

Alveolar-to-arterial oxygen gradient: role in the management of COVID-19 infection mild population

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Abstract

COVID-19 infection is frequently associated with radiological diagnosis of interstitial pneumonia and alteration in gases exchange. We decided to test arterial blood gas assay parameters, in particular alveolar-to-arterial oxygen gradient (AaDO₂), in predicting the need of hospitalization, the survival rate and in identifying pneumonia in patients with SARS-CoV-2 infection.

We conducted an observational prospective study in one of the Emergency Department of our city. We included consecutive patients with symptoms likely related to SARS-CoV-2 infection, confirmed either with positive nasal pharyngeal swabs and/or with suggestive radiological findings. Areas under the curve of the receiver operator characteristic curve were computed to predict need of hospitalization and the presence of pneumonia. Survival curves were analyzed using a Log-rank test. P-value less than 0.05 were considered statistically significant.

We enrolled 825 patients; the final population was composed by 530 patients. Most of them were hospitalized due to complications, the mortality was 14% but no death occurred in the ED. It results that a threshold for AaDO₂ of 27 could predict the need of hospitalization as well as a threshold for AaDO₂ of 24 could identify the presence of pneumonia. Survival curves revealed that patients with a value of AaDO₂ less than or equal to 40 had a better survival. We suggest the application of ABG parameters, in particular AaDO₂, during the first assessment of COVID-19 patients in the ED, because they could be additional tools to help the emergency physician to evaluate the clinical severity of patients.

The study was approved by our local ethics committee with the number 551/2020/Oss/AOUBo.

Introduction

In December 2019 many cases of a new viral pneumonia were registered in Wuhan, China, and on 12 January 2020 WHO, the *World Health Organization*, isolated the genetic sequence of a new Coronavirus, named SARS-CoV-2. Then the virus has spread all over the world and on 11 March 2020 WHO declared a global pandemic¹.

The SARS-CoV-2 infection affects many organs, not only the respiratory system, and clinical features are different from patient to patient, similarly to MERS-CoV (Middle East Respiratory Syndrome Coronavirus) or SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus). The main symptoms are: fever (88%), dry cough (68%), fatigue (38%), dyspnea (19%), myalgia (15%), sore throat (14%), headache (13.6%), nasal congestion (4.8%), diarrhea (4%)^{2,3}. Common radiological findings on chest x-ray, on high resolution thoracic computed tomography (HRCT) and on lung ultrasound (lung US) are those of atypical pneumonia, in particular bilateral peripheral and basal ground glass opacities, consolidation or both¹.

As reported in the recent literature, it could be possible to classify patients with SARS-CoV-2 infection into five different clinical phenotypes, which implies a progressive clinical worsening from the first to the last one⁴.

The diagnosis of the new coronavirus infection (COVID-19) is confirmed by a positive result of real time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs⁵. According to the current studies, the sensitivity of the nasopharyngeal swab is not high especially for mild cases (62,5%). For this reason, for patients with typical symptoms a negative test should be interpreted with caution and a repeat test may be considered. In case of a first negative swab and moderate or severe symptoms, radiological typical findings of the chest may be more sensitive than RT-PCR testing⁶.

Patients with severe infection frequently present arterial hypoxemia and develop an acute respiratory distress syndrome (ARDS) which require, in approximately 5-10% of cases, intensive care unit (ICU) admission and mechanical ventilation⁷.

While patient's oxygenation is evaluated easily by using a pulse oximeter, arterial blood gas assay (ABG) lead to a more precise measure of gas exchange: indeed with this exam it is possible to know the values of arterial partial pressure of oxygen (PaO₂) and arterial partial pressure of carbon dioxide (PaCO₂) in order to better highlight the patient's ventilatory pattern. In this way, it is possible to calculate quickly the ratio of PaO₂ to the fraction of inspired oxygen (FiO₂) defined as PaO₂/FiO₂ (P/F) and the alveolar-to-arterial oxygen gradient (AaDO₂)⁸ the last one obtainable by the following formula:

$$AaDO_2 = [(FiO_2)(\text{Atmospheric pressure} - H_2O \text{ pressure}) - (PaCO_2/0.8)] - PaO_2$$

$$\text{Normal gradient estimate} = (\text{age}/4) + 4$$

It is known that diseases that increase shunt or alter the diffusion barrier for oxygen from the alveoli to the blood can have an impact on these parameters, increasing the value of AaDO₂ and decreasing the value of P/F⁹.

As reported in literature, hypoxemia accompanied by a normal AaDO₂ and by increased PaCO₂ signifies hypoventilation, that is uncommon in COVID-19 pneumonia. Indeed, it is usually accompanied by an increased AaDO₂, signifying either ventilation-perfusion mismatch or intra-pulmonary shunting¹⁰.

The primary aims of this study are to demonstrate the capability of AaDO₂ compared to P/F in predicting the need of hospitalization and the survival in patients with COVID-19 infection and phenotypes 1-4 who present to the Emergency Department⁴. The secondary aim is to evaluate usefulness of these parameters in identifying pneumonia in this cohort of patients.

Methods

We conducted an observational prospective study in the Emergency Department (ED) of Sant'Orsola University Hospital in Bologna, Italy, from 06 March 2020 to 04 April 2020. We considered 18 or older aged consecutive patients admitted to the ED with symptoms likely related to SARS-CoV-2 infection as fever, cough, dyspnea, sore throat, nasal congestion, fatigue, diarrhea, arthralgia, anosmia, ageusia. At the ED presentation, an ABG assay has been made to all these patients, independently to the real need of oxygen support.

We enrolled patients with laboratory confirmation for SARS-CoV-2 infection (positive result of nasal and pharyngeal swabs⁵) and/or with suggestive radiological features of COVID-19 on HRTC and/or lung US^{1,6}. We excluded the patients who presented to our Emergency Department with oxygen support applied by the ambulance service and so with FiO₂ > 21%.

We calculated AaDO₂, the incremental percentage variation between the calculated and the expected aged AaDO₂ (%AaDO₂) and P/F for each patient using arterial blood gas analysis assessed in FiO₂ 21% (ambient air) at the first medical evaluation in the ED. According to the literature, we considered patients with AaDO₂ > 5 mmHg^{10,11,12}.

Patients were followed up until 11 May 2020 recording ED discharge, the need of hospitalization and/or death through data from the hospital records.

Demographic, clinical and laboratory characteristics of the cohort are expressed as means and standard deviation (SD) and as number and percentage as appropriated. Areas under the curve (AUCs) and the 95% confidence interval (CI) of the receiver operator characteristic (ROC) curve were computed to predict need of hospitalization, presence of viral pneumonia and mortality. The optimal AaDO₂, %AaDO₂ and P/F index cut-offs were determined optimizing sensitivity and specificity, privileging sensitivity for our purposes. Survival curves were analyzed using a Log-rank test.

P-value less than 0.05 were considered statistically significant. The analysis was obtained using IBM SPSS Statistics software version 25.

The study was approved by our local ethics committee with the number 551/2020/Oss/AOUBo.

Results

We enrolled 825 consecutive patients admitted to the ED of Sant'Orsola University Hospital in Bologna, Italy. Of these patients, 107 were excluded because of negative swab and radiological findings not suggestive for SARS-CoV-2 pneumonia, 58 were excluded because of a different discharge diagnosis, 61 because they arrived in ED with oxygen support (FiO₂ > 21%) and 69 because of AaDO₂ < 5 mmHg. So, the final study group was composed by 530 patients (**Figure 1**).

Table 1 shows demographic characteristics and comorbidities. Overall, 55.1% (292 of 530 patients) were male, the mean age was 62.5 years old and the median age was 61 years old. Main comorbidities were: hypertension, diabetes, chronic kidney disease (CKD), chronic coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), asthma and active malignancy.

Table 2 shows ABG parameters at the admission in the ED. The pH range varies from 7.20 to 7.64 (mean 7.46); the paO₂ varies from 26 mmHg to 118 mmHg (mean 72 mmHg); the paCO₂ varies from 15 mmHg to 73 mmHg (mean 33 mmHg). The mean value of AaDO₂ was 36 (range 5-83); the mean value of %AaDO₂ was 85% (range 78-384); the mean value of P/F was 344 (range 124-562).

	Gender		Age	Hypertension	Diabetes	COPD	CKD	CAD	Active malignancy	Asthma
	M	F								
n° (%)	292 (55.1)	238 (44.9)		199 (37.5)	58 (10.9)	53 (10)	42 (7.9)	38 (7.2)	28 (5.3)	13 (2.5)
Mean			62.5							
SD			17.9							

Table 1. Abbreviations: M, male; F female; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CAD, coronary artery disease; SD, standard deviation

	pH	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	HCO ₃ ⁻ (mmol/l)	Lac (mmol/l)	SaO ₂ (%)	AaDO ₂	% AaDO ₂	P/F
Mean	7.46	72	33	23.8	1.2	96	36	85	344
SD (min-max)	0.05 (7.20-7.64)	16.1 (26-118)	6.3 (15-73)	3.2 (8.6-39)	0.8 (0.3-8)	4.5 (66-102)	16.8 (5-83)	78 (-78-374)	77 (124-562)

Table 2. Abbreviations: paO₂, arterial partial pressure of oxygen; paCO₂, arterial partial pressure of carbon dioxide; HCO₃⁻, bicarbonates; Lac, lactates; SaO₂, arterial oxygen saturation; DS, standard deviation; min-max, minimum-maximum.

In the study group (n=530), 464 patients (87.5%) received diagnosis of pneumonia and 381 (71.9%) were admitted to the hospital after ED evaluation. Among patients with radiological findings of viral pneumonia, 363 (78.2%) were hospitalized. 122 patients (23%) needed oxygen support, in particular 32 nasal cannula, 41 venturimask, 42 reservoir face mask (FiO₂ = 80%), 6 continuous positive airway pressure, 1 non-invasive mechanical ventilation. No patients were treated with invasive mechanical ventilation in the ED, but 25 required intubation subsequently during the whole hospital stay.

Death at the time of follow up occurred in 78 patients (14.7%). No death occurred in the ED.

The predictive values of AaDO₂, %AaDO₂ and P/F obtained by means of ROC curves are listed in **Table 3**.

The ROC curves and AUC of the AaDO₂, %AaDO₂ and P/F predicting admission to the hospital after ED evaluation are shown in **Figure 2**.

For the prediction of the need for hospitalization AUC were as follows: for AaDO₂ 0.909 (95% C.I. 0.885–0.934), for %AaDO₂ 0.821 (95% C.I. 0.784–0.858), the for P/F 0.859 (95% C.I. 0.828–0.891). Threshold values obtained from ROC curve's analysis were: 27 for AaDO₂ (87% sensitivity and 78% specificity), 52% for %AaDO₂ (78% sens. and 72% spec.), 365 for P/F (80% sens. and 78% spec.).

Out of 168 patients with AaDO₂ less than or equal to 27, only 3 (1.8%) were readmitted in the ED within 7 days and subsequently hospitalized. Of these 3 patients, 2 did not have pneumonia on first chest imaging and, during the second assessment, they showed a worsening of AaDO₂ and P/F values above 27 and under 365 respectively and development interstitial pneumonia.

Data analysis for the prediction of mortality showed following AUC: 0.746 for AaDO₂ (95 % C.I. 0.690–0.803), 0.591 for %AaDO₂ (95% C.I. 0.528–0.655), 0.763 for P/F (95% C.I. 0.702–0.825). Data obtained from the analysis of ROC curve showed that the AaDO₂ threshold value of 40 (70% sens. and 64% spec.) and the P/F threshold value of 300 (78% sens. and 62% spec.) corresponded to acceptable cut off for predicting mortality.

Survival curves are shown in **Figure 3**. Log-rank test revealed statistically significant differences (p < 0.0001) between the population with AaDO₂ less than or equal 40 (23 deaths of 312 patients) and with AaDO₂ more than 40 (55 deaths of 218 patients). Log-rank test revealed also statistically significant differences (p < 0.0001) between the P/F less than or equal to 300 population (48 deaths of 151 patients, 31.8%) and P/F more than 300 population (30 deaths of 379 patients, 7.9%).

For the prediction of pneumonia diagnosis in suspected COVID-19 patient AUC were as following: for AaDO₂ 0.780 (95% CI 0.727–0.833), for %AaDO₂ 0.749 (95% C.I. 0.692–0.807) and 0.748 for P/F (95% C.I. 0.691-0.805). The obtained threshold value were: 24 for AaDO₂ (78% sens. and 60% spec.), 44% for %AaDO₂ (71% sens. and 68% spec.), 370 for P/F (71% sens. and 67% spec.).

	AUC (C.I.)	Threshold value	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Admission						
AaDO ₂	0.909 (0.885-0.934)	27	87	78	91	69
% AaDO ₂	0.821 (0.784-0.858)	52	77	72	87	55
P/F	0.859 (0.828-0.891)	365	80	78	91	57
Pneumonia						
AaDO ₂	0.780 (0.727-0.833)	24	78	60	88	52
% AaDO ₂	0.749 (0.692-0.807)	44	71	68	94	24
P/F	0.748 (0.691-0.805)	370	71	67	94	23
Mortality						
AaDO ₂	0.746 (0.690-0.803)	40	70	64	25	92
% AaDO ₂	0.591 (0.528-0.655)	80	65	51	15	94
P/F	0.763 (0.702-0.825)	300	78	62	32	92

Table 3. Abbreviations: AUC, area under the curve; C.I., confidence interval 95%; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.

Discussion

Considering the impact of COVID-19 interstitial pulmonary involvement on gases exchange, ventilatory/perfusion mismatch and shunting, we decided to test ABG parameters, in particular AaDO₂, %AaDO₂ and P/F, to evaluate the efficacy of this tool to better guide ED physicians in this new challenging clinical condition. Arterial blood gas assay is easily available in an emergency setting and it gives immediately crucial information about pulmonary involvement and respiratory dynamics. Moreover, we decided to use the alveolar-to-arterial oxygen gradient instead of PaO₂ because of its better capability to underline the presence of ventilatory/perfusion mismatch and shunting⁹.

In our cohort, most patients were male and the median age was 61 years old, similarly to that reported for other Italian COVID-19 cases based on data sourced from *Epicentro Epidemiology for public health* (Istituto Superiore di Sanità <https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-dashboard>).

Of 530 enrolled patients, about 72% were hospitalized because of pneumonia diagnosis and based on clinical gestalt. In our study group, the mortality rate (14%) was similar to that recently reported in Italy¹³ and no death was recorded at the time of discharge to the emergency room. Only 23% of the patients required oxygen therapy and no one was intubated during the first evaluation in the ED because they showed initial good responsiveness to the oxygen support, implying the presence of ventilatory-perfusion mismatch instead of intra-pulmonary shunting¹⁰. Moreover, these data could be justified by the characteristics of enrolled patients, who, in most cases, presented with mild symptoms and without need of respiratory support before ED evaluation and a subgroup of them could be otherwise managed in an outpatient setting and not necessarily in the ED.

From statistical analysis, it emerged that in our mild population the AaDO₂ threshold value of 27 could have an higher sensitivity than P/F threshold of 365 in predicting hospital admission after ED evaluation (respectively 87% vs 80%). As far as the prediction of pneumonia is concerned, the AaDO₂ threshold of 24 is better related to the diagnosis of pneumonia in our COVID-19 cohort's patients than P/F. Furthermore, as already known in literature in other clinical conditions, AaDO₂ more than 20 is associated with most serious clinical features that require hospitalization⁷.

In order to enhance the effect of AaDO₂ regardless of the age, we tested the incremental percentage variation between the calculated and the aged expected AaDO₂, but, despite of its statistical significance, it showed poor performances, probably due to the impact of the age itself on patient's COVID prognosis. As a consequence, in clinical practice, we suggest better to use the absolute value of AaDO₂ instead of its incremental percentage.

From the analysis of the survival curves, it results that patients with value of AaDO₂ less than or equal 40 and P/F more than 300 had a better survival, according to the literature in which severe lung injury occurs with highest value of AaDO₂ and worst P/F value¹⁴.

The main limitation of this study is the relatively small cohort, composed by patients with "mild" infection, who are classifiable in the first four clinical phenotypes⁴. We commit to validate and eventually confirm the data obtained in this study enlarging the study group.

Of our best knowledge, this is one of the few studies published until now which analyses patients with SARS-CoV-2 infection in the ED and the first one in which ABG parameters are discussed with particular focus on the role of AaDO₂.

We suggest the application of ABG parameters, in particular AaDO₂, during the first assessment of COVID-19 patients in the ED, because they could be additional tools to help the emergency physician to evaluate the clinical severity of patients.

Declarations

Funding: none

Conflicts of interest/Competing interests: none

Ethics approval: study approved by our local ethics committee with the number 551/2020/Oss/AOUBo

Consent to participate: informed consent was obtained from all individual participants included in the study.

Consent for publication: not applicable

Availability of data and material: the datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability: not applicable

Authors' contributions: all authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Gabriele Farina, Alice Gianstefani, Veronica Salvatore, Martina Anziati, Francesca Baldassarri, Michelle Beleffi, Alfredo Maria Cannizzaro, Elena Casadei, Jacopo Fantini, Eleonora Tubertini. The first draft of the manuscript was written by Gabriele Farina, Alice Gianstefani, Veronica Salvatore, Martina Anziati, Francesca Baldassarri, Michelle Beleffi, Alfredo Maria Cannizzaro, Elena Casadei, Jacopo Fantini, Eleonora Tubertini and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

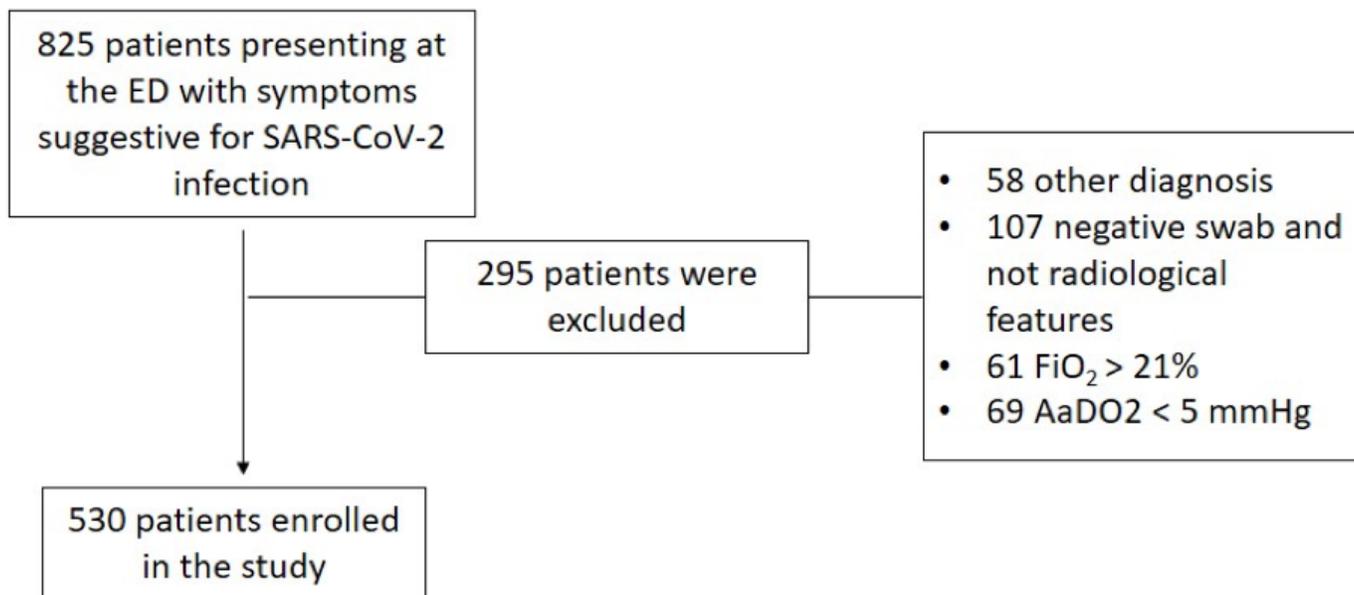
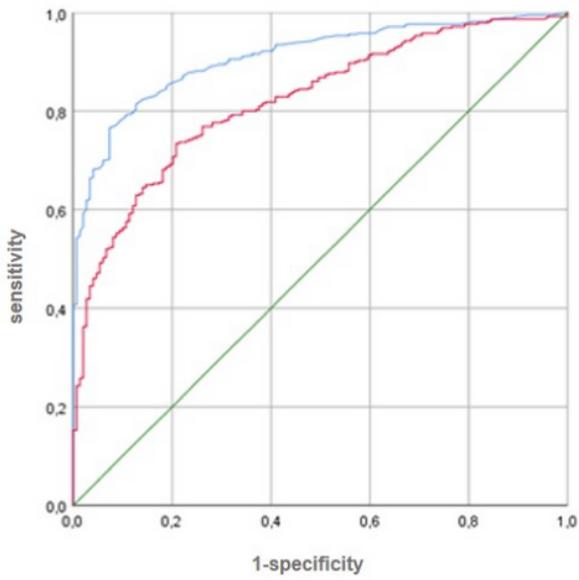
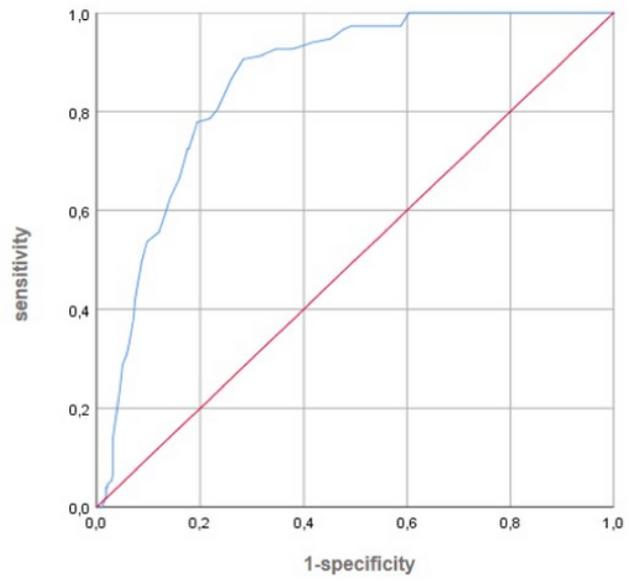


Figure 1

flowchart of patients admitted to the ED with symptoms suggestive for SARS-CoV-2 infection



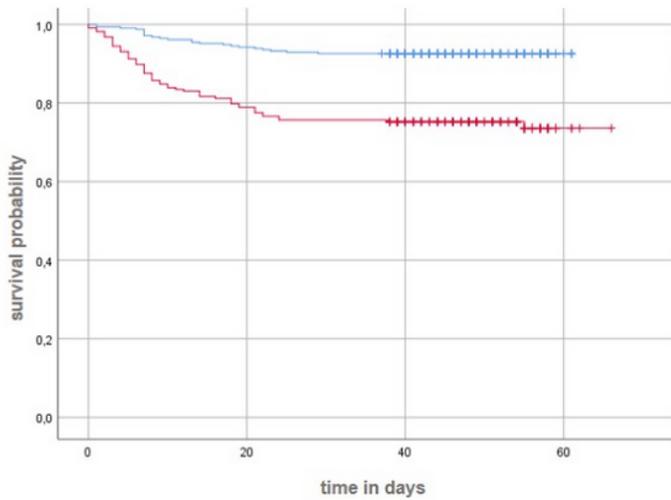
2a. ROC curves for AaDO₂ (blue), %AaDO₂ (red) prediction of admission after ED evaluation



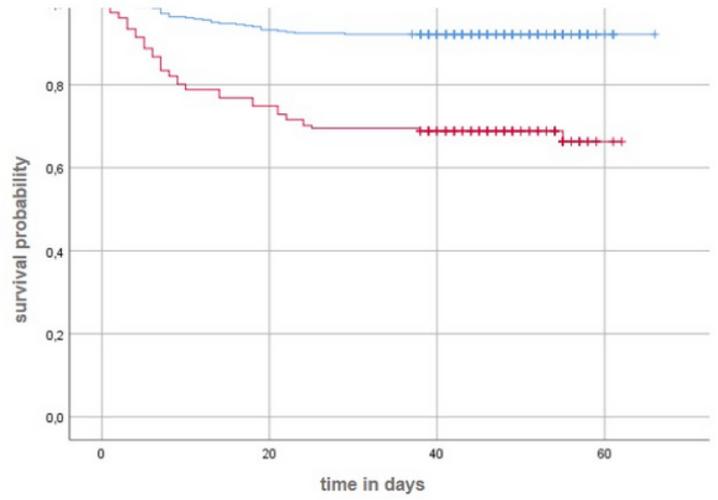
2b. ROC curve for P/F prediction of admission after ED evaluation

Figure 2

ROC curves for P/F, AaDO₂, %AaDO₂ prediction of hospitalization



2a. Kaplan – Meier curves comparing patients with AaDO₂ ≤ 40 (blue) and AaDO₂ > 40 (red)



2b. Kaplan – Meier curves comparing patients with P/F ≥ 300 (blue) and P/F < 300 (red)

Figure 3

Survival curves