

A simple prognostic score based on troponin and presepsin for COVID-19 patients admitted to the emergency department: a single-center pilot study.

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Availability of data and material: the dataset is available upon reasonable motivation.

Abstract. *Background:* The need to determine prognostic factors that can predict a particularly severe or, conversely, the benign course of COVID-19 is particularly perceived in the Emergency Department (ED), considering the scarcity of resources for a conspicuous mass of patients. The aim of our study was to identify some predictors for 30-day mortality among some clinical, laboratory, and ultrasound variables in a COVID-19 patients population. *Methods:* Prospective single-center pilot study conducted in an ED of an University Hospital. A consecutive sample of confirmed COVID-19 patients with acute respiratory failure was enrolled from March 8th, to April 15th, 2020. *Results:* 143 patients were enrolled. Deceased patients (n = 65) were older (81 vs. 61 years, p <0.001), and they had more frequently a history of heart disease, neurological disease, or chronic obstructive pulmonary disease (p-values = 0.026, 0.025, and 0.034, respectively) than survived patients. Troponin I and presepsin had a significant correlation with a worse outcome. Troponin achieved a sensitivity of 77% and a specificity of 82% for a cut-off value of 27.6 ng/L. The presepsin achieved a sensitivity of 54% and a specificity of 92% for a cut-off value of 871 pg/mL. *Conclusion:* In a population of COVID-19 patients with acute respiratory failure in an ED, presepsin and troponin I are accurate predictors of 30-day mortality. Presepsin is highly specific and could permit the early identification of patients who could benefit from more intensive care as soon as they enter the ED. Further validation studies are needed to confirm this result. (www.actabiomedica.it)

Key words: COVID-19, acute respiratory failure, prognostic, biomarkers, presepsin.

Introduction

Since the onset of the COVID-19 epidemic, emergency departments have found themselves on the front line to deal with a rising tide of patients affected by varying degrees of severity of the same clinical syndrome: a viral syndrome that ranges from

asymptomatic or paucisymptomatic up to severe interstitial pneumonia and acute respiratory distress syndrome (1). Establishing which patients can be managed at home and which ones require hospitalization, especially in an intensive care unit, has a particularly relevant value in the context of the COVID-19 epidemic. Many critically ill patients' simultaneities

have dragged various countries' health system into crisis (2-4). In this regard, the search for clinical, laboratory, or imaging predictors has proven very important. The need to identify prognostic factors that can predict a particularly severe or, conversely, the benign trend of COVID-19 patients is particularly perceived in the emergency department's context considering the scarcity of resources and beds for a conspicuous mass of patients (5-7).

Most of the predictors used so far to predict the clinical course of COVID-19 patients have proved to be of modest utility: for example, the assessment of post-exertional oxygen saturation has shown a modest predictive value (8), probably since the respiratory manifestations of COVID-19, although more frequent, are not the only ones, as cardiac or neurological syndromes may also occur (9-11).

We conducted a prospective study to establish which, among the clinical, laboratory, ultrasound variables we measured, could be the best predictor of 30-day mortality in a population of COVID-19 patients with acute respiratory failure in an Emergency Department.

Materials and Methods

Population and data collection

Patients with COVID-19 were prospectively enrolled at the admission in the ED of University Hospital of Bari by consecutive sampling, from March 8th, 2020, to April 15th, 2020. Patients were eligible for acute respiratory distress (i.e., oxygen saturation below 90% in room air) and diagnostic confirmation by SARS-CoV2 genome amplification by real-time polymerase chain reaction on a nasopharyngeal swab. Exclusion criteria were age less than 18 years. Clinical data were registered prospectively without interfering with usual clinical practice.

Our study's primary aim was to identify which clinical, laboratory, or ultrasound data could be the most accurate predictors of the 30-day mortality of COVID-19 patients.

Demographic characteristics (age and sex), comorbidities, type of ventilatory support, concentrations of

serum biomarkers (lactate dehydrogenase, creatine phosphokinase, myoglobin, troponin I, C-reactive protein, D-dimer, presepsin, and lactate), ultrasound evaluation (quantified according to Lung Ultrasound Score and ultrasound evaluation of the diaphragm excursion), respiratory function indices (i.e., partial arterial pressure of oxygen and the inspiratory fraction of oxygen ratio), the ward in which each patient was hospitalized, and clinical outcome 30 days after the evaluation in the emergency room were recorded. The blood sampling on which biomarker searches have been carried out is part of the normal clinical routine of managing patients with respiratory failure in the emergency room. The collection took place within an hour from the evaluation of the attending physician. Lung ultrasound was performed during routine evaluation by the attending emergency physician. Furthermore, the ultrasound evaluation is part of the routine evaluation of patients with respiratory failure belonging to the Emergency Department.

This study is a sub-analysis of a previous study (12) approved by the local Research Ethics Committee: protocol number 6524 del 09/09/2020

Statistical analysis

All the recorded clinical characteristics were compared, dividing patients based on their clinical outcome at 30-day (i.e., death or survival). Quantitative variables were expressed as median (and interquartile range), discrete variables were expressed as absolute frequency (and percentage). The Kruskal-Wallis test, due to the nonparametric distribution of the variables, was performed. The categorical variables were assessed using the chi-square test (or Fisher's exact test, if appropriate).

All the variables of the dataset have been implemented in a multivariate adaptive regression model. Through a stepwise forward process, the less informative variables were eliminated until a 5-variable model was obtained. The variables found to be significant in the latter model were taken individually and implemented in a univariate adaptive regression model to calculate the predictive performance (the dataset was divided into a training dataset, consisting of 80% of the whole dataset, and a test dataset, consisting of the

remaining 20%). ROC curves were drawn to evaluate the area under the curve. Furthermore, the best cut-off was calculated based on the sensitivity and specificity values referred to every predictor considered.

A two-tails p-value \leq of 0.05 was considered statistically significant. A correction for multiplicity by Benjamini and Hochberg technique has been applied when appropriated. The models were compared with each other based on their accuracy, sensitivity, and specificity performances.

We calculated the power of our test (multivariate regression) by estimating a model with up to 5 variables, capable of estimating at least 30% of the mortality variability, with an established significance of 0.05, for a sample of at least 140 patients. With these parameters, the estimated power is 99.9%.

All statistical analyses were generated using the open-source R-CRAN software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). The main packages implemented were “pwr”, “mice”, “compareGroups”, “gamm4”, “ISLR”, and “pROC”, and “cutpointr”.

Results

During the period considered, 143 patients were enrolled. The clinical characteristics of the population are shown in Table 1. The median age was 73 years. Most (60%) of the patients were male. Fifty percent of the sample had a history of hypertension, and a third a history of heart disease. Most patients (53%) were treated with non-invasive ventilation; less than a third of the sample required oxygen therapy alone. Most of the patients were admitted to the respiratory ICU (37%), about 40% were admitted to the Internal Medicine or Infectious Diseases ward, equally distributed. The remaining 25% were admitted to the general ICU unit or the high dependency unit (HDU).

Analyzing the population based on the hospitalization outcome, the deceased patients were on average older than survivors (81 vs. 61 years, $p < 0.001$). Patients who died most frequently had a history of heart disease, neurological disease, or chronic obstructive pulmonary disease (p-values = 0.026; 0.025 and 0.034, respectively) than survivors. They

also had higher lactate dehydrogenase (i.e., LDH; 367 vs. 289 UI/L, $p = 0.002$), myoglobin (260 vs. 87 $\mu\text{g/L}$, $p < 0.001$), troponin I (53.9 vs. 11.5 ng/L, $p < 0.001$), C-reactive protein (109 vs. 64.1 mg/dL, $p < 0.001$), presepsin (892 vs. 518 pg/mL, $p < 0.001$), and D-dimer (1,606 vs. 922 $\mu\text{g/mL}$, $p < 0.001$) values. On average, lactates were higher in the group of deceased patients (1.7 vs. 1.1 mEq/L, $p < 0.001$). The deceased patients had a lower $\text{PaO}_2/\text{FiO}_2$ ratio than the survivors (229 vs. 322 mmHg, $p < 0.001$). Lung ultrasound score was higher (and therefore a greater lung involvement) in deceased than survivors (20 vs. 16, $p = 0.005$).

Through the stepwise exclusion process, a 5-variable predictive model was obtained: age, myoglobin, Troponin I, presepsin, and hospitalization ward. The model is moderately predictive: adjusted square $R = 0.60$, the explained deviance is 56.9%. The Un-Bias Risk Estimator (i.e., UBRE, essentially a scaled Akaike information criterion) is equal to -0.17 (Figure 1). However, in the adaptive model, the only two statistically significant variables were presepsin ($p = 0.04$) and Troponin I ($p = 0.05$).

Using the presepsin alone as a predictor, the model is slightly informative: adjusted square $R = 0.30$, the explained deviance is 30%; UBRE = 0.06. The AUC for the ROC curve is 0.85 (Figure 2). The best cut-off in terms of sensitivity and specificity (0.54 and 0.92, respectively) is 871 pg/mL.

For Troponin I, on the other hand, the model is substantially comparable to the model that uses presepsin in terms of information: adjusted R squared = 0.37, explained deviance equal to 32%; UBRE = -0.006. The AUC for Troponin I ROC is 0.84 (Figure 3). The best cut-off (sensitivity 0.77 and specificity 0.82) is 27.6 ng/L.

Discussion

We derived a simple prognostic score to predict 30-day mortality in a population of COVID-19 patients with acute respiratory failure admitted to the Emergency Department. This score consists of two easily measurable biomarkers in patient serum: troponin I and presepsin.

Table 1. Demographic characteristics, medical history, laboratory values, ultrasound findings and respiratory function indices of the whole sample and divided by outcome (death at 30 days).

		All sample	Survivors	Decesead	P-value
		N = 143	N = 78	N = 65	
Age (years)		73 (61 – 83)	65.5 (55 – 76)	81 (72 – 88)	< 0.001
Sex (Males)		86 (60%)	49 (63%)	37 (59%)	0.585
LU-Score		18 (13 – 22)	16 (12 – 20)	20 (15 – 24)	0.005
Ventilation support					0.015
	None	6 (4%)	4 (5%)	2 (3%)	
	Oxygen	42 (29%)	30 (38.5%)	12 (18.5%)	
	HFNC	14 (10%)	10 (13%)	4 (6%)	
	C-PAP	3 (2%)	1 (1%)	2 (3%)	
	NIV	76 (53%)	32 (41%)	44 (68%)	
	NIV/HFNC	2 (1%)	1 (1%)	1 (1.5%)	
Hypertension		69 (50%)	34 (46%)	35 (55%)	0.393
Obesity		19 (14%)	9 (12%)	10 (16%)	0.733
COPD		29 (21%)	10 (13.5%)	19 (30%)	0.034
Diabetes Mellitus		30 (22%)	11 (15%)	19 (30%)	0.058
Neurological disease		42 (30%)	16 (22%)	26 (41%)	0.025
Cardiovascular disease		46 (33%)	18 (24%)	28 (44%)	0.026
Neoplasm		15 (11%)	8 (11%)	7 (11%)	1.000
LDH (UI/L)		328 (251-429)	289 (240-410)	367 (302-438)	0.002
CPK (UI/L)		132 (71.2-288)	112 (63.5-216)	164 (79.8-436)	0.070
Myoglobin (µg/L)		152 (71.5-312)	87 (55.5-160)	260 (152-673)	<0.001
Troponin I (ng/L)		23.3 (10.1-57)	11.5 (7-23.1)	53.9 (28.9-146)	<0.001
CPR (mg/dL)		84.3 (44.5-140)	64.1 (30.1-114)	109 (70.1-165)	<0.001
D-dimer (µg/mL)		1,094 (632-1,932)	922 (530-1,240)	1,606 (705-3,656)	<0.001
Presepsin (pg/mL)		622 (460-948)	518 (331-673)	892 (574-1,215)	<0.001
Lactate (mEq/L)		1.3 (1-2)	1.1 (1-1.6)	1.7 (1.2-2.7)	<0.001
PaO ₂ /FiO ₂ (mmHg)		281 (186-348)	322 (250-395)	229 (123-324)	<0.001
Diaphragm. thickening (%)		18 (12-23)	20 (13-23)	16 (12-21)	0.169
Inpatient ward					0.001
	Resp. ICU	53 (37%)	29 (37%)	24 (37%)	
	Med. ward	25 (18%)	18 (23%)	7 (11%)	
	Inf. Dis.	28 (20%)	21 (27%)	7 (11%)	
	ICU	22 (15%)	6 (8%)	16 (25%)	
	HDU	14 (10%)	4 (5%)	10 (15%)	
	Surg. ward	1 (0.7%)	0	1 (1.5%)	

LU-score: lung ultrasound score; HFNC: high-flow nasal cannula; C-PAP: continuous positive airways pressure ventilation; NIV: non-invasive ventilation (mostly, in pressure support mode); COPD: chronic obstructive pulmonary disease; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; CRP: C-reactive protein; PaO₂/FiO₂: arterial partial pressure oxygen and inspired fraction of oxygen ratio; Resp. ICU: respiratory intensive care unit; Med. ward: internal medicine ward; Inf. Dis: infectious disease ward; ICU: intensive care unit; HDU: high dependency unit; Surg. ward: surgery ward

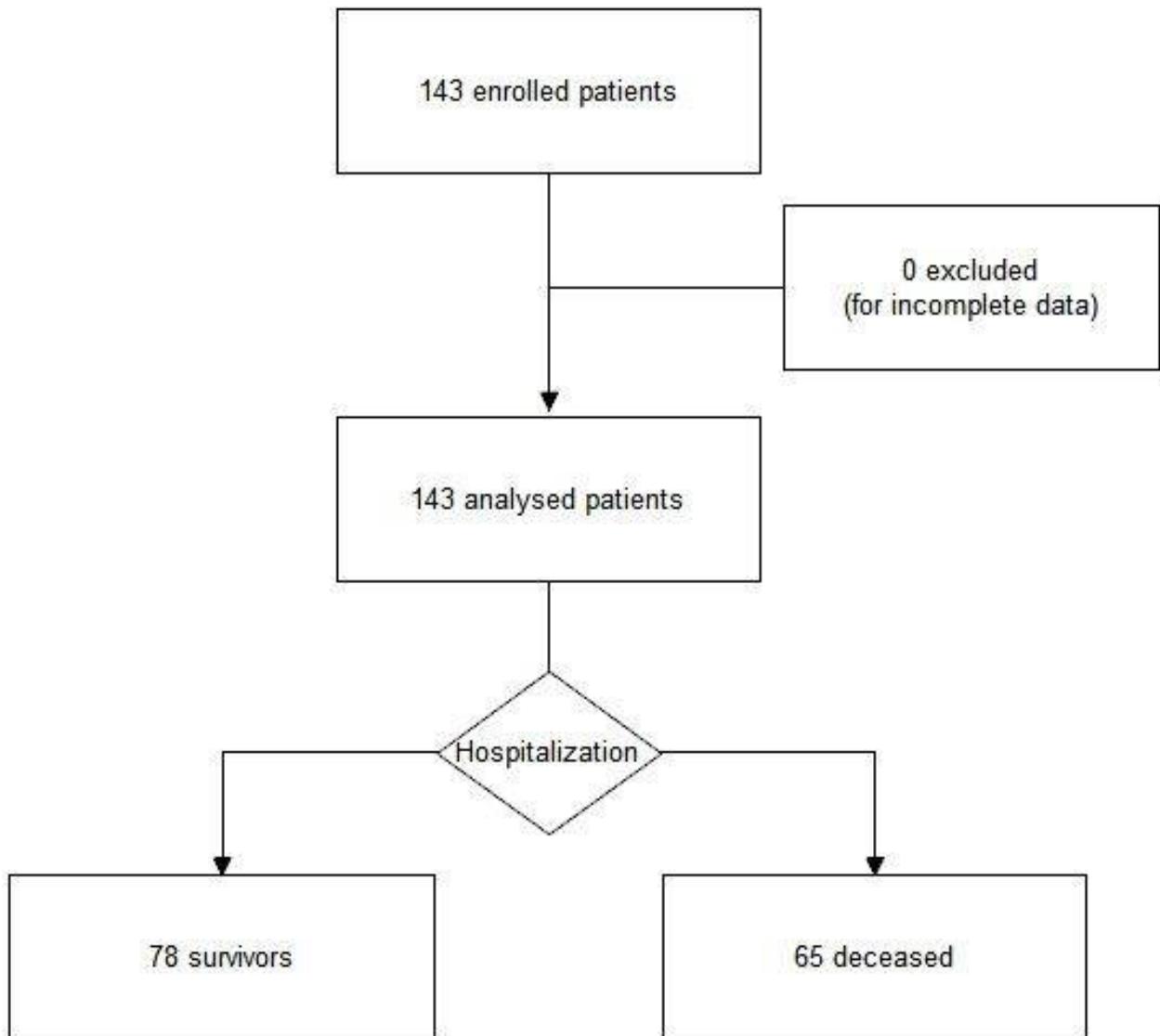


Figure 1. Flowchart of the recruitment and exclusion process. Details on the study method are explained in the main text.

Several studies in the literature have highlighted the prognostic value of cardiovascular injury biomarkers (13-15). Troponin I has shown a discriminatory power to identify patients with a high risk of mortality at six months in an elderly population (16). Furthermore, a prognostic index has also been shown in populations without direct cardiovascular pathologies, such as trauma or septic patients (17,18). In COVID-19 patient populations, troponin I has shown a good prognostic value. Since the beginning of the SARS-CoV2 epidemic, Wuhan's Chinese district's first population

analysis found that patients with worse prognosis had higher levels of troponin I (19). Patients with cardiac injury had a higher mortality rate in the log-rank test, both from symptom onset and admission (Hazard Ratio of 4.26 and 3.41, respectively). Accuracy analysis on a comparable population (Chinese from Wuhan district) showed an AUC for ultra-sensitive Troponin I of 0.86, with a sensitivity of 67% and a specificity of 89% (20). A similar analysis of non-Chinese COVID-19 patient populations subsequently confirmed these observations. An Italian multicenter study found that

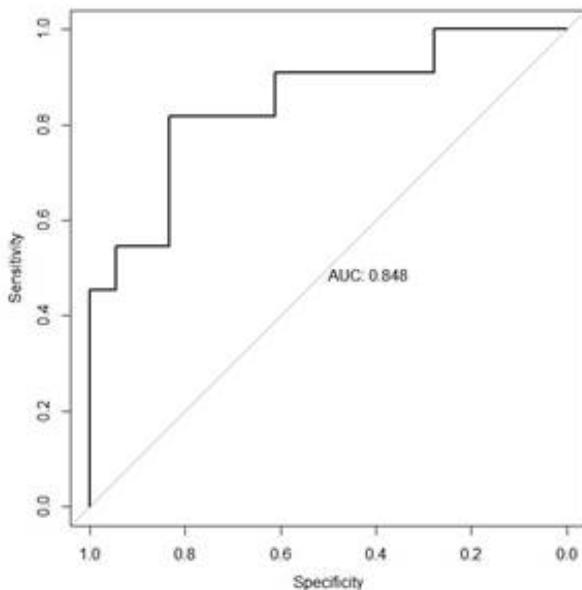


Figure 2. ROC curve for presepsin as a prognostic index of in-hospital mortality. AUC equal to 0.85; sensitivity = 54%, specificity 92% for a cut-off value of 871 pg / mL.

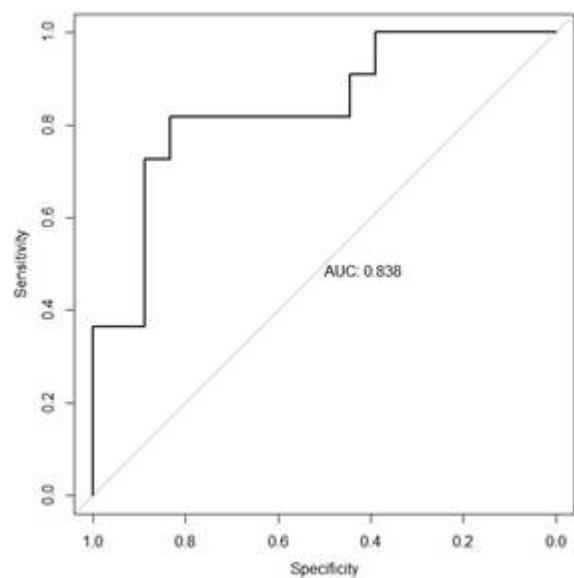


Figure 3. ROC curve for troponin I as a prognostic index of in-hospital mortality. AUC equal to 0.84; sensitivity = 77%, specificity 82% for a cut-off value of 27.6 ng / L.

Table 2. Multivariate regression through a generalized additive mixed model.

	Edf.	Ref. df	Chi-sq.	p-value	Edf.	Ref. df	Chi-sq	p-value
Age	7.50	8.20	12.22	0.151				
Myoglobin	1.16	1.30	0.31	0.564				
Troponin I	1.34	1.59	4.71	0.051	2.72	3.24	33.31	1.3×10^{-06}
Presepsin	1.00	1.00	3.97	0.046	5.57	6.09	20.88	0.001
	Est.	Std. Error	z-value	p-value				
Inpatient ward (intercept)	111.7	67108864.0	0	1				

A 5-variable model was obtained through a stepwise elimination process: age, myoglobin, troponin I, presepsin and ward of destination to predict the clinical outcome of enrolled patients. The model is moderately predictive: adjusted square $R = 0.60$, the explained deviance is 56.9%. The Un-Bias Risk Estimator (UBRE) is equal to -0.17 . However, in the adaptive model, the only two statistically significant variables were presepsin ($p = 0.04$) and Troponin I ($p = 0.05$).

Edf = estimate degree of freedom; Ref.df = reference degree of freedom; Chi.sq: chi-squared test; Est = estimate coefficient; St. Err= standard error.

patients with higher troponin I levels suffered from higher mortality (Hazard Ratio 1.71), regardless of whether they had previous cardiac comorbidity (10).

Similarly, the prognostic role of troponin I in the course of COVID-19 disease was also confirmed in a US patient population (21). Our results confirm the literature produced so far: troponin I is a biomarker capable of predicting COVID-19 patients' mortality, regardless of their cardiovascular comorbidities. It

turned out to be fairly accurate with good sensitivity and specificity. Compared to the first investigations, we found a fair sensitivity: 77% for a 27.6 ng/L cut-off. However, we must underline that compared to the early stages of the epidemic, the implications of the SARS-CoV2 on the coagulation cascade are now known, and therefore a more massive use of anticoagulants is made, i.e., low molecular weight heparin. Therefore, other biomarkers that have proved reliable predictors during

the first epidemic phase, such as the d-dimer, are currently not accurate (22,23). Additionally, we should note that the most frequently deceased patients had a medical history of cardiovascular disease. In any case, the frequency of cardiovascular diseases in the general population and the fact that the predictive value of troponin I remains valid even outside this subpopulation do not diminish the prognostic role of this biomarker.

Presepsin is a molecule that arises from the cleavage of a larger molecule – CD14 – anchored to the membrane of monocytes, macrophages, and polymorphonuclear neutrophils. CD14 is a bacterial lipopolysaccharide recognition receptor (24,25). Presepsin has already proven its prognostic value, particularly in populations with sepsis-related acute respiratory distress syndrome and acquired acute respiratory failure (26-30). Fukada et al., in a small series of patients with COVID-19-related respiratory failure, found that presepsin is more expressed in severe cases than in mild cases (31). Zaninotto et al. demonstrated that presepsin is a more accurate prognostic index than other commonly used biomarkers such as C-reactive protein or procalcitonin (32). Schirinzi et al., in a similar population of COVID-19 patients, obtained an AUC for predictor ability of presepsin of 0.81, therefore comparable to what we obtained (33).

The results we obtained have a double meaning: first, presepsin and troponin I appear to be early predictors, right from the admission to the Emergency Department, of a particularly severe prognosis in an indiscriminate population of patients with COVID-19-related respiratory failure. Furthermore, some predictors, such as the PaO₂/FiO₂ ratio (despite showing a good correlation with the patient's clinical course), are late predictors when respiratory failure is already in an advanced stage (34,35). Additionally, imaging, such as lung ultrasound findings, may not reflect a direct correlation with the severity of COVID-19-related pneumonia (36,37). In other words, the proportion of lung involved in the disease process established by SARS-CoV2 may not directly correlate with the severity of the disease. However, we should also note that patients with more severe ventilatory function indices and more severe lung ultrasound findings may have been treated more intensively. This may have affected the clinical outcome of these patients.

Presepsin is a very specific predictor (92%) of 30-day mortality in COVID-19 patients. Therefore, it can discriminate against patients who will have a particularly severe clinical course from the disease's early stages. The association with troponin I could allow to exploit the greater sensitivity of this biomarker. In this way, it could be possible to have a score composed of two prognostic biomarkers: one more sensitive and one more specific. Even taken alone, presepsin is a sufficiently specific biomarker to identify patients who probably require more aggressive therapy from the early stages of the disease.

Limitations

Ours is a single-center pilot study. The validation of the results obtained by us must be validated with a similar but different population to consider the predictors we detected reliably.

Besides, some assessments, such as lung ultrasound examination or blood gas analysis used as a routine evaluation of patients with respiratory failure, were entered in the decision-making process regarding patients' hospitalization. Therefore, we cannot rule out biases inherent in this aspect of non-concealment. Furthermore, the results we obtained apply exclusively to a population of patients with COVID-19 that refers to the ED. We cannot comment on the clinical course of asymptomatic patients.

Finally, we must note that, like all predictive models, ours is also highly dependent on the variables included in it. We cannot exclude that variables not considered by us may be as much, if not more, predictive than the predictors we obtained.

Conclusion

In a population of COVID-19 patients with COVID-19-related acute respiratory failure in an Emergency Department, presepsin and troponin I proved to be sufficiently accurate predictors of 30-day mortality. Troponin I demonstrated a sensitivity of 77% and a specificity of 82%. Presepsin displayed low sensitivity (54%) but very high specificity (92%); therefore, it could help identify patients who could benefit from

more intensive care as soon as they enter the ED. Further internal and external validation studies are needed to confirm this result.

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.

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APPENDIX - Supplementary Material

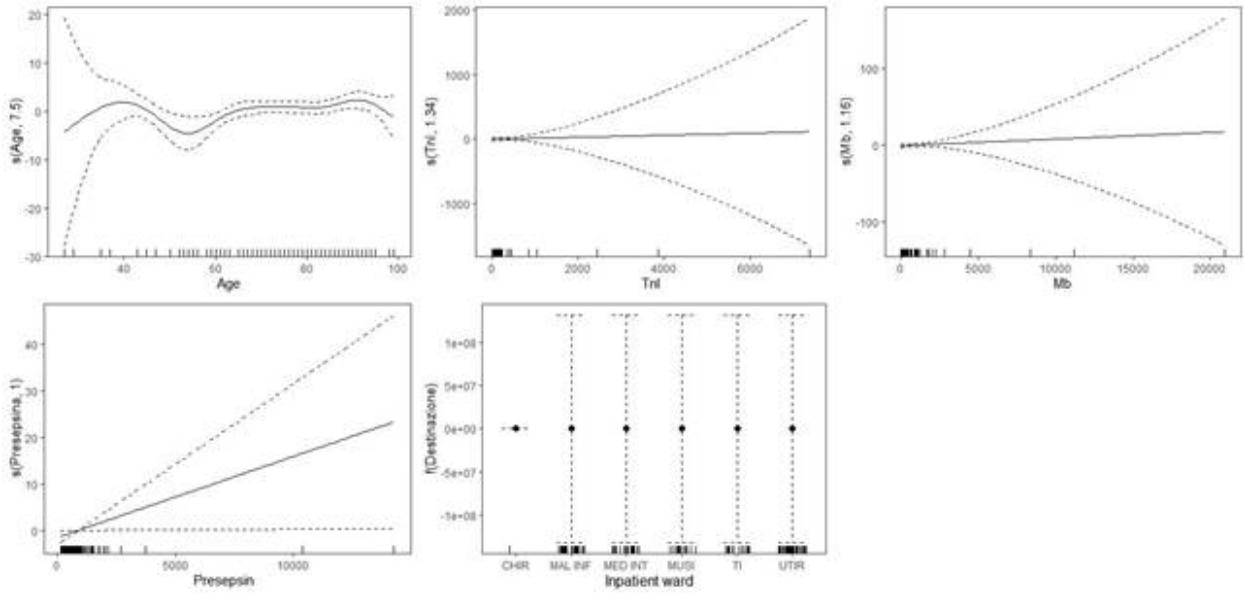


Figure S1. Plots of the variables inserted in the multivariate regression through a generalized additive mixed model. From top right and clockwise: age, troponin I, myoglobin, presepsin and hospitalization ward.