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DESIGN AND DEVELOPMENT OF AN EARLY WARNING SCORE FOR COVID-19 HOSPITALIZED PATIENTS

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Abstract Pandemics pose a major challenge for public health preparedness, requiring a coordinated international response and the development of solid containment plans. Early and accurate identification of high-risk patients in the course of the current COVID-19 pandemic is vital for planning and making proper use of available resources. The purpose of this study was to identify the key variables that account for worse outcomes to create a predictive model that could be used effectively for triage. Through literature review, 44 variables that could be linked to an unfavorable course of COVID-19 disease were obtained, including clinical, laboratory, and X-ray variables. These were used for a 2-round modified Delphi processing with 14 experts to select a final list of variables with the greatest predictive power for the construction of a scoring system, leading to the creation of a new scoring system: the COVID-19 Severity Index. The analysis of the area under the curve for the COVID-19 Severity Index was 0.94 to predict the need for ICU admission in the following 24 hours against 0.80 for NEWS-2. Additionally, the digital medical record of the *Hospital Italiano de Buenos Aires* was electronically set for an automatic calculation and constant update of the COVID-19 Severity Index. Specifically designed for the current COVID-19 pandemic, COVID-19 Severity Index could be used as a reliable tool for strategic planning, organization, and administration of resources by easily identifying hospitalized patients with a greater need of intensive care.

Key words: coronavirus, critical care, hospital administration, early warning score

Resumen ***Diseño y desarrollo de un sistema de alerta temprana para pacientes hospitalizados por COVID-19.*** La pandemia por COVID-19 planteó un desafío para el sistema salud, debido a la gran demanda de pacientes hospitalizados. La identificación temprana de pacientes hospitalizados con riesgo de evolución desfavorable es vital para asistir en forma oportuna y planificar la demanda de recursos. El propósito de este estudio fue identificar las variables predictivas de mala evolución en pacientes hospitalizados por COVID-19 y crear un modelo predictivo que pueda usarse como herramienta de triage. A través de una revisión narrativa, se obtuvieron 44 variables vinculadas a una evolución desfavorable de la enfermedad COVID-19, incluyendo variables clínicas, de laboratorio y radiográficas. Luego se utilizó un procesamiento por método Delphi modificado de 2 rondas para seleccionar una lista final de variables incluidas en el score llamado *COVID-19 Severity Index*. Luego se calculó el Área Bajo la Curva (AUC) del score para predecir el pase a terapia intensiva en las próximas 24 horas. El score presentó un AUC de 0,94 frente a 0,80 para NEWS-2. Finalmente se agregó el *COVID-19 Severity Index* a la historia clínica electrónica de un hospital universitario de alta complejidad. Se programó para que el mismo se actualice de manera automática, facilitando la planificación estratégica, organización y administración de recursos a través de la identificación temprana de pacientes hospitalizados con mayor riesgo de transferencia a la Unidad de Cuidados Intensivos.

Palabras clave: coronavirus, cuidados intensivos, administración hospitalaria, puntaje de alerta temprana

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KEY POINTS
Current knowledge

- Early Warning Scores that detect early and accurately high-risk patients in the course of the current COVID-19 pandemic are vital for planning and making proper use of available resources.

Article´s contribution to knowledge

- COVID-19 Severity Index is an Early Warning Score that was electronically set for an automatic calculation and constant update in COVID-19 patients. This score was used as a tool for strategic planning, organization, and administration of resources during the actual COVID-19 pandemic in a tertiary university hospital in Argentina.

Infectious disease outbreaks constitute a serious problem to global health with a major impact on countries' economies, healthcare systems and resources[1]. The spread of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) known as COVID-19, has already gone into pandemic proportions registering, at the moment of this study, a total of 80 million confirmed cases, 1.7 million deaths and 57 million recovered patients across 215 countries in a short elapse of time[2]. The way in which outbreaks affect countries depends on multiple factors and its impact is difficult to foresee. However, the numbers of infected people and casualties are evidence that despite the attempts to plan in advance, the global healthcare systems remain unprepared[3].

The intensity of staffing needed and the sophisticated training required for the care of patients with viral infections during pandemics result in the fact that a relatively small number of patients could easily overwhelm healthcare systems[4].

Accurate identification of variables related to worse outcomes is key for triaging and adapting the intensity of care that each patient requires, allowing effective strategic planning and a better administration of human and material resources. Moreover, the need for a sensitive and predictive model is mandatory to avoid a delayed recognition of severely ill patients or even those at risk of presenting further complications.

During the early phase of COVID-19 pandemic, Liao et al. propose an early warning score based on an adapted version of the National Early Warning Score 2 (NEWS-2) adding age as a variable to reflect emerging evidence of age as an independent risk factor for survival[5]. In that score, patients were divided into four categories based on the risk of respiratory failure: low, medium, high, and extreme. The score was used to manage the monitoring frequency and to activate a rapid response team.

The NEWS2 is a Early Warning Scores (EWS) that predict deterioration in hospitalized patients[6], but are designed for general hospitalized patients in a non-pandemic scenario. COVID-19 pandemic has now a high proportion of hospitalized patients with a single disease. Therefore, a specific EWS for COVID-19 including laboratory test results, clinical features, and radiological findings[7-12], could improve the detection of high-risk patients with the aim of optimizing the management of hospital resources. This tool is mainly relevant in low-income countries where resources are insufficient, even before the actual pandemic.

Aware of the impact of the current pandemic, *COVID-19 Severity Index was* developed as a triage tool based on the NEWS-2 score, that could rapidly and reliably be used by frontline healthcare personnel to identify high-risk patients.

Materials and methods

A narrative review was conducted to generate a list of possible predictors based on clinical signs and symptoms, comorbidities, laboratory, and radiographic findings. After initial identification of predictive variables, they were subjected to expert analysis through a 2-round Delphi process[13]. The output was a set of potential variables based on expert opinion to be added to the NEWS-2.

The narrative review was conducted in April 2020 using the Ovid MEDLINE and medRxiv database for articles written in English and published until April 2020. The search strategy included terms such as "COVID-19", "Risk Factors", "Respiratory Insufficiency" and "Mortality". Studies were selected on the basis of the following inclusion criteria: population over 18 years of age where signs and symptoms were recorded together with comorbidities, laboratory and radiographic findings and in which all these parameters were valued against the occurrence of death or disease severity in confirmed COVID-19 patients.

To select the final predictive variables a Delphi process was carried on. First experts from both resource-rich and resource-limited settings were recruited, including professionals from Argentina, Chile, and Canada. Participants are involved in the care of critically ill adults and active in medical research areas including critical care, infectious diseases, and pneumology on a daily basis. The first contact was by email to communicate the objective of the study and extend an invitation to participate in both rounds of the Delphi process. The target sample size of expert contributors was 14.

The first round of the Delphi process had a 7-day elapse; it was initiated on April 15th of 2020 and completed by April 22nd of 2020. The questionnaire form was distributed among expert participants who were asked to evaluate the variables gathered from the literature review before mentioned and suggested as potential predictors of worse outcome in COVID-19 patients.

When the participant answered "yes" to the fact that a given variable was valuable as a predictor, they were prompted to evaluate 3 domains: predictive potential, measurement reliability, level of training, and/or resources required to measure and collect the variable[13]. Each domain had 4 possible answers: high (3), moderate (2), minimal (1), or not applicable (0). Finally, there was an option for the participant to make comments regarding each variable. Moreover, they were encouraged to add new variables to the suggested settings.

At the stage of analysis, each answer was given a number between 3 and 0 (high [3], moderate [2], minimal [1], not applicable [0]) based on the strength of the response. The numbers for each domain were tabulated to calculate a weighted effect

(WE) to help to determine the selection threshold. The WE was calculated by following the formula exemplified below, which doubles the weight of the value for predictive potential, adds the value for measurement reliability, and subtracts the value for the level of resources and/or training required.

Weighted Effect = Predictive Potential x2 + Reliability - Resources or Training

eg.: Weighted Effect$_{Asthma}$ = Moderate (2) x2 + Moderate (2) - Minimal (1)
Weighted Effect$_{Asthma}$ = 5

WE was calculated for each variable valued by each expert opinion. The sum of the WE's for a given variable was ranked for a further selection of those with the greatest value achieved whereas WE of variables considered as medical records, were analyzed separately from clinical features.

Afterward, a threshold was chosen based on the desired number of predictors. Then variables in which WE scored above the threshold, were included in a final set of predictor variables. Those variables that were below the threshold, were carefully reviewed by the research team and discharged or included in Round 2 for re-evaluation depending on the value obtained. Any additional variables proposed by participants were evaluated in Round 2 when they were considered clinically distinct from the variables already assessed in Round 1.

The 2nd Round was conducted in a 7-day elapse of time, from 29 April of 2020 to 7 May of 2020. It consisted of re-evaluating selected variables from Round 1 as well as evaluating newly suggested variables. Participants were provided the responses from Round 1, and a threshold procedure similar to the one used in the initial round was used in the second round. Each round demanded 7 days for completion given to each expert consulted who was sent a reminder one day before the deadline. The final set of variables was obtained, and results were analyzed as follows.

The questionnaire was developed using the secure web-based application Google Forms. Participant's own responses from Round 1 were available in Round 2 along with a mean response from the other participants.

This project has been approved by the Ethics Committee for Research Protocols at *Hospital Italiano de Buenos Aires.* Voluntary completion of the questionnaire implied consent and the participants' responses were received and analyzed anonymously.

Results

After analysis, ten articles fulfilled the final inclusion criteria and were, therefore, considered. Sixty-four relevant variables predictors analyzed in these studies were summarized to generate a master list (Supplementary material 1) created using Microsoft Excel to keep track of each predictor variable and the frequency of repetition in other studies as a presumed indicator of its predictive potential and relative commonality. Each variable was organized into the following categories: 1) patient's characteristics; 2) signs and symptoms; 3) scores; 4) laboratory findings; 5) chest x-ray findings; 6) comorbidities. All variables were presented as either binary or continuous variables, depending on how it was presented in the original study.

In the first round of the Delphi process, there was a high level of agreement on the following variables alerting to a worse outcome: age, male gender, dyspnea, d-dimer > 1 µg/ml, lymphopenia, "Sequential Organ Failure Assessment" (SOFA) score, bilateral compromise in chest x-ray and comorbidities such as chronic heart failure, diabetes with end-organ damage and hypertension. The thresholds for age and lymphopenia were discussed in Round 2.

Additionally, there was a high level of agreement to not include: pregnancy, plasma albumin, pro-B-type natriuretic peptide, lactate dehydrogenase, and other comorbidities such as chronic obstructive pulmonary disease (COPD), asthma, chronic renal disease, solid tumor, tuberculosis, active smoking and diabetes without end-organ damage.

Since there was a moderate level of agreement regarding thrombocytopenia, C reactive protein, creatinine serum levels, chest x-ray findings other than bilateral compromise, those variables were discussed in Round 2.

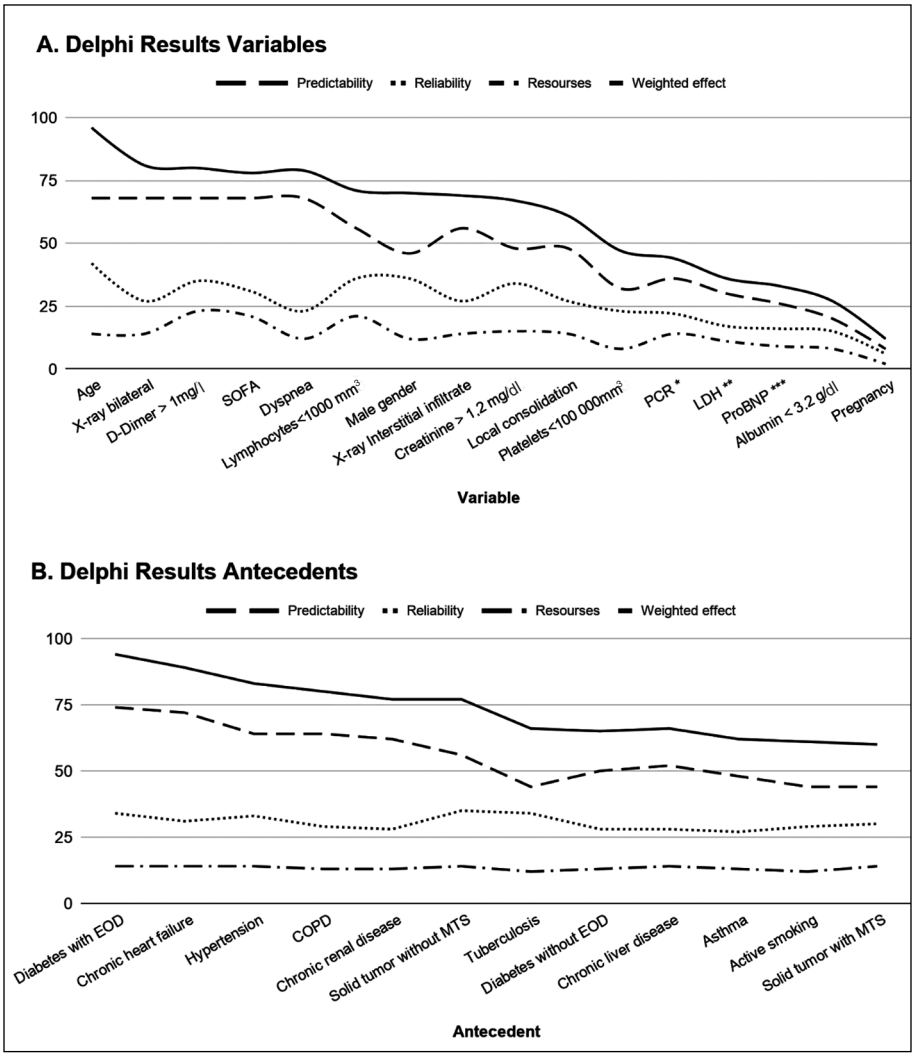
Experts also proposed 2 new variables; findings in pulmonary ultrasound and reticulonodular interstitial pattern in the chest x-ray. These 2 new variables were not considered due to interobserver variability and the need for highly trained professionals to perform and to interpret those studies.

Due to the lack of a specific cut-off value for age and lymphopenia, possible thresholds were proposed to participants. After Round 2, cut-off values for age were defined as follows: low risk for age < 60; moderate risk for ages between 60 and 65; and high risk for age > 65. Regarding lymphopenia, thresholds were: >1000 mm^3, low risk; between 500 and 1000 mm^3, moderate risk; and less than 500 mm^3, high risk.

Variables from Round 1 that did not reach the WE threshold value for immediate consideration, were reassessed. Low platelet count, C-reactive protein, lactate dehydrogenase, and serum creatinine were reconsidered to select the one with a higher predictive value of the worse outcome. Consensus on platelet count <100 000 mm^3 was the variable with higher potential. The list of all potential variables proposed to the Delphi process is available for reference in Supplementary material 2. The final set variables selected from the Delphi process are exposed in Figure 1.

Following the analysis and the application of the modified Delphi process, a final set of selected variables was combined with a modified NEWS-2 score to generate the *COVID-19 Severity Index.* The modifications to NEWS-2 Score are described as follows. In the case that the patient needs supplemental oxygen, he will receive 3 score-points instead of 2. The addition of 1 and 2 score-points related to low blood pressure was eliminated. Low temperature only added 1 score-point if it was less than 35.6 °C instead of 36,1 °C, while 1 point-score was added if the temperature was 38 °C or higher. *COVID-19 Severity Index* score is

Fig. 1.– Delphi process results. A: The trends of the sum of responses to each domain for all 16 variables evaluated in Round 1. B: The trends of the sum of responses to each domain for all 12 antecedents evaluated in Round 1



COPD: chronic obstructive pulmonary disease; EOD: end-organ damage; MTS: metastasis; PCR: protein C reactive; LDH: lactate dehydrogenase

*Values of PCR, proposed were: >10, >100 or > 200 mg/dl
**Values of LDH, proposed were: > 250, > 300 or > 350 U/l
***Values of Pro B-type Natriuretic Peptide, proposed were > 350, > 500 or > 1000 pg/ml

exposed in Figure 2. Patients were divided into four risk categories based on their score (Fig. 3).

The prediction capacity of this score was studied to evaluate its predictive potential of ICU transfer in 24 and 48-hours elapse of time. A group of 220 patients with confirmed COVID-19 was evaluated; 19 of which were unexpectedly transferred to ICU; and 17 of which were transferred to ICU during the first 3 days, one on the 5th day and another on the 6th day of hospitalization.

A comparison between *COVID-19 Severity Index,* NEWS score adapted by Liao et al.[5], and NEWS-2 score was made. All three scores were measured on the first, second, and third day after the hospital admission of the patients.

For those patients who were initially admitted into general wards and were later transferred to the ICU, the score was retrospectively applied for the 72, 48 and 24 hours before the ICU admission, to identify whether they were parameters that could predict the need for more intensive monitoring.

A comparative analysis of the area under the curve (AUC) for the different scores evidenced a better capacity of the *COVID-19 Severity Index* to predict the need for ICU admission. When applied in the 24 hours before ICU admission, the

Fig. 2.– COVID-19 Severity Index

PARAMETERS	3	2	1	0	1	2	3
Age (years)				≤60	61 - 64	≥65	
Male gender			yes	no			
Heart failure			yes	no			
COPD			yes	no			
Diabetes with end - organ damage			yes	no			
Chest X - Ray*				Normal or without bilateral infiltrates	Bilateral infiltrates		
Respiratory rate (breaths per minute)	≤8		9 - 11	12 - 20		21 - 24	≥25
SpO_2 (%)	≤91	92 - 93	94 - 95	≥96			
SpO_2 (%) in COPD	≤83	84 - 85	86 - 87	≥88			
Suplemental O_2	yes			no			
Systolic BP (mmHg)	≤90			90 - 219			≥220
Pulse (Beats per minute)	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Temperature (°C)	≤35		35.1 - 35.5	35.6 - 37.9	38 - 39	≥39.1	
Dyspnoea		yes		no			
D-Dimer** (ng/ml)				≤1000	>1000		
Lymphocytes** (per mm^3)				≥1000	<1000	≤500	
Platelets** (per mm^3)				≥100 000	<100 000		

COPD: chronic obstructive pulmonary disease; SpO_2: peripheral oxygen saturation. BP: blood pressure

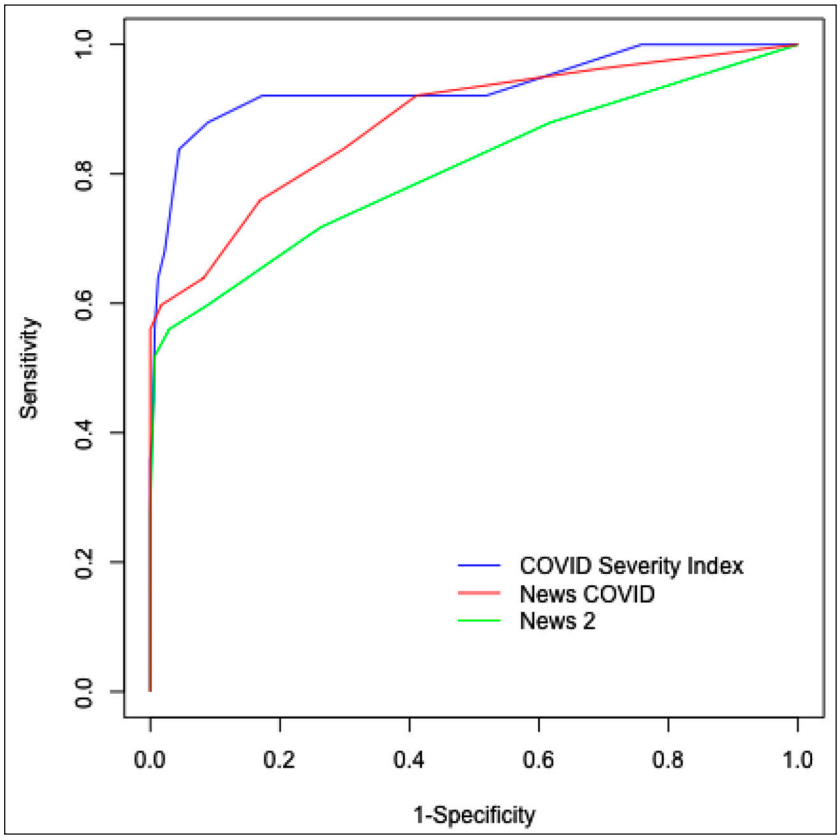
*Chest X-Ray should be analyzed on admission, but it will be reconsidered when a new one is performed.
**If laboratory test results have more than 48 hours, they will not be considered.

Fig. 3.– COVID-19 Severity Index risk chart

SCORE	CLINICAL RISK	ALERT LEVEL	NURSING SURVEILLANCE	RESPONSE	SOLUTION
0-2	Low	Green	Every 12 hours	Standard nursing surveillance	General ward
3-5	Moderate	Yellow	Every 6 hours	Frecuent nursing surveillance	General ward
6-7	High	Orange	Every 2 to 3 hours	Intensive nursing surveillance and physician notification	Evaluate intensive care admission
8 or more	Critical	Red	Continuous monitoring	Immediate physician notification	Intensive care unit

AU-ROC for the score *COVID-19 Severity Index* was 0.94 *vs.* 0.88 for the modified NEWS score developed by *Liao et al.*, and 0.80 for NEWS-2 (Figure 4). When applied in the 48 hours before ICU admission, the AU-ROC for *COVID-19 Severity Index* was 0.88, for the modified NEWS was 0.84, and 0.62 for NEWS-2.

Fig. 4.– Area Under the Curve of COVID Severity Index: 0.93, NEWS COVID: 0.87, proposed by Liao et al. 2 and NEWS-2: 0.8; to predict unexpected ICU transfer in the next 24 hours



Discussion

In this study, an EWS was designed to predict progression towards critical illness among COVID-19 infected patients during hospitalization.

Although NEWS-2 score is the mainly used EWS, there are few published studies on its use in the specific context of COVID-19[14]. A paper published during the early phase of the COVID-19 pandemic offered an EWS based on an adapted version of the NEWS-2 score in which age > 65 years was added to reflect emerging evidence of age as an independent risk factor for survival[5].

The complexity of COVID-19 and the multiple variables involved in its course evidenced the need to search for a more specific score that could be used in this single disease to better discern among patients at risk of presenting severe infection[7–12]. The development and use of a simple tool built on the basis of signs and symptoms with moderate to strong predictive potential, could ideally facilitate the triage process and expedite the care for hospitalized adult patients with COVID-19.

Due to the current lack of evidence, the effort to carry out careful research with a methodologically solid process was paramount. The narrative review allowed the research team to balance information from peer-reviewed articles as well as urgent data reported in preprints.

Additionally, the Delphi method allowed us to merge clinical expertise with theoretical reasoning. Delphi process was chosen with the objective of achieving consensus among a panel of experts on a defined issue, using an iteration of a questionnaire and aggregating the answers to provide feedback to the participants after each completed round. This method, as a way of generating consensus, is widely applied in diverse fields such as program planning and resource assessment, even in the healthcare sector[15]. One of the advantages of using this method is to facilitate the online consensus-building which significantly enabled the participation of experts in the matter from various locations worldwide in the current pandemic scenario[13].

The 10 variables added to the modified NEWS-2 score required for calculation of the risk of developing a critical illness are usually available at Hospital admission. *COVID-19 Severity Index* is a dynamic tool designed to be actualized with the clinical changes of the patient, with

the aim of detecting clinical deterioration within 24 to 48 hours prior to ICU transfer.

Additionally, the digital medical record of the Hospital Italiano de Buenos Aires was electronically set for an automatic calculation and constant update of the COVID-19 Severity Index as soon as the latest laboratory results and vital signs were recorded. This provided real-time information for deciding the most suitable area of care for each patient[16]. Likewise, since it is a relatively simple score, it can also be calculated manually.

Even though *COVID-19 Severity Index* has a short scale validation, it was designed by experts' opinions. Opinions may be impacted by experts' training, exposure, and expertise. The application of the present score is being carried out in patients at the Hospital Italiano de Buenos Aires to define the intensity of nursing monitoring required.

The COVID-19 Severity Index was Specifically designed for the current COVID-19 pandemic. This score may serve as a reliable tool for strategic planning, organization and administration of resources by easily distinguishing hospitalized patients with a higher risk of ICU transfer.

Final disclosures: In a scientific letter previously presented to *Medicina Intensiva*[17] a simplified summary of this work was presented, with a stating of the variables included in the score, without mention of the elements that led to its construction. Here we present a detailed description and precise information of the concrete methodology used for the design of the score, including a narrative review (summarized in the master table in Supplementary Material 1) where 44 variables were analyzed. We also describe how the modified Delphi process was applied and how the weighted effect of each of these variables was calculated based on the experts' opinions (reflected in Fig. 1). In addition, we include here the graphical comparison of the AUROC of the designed model in order to compare it to other early warning systems. These factors were not analyzed in the scientific letter[17]. The research team considers that the methodology applied in the design of this early warning system is as relevant as the variables included in it. The design and process through which the Early Warning System was built is novel and allowed us, in just 3 months, to identify potentially critical patients. It should also be mentioned that our study was initially released in a *medRxiv*[18]. Its dissemination was a way of contributing to the scientific community by sharing this tool that proved so useful to us in our institution.

Conflict of interest: None to declare

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Suplementary material 1

Trials Variable	Comments	Difference	Guan WJ, et al Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age	> 65%	significant	13%	27%	< 0.001
Gender (Male)		not significant			
Pregnancy		unevaluated			
Predictive scores					
SOFA score		unevaluated			
Signs and symptoms					
Heart rate		not significant			
Respiratory rate (breaths per minute)		unevaluated			
Systolic blood pressure		unevaluated			
SpO_2 (Ambient air)		unevaluated			
Fever		not significant			
Cough		not significant			
Days symptoms onset to dyspnoea		not significant			
Dyspnoea %		significant	139/926 (15.0)	65/173 (37.6)	< 0.001
Expectoration		not significant			
Fatigue		not significant			
Myalgia		not significant			
Haemoptysis		not significant			
Gastrointestinal symptoms		not significant			
Headache		not significant			
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated			
PCO_2, mmHg		unevaluated			
"Blood routine					
Hemoglobin	g/dl	significant	134.0 (119.0-148.0)	135.0 (120.0-148.0)	< 0.001
Red blood cell		unevaluated			
Red blood cell distribution		unevaluated			
White cell count		unevaluated			
Neutrophil count		unevaluated			
Lymphocytes	< 1.5* 10^9/l N°/total N° (%)	significant	584/736 (79.3)	147/154 (95.5)	< 0.001
Neutrophil-to-lymphocyte ratio		unevaluated			
Platelets	< 150* 10^9/l N°/total N° (%)	significant	315/869 (36.2)	225/713 (31.6)	< 0.001
Liver and renal function					
Albumin level		unevaluated			
Aspartate aminotransferase (ASAT)	> 40 U/liter N°/total N° (%)	significant	112/615 (18.2)	56/142 (39.4)	< 0.001
Alanine aminotransferase (ALAT)	> 40 U/liter N°/total N° (%)	significant	120/606 (19.8)	38/135 (28.1)	0.043
Total bilirubin		not significant			
Direct bilirubin		unevaluated			
Creatine phosphokinase (CPK)		not significant			
Cretinine	≥ 133 µmol/l N°/total N° (%)	significant	6/614 (1.0)	6/138 (4.3)	
Urea		unevaluated			
BUN, mmol/L		unevaluated			
Cardiac function					
Myoglobin		unevaluated			
Troponin		unevaluated			
N-terminal pro b Natriuretic Peptide		unevaluated			
Inflammatory and coagulation					
Hypersensitive C-reactive protein	≥ 10 mg/liter N°/total N° (%)	significant	371/658 (56.4)	110/135 (81.5)	< 0.001
Procalcitonin (PCT)	≥ 0.5 ng/ml N°/total N° (%)	significant	19/516 (3.7)	16/117 (13.7)	< 0.001
Lactate dehydrogenase (LDH)	≥ 250 U/liter N°/total N° (%)	significant	205/551 (37.2)	72/124 (58.1)	< 0.001
D-Dimer	≥ 0.5 mg/liter - N°/total N° (%)	significant	195/451 (43.2)	65/109 (59.6)	
Prothrombin time		unevaluated			
Activated partial thromboplastin time		unevaluated			
Chest X-Ray					
Ground glass opacity	N°/total N° (%)	significant	37/926 (4.0)	18/173 (10.4)	< 0.001
Interstitial opacity	N°/total N° (%)	significant	7/926 (0.8)	5/173 (2.9)	0.028
Local patchy shadowing	N°/total N° (%)	significant	56/926 (6.0)	21/173 (12.1)	0.007
Bilateral patchy shadowing	N°/total N° (%)	significant	65/926 (7.0)	35/173 (20.2)	< 0.001
Comorbidity					
Tabaquism	Current smokers	significant	12%	17%	< 0.001
Chronic obstructive pulmonary disease		significant	6/926 (0.6)	6/173 (3.5)	0.006
Heart Failure		unevaluated			
Diabetes	n positive/total (%)	significant	53/926 (5.7)	28/173 (16.2)	< 0.001
Hypertension	n positive/total (%)	significant	123/926 (13.3)	41/173 (23.7)	< 0.001
Cardiovascular disease	n positive/total (%)	significant	27/1099 (2.5)	17/926 (1.8)	0.005
Cerebrovascular diseases		not significant			
Malignant tumor		not significant			
Chronic renal disease		not significant			
Chronic liver disease		unevaluated			
Pulmonary tuberculosis		unevaluated			
Chronic digestive disorders		unevaluated			
Immunodeficiency		not significant			

Trials Variable	Comments	Difference	Bai, Fang, Zhou, Bai, Liu, Chen, Xu, Xia, et al Patients w/o severe/critical progress	 Patients with severe/critical progress	p-value
Patient characteristics					
Age		significant	48.51 ± 12.04	59.13 ± 10.66	OR 5.334, 95% CI (1.800-15.803)
Gender (Male)		not significant	–	–	–
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		not significant	–	–	–
Respiratory rate (breaths per minute)		significant	20.01 ± 1.24	20.77 ± 1.87	p = 0.013
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	–	–	–
Fever		significant	94%	82%	p = 0.038
Cough		not significant	–	–	–
Days symptoms onset to dyspnoea		significant	0.63 ± 2.16	2.16 ± 3.89	p = 0.013
Dyspnoea %		significant	13%	37%	p = 0.001
Expectoration		not significant	–	–	–
Fatigue		not significant	–	–	–
Myalgia		not significant	–	–	–
Haemoptysis		significant	1%	9%	p = 0.040
Gastrointestinal symptoms		not significant	–	–	–
Headache		not significant	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		not significant	–	–	–
PCO_2, mmHg		significant	39.80 ± 4.7	37.48 ± 5.03	p = 0.014
Blood routine					
Hemoglobin		unevaluated	–	–	–
Red blood cell		unevaluated	–	–	–
Red blood cell distribution		unevaluated	–	–	–
White cell count		not significant	–	–	–
Neutrophil count	×10 e 9 /l	not significant	3.54 ± 1.90	4.15 ± 2.29	p = 0.001
Lymphocytes	×10 e 9 /l	significant	1.12 ± 0.36	0.90 ± 0.4	OR 3.459, 95% CI (1.067-11.209)
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets		unevaluated	–	–	–
Liver and renal function					
Albumin level	g/l	significant	39.73 ± 4.21	36.21 ± 5.34	OR 4.01, 95% CI (1.216–13.223)
Aspartate aminotransferase (ASAT)	U/l	significant	26.70 ± 12.81	39.37 ± 30.7	p = 0.007
Alanine aminotransferase (ALAT)	U/l	significant	24.80 ± 21.13	35.25 ± 31.4	p = 0.04
Total bilirubin		not significant	–	–	–
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		unevaluated	–	–	–
Cretinine	µmol/l	significant	65.44 ± 15.24	75.19 ± 27.78	p = 0.025
Urea	µmol/l	significant	4.13 ± 1.38	5.20 ± 2.24	p = 0.003
BUN, mmol/L		unevaluated	–	–	–
Cardiac function					
Myoglobin		significant	21.81 ± 14.85	46.62 ± 53.4	p = 0.013
Troponin		not significant	–	–	–
N-terminal pro b Natriuretic Peptide	pg/ml	significant	141.05 ± 200.42	467.24 ± 773.60	p = 0.020
Inflammatory and coagulation					
Hypersensitive C-reactive protein	ng/ml	significant	31.88 ± 30.28	59.37 ± 49.9	p = 0.001
Procalcitonin (PCT)		not significant	–	–	–
Lactate dehydrogenase (LDH)	u/l	significant	251.65 ± 60.02	331.24 ± 138.03	
D-Dimer		not significant	–	–	–
Prothrombin time		not significant	–	–	–
Activated partial thromboplastin time		not significant	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity					
Tabaquism		unevaluated	–	–	–
Chronic obstructive pulmonary disease		not significant	–	–	–
Heart Failure		unevaluated	–	–	–
Diabetes		not significant	–	–	–
Hypertension		significant	9	19	OR 5.093, 95% CI (1.236-20.986)
Cardiovascular disease		unevaluated	–	–	–
Cerebrovascular diseases		significant	6	22	p = 0.001
Malignant tumor		not significant	–	–	–
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		unevaluated	–	–	–
Pulmonary tuberculosis		not significant	–	–	–
Chronic digestive disorders		not significant	–	–	–
Immunodeficiency		unevaluated			

Trials Variable	Comments	Difference	Caramelo et al Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age		significant	< 60	> 60	18.8161, 95% CI (7.1997-41.5517)
Gender (Male)		significant	0	1	1.8518, 95% CI (1.5996-2.1270)
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		unevaluated	–	–	–
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	–	–	–
Fever		unevaluated	–	–	–
Cough		unevaluated	–	–	–
Days symptoms onset to dyspnoea		unevaluated	–	–	–
Dyspnoea %		unevaluated	–	–	–
Expectoration		unevaluated	–	–	–
Fatigue		unevaluated	–	–	–
Myalgia		unevaluated	–	–	–
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		unevaluated	–	–	–
Headache		unevaluated	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated			
PCO_2, mmHg		unevaluated	–	–	–
Blood routine			–	–	–
Hemoglobin		unevaluated			
Red blood cell		unevaluated	–	–	–
Red blood cell distribution		unevaluated	–	–	–
White cell count		unevaluated	–	–	–
Neutrophil count		unevaluated	–	–	–
Lymphocytes		unevaluated	–	–	–
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets		unevaluated	–	–	–
Liver and renal function			–	–	–
Albumin level		unevaluated			
Aspartate aminotransferase (ASAT)		unevaluated	–	–	–
Alanine aminotransferase (ALAT)		unevaluated	–	–	–
Total bilirubin		unevaluated	–	–	–
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		unevaluated	–	–	–
Cretinine		unevaluated	–	–	–
Urea		unevaluated	–	–	–
BUN, mmol/L		unevaluated	–	–	–
Cardiac function					
Myoglobin		unevaluated			
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unevaluated	–	–	–
Inflammatory and coagulation			–	–	–
Hypersensitive C-reactive protein		unevaluated			
Procalcitonin (PCT)		unevaluated	–	–	–
Lactate dehydrogenase (LDH)		unevaluated	–	–	–
D-Dimer		unevaluated	–	–	–
Prothrombin time		unevaluated	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray		–	–	–	
Ground glass opacity		unevaluated			
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity			–	–	–
Tabaquism		unevaluated			
Chronic obstructive pulmonary disease		significant	data not available	data not available	7.7925, 95% CI (5.5446-10.4319)
Heart Failure		unevaluated	–	–	–
Diabetes		significant	data not available	data not available	4.62, 95% CI (4.44-4.82)
Hypertension		significant	data not available	data not available	12.74, 95% CI (12.52-12.88)
Cardiovascular disease		significant	data not available	data not available	12.8328, 95% CI (10.2736-15.8643)
Cerebrovascular diseases		unevaluated	–	–	–
Malignant tumor		not significant	data not available	data not available	0.39, 95% CI (0.34-0.45)
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		unevaluated	–	–	–
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		unevaluated	–	–	–
Immunodeficiency		unevaluated			

Trials Variable	Comments	Gong, Ou, et al Difference	Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age		significant	45.0 (33.0, 62.0)	63.5 (54.5, 72.0)	p < 0.01
Gender (Male)		not significant	–	–	p = 0.3
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		significant	20.0 (20.0, 20.0)	20.0 (20.0, 22.0)	p = 0.04
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	97.9 (96.7, 98.8)	96.8 (95.2, 97.8)	p = 0.02
Fever		not significant	26.1%	42.9%	p = 0.11
Cough		unevaluated	–	–	–
Days symptoms onset to dyspnoea		unevaluated	–	–	–
Dyspnoea %		unevaluated	–	–	–
Expectoration		unevaluated	–	–	–
Fatigue		unevaluated	–	–	–
Myalgia		unevaluated	–	–	–
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		not significant	–	–	p = 0.1
Headache		unevaluated	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		significant	12.9 (10.7, 15.7)	10.9 (9.6, 13.0)	p = 0.04
PCO_2, mmHg		unevaluated	–	–	–
Blood routine					
Hemoglobin	g/l	significant	136.8 (16.7)	128.9 (17.3)	p = 0.02
Red blood cell	10E12/l	significant	4.5 (0.6)	4.2 (0.6)	p = 0.02
Red blood cell distribution	%	significant	12.2 (11.8, 12.7)	12.8 (12.3, 13.1)	p < 0.01
White cell count	*10^9/l	significant	4.6 (3.7, 5.6)	5.2 (4.4, 6.7)	p = 0.03
Neutrophil count	*10^9/l	significant	2.8 (2.0, 3.6)	3.7 (2.8, 5.2)	p < 0.01
Lymphocytes	*10^9/l	significant	1.3 (1.0, 1.8)	1.0 (0.8, 1.4)	p < 0.01
Neutrophil-to-lymphocyte ratio		significant	1.9 (1.4, 2.9)	3.7 (2.0, 6.7)	p < 0.01
Platelets	*10^9/l	not significant	180.0 (147.0, 221.0)	167.0 (139.5, 200.0)	p = 0.09
Liver and renal function					
Albumin level	g/l	significant	39.7 (4.3)	34.2 (5.1)	p < 0.01
Aspartate aminotransferase (ASAT)	U/l	significant	20.8 (17.4, 27.1)	33.5 (27.4, 46.5)	p < 0.01
Alanine aminotransferase (ALAT)	U/l	not significant	21.0 (14.2, 32.4)	23.0 (15.1, 40.5)	p = 0.33
Total bilirubin	µmol/l	significant	9.6 (6.5, 14.1)	12.3 (8.6, 20.4)	p = 0.03
Direct bilirubin	µmol/l	significant	3.9 (2.7, 5.2)	5.2 (3.4, 7.8)	p < 0.01
Creatine phosphokinase (CPK)	U/l	significant	76.5 (50.0, 111.0)	111.5 (72.5, 168.5)	p < 0.01
Cretinine	µmol/l	not significant	58.8 (47.6, 76.7)	57.0 (42.5, 80.7)	p = 0.52
Urea		unevaluated	–	–	–
BUN, mmol/L	mmol/l	significant	3.9 (3.2, 4.6)	4.7 (3.1, 7.2)	p = 0.08
Cardiac function					
Myoglobin		unevaluated	–	–	–
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unevaluated	–	–	–
Inflammatory and coagulation					
Hypersensitive C-reactive protein	mg/l	significant	5.0 (5.0, 19.5)	35.5 (21.6, 72.3)	p < 0.01
Procalcitonin (PCT)	ng/ml	significant	0.0 (0.0, 0.1)	0.2 (0.1, 0.3)	p < 0.01
Lactate dehydrogenase (LDH)	U/l	significant	175.5 (148.5, 219.5)	296.0 (203.0, 407.0)	p < 0.01
D-Dimer	µg/l	not significant	990.0 (600.0, 1380.0)	1225.0 (6.6, 1720.0)	p = 0.25
Prothrombin time		unevaluated	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity					
Tabaquism		unevaluated	–	–	–
Chronic obstructive pulmonary disease		unevaluated	–	–	–
Heart Failure		unevaluated	–	–	–
Diabetes		unevaluated	–	–	–
Hypertension		unevaluated	–	–	–
Cardiovascular disease		unevaluated	–	–	–
Cerebrovascular diseases		unevaluated	–	–	–
Malignant tumor		unevaluated	–	–	–
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		unevaluated	–	–	–
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		unevaluated	–	–	–
Immunodeficiency		unevaluated			

Trials Variable	Comments	Difference	Lu, Hu, Fan, Liu, Yin, et al Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age		significant	≥ 60	< 60	p = 0.03
Gender (Male)		not significant	–	–	p = 0.43
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		unevaluated	–	–	–
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	–	–	–
Fever		significant	–	–	p = 0.02
Cough		not significant	–	–	p = 0.65
Days symptoms onset to dyspnoea		not significant	–	–	p = 0.72
Dyspnoea %		not significant	–	–	p = 0.28
Expectoration		unevaluated	–	–	–
Fatigue		not significant	–	–	p = 0.28
Myalgia		not significant	–	–	p = 0.81
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		not significant	–	–	p = 0.08
Headache		not significant	–	–	p = 0.33
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated	–	–	–
PCO_2, mmHg		unevaluated	–	–	–
Blood routine					
Hemoglobin		not significant	–	–	–
Red blood cell		not significant	–	–	–
Red blood cell distribution		unevaluated	–	–	–
White cell count	*10^9/l > 10	significant	4.6 (3.6-6.6)	5.8 (4.0-8.7)	p < 0.001
Neutrophil count		significant	3.3 (2.1-5.2)	5.0 (2.8-7.5)	p < 0.001
Lymphocytes	*10^9/l < 1.1	significant	0.9 (0.6-1.3)	0.6 (0.4- 0.9)	p < 0.001
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets		unevaluated	–	–	–
Liver and renal function					
Albumin level	g/l <34	significant	35.0 (31.9-38.0)	31.4 (29.2-35.5)	p < 0.001
Aspartate aminotransferase (ASAT)		unevaluated	–	–	–
Alanine aminotransferase (ALAT)	U/l >40	significant	22.0 (16.0-34.0)	28.0 (17.0-42.0)	p = 0.02
Total bilirubin		not significant	–	–	–
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		unevaluated	–	–	–
Cretinine		not significant	–	–	–
Urea		unevaluated	–	–	–
BUN, mmol/L		unevaluated	–	–	–
Cardiac function					
Myoglobin		unevaluated	–	–	–
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unevaluated	–	–	–
Inflammatory and coagulation					
Hypersensitive C-reactive protein	mg/l	significant	25.7 (8.5-36.6)	35.8 (25.2-37.9)	p < 0.001
Procalcitonin (PCT)		unevaluated	–	–	–
Lactate dehydrogenase (LDH)		unevaluated	–	–	–
D-Dimer	mg/l	significant	0.2 (0.1-0.7)	0.5 (0.3-2.3)	p < 0.001
Prothrombin time		not significant	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		not significant	–	–	–
Comorbidity					
Tabaquism		unevaluated	–	–	–
Chronic obstructive pulmonary disease		not significant	–	–	p = 0.24
Heart Failure		unevaluated	–	–	–
Diabetes		not significant	–	–	p = 0.96
Hypertension		not significant	–	–	p = 0.14
Cardiovascular disease		not significant	–	–	p = 0.11
Cerebrovascular diseases		not significant	–	–	p = 0.60
Malignant tumor		unevaluated	–	–	–
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		not significant	–	–	p = 0.52
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		unevaluated	–	–	–
Immunodeficiency		unevaluated			

Trials Variable	Comments	Difference	Qi, Jian, et al Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age		not significant	32.00 (26.00-46.50)	41.00 (26.00-47.00)	p = 0.72
Gender (Male)		not significant	–	–	p = 0.10
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		unevaluated	–	–	–
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	–	–	–
Fever		unevaluated	–	–	–
Cough		unevaluated	–	–	–
Days symptoms onset to dyspnoea		unevaluated	–	–	–
Dyspnoea %		unevaluated	–	–	–
Expectoration		unevaluated	–	–	–
Fatigue		unevaluated	–	–	–
Myalgia		unevaluated	–	–	–
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		unevaluated	–	–	–
Headache		unevaluated	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated	–	–	–
PCO_2, mmHg		unevaluated	–	–	–
Blood routine					
Hemoglobin		unevaluated	–	–	–
Red blood cell		unevaluated	–	–	–
Red blood cell distribution		unevaluated			
White cell count	*10^9/l	not significant	5.09 (3.70-6.89)	4.30 (3.56-4.66)	p = 0.14
Neutrophil count	*10^9/l	unevaluated	–	–	–
Lymphocytes	*10^9/l	not significant	1.38 (1.16-1.93)	1.22 (0.91-1.40)	p = 0.17
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets		unevaluated	–	–	–
Liver and renal function					
Albumin level		unevaluated	–	–	–
Aspartate aminotransferase (ASAT)		unevaluated	–	–	–
Alanine aminotransferase (ALAT)		unevaluated	–	–	–
Total bilirubin		unevaluated	–	–	–
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		unevaluated	–	–	–
Cretinine		unevaluated	–	–	–
Urea		unevaluated	–	–	–
BUN, mmol/L		unevaluated	–	–	–
Cardiac function					
Myoglobin		unevaluated	–	–	–
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unevaluated	–	–	–
Inflammatory and coagulation					
Hypersensitive C-reactive protein		unevaluated	–	–	–
Procalcitonin (PCT)		unevaluated	–	–	–
Lactate dehydrogenase (LDH)		unevaluated	–	–	–
D-Dimer		unevaluated	–	–	–
Prothrombin time		unevaluated	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity					
Tabaquism		unevaluated	–	–	–
Chronic obstructive pulmonary disease		unevaluated	–	–	–
Heart Failure		unevaluated	–	–	–
Diabetes		unevaluated	–	–	–
Hypertension		unevaluated	–	–	–
Cardiovascular disease		unevaluated	–	–	–
Cerebrovascular diseases		unevaluated	–	–	–
Malignant tumor		unevaluated	–	–	–
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		unevaluated	–	–	–
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		unevaluated	–	–	–
Immunodeficiency		unevaluated			

Trials Variable	Comments	Difference	Shi, Yu, et al Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age		significant	< 50	≥ 50	p < 0.001
Gender (Male)		significant	–	–	p = 0.03
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		unevaluated	–	–	–
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	–	–	–
Fever		unevaluated	–	–	–
Cough		unevaluated	–	–	–
Days symptoms onset to dyspnoea		unevaluated	–	–	–
Dyspnoea %		unevaluated	–	–	–
Expectoration		unevaluated	–	–	–
Fatigue		unevaluated	–	–	–
Myalgia		unevaluated	–	–	–
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		unevaluated	–	–	–
Headache		unevaluated	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated	–	–	–
PCO_2, mmHg		unevaluated	–	–	–
Blood routine					
Hemoglobin		unevaluated	–	–	–
Red blood cell		unevaluated	–	–	–
Red blood cell distribution		unevaluated	–	–	–
White cell count		unevaluated	–	–	–
Neutrophil count		unevaluated	–	–	–
Lymphocytes		unevaluated	–	–	–
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets		unevaluated	–	–	–
Liver and renal function					
Albumin level		unevaluated	–	–	–
Aspartate aminotransferase (ASAT)		unevaluated	–	–	–
Alanine aminotransferase (ALAT)		unevaluated	–	–	–
Total bilirubin		unevaluated	–	–	–
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		unevaluated	–	–	–
Cretinine		unevaluated	–	–	–
Urea		unevaluated	–	–	–
BUN, mmol/L		unevaluated	–	–	–
Cardiac function					
Myoglobin		unevaluated	–	–	–
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unevaluated	–	–	–
Inflammatory and coagulation					
Hypersensitive C-reactive protein		unevaluated	–	–	–
Procalcitonin (PCT)		unevaluated	–	–	–
Lactate dehydrogenase (LDH)		unevaluated	–	–	–
D-Dimer		unevaluated	–	–	–
Prothrombin time		unevaluated	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity					
Tabaquism		not significant	data not available	data not available	p = 0,331
Chronic obstructive pulmonary disease		unevaluated	–	–	–
Heart Failure		unevaluated	–	–	–
Diabetes		significant	data not available	data not available	p = 0,009
Hypertension		significant	data not available	data not available	p < 0.001
Cardiovascular disease		significant	data not available	data not available	p = 0,003
Cerebrovascular diseases		unevaluated	–	–	–
Malignant tumor		not significant	data not available	data not available	p = 0,025
Chronic renal disease		not significant	data not available	data not available	p = 0,101
Chronic liver disease		not significant	data not available	data not available	p = 0,877
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		unevaluated	–	–	–
Immunodeficiency		unevaluated			

Trials		Xie, Hungerford, Chen, Abrams, Li, Wang, et al			
Variable	Comments	Difference	Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age		significant	56·0 (47·8, 67·0)	69·00 (62·0, 76·0)	p < 0·001
Gender (Male)		not significant	–	–	–
Pregnancy		not significant	–	–	–
Predictive scores					
SOFA score		significant	2·0 (1·0, 2·0)	4·0 (2·0, 5·0)	p < 0·001
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		unevaluated	–	–	–
Systolic blood pressure		not significant	–	–	–
SpO_2 (Ambient air)		significant	97·0 (95·0, 98·0)	92·0 (83·8, 96·0)	p < 0·001
Fever		unevaluated	–	–	–
Cough		unevaluated	–	–	–
Days symptoms onset to dyspnoea		unevaluated	–	–	–
Dyspnoea %		unevaluated	–	–	–
Expectoration		unevaluated	–	–	–
Fatigue		unevaluated	–	–	–
Myalgia		unevaluated	–	–	–
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		unevaluated	–	–	–
Headache		unevaluated	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated	–	–	–
PCO_2, mmHg		unevaluated	–	–	–
Blood routine					
Hemoglobin		unevaluated	–	–	–
Red blood cell		unevaluated	–	–	–
Red blood cell distribution		unevaluated	–	–	–
White cell count	*10^9/l	significant	5·4 (4·0, 7·2)	9·0 (5·9, 13·4)	p < 0·001
Neutrophil count		unevaluated	–	–	–
Lymphocytes	*10^9/l	significant	0·98 (0·75, 1·52)	0·57 (0·43, 0·82)	p < 0001
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets	*10^9/l	significant	207·0 (161·0, 278·0)	159·0 (114·5, 220·5)	p < 0·001
Liver and renal function					
Albumin level		significant	35·6 (32·7, 37·9)	31·3 (28·2, 34·3)	p < 0·001
Aspartate aminotransferase (ASAT)		significant	30·0 (21·5, 44·0)	42·0 (26·0, 64·0)	p < 0.001
Alanine aminotransferase (ALAT)		significant	23·0 (15·0, 37·0)	28·0 (19·0, 44·0)	p = 0·026
Total bilirubin	umol/l	significant	8·4 (6·5, 11·9)	12·7 (9·0, 18·8)	p < 0·001
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		not significant	–	–	–
Cretinine	U/l	significant	66·0 (56·0, 83·0)	85·0 (66·0, 109·0)	p < 0·001
Urea		unevaluated	–	–	–
BUN, mmol/L	mmol/l	significant	4·4 (3·3, 6·0)	8·0 (5·7, 11·9	p < 0·001
Cardiac function					
Myoglobin		unevaluated	–	–	–
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unevaluated	–	–	–
Inflammatory and coagulation					
Hypersensitive C-reactive protein	mg/dl	significant	39·0 (10·7, 80·6)	97·2 (47·2, 148·8)	p < 0.001
Procalcitonin (PCT)		unevaluated	–	–	–
Lactate dehydrogenase (LDH)	U/l	significant	295 (216, 388)	505(371, 670)	p < 0·001
D-Dimer	≥ 1.0 mg/liter – N°/total N° (%)	significant	46 (37·7%)	108 (79·4%)	p < 0·001
Prothrombin time		unevaluated	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity					
Tabaquism		not significant	–	–	–
Chronic obstructive pulmonary disease		significant	2 (1·4%)	13 (8·4%)	p = 0·006
Heart Failure		significant	1 (0·7%)	12 (7·8%)	p = 0·003
Diabetes		not significant	–	–	–
Hypertension		significant	47 (32·6%)	80 (51·9%)	p < 0·001
Cardiovascular disease		unevaluated	–	–	–
Cerebrovascular diseases		unevaluated	–	–	–
Malignant tumor		unevaluated	–	–	–
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		unevaluated	–	–	–
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		unevaluated	–	–	–
Immunodeficiency		unevaluated			

Trials			Yan, Zhang, Xiao, et al		
Variable	Comments	Difference	Patients w/o severe/critical progress	Patients with severe/critical progress	XGBoost algorithm
Patient characteristics					
Age		unpublished analysis	–	–	–
Gender (Male)		unpublished analysis	–	–	–
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		unevaluated	–	–	–
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	–	–	–
Fever		unpublished analysis	–	–	–
Cough		unpublished analysis	–	–	–
Days symptoms onset to dyspnoea		unevaluated	–	–	–
Dyspnoea %		unpublished analysis	–	–	–
Expectoration		unevaluated	–	–	–
Fatigue		unevaluated	–	–	–
Myalgia		unevaluated	–	–	–
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		unevaluated	–	–	–
Headache		unevaluated	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated	–	–	–
PCO_2, mmHg		unevaluated	–	–	–
Blood routine					
Hemoglobin		unevaluated	–	–	–
Red blood cell		unevaluated	–	–	–
Red blood cell distribution		unevaluated	–	–	–
White cell count		unpublished analysis	–	–	–
Neutrophil count		unpublished analysis	–	–	–
Lymphocytes		significant	> 14%	< 14%	7.5% relative importance
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets		unevaluated	–	–	–
Liver and renal function					
Albumin level		unpublished analysis	–	–	–
Aspartate aminotransferase (ASAT)		unevaluated	–	–	–
Alanine aminotransferase (ALAT)		unevaluated	–	–	–
Total bilirubin		unevaluated	–	–	–
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		unevaluated	–	–	–
Cretinine		unevaluated	–	–	–
Urea		unpublished analysis	–	–	–
BUN, mmol/L		unevaluated	–	–	–
Cardiac function					
Myoglobin		unevaluated	–	–	–
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unpublished analysis	–	–	–
Inflammatory and coagulation					
Hypersensitive C-reactive protein	nmg/l	significant	< 41.2	> 41.2	4% relative importance
Procalcitonin (PCT)		unpublished analysis	–	–	–
Lactate dehydrogenase (LDH)	U/l	significant	< 365	> 365	35% relative importance
D-Dimer		unpublished analysis	–	–	–
Prothrombin time		unevaluated	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity					
Tabaquism		unevaluated	–	–	–
Chronic obstructive pulmonary disease		unevaluated	–	–	–
Heart Failure		unevaluated	–	–	–
Diabetes		unevaluated	–	–	–
Hypertension		unevaluated	–	–	–
Cardiovascular disease		unevaluated	–	–	–
Cerebrovascular diseases		unevaluated	–	–	–
Malignant tumor		unevaluated	–	–	–
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		unevaluated	–	–	–
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		unevaluated	–	–	–
Immunodeficiency		unevaluated			

Trials Variable	Comments	Difference	Yuan, Yin, et al Patients w/o severe/critical progress	Patients with severe/critical progress	p-value
Patient characteristics					
Age		significant	55 (35-60)	68 (63-73)	p = 0.003
Gender (Male)		not significant	–	–	
Pregnancy		unevaluated	–	–	–
Predictive scores					
SOFA score		unevaluated	–	–	–
Signs and symptoms					
Heart rate		unevaluated	–	–	–
Respiratory rate (breaths per minute)		unevaluated	–	–	–
Systolic blood pressure		unevaluated	–	–	–
SpO_2 (Ambient air)		unevaluated	–	–	–
Fever		not significant	–	–	–
Cough		not significant	–	–	–
Days symptoms onset to dyspnoea		unevaluated	–	–	–
Dyspnoea %		significant	6%	100%	< 0.0001
Expectoration		unevaluated	–	–	–
Fatigue		unevaluated	–	–	–
Myalgia		not significant	–	–	–
Haemoptysis		unevaluated	–	–	–
Gastrointestinal symptoms		unevaluated	–	–	–
Headache		unevaluated	–	–	–
Laboratory testing					
Blood oxygen content					
PO_2, mmHg		unevaluated	–	–	–
PCO_2, mmHg		unevaluated	–	–	–
Blood routine					
Hemoglobin		unevaluated	–	–	–
Red blood cell		unevaluated	–	–	–
Red blood cell distribution		unevaluated	–	–	–
White cell count		unevaluated	–	–	–
Neutrophil count		unevaluated	–	–	–
Lymphocytes		unevaluated	–	–	–
Neutrophil-to-lymphocyte ratio		unevaluated	–	–	–
Platelets		unevaluated	–	–	–
Liver and renal function					
Albumin level		unevaluated	–	–	–
Aspartate aminotransferase (ASAT)		unevaluated	–	–	–
Alanine aminotransferase (ALAT)		unevaluated	–	–	–
Total bilirubin		unevaluated	–	–	–
Direct bilirubin		unevaluated	–	–	–
Creatine phosphokinase (CPK)		unevaluated	–	–	–
Cretinine		unevaluated	–	–	–
Urea		unevaluated	–	–	–
BUN, mmol/L		unevaluated	–	–	–
Cardiac function					
Myoglobin		unevaluated	–	–	–
Troponin		unevaluated	–	–	–
N-terminal pro b Natriuretic Peptide		unevaluated	–	–	–
Inflammatory and coagulation					
Hypersensitive C-reactive protein		unevaluated	–	–	–
Procalcitonin (PCT)		unevaluated	–	–	–
Lactate dehydrogenase (LDH)		unevaluated	–	–	–
D-Dimer		unevaluated	–	–	–
Prothrombin time		unevaluated	–	–	–
Activated partial thromboplastin time		unevaluated	–	–	–
Chest X-Ray					
Ground glass opacity		unevaluated	–	–	–
Interstitial opacity		unevaluated	–	–	–
Local patchy shadowing		unevaluated	–	–	–
Bilateral patchy shadowing		unevaluated	–	–	–
Comorbidity					
Tabaquism		unevaluated	–	–	–
Chronic obstructive pulmonary disease		unevaluated	–	–	–
Heart Failure		unevaluated	–	–	–
Diabetes		signficant			p = 0.001
Hypertension		signficant			p = 0.003
Cardiovascular disease		signficant			p = 0.041
Cerebrovascular diseases		not significant	–	–	–
Malignant tumor		not significant	–	–	
Chronic renal disease		unevaluated	–	–	–
Chronic liver disease		unevaluated	–	–	–
Pulmonary tuberculosis		unevaluated	–	–	–
Chronic digestive disorders		not significant	–	–	–
Immunodeficiency		unevaluated			

Study	Number of patients	Population	Reference	doi
Bai, Fang, Zhou, Bai, Liu, Chen, Xu, Xia et al	133	Chinese	medRxiv (2020)	10.1101/2020.03.20.20037325
Caramelo, et al	Unknown	Chinese	medRxiv (2020)	10.1101/2020.02.24.20027268
Gong, Ou, et al	189	Chinese	medRxiv (2020)	10.1101/2020.03.17.20037515
Lu, Hu, Fan, Liu, Yin, et al org/10.1101/2020.02.20.20025510	577	Chinese	medRxiv (2020)	https://doi.
Qi, Jiang, et al	52	Chinese	medRxiv (2020)	10.1101/2020.02.29.20029603
Shi, Yu, et al	478	Chinese	Critical Care 2020, 24:108	10.1186/s13054-020-2833-7
Xie, Hungerford, Chen, Abrams, Li, Wang, et al	299	Chinese	medRxiv (2020)	10.1101/2020.03.28.20045997
Yan, Zhang, Xiao et al	375	Chinese	medRxiv (2020)	10.1101/2020.02.27.20028027
Yuan, Yin, et al	27	Chinese	medRxiv (2020)	10.1371/journal.pone.0230548
W.J. Guan, et al	1099	Chinese	medRxiv (2020)	10.1101/2020.02.06.20020974
Guang, et al	21	Chinese	J Clin Invest 2020	0.1172/JCI137244

Supplementary material 2
List of all potential variables proposed to the Delphi process

Patients' characteristics
Age
Gender (Male)
Pregnancy
Days symptoms onset to admission

Predictive scores
SOFA score

Signs and symptoms
Heart rate
Respiratory rate (breaths per minute)
Systolic blood pressure
SpO_2 (Ambient air)
Fever
Cough
Days symptoms onset to dyspnoea
Dyspnoea %
Expectoration
Fatigue
Myalgia
Haemoptysis
Gastrointestinal symptoms
Headache

Laboratory testing
Blood oxygen content
- PO_2, mmHg
- PCO_2, mmHg

Blood routine
- Hemoglobin
- Red blood cell
- Red blood cell distribution
- White cell count
- Neutrophil count
- Lymphocytes
- Neutrophil-to-lymphocyte ratio
- Platelets

Liver and renal function
- Albumin level
- Aspartate aminotransferase (ASAT)
- Alanine aminotransferase (ALAT)
- Total bilirubin
- Direct bilirubin
- Creatine phosphokinase (CPK)
- Creatinine
- Urea
- BUN, mmol/L

Cardiac function
- Myoglobin
- Troponin
- N-terminal pro b Natriuretic Peptide

Inflammatory and coagulation
- Hypersensitive C-reactive protein
- Procalcitonin (PCT)
- Lactate dehydrogenase (LDH)
- D-Dimer
- D-Dimer $\geq$ 1.0
- Prothrombin time
- Activated partial thromboplastin time

Chest X-Ray
Ground glass opacity
Interstitial opacity
Local patchy shadowing
Bilateral patchy shadowing

Comorbidity
Tabaquism
Chronic obstructive pulmonary disease
Heart Failure
Diabetes with end-organ damage
Diabetes without end-organ damage
Hypertension
Cardiovascular disease
Cerebrovascular diseases
Malignant tumor
Chronic renal disease
Chronic liver disease
Pulmonary tuberculosis
Chronic digestive disorders
Immunodeficiency