fortune Journals

Research Article

ARCHIVES OF
CLINICAL AND
BIOMEDICAL RESEARCH

ISSN: 2572-5017

Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study

Michel Ducher[1], Christelle Elias[2,3], Nans Florens[4], Maelys Granal[5], Mitra Saadatian-Elahi[2,3], Laetitia Henaff[2,3], Philippe Vanhems[2,3], Jean-Pierre Fauvel[4,5]*

Abstract

Purpose: Propose a carefully developed prediction clinical tool to predict unfavourable outcome at admission of a SARS-CoV2–infected patient.

Methods: This study is a *post-hoc* analysis of the NOSO-COR study, a multicentre prospective, observational study. All patients infected by SARS-CoV2 hospitalised in the Lyon-University hospitals from 8-March-2020 to 2-June-2020 were included. The database was split into a learning dataset (80%) and a validation dataset (20%). The primary composite outcome was the need for mechanical ventilation and/or transfer to intensive care unit and/or death within 21 days of admission. The PREDICT-COVID risk prediction tool was developed using a Bayesian network.

Results: Data from 823 patients were analysed: age 70.6±16.9 years; BMI 26.7±5.4 kg/m2. Out of the 44 recorded variables, 11 that were the most linked to the primary outcome criteria were retained to develop the risk prediction tool. The primary composite endpoint was met by 36.5% of patients and 15.9% of patients died. The 5 most informative predictors were: C-Reactive-Protein, neutrophil-to-lymphocyte ratio, aspartate transaminase, shortness of breath, and prothrombin time. The final optimised models that used 11 variables had a mean±SD area under the receiver operating characteristic curve of 0.76±0.06, sensitivity of 55.5±7.0%, specificity of 78.6±4.6%, for the prediction of the primary outcome in patients hospitalised for COVID-19. The performance of the PREDICT-COVID prediction tool to predict the primary outcome of the validation dataset had accuracy of 77.6%.

Conclusions: The PREDICT-COVID prediction tool that uses 11 routinely determined variables to predict an unfavourable course at admission for COVID-19 had satisfactory performance.

Keywords: Bayesian Network; Covid-19; Epidemiology; Mortality; Risk Prediction; Sars-cov-2.

Abbreviations: Alanine Transaminase- ALT; Area under the Receiver-Operating-Characteristic- AUC-ROC; Aspartate Transaminase- AST; Body Mass Index- BMI; C-Reactive Protein- CRP; Intensive Care Unit- ICU; Interquartile Range- IQR; Lactate Dehydrogenase- LDH; Negative Predictive Value- NPV; Positive Predictive Value- PPV; Receiver-Operating Characteristic- ROC; Standard Deviation- SD; Tree Augmented Naive Algorithm- TAN.

Affiliation:

[1]Hospices Civils de Lyon, Pharmacie Groupement hospitalier Nord (P Garraud), EMR3738 Ciblage thérapeutique en oncologie, Université Claude Bernard Lyon 1, Lyon, France

[2]Hospices Civils de Lyon, Service d'Hygiène, Epidémiologie, Infectiovigilance et Prévention, Hôpital Edouard Herriot, 5 place d'Arsonval, Lyon, Cedex F-69437, France

[3]Équipe Épidémiologie et Santé Internationale, Laboratoire des Pathogènes Emergents – Fondation Mérieux, Centre International de Recherche en Infectiologie, Institut National de la Santé et de la Recherche Médicale U1111, Centre National de la Recherche Scientifique, UMR5308, Ecole Normale Supérieure de Lyon, Université Claude Bernard Lyon 1, 21, Avenue Tony Garnier, Lyon, F-69007, France

[4]Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Néphrologie, hypertension, dialyse, Lyon, Cedex F-69437, France

[5]Université de Lyon, UMR 5558, Faculté de Médecine Laennec, Rue Guillaume Paradin, BP8071 Lyon, Cedex F-69376, France

***Corresponding author:**

Jean-Pierre Fauvel, Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Néphrologie, hypertension, dialyse, Lyon, Cedex F-69437, France.

Citation: Michel Ducher, Christelle Elias, Nans Florens, Maelys Granal, Mitra Saadatian-Elahi, Laetitia Henaff, Philippe Vanhems, Jean-Pierre Fauvel. Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study. Archives of Clinical and Biomedical Research 6 (2022): 663-672.

Received: July 25, 2022
Accepted: August 01, 2022
Published: August 23, 2022

Ducher M et al., Arch Clin Biomed Res 2022
DOI:10.26502/acbr.50170278

Introduction

The COVID-19 pandemic has raised health concerns around the world. The clinical signs of COVID-19 that lead patients to hospital are well known: fever, cough, fatigue, headache, and shortness of breath [1, 2]; while the most frequently reported prognostic predictors are: age, sex, co-morbidities, body temperature, C-reactive protein (CRP), creatininemia, lymphocyte count, and lung imaging characteristics [3-10]. With more than 90% of deaths occurring in patients over the age of 60 years, and a predominance of males, French data are consistent with that reported worldwide [3-9]. However, the COVID-19 hospitalised case fatality rate varies among countries; from 32.2% in the UK [3] to 7.2% in Italy [11], and 2.3% in China [12]. The differences in mortality/case fatality rates were attributed to a higher proportion of elderly people or criteria for hospitalisation, if the methods for classifying and reporting deaths due to COVID-19 were the same. In many countries, the capacity of intensive care units (ICU) was exceeded during the first COVID-19 wave, and this was also the case in France in the north-east and in the Paris regions. Thus, it is of major interest to forecast as soon as possible the clinical course of COVID-19. To this end, many prediction tools have been developed. As pointed out by Wynants et al. [10], these models are poorly presented and have a high risk of bias, raising concerns that their predictions may be unreliable when applied in daily practice. Recently, a properly developed prediction tool was proposed using a large UK database [3]. The primary outcome measure was hospital fatality within 4 weeks of admission. The prediction tool finally proposed uses prognostic scores which, according to the authors [3], has the advantage of being usable at the bedside, without complex equations and without an online calculator or mobile application. Using available data from the French NOSO-COR study [13] and Bayesian methods derived from artificial intelligence [14], the main objective of the present analysis was to carefully develop a tool to predict the risk of unfavourable outcomes following the admission of a patient for COVID-19. This predictive tool should help physicians and healthcare decision-makers to manage the current COVID-19 epidemic.

Methods

This is a post hoc analysis of the NOSO-COR study [13], an international multicentre prospective, observational, hospital-based study in adults. The data were restricted to patients hospitalised in the Lyon University hospitals. The main criterion for hospitalisation was "need for oxygen therapy" (i.e. O^2 saturation <90% in room air), if this was not the case then patients were not hospitalised. Demographic and clinical data were collected using specifically designed case report forms. An internal monitoring was implemented to detect transcription errors. The NOSO-COR study included all patients with a cough and/or fever greater than 37.8°C at admission for whom SARS-Cov-2 infection was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab. The NOSO-COR study was approved by the ethics committee of Ile de France V on 8 March 2020 (Comité de Protection des Personnes Ile de France 5). According to French law, patients received a written information form and gave their oral consent to the use of their anonymised data for research purposes. The trial was registered on ClinicalTrials (NCT04290780). The present analysis that considered data of patients with a positive SARS-Cov-2 RT-PCR was also registered on ClinicalTrials (NCT04412031) on 2 June 2020. The present paper follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) [15] statement.

Database

Anonymised data for patients who were tested positive for Sars-Cov2 and hospitalised in the Hospices Civils de Lyon (Lyon, France) were extracted from the NOSO-COR database [13] on 2 June 2020 (the initial source of which was electronic medical records); the study period was therefore from the 8 March 2020 to the 2 June 2020. The data extracted concerned the following. Clinical course of the patient: date of symptoms onset, date of admission to the hospital, date of admission to ICU, as well as vital status at 7, 15, and 21 days. Patient characteristics at admission: age, sex, body mass index (BMI), smoking status, and whether or not they were a healthcare professional. Clinical signs at admission: temperature, cough, fatigue, irritability, abnormal lung auscultation, shortness of breath, pain, myalgia, nausea, runny nose, headache, ageusia, anosmia, diarrhoea, nasopharyngeal discomfort, red eye, confusion, heart failure, sore throat, and coma. Comorbidities (disease or condition present in the patient at hospital admission): cardiac comorbidities, hypertension, liver comorbidities, hypothyroidism, rheumatological comorbidities, neurological comorbidities, diabetes (type 1 or 2), renal comorbidities, pulmonary comorbidities, cancer, and immunodeficiency (for modelling only the number of comorbidities was considered). Paramedical exams at admission: lung X-ray, CRP, haemoglobin, white cell count, lymphocyte count, creatinine, natraemia, serum potassium, prothrombin time, aspartate transaminase (AST), and alanine transaminase (ALT). Variables with more than 25% missing values (LDH, 66.7%, and alcohol consumption, 43.7%) were excluded from the analysis. For Bayesian modelling, continuous variables were divided into classes of clinical relevance (age, BMI, temperature) or into five classes (best tested discretisation). The database was separated in two separate datasets at random; the learning dataset that contained data for 80% of the patients was used for the development of the models (Bayesian network and logistic regression) and the validation dataset that contained data for 20% of the patients was used for the internal validation of the model.

Citation: Michel Ducher, Christelle Elias, Nans Florens, Maelys Granal, Mitra Saadatian-Elahi, Laetitia Henaff, Philippe Vanhems, Jean-Pierre Fauvel. Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study. Archives of Clinical and Biomedical Research 6 (2022): 663-672.

Ducher M et al., Arch Clin Biomed Res 2022
DOI:10.26502/acbr.50170278

Primary Outcome

The primary composite outcome included: need for mechanical ventilation and/or transfer to ICU and/or death within 21 days of admission. For all patients included in the present analysis (who were all SARS-CoV-2 -infected), the need for mechanical ventilation and/or transfer to an ICU, and/or the occurrence of death was considered, regardless of pre-existing conditions that may have contributed to or caused the need for mechanical ventilation and/or transfer to an ICU, and/or death.

Prediction Model

A Bayesian model was used to develop the prediction tool. A Bayesian network is a directed acyclic graph that includes nodes and arrows. Each node represents a variable (and its modalities), and each arrow represents a probabilistic dependency between the parent variable and the child variable. The Tree Augmented Naive (TAN) algorithm was used to build the structure of the Bayesian network. The TAN algorithm applies three rules: i) each node is independently linked to the target node (i.e. primary criteria); ii) each node is also linked to a unique parent node; iii) among all possible structures, the structure that maximises the overall mutual information (mutual information measures the strength of the relationship between each variable and the target) between nodes is selected [16]. The next step consists in estimating conditional probability tables, using the expectation maximisation algorithm. The expectation maximisation algorithm is an iterative procedure to compute the maximum likelihood estimation in the presence of missing or hidden data. In the maximum likelihood estimation, the aim was to estimate the model parameters for which the observed data were the most likely. This step is the so-called "learning step" that allows to develop the Bayesian network using the learning PREDICT-COVID dataset. The software used to create the model was RapidMiner Studio® version 9.7 with the W-BayesNet (TAN) Weka 3® Machine Learning Group extension.

Optimisation of the Prediction Tool

The binding strengths between the variables and the target (unfavourable course) were evaluated by the proportion of variance reduction [17]. This method, based on variance decomposition, makes it possible to completely explore the space of the inputs to the model and to take into account interactions as well as non-linear responses [17]. The sensitivity analysis makes it possible to classify the variables of the model and to reduce their number, retaining the most relevant variables. Thus, to improve the ergonomics of the model and make it usable in clinical practice, the number of variables was reduced while preserving the performance of the prediction network. A regression logistic model was also used to confirm the performance of the Bayesian model. The software used to create the logistic regression model was RapidMiner Studio® version 9.7 Weka 3® Machine Learning Group extension. The performance of the optimised developed prediction tool used a 10-fold cross validation to determine mean ± standard deviation (SD) area under the receiver-operating-characteristics (AUC-ROC) curve and accuracy. Performance of the optimised developed model to predict the clinical course of the patients of the validation dataset was investigated using the AUC-ROC curve, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The software used was RapidMiner Studio® version 9.7 with the W-BayesNet (TAN) Weka 3® Machine Learning Group extension. The prediction tool was published online using Netica® version 5.19 (Norsys corporation®).

Statistics, Calibration, and Validation of the Models

Quantitative variables are described in terms of means and SD if normal distribution, or median and interquartile range [IQR] otherwise, and qualitative variables in percentages. Missing data were imputed using Bayesian imputation. All the variables were analysed as categorical; clinical variables (i.e. age, temperature and BMI) were classified according to medically recognized thresholds, and laboratory values were classified by frequency into 5 categories. Interactions between variables were not investigated. The number of predictive variables was first reduced to 11 using the variance reduction. The calibration of the Bayes Network used the Weka® learning algorithm that determines the maximum weight spanning tree and returns a Naive Bayes network augmented with a tree [18]. In contrast, the supervised structure of the logistic regression using the 11 selected predictive variables did not require any calibration. The sample size could not be calculated for the development of the prediction tool because at this stage there were too many unknown parameters such as the number and type of variables. The software used was MedCalc® version 11.5.1.0. The validation dataset that contained data for 20% of the patients was used for the internal validation of the model. The performance of the model was assessed by C statistic.

Results

Study Population

A total of 1100 patients were selected on 2 June 2020. Wrongly selected patients (nosocomial infection, n=266; under 18 years of age, n=3), and patients whose admission date was unknown (n=8) were excluded from this analysis; thus, data from 823 patients were analysed. The main criteria for hospitalisation was "need for oxygen therapy" (i.e. O^2 saturation <90% in room air), unless patients were not hospitalised. The mean ± SD age of the patients was 70.6 ± 16.9 years (range: 19 to 102 years), that of BMI was 26.7 ± 5.4 kg/m² (range: 11 to 46 kg/m²), and the median total

Ducher M et al., Arch Clin Biomed Res 2022
DOI:10.26502/acbr.50170278

number of comorbidities was 2 (range: 2 to 8). The most frequent comorbidity was hypertension (45.1%), and 23.4% of the patients were diabetics. The most frequent clinical signs reported at admission were abnormal lung auscultation (68.0%), fatigue (67.0%), and cough (66.7%; e-Table 1). Sex, age, smoking status, temperature, renal comorbidity, diabetes, lung auscultation, fatigue, cough, shortness of breath, diarrhoea, pain, headache, runny nose, myalgia, coma

e-Table 1: Patient characteristics at admission and frequency of occurrence of key components of the primary composite criteria within 21 days of admission.

Characteristics of the patients	Mean	SD	N Filled (%)	N	Distribution (%)
Sex			100		
M				458	55.8
F				365	44.2
Age (years)	70.5	16.9	100		
Younger than 41				55	6.7
From 41 to 60				148	17.9
From 61 to 70				157	19
From 71 to 80				184	22.3
Older than 80				79	34.1
Smoking Status			75		
Current smoker				32	5.3
Never smoked				387	62.5
Previous smoker				198	32.1
Temperature (Celsius)	37.9	1	89.2		
Lower than 37.5				216	29.5
From 37.5 to 39				439	59.7
Greater than 39				79	10.7
Body mass index (kg/m²)	26.7	5.4	76.5		
Lower than 18.5				36	5.7
From 18.5 to 24.9				215	34.2
From 25 to 29.9				222	35.3
Greater than 29.9				157	24.8
Healthcare professional			100		
Yes				20	2.4
Comorbidities			N Filled (%)	N	Distribution (%)
Number of Comorbidities			88.7 to 100		
0				161	19.5
1				163	19.8
2				190	23
3				152	18.5
4				91	11.2
5				39	4.7
6				16	1.9
7				9	1.1
8				2	0.2
Hypertension			88.7		
Yes				330	45.1
Cardiac comorbidity			100		
Yes				366	44.5
Diabetes			100		
Yes				193	23.4
Neurologic comorbidity			100		
Yes				150	18.2
Cancer			100		
Yes				135	16.4
Renal comorbidity			100		
Yes				115	14
Pulmonary comorbidity			100		
Yes				109	13.2
Rheumatologic comorbidity			88.7		

Citation: Michel Ducher, Christelle Elias, Nans Florens, Maelys Granal, Mitra Saadatian-Elahi, Laetitia Henaff, Philippe Vanhems, Jean-Pierre Fauvel. Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study. Archives of Clinical and Biomedical Research 6 (2022): 663-672.

Ducher M et al., Arch Clin Biomed Res 2022
DOI:10.26502/acbr.50170278

Yes				72	9,9
Hypothyroidism			88.7		
Yes				62	8.5
Liver comorbidity			89.7		
Yes				48	6.5
Immuno deficiency			100		
Yes				44	5.3
Clinical signs			N Filled (%)	N	Distribution (%)
Lung auscultation			92.3		
Abnormal				518	68
Fatigue			99.9		
Yes				551	67
Cough			99.9		
Yes				550	66.7
Shortness of breath			99.9		
Yes				467	56.7
Diarrhea			99.9		
Yes				216	26.2
Pain			99.9		
Yes				210	25.5
Myalgia			100		
Yes				133	16.1
Headache			99.9		
Yes				108	13.1
Nausea			100		
Yes				104	12.6
Irritability			99.9		
Yes				89	10.8
Runny nose			99.9		
Yes				72	8.7
Ageusia			98.5		
Yes				59	7.3
Anosmia			98.5		
Yes				55	6.8
Nasopharyngeal discomfort			92.2		
Yes				49	6.5
Heart failure at admission			88.7		
Yes				39	5.3
Sore throat			100		
Yes				32	3.9
Coma at admission			92.2		
Yes				6	0.8
Red eye			92.2		
Yes				3	0.4
Paramedical entrance exam	Mean/Median	SD/IQR	N Filled (%)	N	Distribution (%)
Lung X-Ray			78.6		
Abnormal				570	88.1
Natraemia (mmol/L)	137	[134-139]	97.2		
Serum potassium (mmol/L)	4.1	[3.7-4.4]	96.7		
Creatininaemia (µmol/L)	82	[66-106]	97.1		
C-Reactive Protein (mg/L)	70	[29-136]	88.4		
Haemoglobin (g/dL)	131	20	97.8		
Prothrombin time ratio ()	80	[68-89]	76.2		
White blood cells (G/L)	6.4	[4.8-8.6]	97.7		
Neutrophil to lymphocyte ratio ()	5	[3.0-8.9]	97.3		
Aspartate transaminase (UI/L)	45	[32-65]	78		
Alanine transaminase (UI/L)	27	[17-47]	80.6		

Citation: Michel Ducher, Christelle Elias, Nans Florens, Maelys Granal, Mitra Saadatian-Elahi, Laetitia Henaff, Philippe Vanhems, Jean-Pierre Fauvel. Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study. Archives of Clinical and Biomedical Research 6 (2022): 663-672.

Ducher M et al., Arch Clin Biomed Res 2022
DOI:10.26502/acbr.50170278

at admission, lung X-Ray, creatininaemia, CRP, prothrombin time ratio, white blood cell count, neutrophil-to-lymphocyte ratio, ALT, and AST were significantly different between patients with an unfavourable and those with a favourable outcome (e-Table 2). The mean proportion of missing values was 5.2%, ranging from 0% for age and sex, to 25.0% for smoking status (e-Table 1). The primary composite endpoint (need for mechanical ventilation and/or transfer to ICU and/or death within 21 days of admission) was met by 36.5% of patients; 34.6% of patients required mechanical ventilation and/or transfer to an ICU. The case fatality rate was 15.9%.

Models to Predict the Primary Composite Outcome: Need for Mechanical Ventilation and/or Transfer to an ICU and/or Death within 21 Days of Admission

Using a Bayesian network, variables were first classified according to the variance reduction, (Table 1). The 11 retained variables that were the most linked to the primary outcome criteria are listed in Table 2. The 5 most informative variables to predict the primary outcome, in descending order, were: CRP, neutrophil-to-lymphocyte ratio, AST, shortness of breath, and prothrombin time (Table 1). The ten-fold cross validation of the optimised Bayesian model

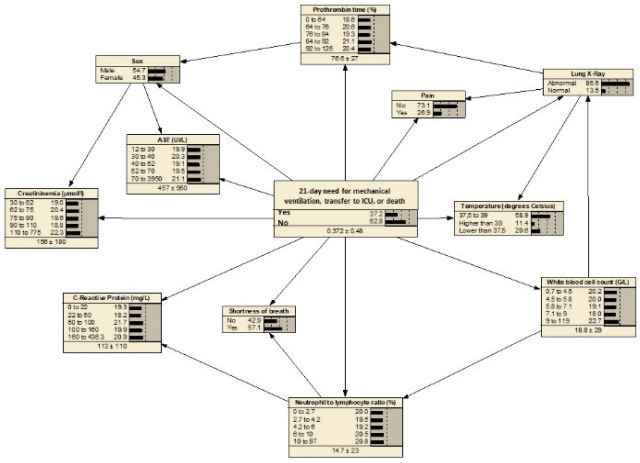

Figure 1: Structure of the optimised Bayesian network to predict an unfavourable course in patients hospitalised for the COVID-19 disease. Values for each modality of each variable represent the distribution expressed as a percentage.

e-Table 2: Patient characteristics at admission in both the favourable and the unfavourable groups.

		Favourable outcome				Unfavourable outcome				
Characteristics of the patients	N total	Mean/ Median	SD/IQR	N	(%)	Mean/ Median	SD/IQR	N	(%)	p
Sex	823									<0.001
M				198	65.8			260	50.2	
F				103	34.2			262	49.8	
Age (years)	823	69.2	17.8			72.7	14.9			0.03
Lower than 41				8	2.7			47	9,0	0.011
From 41 to 60				52	17.3			96	18.4	
From 61 to 70				61	20.3			96	18.4	
From 71 to 80				73	24.5			111	21.3	
Greater than 80				107	35.6			172	33,0	
Smoking Status	617									0.002
Current smoker				12	5.2			20	5.2	
Never smoked				125	54.1			262	67.9	
Previous smoker				94	40.7			104	26.9	
Temperature (Celsius)	734	38.1	1			37.8	1			<0.001
Lower than 37.5				49	19.1			167	34.9	<0.001
From 37.5 to 39				170	66.4			269	56.3	
Greater than 39				37	14.5			42	8.8	
Body mass index (kg/m²)	630	26.3	[23.5-30.4]			26.3	[23.1-29.7]			0.28
Lower than 18.5				7	2.9			29	7.4	0.054
From 18.5 to 24.9				86	36			90	23	
From 25 to 29.9				79	33.1			143	36.6	
Greater than 29.9				67	28			129	33	
Healthcare professional	823									0.058
Yes				3	1			17	3.3	

Citation: Michel Ducher, Christelle Elias, Nans Florens, Maelys Granal, Mitra Saadatian-Elahi, Laetitia Henaff, Philippe Vanhems, Jean-Pierre Fauvel. Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study. Archives of Clinical and Biomedical Research 6 (2022): 663-672.

Ducher M et al., Arch Clin Biomed Res 2022
DOI:10.26502/acbr.50170278

Table 3: Performance of the developed optimised Bayesian model (11 variables) to predict the primary outcome of the validation dataset (remaining 20% of the patients, n=165).

Parameters used to evaluate the performance	
AUC-ROC curve	0.78
Accuracy	77.60%
Sensitivity	67.90%
Specificity	76.20%
Positive predictive value	59.40%
Negative predictive value	82.50%

developed using the learning dataset (80% of the patients, n=658) and the 11 analysed variables provided a mean ±SD AUC-ROC of 0.76 ± 0.06,a mean ± SD error rate of 29.2 ± 6.5%, a mean sensitivity of 55.5±7.0% and a mean specificity of 78.6±4.6%. The ten-fold cross-validation of the logistic regression model developed using the learning dataset (80% of the patients, n=658) and the 11 analysed variables for the primary composite outcome had a mean ± SD AUC-ROC of 0.76 ± 0.08, a mean ± SD error rate of 27.4 ± 11.0%, a mean sensitivity of 46.2±5.3% and a mean specificity of 82.2±4.7%. The performance of the developed optimised Bayesian model to predict the primary outcome in the validation dataset (the remaining 20% of the patients, n=165) had an AUC-ROC of 0.78, an accuracy of 77.6%, a sensitivity of 67.9%, a specificity of 76.2%, a PPV of 59.4%, and NPV of 82.5% (Table 3). The structure of the optimised Bayesian network using 11 variables to assess the primary outcome criteria is presented in Figure 1.

Discussion

Using data from a large and recent prospective cohort of COVID-19 patients, the PREDICT-COVID prediction tool was carefully built using a Bayesian model to predict the need for mechanical ventilation, transfer to an ICU or death within 21 days of hospital admission. The clinical characteristics and clinical course of COVID-19 patients hospitalised in Lyon were similar to those reported in California [6], New York City [9], and Italy [5,7,8], which supports the generalisability of the proposed prediction tool. Many clinical decision tools to predict the clinical course of patients admitted to hospital with COVID-19 have been proposed; many of these were designed to predict the risk of mortality, while few were designed to predict progression to more serious or critical illness (reviewed by Wynants et al. [10]). However, the proposed clinical prediction tools are poorly presented and are at high risk of selection bias; sufficient information is not provided to replicate these studies concerning the selection of patients and data, and the methodology used [10]. Few studies report missing data, and, even when this was the case, the authors do not explain how these values were replaced, which is crucial for the construction of clinical prediction tools. In addition, internal validation is not always carried out or clearly presented. Without a careful internal validation an overfitting of the model to the data is to be expected explaining that their reported performance is probably optimistic [10]. Contrary to previously published models, the methodology used to develop the prediction models by Knight et al. [3] as well as the one proposed herein follows the published recommendations concerning the information on source data, the presentation of the inclusion and exclusion criteria of the prospectively included population, the explanation of the judgment criterion, the management of missing data, the explanation of the model used, the methodology used for internal validation, and the model performance measures and their interpretations [19]. Seven of the 11 selected prognostic variables included in the PREDICT-COVID prediction tool proposed herein are included among those cited in the other proposed prediction tools [10]. Compared to the 4C Mortality Score [3], the PREDICT-COVID prediction tool uses identical (CRP, sex) or similar (shortness of breath, creatinine) variables but also variables that are not included in the 4C Mortality Score (neutrophil-to-lymphocyte ratio, AST, prothrombin time, white blood cell count, temperature, chest X-ray, pain). Although increasing age is reported as a risk for poor outcomes [3,8,9,20-23], herein patients with an unfavourable outcome were slightly but significantly older, but this was not retained in the prediction tool presented. Similarly, a high BMI was also reported as a risk factor [22,23], but this was not the case in the 4C Mortality Score [3] and in the PREDICT-COVID prediction tool proposed herein. This suggests that age and BMI may explain a higher rate of hospitalisation in COVID-19 patients rather than an unfavourable outcome. It should be noted that, as in many centres, access to ICU in the Hospices Civils de Lyon was limited for the oldest and most fragile patients. It is surprising that the variable "shortness of breath" is predictive. Nevertheless, this variable is also predictive in other published scores such as in the 4C Mortality Score [3]. The "shortness of breath" variable takes into account the patient's feeling, and the subjective character of the patient with regard to his/her respiratory discomfort could therefore explain why it is predictive. Another interesting point is that among the 11 variables retained herein, the majority were laboratory parameters, and these represented 6 of the 7 most predictive variables. Among these laboratory parameters, only AST and prothrombin time are not among the parameters most frequently retained by other predictive tools. The difference between the selected variables could also be explained by the different main outcome measures used by the different prediction tools. The performance of the logistic regression model, which is the most commonly used method in medicine to calculate the risk of an event according to exposure, was similar to that of the Bayesian model. However, Bayesian

models have many advantages over logistic regression models; for instance, as they do not use any a priori hypothesis, explanatory variables can be co-linear (e.g. white blood cell count and neutrophil-to-lymphocyte ratio), and as they are based on conditional probabilities, the associations between variables are taken into account even if they are not linear. In addition, Bayesian networks are applicable in case of missing data that are frequent in clinical practice, which could be considered the most important advantage as in absence of a single variable a logistic regression model will not be able to calculate a prediction score for an individual. This explains, in part, why Bayesian models are increasingly used to develop risk prediction tools [16]. Similarly, Knight et al. [3] also developed a prediction tool using artificial intelligence (XGBoost) and the results of the proposed prediction tool were only slightly better than those of the 4C Mortality Score that used a logistic regression. Finally, internal validity tests of the PREDICT-COVID proposed herein are satisfactory and similar to those reported for the 4C Mortality Score prediction tool. If both prediction tools are easy to use in clinical practice, the PREDICT-COVID prediction tool can provide a prediction score in case of missing values that are frequent in clinical setting. Furthermore, in the digital age, the PREDICT-COVID prediction tool was developed to be usable online in order to facilitate its use, dissemination, and external validation. The present study has some limitations. The endpoint was independent of the comorbidities of the patient infected with SARS-Cov-2. This method was chosen because there is no consensus to formally attribute death to SARS-Cov-2. Furthermore, as recommended by Piccininni et al. [8] total mortality captures indirect deaths, such as those related to a healthcare system under crisis, yielding a more complete picture of the pandemic's consequences. The NOSO-COR study, from which the data were extracted, was designed at the early stage of the pandemic in France. Not all risk factors for worsening were clearly documented at that time. Data collection was based on a clinical approach collecting the main symptoms of COVID-19 patients on arrival in the emergency department, i.e. at the very beginning of their hospital management. Unfortunately, the NOSO-COR project did not include the collection of blood pressure, O^2 flow, or O^2 saturation data. However, some of the variables included in the predictive tool (weakness, coma, pain, shortness of breath) are related to these clinical characteristics, which at least partially explains this missing information. It should also be noted that the majority of inpatient COVID-19 worsening prediction tools, including the Mortality 4C tool, do not consider these variables, which have predictive value at a later stage of management such as in the ICU. In addition, medications were not recorded in the NOS-COR database and thus not analysed; this could be considered as a limitation of the study, but the number of medications received by such patients would have resulted in a too great number of variables for this to have been considered in the construction of the models. In the same way, the total number of explanatory variables was limited due to the increased mathematical combinatory; and was related to the number of subjects included in the learning dataset. After a classification based on variance reduction, somewhat arbitrarily, only the 11 most relevant variables were selected. Thus, using 11 variables, the prediction model offers a good compromise between performance and ergonomics. As Lindsell et al. [24] point out, the proposed PREDICT-COVID prediction tool, which can be used as both a prognostic and predictive tool, does not guide the health care team on the effectiveness of treatment, which is more informative than a simple prognosis. It would have been of interest to be able to compare the results obtained with the PREDICT-COVID prediction tool with those already reported, in particular with the prediction tool proposed by knight et al. [3]. The main limitation of the present study is that, although carefully developed from data controlled by internal monitoring, the results have to be externally validated using similar data sources and prove its effectiveness in a pragmatic trial. However, this clinical prediction tool might be repeated in the same location to detect a change regarding predictors of outcomes according to care improvement by time. In conclusion, the proposed PREDICT-COVID optimised prediction tool that uses 11 routinely determined variables to predict an unfavourable course at admission for COVID-19 had satisfactory performance. Before its use in clinical practice, external validation must be undertaken.

Acknowledgments

We thank Dr. Philip Robinson for manuscript preparation and critical reading of the manuscript.

Ethics Approval and Consent to Participate

The NOSO-COR study was approved by the ethics committee of Ile de France V on 8 March 2020 (Comité de Protection des Personnes Ile de France 5). According to French law, patients received a written information form and gave their oral consent to the use of their anonymised data for research purposes. The trial was registered on ClinicalTrials (NCT04290780). The present analysis that considered data of patients with a positive SARS-Cov-2 RT-PCR was also registered on ClinicalTrials (NCT04412031) on 2 June 2020.

Funding

This analysis was conducted without any specific funding. The NOSO-COR project was supported by partial funding by REACTING (Research and Action targeting emerging infectious diseases) INSERM, France and a donation from Fondation AnBer (http://fondationanber.fr/). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest Statement

Authors have no conflicts of interest to disclose.

Contribution Statement

Michel Ducher: Conceptualisation, methodology, formal analysis, review, and editing. Christelle Elias: Preparation and data collection, review, and editing. Jean-Pierre Fauvel: Conceptualisation, formal analysis, writing original draft. Nans Florens: Review and editing. Maelys Granal: Review and editing. Laetitia Henaff: Preparation and data collection. Mitra Saadatian-Elahi: Preparation and data collection. Philippe Vanhems: Conceptualisation, review, and editing.

Key Points

- Patients hospitalised for COVID-19 are likely to develop serious complications.
- Robust models that predict the prognosis of COVID-19 are necessary.
- Using a Bayesian network, the PREDICT-COVID prediction tool was developed.

References

1. Williamson E, Walker AJ, Bhaskaran KJ, et al. Open SAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. Ben Goldacre Nature 584 (2020): 430-436.
2. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA 323 (2020): 1775-1776.
3. Knight SR, Ho A, Pius R, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score BMJ 370 (2020) :m3339.
4. Deng G, Yin M, Chen X, et al. Clinical determinants for fatality of 44,672 patients with COVID-19. Crit Care 24 (2020):179.
5. Colaneri M, Sacchi P, Zuccaro V, et al. Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020. Euro Surveill 25 (2020): 2000460.
6. Lewnard JA, Liu VX, Jackson ML, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. BMJ 369 (2020): m1923.
7. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 323 (2020): 1574-1581.
8. Piccininni M, Rohmann JL, Foresti L, et al. Use of all cause mortality to quantify the consequences of covid-19 in Nembro, Lombardy: descriptive study. BMJ 369 (2020): m1835.
9. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 6 (2020): 1763-1770.
10. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ 369 (2020): m2204.
11. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA 323 (2020): 1335.
12. Novel Coronavirus Pneumonia Emergency. Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) China CDC Weekly. 2 (2020): 113-122.
13. Saadatian-Elahi M, Picot-Sanchez V, Henaff L, et al. Protocol for a multicentre study of nosocomial SARS-CoV2 transmission The NOSO-COR Project (2020).
14. Siga MM, Ducher M, Florens N, et al. Prediction of all-cause mortality in haemodialysis patients using a Bayesian network. Nephrol Dial Transplant 1 (2020): 1420-1425.
15. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 162(2015): 55-63.
16. Friedman N, Geiger D, Goldszmidt M. Bayesian network classifiers. Machine Learning 29 (1997): 131-163.
17. Pappenberger F, Ratto, Vandenberghe MV. Review of sensitivity analysis methods. In P.A.Vanrolleghem, éditeur: Modelling aspects of water framework directive implementation. (2010): 191-265.
18. Friedman N, Geiger D, Goldszmidt M. Bayesian network classifiers. Machine Learning 29 (1997): 131-163.
19. Leisman DE, Harhay MO, LedererDJ, et al. Development and Reporting of Prediction Models: Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. Critical care medicine 48 (2020): 623-633.
20. Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med 180 (2020): 1081-1089.
21. Gong J, Ou J, Qiu X, et al. A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis 71 (2020): 833-840.

Citation: Michel Ducher, Christelle Elias, Nans Florens, Maelys Granal, Mitra Saadatian-Elahi, Laetitia Henaff, Philippe Vanhems, Jean-Pierre Fauvel. Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study. Archives of Clinical and Biomedical Research 6 (2022): 663-672.

22. Caussy C, Pattou F, Wallet F, et al. Prevalence of obesity among adult inpatients with COVID-19 in France. Lancet Diabetes Endocrinol 8 (2020): 562-564.

23. Gupta S, Hayek SS, Wang W, et al. Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US. JAMA Intern Med 180 (2020): 1436-1447.

24. Lindsell CJ, Stead WW, Johnson KB. Action-Informed Artificial Intelligence-Matching the Algorithm to the Problem. JAMA 323 (2020): 2141-2142.

Citation: Michel Ducher, Christelle Elias, Nans Florens, Maelys Granal, Mitra Saadatian-Elahi, Laetitia Henaff, Philippe Vanhems, Jean-Pierre Fauvel. Use of Artificial Intelligence to Predict Intensive Care Admission or Death in Patients Hospitalised for COVID-19: The PREDICT-COVID Study. Archives of Clinical and Biomedical Research 6 (2022): 663-672.