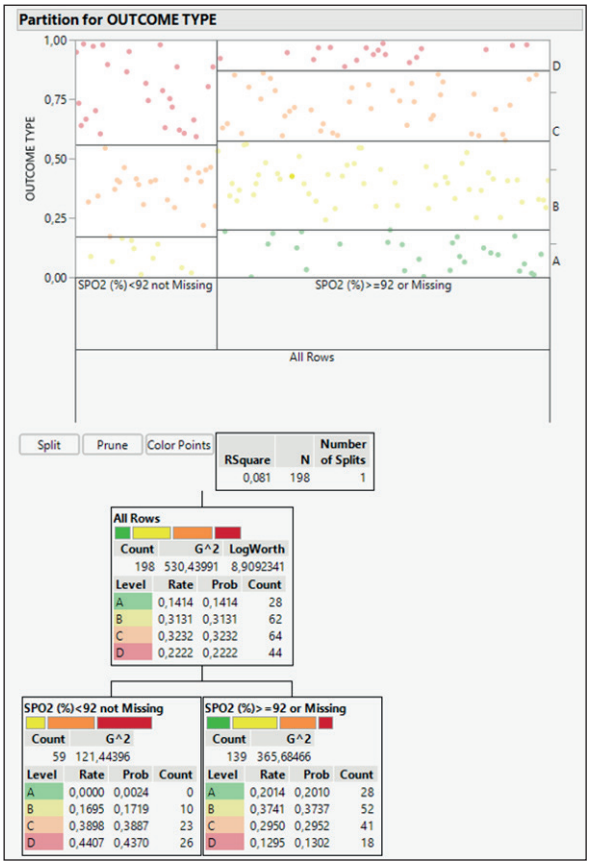

Figure 5. Sum of G^2 values for the split sets and view of the optimal first split using SpO_2 with a cut-off point of 92 (A= mild outcome; B= moderate outcome; C= severe outcome; D= critical outcome).

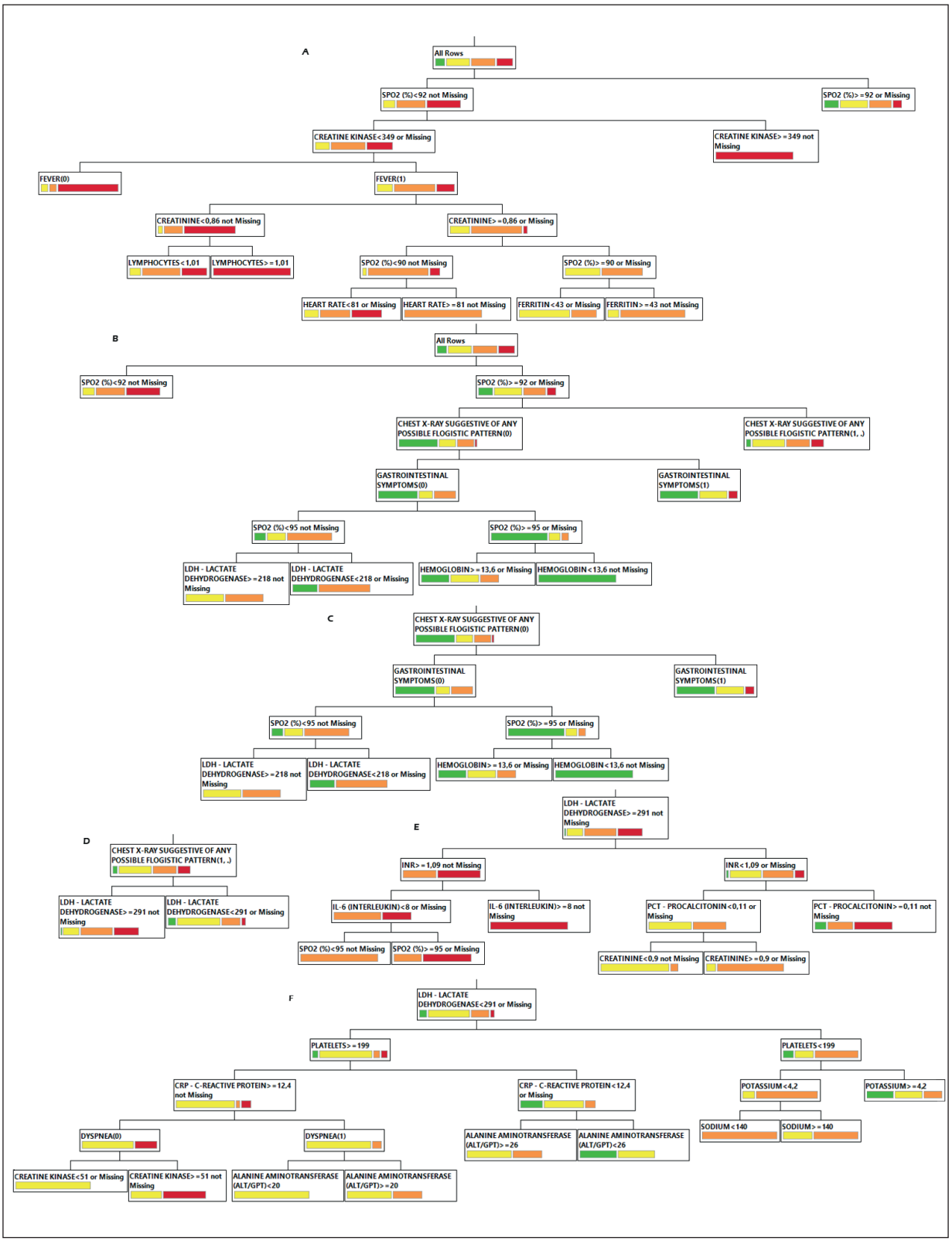

Figure 6. Decision tree split for better view (Panel A: As if $SpO_2 < 92$; Panel B: As if $SpO_2 \geq 92$; Panel C: As if $SpO_2 \geq 92$ and CHEST X-RAY negative; Panel D: As if $SpO_2 \geq 92$ and CHEST X-RAY positive; Panel E: As if $SpO_2 \geq 92$, CHEST X-RAY positive and LDH > 291; Panel F: As if $SpO_2 \geq 92$, CHEST X-RAY positive and LDH < 291).

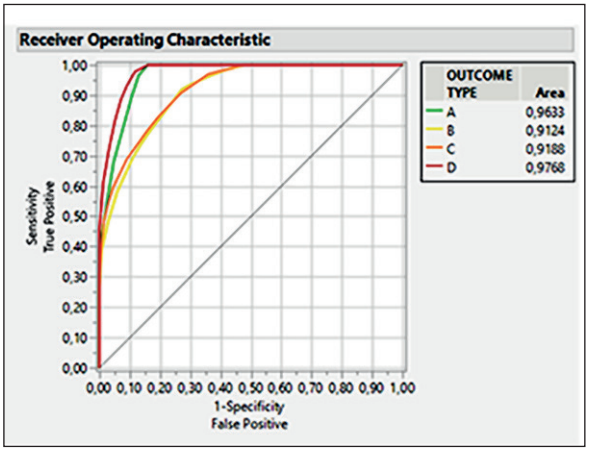

Figure 7. Receiver operating characteristic (ROC) curves (outcome type A= mild; B= moderate; C= severe; D= critical).

have been developed[22-24]. However, as the latest version of a living systematic review published in BMJ recently highlighted, all 232 prediction models for the diagnosis and prognosis of COVID-19 "remain at high or unclear risk of bias" and still need to be validated[25].

Our study has some limitations. First, the dataset was based on a relatively small, single hospital-based cohort. In this regard, this can be seen as a preliminary study with the aim of developing a new approach. The dataset considered here can represent a training environment for the predictive model, which could be enlarged in a second step of the work by considering a larger population of patients, as mentioned above, and conducting model testing and validation. Therefore, a confirmatory study is recommended and will be our next step. Second, the variables used were those typically obtainable outside the hospital setting, but analytic methods may not be the same in every setting.

Despite these limitations, the present prediction model is strong because the entry values in the confusion matrix (Table II) are concentrated close to the main diagonal, as described in the results. Moreover, the RT-PCR result was not considered in the decision tree, suggesting that testing is not an influencing outcome. These data are even more important if we hypothesize that COVID-19 outbreaks could coincide with seasonal influenza and other viruses causing respiratory diseases, which could be difficult to differentiate because of their similar clinical features (fever, fatigue, dry cough, and expiratory dyspnea). Further studies should address this issue.

Conclusions

To sum up, we developed a machine learning-based tool to predict the need for hospitalization and to assist general practitioners in the primary care setting. Our tool might have potentially important implications for the optimization of quality of care in terms of hospitalization appropriateness, saving resources and decreasing pressure on hospitals, which continue to have a heavy impact on managing the pandemic correctly.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Table II. Most likely outcome in case of prediction error (outcome type A = mild; B = moderate; C = severe; D = critical).

	Most likely outcome in prediction				
Outcome	**A**	**B**	**C**	**D**	**Total**
A	**15**	**10**	**2**	**1**	28
B	**3**	**46**	**9**	**4**	62
C		**12**	**46**	**6**	64
D	**1**		**4**	**39**	44
Total	19	68	61	50	198

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