Acta Biomed 2021; Vol. 92, N. 2: e2021202 DOI: 10.23750/abm.v92i2.11086

Artificial neural network model from a case series of COVID-19 patients: a prognostic analysis

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Abstract. Background and aim: There is a need to determine which clinical variables predict the severity of COVID-19. We analyzed a series of critically ill COVID-19 patients to see if any of our dataset's clinical variables were associated with patient outcomes. Methods: We retrospectively analyzed the data of COVID-19 patients admitted to the ICU of the Hospital in Pordenone from March 11, 2020, to April 17, 2020. Patients' characteristics of survivors and deceased groups were compared. The variables with a different distribution between the two groups were implemented in a generalized linear regression model (LM) and in an Artificial Neural Network (NN) model to verify the "robustness" of the association with mortality. Results: In the considered period, we reviewed the data of 22 consecutive patients: 8 died. The causes of death were a severe respiratory failure (3), multi-organ failure (1), septic shock (1), pulmonary thromboembolism (2), severe hemorrhage (1). Lymphocyte and the platelet count were significantly lower in the group of deceased patients (p-value 0.043 and 0.020, respectively; cut-off values: 660/mm3; 280,000/mm3, respectively). Prothrombin time showed a statistically significant trend (p-value= 0.065; cut-off point: 16.8/sec). The LM model (AIC= 19.032), compared to the NN model (Mean Absolute Error, MAE = 0.02), was substantially alike (MSE 0.159 vs. 0.136). Conclusions: In the context of critically ill COVID-19 patients admitted to ICU, lymphocytopenia, thrombocytopenia, and lengthening of prothrombin time were strictly correlated with higher mortality. Additional clinical data are needed to be able to validate this prognostic score. (www.actabiomedica.it)

Key words: COVID-19, Prognostic, Artificial Neural Network, Machine Learning, ICU, Mortality

Introduction

Since the global outbreak of COVID-19 (caused by the coronavirus called SARS-CoV2) in the Wuhan district in China has started, the need has arisen to detect the predictors of the severe form of the disease that roughly affects 5% of symptomatic patients (1). COVID-19 seems to cover a wide range of severity: from asymptomatic forms or substantially with few clinical manifestations to critical conditions capable of determining the patient's death (2).

After the early stages, studying most critically ill patients, some cytokines seemed to be more represented in advanced disease stages. Some interleukin appeared to be more expressed in patients with forms of severe respiratory failure (3). Interleukin-6 has been identified as a prognostic factor by different research groups (4,5). Based on these findings, anti-interleukin-6

drugs were also used to treat COVID-19 critically ill patients (6,7). The hypothesis - so far, never proven – is that in addition to being a statistical association, interleukin-6 is implicated in the COVID-19 pathogenetic mechanism. Unfortunately, the measurement of IL-6 is not always rapidly accessible to every hospital. To date, no high-quality data are supporting the use of many drugs used during the epidemic (8). With the advent of Data Science, the availability of vast databases containing numerous variables has encouraged the search for factors related to different outcomes, the main one being mortality, through increasingly advanced machine learning and deep learning models and techniques (9,10).

We have intended to study a series of critically ill patients from COVID-19 to verify if any clinical variables recorded are associated with patient outcomes. We also built a classic regression model and a neural network model to compare and assess the best performing one.

Material and Methods

Patients

We retrospectively analyzed the data of COVID-19 patients admitted to the general intensive care unit (ICU) of the "Santa Maria degli Angeli" Hospital in Pordenone from March 11, 2020, to April 17, 2020. The only two inclusion criteria were: at least one reverse transcription-polymerase chain reaction (RT-PCR) test positive for SARS-CoV2 and a clinical condition that required ICU admission. The exclusion criteria were: age below 18 years, pregnancy, trauma, post-cardiac arrest status, or patient transferred from another hospital. Each patient gave informed consent for data acquisition as a case series, and the European Privacy Regulation 2016/679 for General Data Protection Regulation (GDPR) was respected.

The following clinical and biochemical data at admission were collected: age, sex, length of stay in ICU, duration of invasive mechanical ventilation, presence of fever, cough, asthenia/myalgia, diarrhea or other symptoms at the admission, any comorbidity as: smoking, diabetes mellitus, obesity, hypertension, metabolic syndrome or neoplasm, blood gas analysis values at the time of admission: pH, partial pressure of oxygen (pO2), partial pressure of carbon dioxide (pCO2), arterial oxygen saturation (SaO2), inspiratory fraction of oxygen (FiO2) and PaO2/FiO2 ratio, white blood cell counts, neutrophilis, lymphocyte count, hemoglobin (Hb), platelet count, C-reactive protein, procalcitonin, creatinine, glucose, sodium (Na) and potassium (K), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, prothrombin time (PT), activated thromboplastin time (aPTT), D-dimer, fibrinogen, interleukin 6 (Il-6), administration of therapeutic drugs, including: hydroxychloroquine (and duration of the therapy), azithromycin (duration of the treatment), lopinavir/ritonavir, darunavir/cobicistat, methylprednisolone (duration of steroid therapy), tocilizumab or sarilumab, any microbiological findings.

Statistical Analysis

All characteristics of the patients in the survivor and deceased groups were compared. The Kruskal-Wallis test assessed continuous variables with non-parametric distributions. The categorical variables were assessed using the chi-square test (or Fisher's exact test, if appropriate). The parameters that showed a different distribution (p-value ≤ 0.05 or close to this value) between the two groups were implemented in a generalized linear regression model (LM) and in an Artificial Neural Network (NN) model to verify the "robustness" of the association with mortality. The missing values have been omitted from the initial dataset. Continuous variables were scaled by the logarithmic transformation according to a scale from 0 to 1. All statistical analyzes were generated using the open-source R-CRAN software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria). In particular, the following libraries have been implemented: "compareGroups", "neuralnet", "caTools", "boot", "pylr", "caret" and "OptimalCutpoints".

Development of the Artificial Neural Network Model

In the training group (n = 18), 18 (80%) patients were randomly selected to train the network, while 4 (20%) for cross-validation was amplified by

bootstrapping ten replications. Variables found to be significantly distributed in the two groups were entered into the NN model. A total of 18 patients in the training group were selected to train the network, and the remaining four patients were considered for testing, once replicated ten times through bootstrapping. The search space of network configuration was based empirically on the number of features and the quantity of our available data. After that, a grid search was conducted to establish the best network configuration based on our cross-validation group's criteria. We built a two-layer feedforward neural network with 5 and 3 hidden nodes, respectively, and one output neuron in model 1 (Figure 1). The performance of the NN model was evaluated by the mean absolute error (MAE). The NN model was compared to the LM model by comparing the mean squared error (MSE).

Results

We reviewed the data of 22 patients admitted during the study period: 8 of these died (Table 1). The median age was 66.8 years. The causes of death were: severe respiratory failure (3 cases), multi-organ failure (1 case), septic shock (1 case), pulmonary thromboembolism (2 cases), severe hemorrhage (1 case). The characteristics of the variables considered for the two groups are shown in Table 1.

None but two variables showed a significant difference in distribution between the two groups: the lymphocyte count and the number of platelets (respectively p-value 0.043 and 0.020). The prothrombin time showed a trend of significance (p-value 0.065). The cut-off values with greater diagnostic accuracy (based on the largest AUC) were: for the lymphocyte count 660/mm3 (AUC = 0.80; 95% CI 0.59 - 1.00); for platelet count 280,000/mm3 (AUC = 0.80; 95% CI 0.61-0.99); for the prothrombin time 16.8 sec (AUC = 0.74; 95% CI 0.52-0.97) (Figure S1 in Appendix).

In the LM model (AIC= 19.032), PT showed a trend approaching significance (p-value for lymphocyte count, platelets count, PT of 0.133, 0.203, and 0.058, respectively). Lymphocyte and platelet count showed an inverse relationship (exponent value: -0.729 and -0.505), while we verified a direct relationship between mortality and prothrombin time (exponent value: 0.888) (Figure 2).

By applying the NN model, we obtained a well-performed model (MAE = 0.02). Although the MSE is higher for the NN model than for the LM model (0.187 vs. 0.096) in the training dataset, the

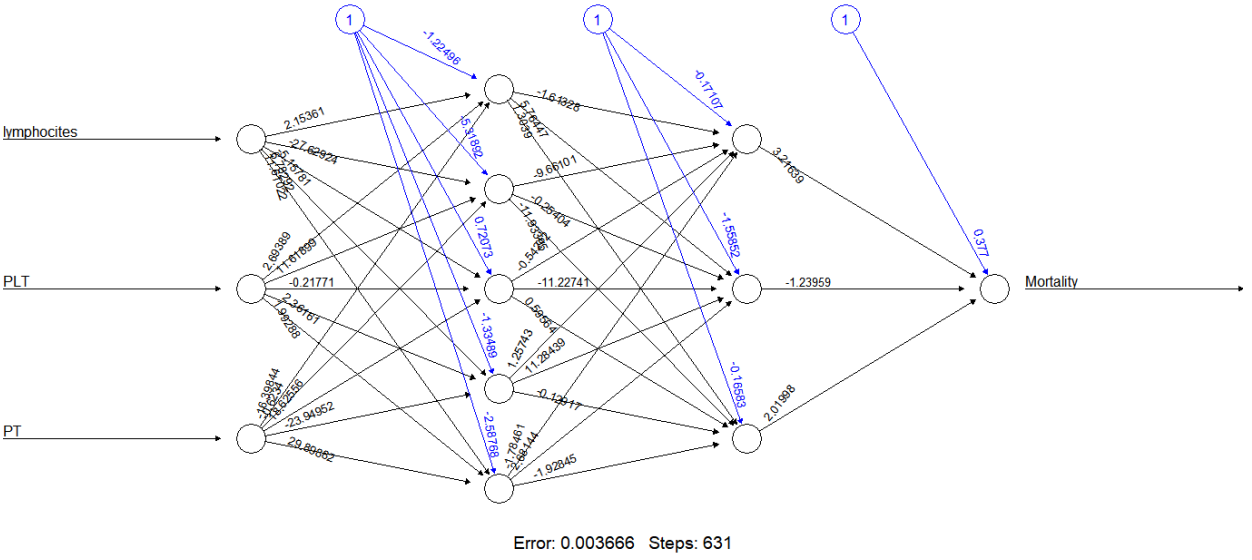

Figure 1. Artificial neural network model. Mean Absolute Error = 0.02 (See the main text for details).

Table 1. Demographic, clinical, laboratory and therapeutic characteristics of surviving and deceased critically ill patients from COVID-19. In brackets the first and third quartiles.

	Survivors (n=14)	**Deads (n=8)**	**Overall p-value**
Age (years)	65.0 [58.5-75.2]	71.5 [63.8-76.5]	0.608
Sex (males)	11 (78.6%)	8 (100%)	0.273
LOS in ICU (days)	17.0 [11.8-27.8]	17.5 [10.2-21.8]	0.584
Lenght of MV (days)	13.0 [9.00-14.0]	12.0 [8.75-16.8]	0.813
Delay before therapy	7.50 [4.00-15.8]	8.50 [7.25-10.5]	0.706
Fever	13 (92.8%)	8 (100%)	1.000
Cough	11 (78.6%)	7 (87.5%)	1.000
Asthenia / myalgia	2 (14.3%)	2 (25%)	0.602
Diarrhea	0	1 (12.5%)	0.364
Other symptoms	4 (28.6%)	2 (25%)	0.745
Smoking	1 (7.1%)	0	1.000
Diabetes mellitus	3 (21.4%)	2 (25%)	1.000
Obesity	2 (14.3%)	3 (37.5%)	0.325
Hypertension	6 (42.9%)	5 (62.5%)	0.659
Metabolic syndrome	4 (28.5%)	5 (62.5%)	0.187
Neoplasm	1 (7.1%)	1 (12.5%)	0.606
pH	7.48 [7.46-7.51]	7.47 [7.47-7.49]	0.672
pO_2 (mmHg)	55.9 [48.5-61.8]	77.0 [67.2-83.8]	0.160
pCO_2 (mmHg)	30.5 [30.0-31.0]	35.0 [32.8-35.0]	0.244
FiO_2	33.5 [21.0-74.0]	65.0 [52.5-77.5]	0.258
PiO_2/FiO_2	151 [85.0-193]	120 [96.8-135]	0.680
SaO_2 (%)	91.0 [87.0-93.8]	92.0 [83.0-96.0]	0.525
WBC (/mm^3)	10,185 [7,782-10,395]	8,055 [3,725-9,648]	0.195
Neutrophilis (/mm^3)	8,900 [6,220-9,400]	7,190 [3,392-8,655]	0.405
Lymphocytes (/mm^3)	***910 [660-1150]***	***535 [395-622]***	***0.043****
Hb (g/dL)	13.5 [12.3-14.1]	12.1 [11.5-13.4]	0.194
Platelets (/mm^3)	***282 [210-376]***	***165 [150-235]***	***0.020****
C-reactive protein (mg/dL)	13.4 [10.6-21.0]	15.6 [12.8-17.9]	0.946
Procalcitonin (ng/mL)	0.28 [0.17-0.46]	0.28 [0.14-0.66]	0.891
Creatinine (mg/dL)	0.86 [0.81-1.20]	0.91 [0.86-1.05]	0.585
Glucose (mg/mL)	155 [118-240]	118 [103-182]	0.219
Na (mEq/L)	135 [133-139]	136 [135-138]	0.537
K (mEq/L)	4.35 [3.60-4.53]	3.85 [3.48-4.50]	0.351

	Survivors (n=14)	**Deads (n=8)**	**Overall p-value**
AST (UI/L)	45.0 [31.8-95.8]	89.5 [67.8-111]	0.505
ALT (UI/L)	38.0 [25.2-55.8]	58.0 [36.8-75.5]	0.177
LDH (UI/L)	488 [393-603]	491 [488-522]	0.910
Bilirubin tot (mg/dL)	.	0.95 [0.80-1.55]	.
PT (sec)	***14.6 [12.9-15.7]***	***15.9 [14.6-17.6]***	***0.065****
aPTT (sec)	29.0 [28.0-31.3]	29.8 [28.9-31.7]	0.473
Fibrinogen (mg/dL)	835 [736-962]	685 [649-744]	0.104
D-dimer (µg/mL)	.	3,844 [2,173-5,514]	.
Il-6 (pg/mL)	12.7 [9.35-13.3]	24.0 [24.0-24.0]	0.180
Hydroxychloroquine (cases)	14 (100%)	8 (100%)	.
Duration of Hydroxy. (days)	14.0 [10.2-16.5]	10.0 [8.50-17.0]	0.475
Azithromycin (cases)	8 (57.1%)	3 (37.5%)	0.659
Duration of Azitr. (days)	5.00 [0.00-5.00]	0.00 [0.00-3.50]	0.355
Lopinavir+ritonavir (cases)	4 (28.6%)	3 (37.5%)	1.000
Darunavir+cobicistat (cases)	13 (92.9%)	7 (87.5%)	1.000
Duration of anti-retroviral therapy (days)	14.0 [10.0-14.8]	10.0 [7.00-13.2]	0.390
Metylprednisolone (cases)	10 (71.4%)	7 (87.5%)	0.613
Duration of steroid therapy (days)	8.00 [7.00-13.2]	9.00 [6.50-14.0]	0.845
Tocilizumab (cases)	3 (21.4%)	1 (12.5%)	1.000
Other microbiological isolations	2 (14.3%)	4 (50%)	0.162

performance of the two models in the cross-validation dataset is substantially equivalent (MSE 0.136 vs. 0.159) (Figure 3).

Discussion

The main finding of our study is that lymphocyte count, platelets count, and prothrombin time at ICU admission correlate with COVID-19 mortality in critically ill patients. While lymphocytopenia has been previously described in the early stage of COVID-19, our data suggest that lymphocytopenia may be observed even in the subsequent advanced and critical stages of illness and correlates with a worse prognosis. Yang et al. showed biphasic kinetics in lymphocyte count: in the early stages, there is a decreasing trend that can overlap with the critical phase of the disease and can last up to 15 days from the beginning of the disease (11). Our Center's average hospitalization time in intensive care is 17 days, so a late increase in the lymphocyte count not detected by our analyzes may be possible. Liu et al. showed a similar lymphocyte count trend, underlining the relationship between neutrophils and lymphocytes as a predictor of poor prognosis (12).

Literature reports thrombocytopenia as a possible manifestation of COVID-19, mostly in the context of disseminated intravascular coagulation (DIC) (13-15). Our data do not confirm these observations, although they cannot rule out subclinical forms of DIC. The activated thromboplastin time does not reveal any elongation in any of the two groups. A recent meta-analysis has shown that thrombocytopenia is related

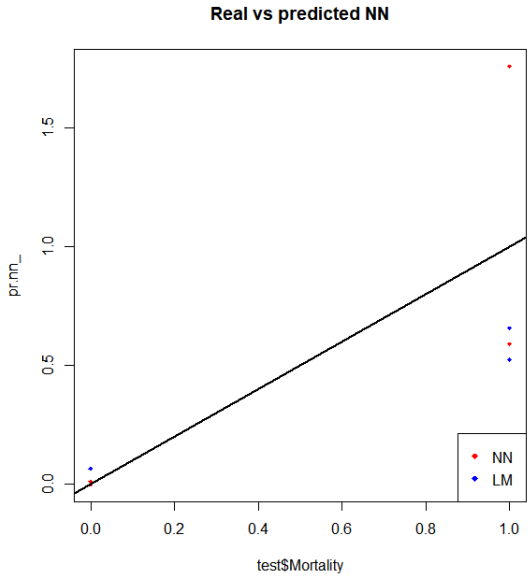

Figure 2. Comparison between real and predicted values for the NN model (red dots) and LM model (blue dots). Mean Square Errors are 0.187 and 0.096 respectively, for the training dataset, and 0.136 vs. 0.159, for cross-validation dataset.

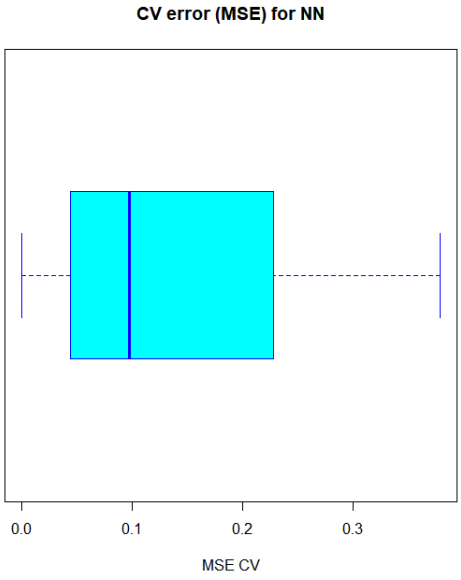

Figure 3. Cross-validation error for NN model. The Mean Square Error is 0.136 (See main text for details).

to the most severe forms of COVID-19 and seems to be a linear relationship between a decrease in platelet count and mortality (16). Although it cannot be ruled out that this may be a non-specific manifestation of widespread organ damage and, therefore, multi-organ failure (i.e., severe sepsis, severe trauma, etc.), it is conceivable this laboratory finding could have a double meaning. It could be an epiphenomenon of the pathophysiological mechanism produced by SARS-CoV2. On the other side, it could be implicated in the determinism of the death of critically ill patients from COVID-19 (17,18).

The prolongation of prothrombin time has also been shown to hold a prognostic significance (19). This laboratory finding could be the expression of a wider dysfunction of the coagulation system (20). The incidence of thromboembolic phenomena in these patients appears to be high (21). In this regard, we observed that two out of 8 patients died for pulmonary thromboembolism, and a third case had coagulation disorders resulting in hemorrhagic shock. A Dutch series of about 180 COVID-19 patients revealed an incidence of about 30% for thromboembolic events (pulmonary embolism, deep vein thrombosis, myocardial infarction, and stroke) (22).

None of the blood gas variables nor the therapeutic drugs used showed a significant difference between the two groups of patients (23-26). While Liu and colleagues highlighted a direct correlation between interleukin-6 values and disease severity, we have not been able to verify any different distribution between survivors and non-survivors (27). Others have shown a similar pattern, with a cytokine increase parallel to the disease's clinical worsening (28).

We noticed that most of the patients were male. This difference seems to confirm a larger series: male sex seems to be affected more frequently by SARS-CoV2 and has a more severe illness course (29,30). In contrast with previous reports, our dataset does not show evidence of worse prognosis in patients with cardiovascular or multiple comorbidities.

As reported in the literature, most patients admitted to the ICU (14/22 patients) showed a bacterial infection with microbiological isolation on blood or bronchoalveolar lavage. Indeed, four patients out of 8 died in total, had positive blood culture (two patients with Klebsiella pneumoniae multi-S and Citrobacter Koseri, related to 2 severe respiratory failures; one case

Table 2. Bacterial isolates and causes of death of patients who died from COVID-19.

ID	Outcome (1 = dead)	Isolates from bronchoalveolar lavage	Isolates from blood culture	Cause of death
1	0	Pseudomonas MDR e CMV		0
2	0			0
3	1	0	0	Hemorrhagic shock
4	0	E.aerogenes	0	0
5	1	E.coli, Proteus e P. aeruginosa	K. pneumoniae ESBL + Enterobacter	Pulmonary Embolism
6	0	0	0	0
7	0	0	K. pneumoniae toti-s	0
8	0	K. oxytoca		0
9	1	0	S. epidermidis toti-s	Pulmonary Embolism
10	1	P.aeruginosa	0	Septic shock
11	0	Candida	0	0
12	0	0	0	0
13	0	0	Pseudomonas MDR	0
14	1	0	Klebsiella multi-S + citrobacter koseri	Respiratory failure
15	1		Klebsiella multi-S + citrobacter koseri	Respiratory failure
16	0	MRSA	0	0
17	0	0	E. cloacae	0
18	0	0	0	0
19	1	0		Multiorgan failure
20	0	0	0	0
21	1	0	0	Respiratory failure
22	0		Candida albicans	0

of pulmonary embolism presented a Klebsiella pneumoniae ESBL and Enterobacter aerogenes; the other case of pulmonary embolism present central line-associated bloodstream infection caused by Staphylococcus epidermidis) (Table 2). In the only case of septic shock, Pseudomonas aeruginosa MDR was isolated from the bronchoalveolar lavage.

The comparison between the NN model and the LM model shows that the correlation between the proposed predictive model and the outcome of mortality is robust. Even though the limited sample size did not improve the two models tested through a larger training dataset, the predictive models are sufficiently performing. Beyond the value that single variables have in a predictive score, we have shown that their predictive power is high enough to be carefully considered in further studies with a larger population size. Furthermore, the nature of the variables implemented in the two models confirms the role of the coagulation cascade in delineating the outcome of critically ill COVID-19 patients. The future goal will be to focus on therapeutic efforts on the patients most at risk promptly.

Limitations

The main limit of our study is the small sample size. However, this is a preliminary analysis, and data will increase with the continuation of the COVID-19 pandemic. In any case, the statistical significance achieved for the collected variables indicates the strength of the correlation. The limited sample sizes do not allow to establish whether other variables can be correlated with the outcome of critically ill patients with COVID-19.

Additional clinical data are needed to validate the prognostic score obtained by us externally.

Conclusion

In critically ill COVID-19 patients admitted to our ICU, lymphocytopenia, thrombocytopenia, and lengthening of prothrombin time were correlated with higher mortality. These results may support clinicians in the early appropriate medical management of patients with COVID-19.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' contributions: SV designed the study, collected the data, drafted the first draft and supervised the final draft; DO designed the study, performed the statistical analysis, drafted the first draft and supervised the final draft; FC designed the study, drafted the first draft and supervised the final draft; MC collected the data, supervised the final draft; SF collected the data; AC collected the data; TP collected the data and supervised the final draft; DCT collected the data; MT collected the data; AG collected the data; NDA supervised the final draft; LV supervised the final draft; TB supervised the final draft.

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Received: 6 December 2020
Accepted: 12 January 2021
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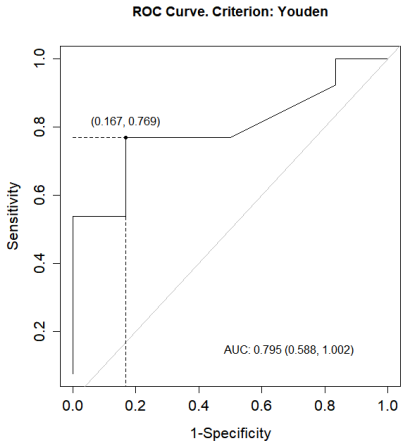
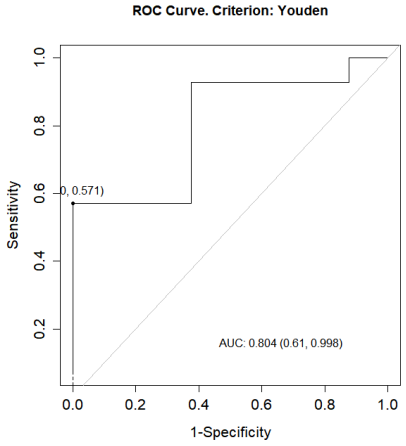
APPENDIX

A)



B)



C)

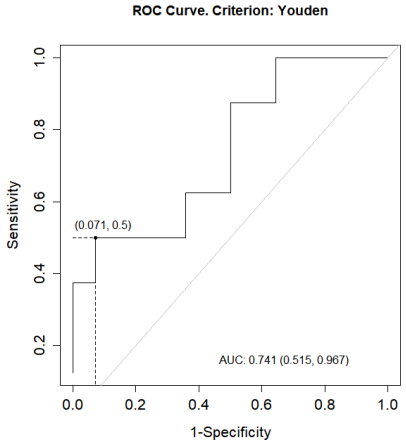


Figure S1. A) ROC for lymphocyte count. Cut-off point 660/mm^3 (AUC=0.80; 95%CI 0.59-1.00; Sens 0.77; Spec 0.83; PPV 0.91; NPV 0.63). B) ROC for platelet count. Cut-off point: 280,000/mm^3 (AUC=0.80; 95%CI 0.61-0.99; Sens 0.57; Spec 1.00; PPV 1.00; NPV 0.57). C) ROC for prothrombin time. Cut-off point 16.8/sec (AUC=0.74; 95%CI 0.52-0.97; Sens 0.50; Spec 0.93; PPV 0.80; NPV 0.76). AUC: area under the ROC; Sens: Sensitivity; Spec; Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value).