

# Predictors of Intensive Care Unit admission in patients with coronavirus disease 2019 (COVID-19)

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## Abstract

Italy is currently experiencing an epidemic of coronavirus disease 2019 (Covid-19). Aim of our study is to identify the best predictors of Intensive Care Unit (ICU) admission in patients with Covid-19. We examined 28 patients admitted to the Emergency Department (ED) and subsequently confirmed as cases of Covid-

19. Patients received, at the admission to the ED, a diagnostic work-up including: patient history, clinical examination, an arterial blood gas analysis (whenever possible performed on room air), laboratory blood tests, including serum concentrations of interleukin 6 (IL-6), lung ultrasound examination and a computed tomography (CT) scan of the thorax. For each patient, as gas exchange index through the alveolocapillary membrane, we determined the alveolar-arterial oxygen gradient (AaDO<sub>2</sub>) and the alveolar-arterial oxygen gradient augmentation (AaDO<sub>2</sub> augmentation). For each patient, as measurement of hypoxemia, we determined oxygen saturation (SpO<sub>2</sub>), partial pressure of oxygen in arterial blood (PaO<sub>2</sub>), PaO<sub>2</sub> deficit and the ratio between arterial partial pressure of oxygen by blood gas analysis and fraction of inspired oxygen (P/F). Patients were assigned to ICU Group or to Non-ICU Group basing on the decision to intubate. Areas under the curve (AUC) and receiver operating characteristic (ROC) curve were used to compare the performance of each test in relation to prediction of ICU admission. Comparing patients of ICU Group (10 patients) with patients of Non-ICU Group (18 patients), we found that the first were older, they had more frequently a medical history of malignancy and they were more frequently admitted to ED for dyspnea. Patients of ICU Group had lower oxygen saturation, PaO<sub>2</sub>, P/F and higher heart rate, respiratory rate, AaDO<sub>2</sub>, AaDO<sub>2</sub> augmentation and lactate than patients of Non-ICU Group. ROC curves demonstrate that age, heart rate, respiratory rate, dyspnea, lactate, AaDO<sub>2</sub>, AaDO<sub>2</sub> augmentation, white blood cell count, neutrophil count and percentage, fibrinogen, C-reactive protein, lactate dehydrogenase, glucose level, international normalized ratio (INR), blood urea and IL-6 are useful predictors of ICU admission. We identified several predictors of ICU admission in patients with Covid-19. They can act as fast tools for the early identification and timely treatment of critical cases since their arrival in the ED.

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Key words: arterial blood gas analysis; alveolar-arterial oxygen gradient; hypoxemia; dyspnea; lactate.

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## Introduction

A novel beta coronavirus (2019-nCoV) was identified in a cluster of hospitalized patients with pneumonia of unknown cause in Wuhan, China, in December 2019 and January 2020 [1]. The pathogen was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) considering its phylogenetic similarity to SARS-CoV [1]. The World Health Organization (WHO) declared coronavirus disease 2019 (Covid-19) a public health emergency of international concern [2]. Covid-19 has spread rapidly throughout China causing a wide spectrum of clinical pictures [3]. Italy is currently experiencing an epidemic of Covid-19 which emerged in the region of Lombardy [4], progressing rapidly in all the country.

Covid-19 caused thousands of deaths and stressed national health system, especially with regard to Intensive Care Units (ICU) [5]. Nowadays little evidence exists about the predictors of ICU admission in patients with Covid-19, in fact only clinical features and laboratory parameters have been evaluated. A recent retrospective case series of 1591 critically ill patients with laboratory-confirmed Covid-19 admitted to ICUs in Lombardy (Italy), showed as the majority were older men [6]. Many laboratory abnormalities (increased white blood cell count, neutrophil count, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine, cardiac troponin, D-dimer, prothrombin time, procalcitonin and C-reactive protein, decreased lymphocyte count and albumin) were cited as predictive of adverse outcome in patients with Covid-19 [7]. There are no studies about the prognostic utility of arterial blood gas analysis in patients with Covid-19. The aim of our study is to evaluate clinical features, laboratory parameters and arterial blood gas analysis variables, identifying the best predictors of ICU admission in patients with Covid-19.

## Materials and Methods

This observational study was conducted in the Emergency Department (ED) of C.T.O. Hospital in Naples (Italy) from 11 March 2020 to 25 April 2020. Our research satisfies the Helsinki criteria. We examined 28 consecutive patients admitted to the ED for respiratory symptoms (cough, fever, dyspnea) or syncope or chest pain or headache or myalgia or gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain or discomfort) [8] and subsequently confirmed as cases of Covid-19 using real-time reverse-transcription Polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens, only laboratory-confirmed cases were included in the analysis. All patients have been clinically followed for at least 30 days from their admission to the ED. Patients received, at the admission to the ED, a diagnostic work-up including: patient history, clinical examination, an arterial blood gas analysis (whenever possible performed on room air), laboratory blood tests including serum concentrations of Interleukin 6 (IL-6), lung ultrasound examination and a computed tomography (CT) scan of the thorax. Laboratory blood tests and lung ultrasound examination data have been collected within 1 h

from the arrival of the patients at the ED. For each patient, as gas exchange index through the alveolocapillary membrane, we determined the alveolar-arterial oxygen gradient (AaDO<sub>2</sub>) [9] and the alveolar-arterial oxygen gradient augmentation (AaDO<sub>2</sub> augmentation) (Box 1). Measurements of arterial blood gases were obtained while the patient breathed room air. Using the estimated normal gradient [10] we calculated the alveolar-arterial oxygen gradient augmentation (Box 1) [11].

For each patient, as measurement of hypoxemia [12], we determined oxygen saturation (SpO<sub>2</sub>), PaO<sub>2</sub>, PaO<sub>2</sub> deficit (11) [13] and (PaO<sub>2</sub>)/FiO<sub>2</sub> or P/F (Box 1). Based on the decision to intubate and the consequently ICU admission, the 28 patients were assigned to the ICU Group (ICUG) (10 patients) or to the Non-ICU Group (NICUG) (18 patients). Endotracheal intubation was performed for patients with PaO<sub>2</sub>/FiO<sub>2</sub> ≤150 mmHg [14] and in case of failure to reach the established targets (SpO<sub>2</sub> ≥94% and a respiratory rate ≤25 breaths/min) after 120 min of continuous positive airways pressure (CPAP) [15]. Data were analyzed using SPSS version 21.0 (SPSS, Chicago, IL, USA). Continuous data are expressed as mean ± 1 standard deviation and categorical variables as percentages. Quantitative variables were compared by using Student's *t*-test while chi-square distribution was used to compare categorical variables. A p-value < 0.05 was considered statistically significant. Areas Under the Curve (AUC) and Receiver Operating Characteristic (ROC) curve were used to compare the performance of each different test in relation to the prediction of ICU admission. The Logistic Regression Analysis was used to evaluate which variables are the most powerful to predict the ICU admission.

## Results

Our study population included 28 patients (16 males) with a mean age of 56 years. The symptoms at onset of illness were fever (57%), dyspnea (32%), gastrointestinal symptoms (14%), cough (11%), myalgia (7%), headache (7%), syncope (7%), chest pain (7%). Considering the 10 ICU patients, one was directly treated with the endotracheal intubation, while the other 9 patients were treated with continuous positive airways pressure (CPAP) for at least 120 min (the mean of the Positive End-Expiratory Pressure, PEEP) used was 9,67 cmH<sub>2</sub>O while the mean of fraction of

### Box 1.

The alveolar-arterial oxygen gradient was calculated as follows:

AaDO<sub>2</sub> (mmHg), 150 - (1.25 x PaCO<sub>2</sub>) - PaO<sub>2</sub>,

where PaCO<sub>2</sub> is the partial pressure of carbon dioxide in arterial blood (mmHg) and PaO<sub>2</sub> is the partial pressure of oxygen in arterial blood (mmHg). Measurements of arterial blood gases were obtained while the patient breathed room air. The estimated normal gradient (mmHg) was calculated as follows:

(Age/4) + 4.

The alveolar-arterial oxygen gradient augmentation was calculated as follows:

AaDO<sub>2</sub> augmentation (mmHg), AaDO<sub>2</sub> - estimated normal gradient.

Owing to the natural decline in normal arterial oxygen levels with age, the estimated normal PaO<sub>2</sub> (mmHg) was calculated as follows:

100 - Age/3.

The PaO<sub>2</sub> deficit was calculated as follows:

PaO<sub>2</sub> deficit (mmHg), estimated normal PaO<sub>2</sub> - arterial blood gas analysis PaO<sub>2</sub>.

The P/F was calculated as the ratio between arterial partial pressure of oxygen by blood gas analysis (in mmHg) and fraction of inspired oxygen.

inspired oxygen (FiO<sub>2</sub>) was 95,55%) before the endotracheal intubation that was performed because CPAP treatment failed to reach the established targets (SpO<sub>2</sub> ≥94% and a respiratory rate ≤25 breaths/min). Considering the 18 Non-ICU patients, 12 patients didn't require oxygen supplementation, 2 patients were treated with conventional nasal cannula (mean of FiO<sub>2</sub> was 28%), 1 patient was treated with Venturi mask (FiO<sub>2</sub> was 60%) and the last 3 patients were treated with CPAP (the mean of PEEP used was 10 cmH<sub>2</sub>O while the mean of FiO<sub>2</sub> was 50%).

The baseline characteristics and the laboratory findings at the admission to the ED of the two subgroups are detailed in Table 1 and in Table 2, respectively. Comparing patients of the ICU Group with patients of the Non-ICU Group, the first were older, they had more frequently medical history of malignancy and they were more frequently admitted to the ED for dyspnea (Table 1, all p<0.05). Patients of the ICU Group had lower oxygen saturation, PaO<sub>2</sub>, PaCO<sub>2</sub>, P/F and higher heart rate, respiratory rate, AaDO<sub>2</sub>, AaDO<sub>2</sub> augmentation and lactate levels than patients of the Non-ICU Group (Table 1, all p<0.05). Considering laboratory findings, at the admission to the ED, patients of the ICU Group had lower

lymphocyte count, lymphocyte percentage, monocyte percentage, albumin level and higher white blood cell count, neutrophil count, neutrophil percentage, C-reactive protein, INR, fibrinogen, lactate dehydrogenase, blood urea, glucose, Interleukin 6 than patients of the Non-ICU Group (Table 2, all p<0.05).

The receiver operating characteristic curve of epidemiological characteristics, medical history, vital signs and symptoms (Figure 1) demonstrates that age, heart rate, respiratory rate and dyspnea are useful in predicting ICU admission, while testing the ability to predict ICU admission of medical history of malignancy, it showed an AUC of 0.611. The receiver operating characteristic curve of arterial blood gas analysis parameters (Figure 2) demonstrates that lactate levels, AaDO<sub>2</sub> and AaDO<sub>2</sub> augmentation are useful in predicting ICU admission. The receiver operating characteristic curve of laboratory findings at the admission to the ED (Figure 3) demonstrates that INR, lactate dehydrogenase (LDH), blood urea, C-reactive protein, fibrinogen, neutrophil percentage, Interleukin 6, neutrophil count, glucose and white blood cell count are useful in predicting ICU admission, while testing the ability to predict ICU admission of lymphocyte count, monocyte percentage, albu-

**Table 1. Baseline characteristics at the admission to the Emergency Department of the two subgroups.**

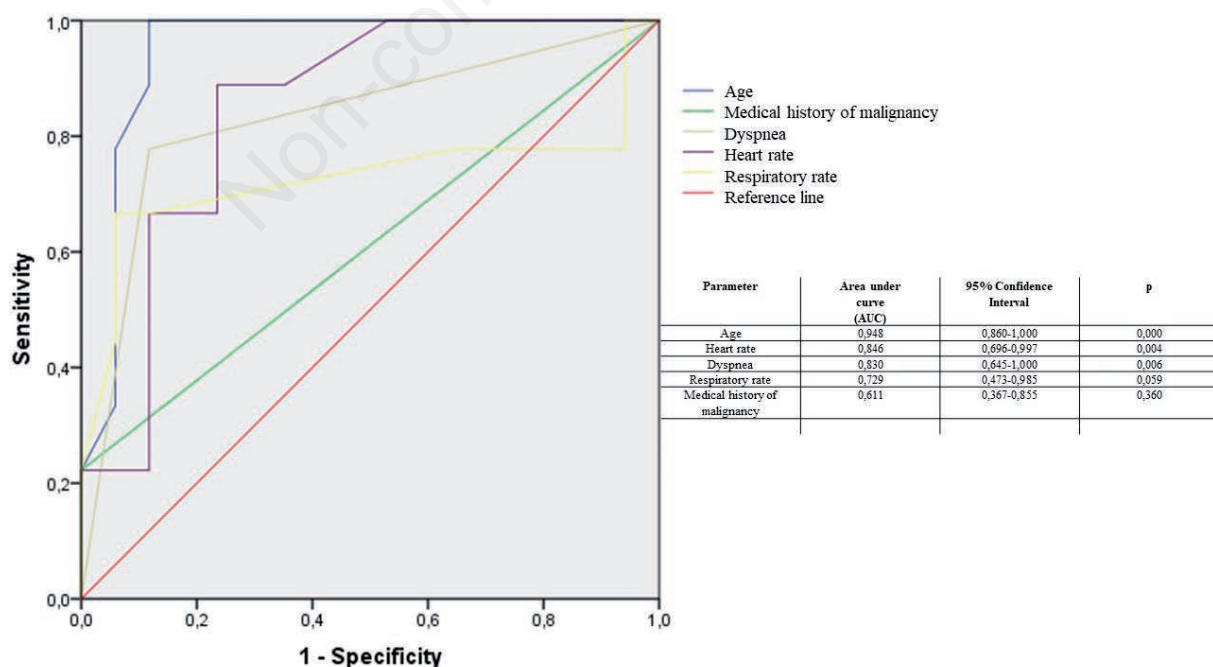
	ICUG (n=10)	NICUG (n=18)	p
Age (years)	73±7.44	47±12.62	0.000
Sex (female)	20%	55%	0.073
Medical history of arterial hypertension	40%	17%	0.130
Medical history of chronic obstructive pulmonary disease or asthma	30%	22%	0.553
Medical history of diabetes	20%	5%	0.209
Medical history of malignancy	20%	0%	0.039
Medical history of atrial fibrillation	10%	5%	0.620
Medical history of ischemic heart disease	30%	5%	0.059
Fever	70%	50%	0.323
Dyspnea	70%	11%	0.001
Gastrointestinal symptoms	10%	17%	0.644
Cough	0%	17%	0.185
Myalgia	0%	11%	0.291
Headache	0%	11%	0.291
Syncope	10%	5%	0.676
Chest pain	0%	11%	0.291
Systolic BP (mm Hg)	130.1±30.9	127.5±17.2	0.776
Diastolic BP (mm Hg)	76.7±14.79	73.1±11.2	0.476
Body temperature (°C)	36.1±1.0	36.5±0.5	0.220
Heart rate (bpm)	91.4±17.9	73.4±12.5	0.004
Respiratory rate (breaths/min)	24.4±7.7	17.9±3.0	0.005
Oxygen saturation (%)	86.9±11.7	97.3±2.1	0.001
PaO <sub>2</sub> (mmHg)	56.3±14.2	78.3±10.0	0.005
PaCO <sub>2</sub> (mmHg)	31.7±5.1	37±5.8	0.029
PaO <sub>2</sub> /FiO <sub>2</sub>	234.6±146.4	362.7±59.9	0.006
PaO <sub>2</sub> deficit (mmHg)	17.2±15.11	6.3±7.8	0.08
pH	7.49±0.06	7.45±0.06	0.172
AaDO <sub>2</sub> (mmHg)	56.6±17.5	25.9±9.7	0.001
AaDO <sub>2</sub> augmentation (mmHg)	32.7±19.1	10.3±8.00	0.003
Lactate level (mmol/L)	1.7±0.5	0.7±0.2	0.000

ICUG, Intensive Care Unit Group; NICUG, Non- Intensive Care Unit Group; BP, blood pressure; PaO<sub>2</sub>, partial pressure of oxygen in arterial blood; PaCO<sub>2</sub>, partial pressure of carbon dioxide in arterial blood; AaDO<sub>2</sub>, alveolar-arterial oxygen gradient.

**Table 2. Laboratory findings at the admission to the Emergency Department of the two subgroups.**

	ICUG (n=10)	NICUG (n=18)	p
White blood cell count ( $\times 10^3/\mu\text{L}$ )	8.87 $\pm$ 3.31	5.11 $\pm$ 1.41	0.000
Neutrophil count ( $\times 10^3/\mu\text{L}$ )	7.66 $\pm$ 3.23	3.24 $\pm$ 1.36	0.000
Neutrophil percentage	85.34 $\pm$ 5.68	62.04 $\pm$ 12.21	0.000
Lymphocyte count ( $\times 10^3/\mu\text{L}$ )	0.78 $\pm$ 0.34	1.39 $\pm$ 0.57	0.007
Lymphocyte percentage	9.51 $\pm$ 3.88	28.10 $\pm$ 10.28	0.000
Eosinophil count ( $\times 10^3/\mu\text{L}$ )	0.04 $\pm$ 0.10	0.06 $\pm$ 0.12	0.588
Eosinophil percentage	0.30 $\pm$ 0.71	1.62 $\pm$ 2.59	0.149
Basophil count ( $\times 10^3/\mu\text{L}$ )	0.02 $\pm$ 0.01	0.02 $\pm$ 0.04	0.744
Basophil percentage	0.21 $\pm$ 0.10	0.32 $\pm$ 0.23	0.202
Monocyte count ( $\times 10^3/\mu\text{L}$ )	0.36 $\pm$ 0.19	0.42 $\pm$ 0.15	0.365
Monocyte percentage	4.62 $\pm$ 2.55	9.08 $\pm$ 3.57	0.003
C-reactive protein (mg/L)	171.59 $\pm$ 101.47	20.55 $\pm$ 38.14	0.000
Procalcitonin ( $\mu\text{g/L}$ )	2.30 $\pm$ 5.98	0.10 $\pm$ 0.19	0.125
INR	1.42 $\pm$ 0.25	1.07 $\pm$ 0.05	0.000
D-dimer ( $\mu\text{g/L}$ )	6227.60 $\pm$ 17364.92	268.22 $\pm$ 323.75	0.151
Fibrinogen (mg/dL)	651.11 $\pm$ 302.77	363.55 $\pm$ 125.75	0.002
Lactate dehydrogenase (U/L)	748.70 $\pm$ 543.80	189.94 $\pm$ 51.89	0.000
Albumin level (g/dL)	3.45 $\pm$ 0.36	4.39 $\pm$ 0.55	0.000
Alanine aminotransferase (U/L)	52.80 $\pm$ 47.62	28.89 $\pm$ 17.2	0.064
Serum creatinine (mg/dL)	0.96 $\pm$ 0.27	0.85 $\pm$ 0.22	0.274
Blood urea (mg/dL)	74.20 $\pm$ 25.53	34.61 $\pm$ 8.27	0.000
Sodium (mmol/L)	136.70 $\pm$ 4.22	138.72 $\pm$ 2.08	0.099
Potassium (mmol/L)	4.22 $\pm$ 0.62	4.02 $\pm$ 0.36	0.294
Glucose (mg/dL)	145.10 $\pm$ 44.07	101.67 $\pm$ 23.02	0.002
Interleukin 6 (pg/mL)	58.51 $\pm$ 48.63	14.03 $\pm$ 19.21	0.006

ICUG, Intensive Care Unit Group; NICUG, non-ICU Group; INR, international normalized ratio.



**Figure 1. Receiver operating characteristic (ROC) curve comparing accuracy of epidemiological characteristics, medical history, vital signs and symptoms in relation to the prediction of ICU admission in patients with Covid-19.**

min and lymphocyte percentage, they showed an AUC of 0.236-0.148-0.093-0.044, respectively. From the Logistic Regression Analysis we obtained the following two equations:

$$P=1/1+e^{-(274.480+0.905 \times \text{lactate dehydrogenase})}$$

$$P=1/1+e^{-(210.877+175.594 \times \text{lactate level})}$$

This model allows 100% correct classification of patients into the two different groups. Critical values were >303.29 for lactate dehydrogenase and >1.201 for lactate level.

## Discussion

Most patients with Covid-19 have mild symptoms, while some others may develop severe complications including Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure leading to ICU admission and death. Emergency physicians should identify patients with severe symptoms, hypoxemia with the need for oxygen supplementation, or high risk for clinical deterioration that require admission for further management and monitoring [16]. In our study, among epidemiological characteristics, the best predictor of ICU admission in patients with Covid-19 was the age (AUC 0.948) as previously demonstrated by Wang *et al.* [17]. In our population there was not a good predictor of ICU admission among coexisting medical conditions, in fact medical history of malignancy was more frequent in the ICU Group than in the Non-ICU Group ( $p<0.05$ ) but it showed an AUC of just 0.611. Among symptoms at ED presentation, dyspnea was a good predictor of ICU admission showing an AUC of 0.830, while among vital signs the best predictors were heart rate and respiratory rate (AUC 0.846-0.729, respectively). These clinical findings are attributable

to hypoxemia that represents the main pathophysiological complication of patients with pneumonia. In particular, the development of hypoxemia reflects the severity of lung involvement (interstitium inflammation and alteration of the alveolar ventilation) leading to intrapulmonary shunt in the affected zone [18]. Shunt is a condition whereby blood from the right side of the heart enters the left side without taking part in any gas exchange and it can be caused by pneumonia and ARDS [12]. There are different measurement of hypoxemia and among them, in our study, oxygen saturation, PaO<sub>2</sub> and P/F showed a statistically significant difference between the two groups (all  $p<0.05$ ), underlining the major grade of hypoxemia of the ICU group patients since their admission to the ED. The AaDO<sub>2</sub> is an index of gas exchange and indicates the integrity of the alveolo-capillary membrane being influenced by diffusion gradient, ventilation-perfusion imbalance and true shunt [9]. In our study, ICU group patients had higher AaDO<sub>2</sub> and AaDO<sub>2</sub> augmentation than non-ICU group patients (all  $p<0.05$ ) underlining the alveolo-capillary membrane damage and the consequent worsening of gas exchange in the ICU group since their admission to the Emergency Department. Furthermore, AaDO<sub>2</sub> and AaDO<sub>2</sub> augmentation showed an excellent and a good accuracy (AUC of 0.952 and 0.810 respectively) to predict ICU admission in patients with Covid-19 since their arrival in the Emergency Department. Among arterial blood gas analysis parameters, lactate level was higher in the ICU Group (1.7±0.5 mmol/L) than in the Non-ICU Group (0.7±0.2 mmol/L) with statistical significance. Furthermore lactate showed an excellent accuracy (AUC 1.000) to predict ICU admission, since it can be used as an early marker of reduced tissue oxygenation, organ failure and occult shock before any detectable changes occur in patients' vital signs [19].

White blood cell count, neutrophil count and neutrophil percentage were higher in the ICU Group than in the non-ICU Group with statistical significance and, in particular, neutrophil percentage

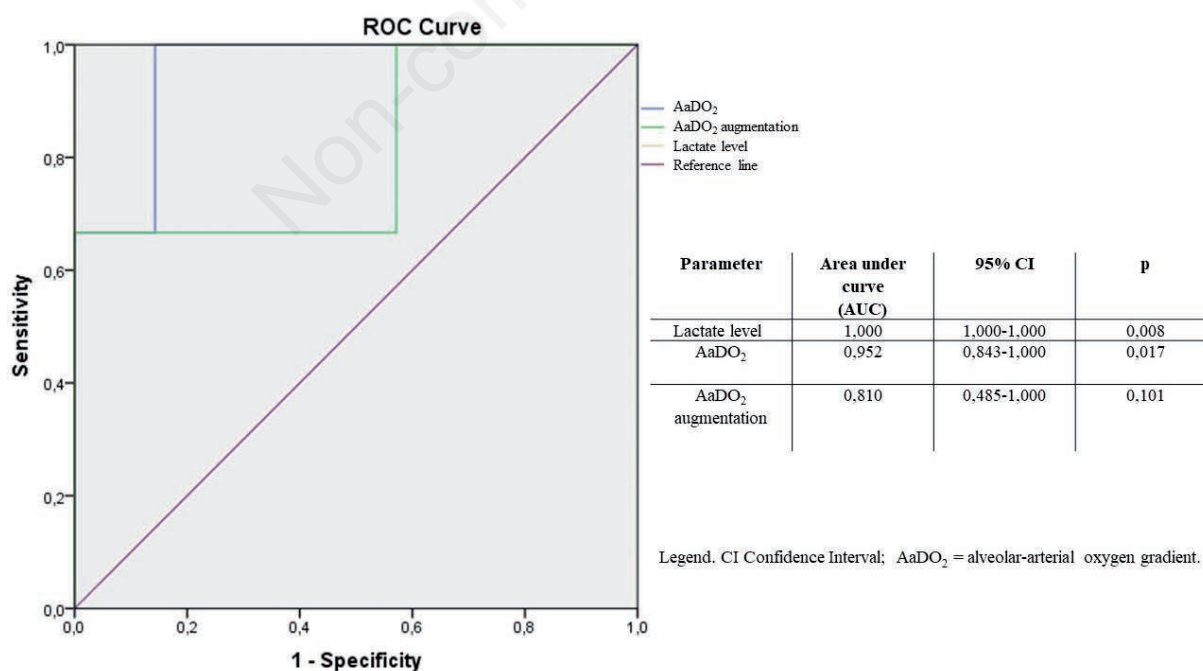


Figure 2. Receiver operating characteristic (ROC) curve comparing accuracy of arterial blood gas analysis parameters at the admission to the Emergency Department in relation to the prediction of ICU admission in patients with Covid-19.

showed an excellent accuracy (AUC 0.954) and white blood cell count and neutrophil count a good accuracy (AUC 0.847 and 0.898, respectively), to predict ICU admission in patients with Covid-19. This can be explained by the increased severity of Systemic Inflammatory Response Syndrome (SIRS) in the ICU patients compared to the Non-ICU patients and also by possible bacterial over-infections. Recently, Barnes *et al.* suggested that the severe symptoms of Covid-19, including ARDS, could be caused by Neutrophil Extracellular Traps (NETs), since they found lung infiltration of neutrophils in an autopsy specimen from a patient who succumbed to Covid-19 [20]. Lymphocyte count and lymphocyte percentage were reduced below the normal values in the majority of patients included in the study (2019-nCoV might mainly act on lymphocytes, especially T- lymphocytes, just like SARS-CoV [21]) and they were reduced more profoundly in the ICU Group than in the non-ICU Group (all  $p < 0.05$ ), but they failed to predict ICU admission, AUC of 0.236 and 0.044, respectively). In our study, the levels of non-specific inflammation parameters, such as fibrinogen, C-reactive protein and lactate dehydrogenase were higher in the ICU Group than in the non-ICU Group with statistical significance and they showed an excellent accuracy to predict ICU admission (AUC 0.959, 0.969 and 0.980, respectively). Considering the inflammatory status, it is not surprising that in our study glucose level was significantly higher in the ICU Group than in the non-ICU Group and it showed a good accuracy (AUC 0.816) to predict ICU admission. Comparing the ICU Group with the non-ICU Group, we found in the first group higher international normalized ratio (INR) and lower albumin level indicating that critical patients developed liver failure besides the fact that the angiotensin-converting enzyme 2 (ACE 2), a key receptor for the SARS-CoV-2 viral entry, is also expressed by cholangiocytes in liver and enterocytes in intestine [22]. Furthermore, INR showed an excellent accuracy (AUC 1.000) to predict ICU admission. In our study, blood urea was significantly higher in the ICU

Group than in the non-ICU Group, showing an excellent accuracy (AUC 0.949) to predict ICU admission. This finding can be explained by the hypoperfusion-related injury of the renal tubules due to cytokine storm and also by the fact that podocytes and tubule epithelial cells express the ACE2 receptor [23]. Furthermore, the ICU patients are probably more dehydrated than the non-ICU patients. A large number of data suggest that cytokine storm, in critical patients with Covid-19, is an important cause of death [24]. Therefore, considering that interleukin-6 (IL-6) plays an important role in cytokine release syndrome, it is not surprising that in our study IL-6 was significantly higher in the ICU Group than in the non-ICU Group and that it showed an excellent accuracy (AUC 0.929) to predict ICU admission. Basing on the results of Logistic Regression Analysis, lactate dehydrogenase and lactate level seem to be the most powerful variables to predict the ICU admission. Probably the elevated serum LDH concentration in the ICU patients reflects cellular hypoxia and tissue necrosis, while the elevated lactate level can be due to hypoxia and to the high respiratory rate generating fatigue of the respiratory muscles.

The main limitation of our study is that the population sample could be larger, but considering that the pandemic had a limited extension in the south of Italy a group of only 28 patients could be representative of how this health emergency has been managed in a southern Italy hospital.

## Conclusions

We identified several predictors of ICU admission in patients with Covid-19. They can act as fast tools for the early identification and timely treatment of critical cases since their arrival in the Emergency Department.

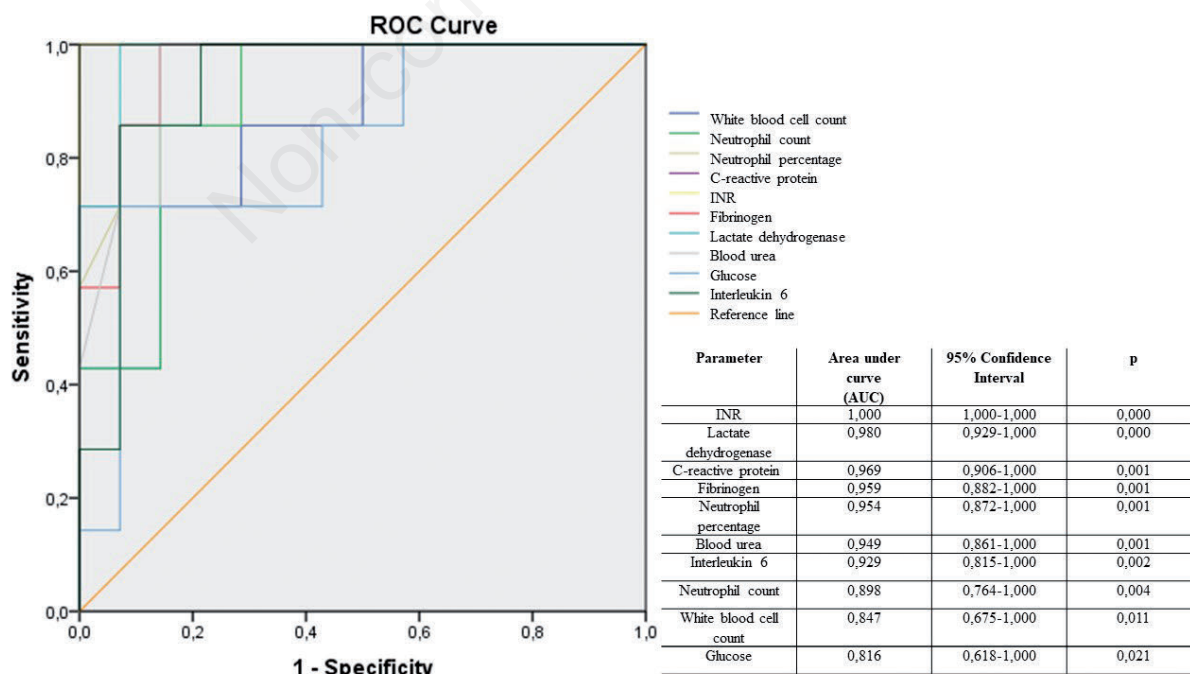


Figure 3. Receiver operating characteristic (ROC) curve comparing accuracy of laboratory findings at the admission to the Emergency Department in relation to the prediction of ICU admission in patients with Covid-19.

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