Role of ROX Index in the first assessment of COVID-19 patients in the Emergency Department

Alice Gianstefani
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Gabriele Farina
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Veronica Salvatore
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Francesca Alvau
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Maria Laura Artesiani
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Sara Bonfatti
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Francesca Campinoti
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Ilaria Caramella
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Michele Ciordinik (michele.ciordinik@studio.unibo.it)
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Andrea Lorusso
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Sara Nanni
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Daniela Nizza
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Stefano Nava
Respiratory Disease Clinic, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy
Fabrizio Giostra
Emergency Department, University of Bologna Hospital of Bologna Sant'Orsola-Malpighi, Bologna, Italy

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Abstract

Background: In Italy, since the first symptomatic cases of Coronavirus disease 2019 (COVID-19) appeared in late February 2020, 205.463 cases of Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) were reported as of April 30, causing an high rate of hospital admission through the Emergency Department (ED).

Objectives: The aim of the study was to evaluate the accuracy of ROX index in predicting hospitalization and mortality in patients with suspected diagnosis of COVID-19 in the ED. Secondary outcomes were to assess the number of readmissions and the variations of ROX index between first and second admission.

Methods: This is an observational prospective monocentric study, conducted in the ED of Policlinico Sant'Orsola-Malpighi in Bologna. We enrolled 1371 consecutive patients with suspected COVID-19 and ROX index was calculated in 554 patients. Patients were followed until hospital discharge or death.

Results: ROX index value < 25.7 was associated with hospitalization (AUC=0.737, 95%CI 0.696–0.779, p<0.001). ROX index < 22.3 is statistically related with higher 30-days mortality (AUC= 0.764, 95%CI 0.708-0.820, p<0.001). 8 patients were discharged and returned in the ED within the following 7 days, their mean ROX index was 30.3 (6.2; range 21.9-39.4) at the first assessment and 24.6 (5.5; 14.5-29.5) at the second assessment, (p=0.012).

Conclusion: ROX index, together with laboratory, imaging and clinical findings, can help discriminate patients suspected for COVID-19 requiring hospital admission, their clinical severity and their mortality risk. Furthermore, it can be useful to better manage these patients in territorial healthcare services, especially in the hypothesis of another pandemic.

Introduction

In late December 2019, clusters of severe atypical pneumonia were identified in Wuhan and in the Hubei Province of China. In Italy, since the first reports of symptomatic cases of Coronavirus disease 2019 (COVID-19) in late February 2020, 205.463 cases of Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) infection have been reported as of April 30, 2020. The curve of reported cases in the Italian epidemic shows a growing trend of new diagnoses until March 20, followed by a constant decrease due to government restriction**.** According to the indication of the World Health Organization the diagnosis is based on the positivity of real-time reverse transcription polymerase chain reaction (RT-PCR) test of oral and nasopharyngeal swabs [2], however the sensitivity and specificity are poorly characterized, and the "window period" after acquisition in which testing is most likely to produce false-negative results is not well known [3]. As a consequence, in real clinical practice also specific radiological patterns on computed tomography (CT) and on lung ultrasound are considered able to convey diagnosis and influence patient management [4].

The most frequent severe manifestation of infection appears to be interstitial pneumonia, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging [5] with a prevalence of hypoxic respiratory failure of 19% [6, 7]. These patients may show at admission to the Emergency Department (ED) an atypical presentation of their symptoms, characterized by mild increase in respiratory rate, in face of severe hypoxia probably due to their normal or only partially impaired respiratory mechanics. This particular "phenotype" has been defined as *L* (i.e. low elastance) versus the form closer to Acute Respiratory Distress Syndrome (ARDS), named as *H* (i.e. high elastance). This latter been characterized by worst prognosis, and in most cases representing an evolution of phenotype *L* [8]. At the same time, a large cohort of patients exhibits mild symptoms (myalgia, cough, fever, headache) at first presentation. Since the evolution of the disease is yet not well known with a possible sudden deterioration, one of the challenges that emergency physicians have to face is the early detection of patients who need to be hospitalized and of those who can be directly and safely discharged. This is even more important when dealing with a rapidly spreading global pandemic like COVID-19, that has the potential to overwhelm hospital capacity [9]. Hence the need of rapid and simple tools for emergency physician able to support critical clinical decisions. We tested ROX index (Respiratory rate – OXygenation), which was firstly described by Roca et al in 2016 [10] as the ratio of peripheral oxygen saturation (SpO_2) and fraction of inspired oxygen (FiO_2), to Respiratory Rate (RR). ROX index was introduced to predict the need for mechanical ventilation (MV) in patients with hypoxemic acute respiratory failure (ARF) resulting from pneumonia/ARDS treated with high-flow nasal cannula (HFNC). To the best of our knowledge, the ROX index has not yet been applied in COVID-19 patients nor in patient's initial assessment in the ED.

The primary aim of this prospective observational study was to evaluate the reliability and accuracy of the ROX index in predicting the need of hospitalization and the risk of mortality in patients with suspected diagnosis of COVID-19 as they arrive in the ED. Secondary outcomes were to assess the number of readmissions in patients initially discharged and the variations of ROX index in the time frame between first and second admission.

Methods

Study design

This is an observational prospective monocentric study, conducted in the ED of Policlinico Sant'Orsola-Malpighi in Bologna, Italy, from 13th of March to 3rd of April 2020. We enrolled 1371 consecutive patients with suspected COVID-19 admitted to the ED in a dedicated area. Symptoms such as fever, cough, dyspnea, sore throat, rhinorrhea, headache, fatigue, conjunctivitis, diarrhea, and smell or taste aberrancies were considered likely related to SARS-CoV-2 infection. The local ethics committee approved this study (551/2020/Oss/AOUBo).

Participants

Our analysis included patients with confirmed SARS-CoV-2 infection determined by positive result on RT-PCR test of oral and nasopharyngeal swabs, at initial test or in a repeated one during hospitalization, and patients with positive imaging findings on CT or lung ultrasound (interstitial pneumonia) but negative result on nasopharyngeal swabs test, who didn't reach alternative diagnosis when discharged from hospital (inclusion criteria). We consider these criteria the best available in the period of enrollment based on the knowledge up to that time.

Data collection

At the time of admission to the ED, we collected demographic data, medical history and respiratory variables, such as SpO_2, FiO_2 and RR. Based on these data, ROX index was calculated using the formula: $(SpO_2/FiO_2)/RR$. National Early Warning Score 2 (NEWS2) was also calculated; it includes respiratory rate, hypercapnic respiratory failure occurrence, supplemental O2 needing, temperature, systolic blood pressure, cardiac rate and level of consciousness [11]. Additionally, all the patients underwent arterial blood gas (ABG) analysis, and at least one imaging test (chest X-rays, lung ultrasound, and high-resolution thoracic CT). Blood tests were performed according to clinical evaluation. Patients were followed up until hospital discharge or death and medical records were extracted from the registry. The following data were extracted: hospitalization and 30-days mortality.

Statistical analysis

Demographic, clinical and laboratory characteristics of the cohort are expressed as means and standard deviation (SD) and as number and percentage as appropriated. Continuous variables were compared using ANOVA T-test or Mann-Whitney and frequencies using the chi-squared test. 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 risk of 30-days mortality. The optimal ROX index cut-off was determined optimizing sensitivity and specificity, favoring sensitivity for our purposes. P-value less than 0.05 were considered significant. Statistical analysis was obtained using IBM SPSS Statistics software version 25.

Patient and public involvement

Due to the nature of pandemic crisis it was not possible to involve patients in the design, or conduct, or reporting, or dissemination plans of the study.

Results

Among 1371 patients admitted to the COVID area of our ED, we identified 554 patients who met the inclusion criteria [Figure 1].

Age was 61.5 ± 19 years, comparable to the one described in international literature [5]. In our population males represented 53.4% (N=296) and females 46.6% (N=258), which is consistent with Italian data [1]. Baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics of the cohort (n=554).

Age, years	61.5 ± 19
Sex, n (%)	
Male	296 (53.4)
Female	258 (46.6)
Comorbidities, n (%)	
Hypertension	204 (36.3)
Use of RAAS inhibitors	52 (9.4)
Use of ARBs inhibitors	55 (9.9)
Diabetes mellitus	62 (11.2)
COPD	58 (10.5)
Asthma	13 (2.3)
Other respiratory diseases	22 (4)
Ischemic heart disease	41 (7.4)
Active cancer	33 (6)
Chronic kidney disease	46 (6.6)
Previous TIA/stroke	26 (4.7)
Liver disease	22 (4)
Cognitive impairment	72 (13)
Onset of symptoms, days	6.5 ± 5.2
Clinical features at ED admission, n (%)	
Fever	461 (83.4)
Dyspnea	209 (37.8)
Cough	315 (57)
Conjunctivitis	8 (1.4)
Rhinorrhea	21 (3.8)
Sore throat	39 (7.1)
Headache	45 (8.1)
Asthenia	90 (16.3)
Myalgia/Arthralgia	67 (12.1)
Diarrhea	81 (14.6)

Anosmia	29 (5.2)
Ageusia/Dysgeusia	51 (9.2)
Syncope	6 (1.1)
Respiratory rate, breaths/min	20 ± 5
Heart rate, beats/min	90 ± 16
Arterial pressure, systolic – diastolic, mmHg	127 ± 22 – 75 ± 13
Body temperature, °C	37.1 ± 0.8
SpO_2, %	96.2 ± 3.7

Data are presented as number (n) and percentage (%) for dichotomous values or average and standard deviation for continuous values. RAAS, renin–angiotensin–aldosterone system; ARBS, angiotensin-receptor blockers; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

Main comorbidities were hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic kidney disease, ischemic heart disease and asthma. Patients arrived at the ED 6.3 ± 5.2 days after the onset of symptoms [Table 1]. Most patients (93.7%) were neurologically normal with a 15/15 Glasgow Coma Scale (GCS). Respiratory variables registered at admission were SpO_2 (95.7% ± 3.9), RR (20 breaths/min ± 5.5) and FiO_2 (536 patients with FiO_2 21% and 18 with FiO_2 > 21%, being this last value based on that reported on Ventimask kit used in our ED).

Laboratory findings are listed in Table 2.

Table 2. Laboratory tests and arterial blood gas.

Laboratory tests	
White Blood Count – n/mmc	7788 ± 5421
Neutrophils – n/mmc	6091 ± 6547
Lymphocytes – n/mmc	1673 ± 2906
Eosinophils – n/mmc	0.541 ± 0.1332
Platelets – n/mmc	221 ± 90
aPTT	1.80 ± 13
INR	1.2 ± 0.6
Creatinine – mg/dl	1.07 ± 0.99
Urea – mg/dl	44.2 ± 36.5
Sodium – mmol/L	138 ± 4.7
Potassium– mmol/L	4.1 ± 0.5
Lactate dehydrogenase – U/L	288 ± 185
C-Reactive Protein – mg/dl	6.2 ± 7.2
Procalcitonin – ng/ml	1.7 ± 12
Arterial blood gas	
pH	7.42 ± 0.53
PaO_2 – mmHg	75 ± 20.1
$PaCO_2$ – mmHg	33.7 ± 6.6
$SatO_2$	96 ± 4.5
P/F	349.7 ± 97.2
HCO_3 – mmHg	23.8 ± 3.3
Blood Lactate – mmol/L	1.2 ± 1

Data are presented as number (n) and percentage (%) for dichotomous values or average and standard deviation for continuous values.

In 4.9% of the admissions blood tests were not performed due to mild symptoms. Lymphopenia was present in 44% of the population. Patients often presented with normal white blood count (7788/mmc ± 5421), elevated C-reactive protein (6.2 mg/dl ± 7.2, 0.02-40.7 mg/dl) and lactate dehydrogenase (288 U/L

± 185). In the majority of cases arterial blood gas analysis showed normal value of pH and hypocapnia [Table 2].

Viral pneumonia was confirmed at imaging in 485 patients (87.5%). ROX index in our overall population was 24.3 ± 6.5.

Baseline characteristics of the discharged and hospitalized patients are listed in Table 3.

Table 3. Baseline characteristic of the cohort comparing discharged and hospitalized patients.

	Discharged (n=170)	Hospitalized or death (n=384)	P value
Age, years	46.7 ± 14.8	68 ± 17	<0.001
Sex, n (%)			0.001
Male	72 (42.4)	224 (58.3)	
Female	98 (57.6)	160 (41.7)	
Comorbidities, n (%)			
Hypertension	23 (13.5)	181 (47.1)	<0.001
Use of RAAS inhibitors	5 (2.9)	47 (12.2)	<0.001
Use of ARBs inhibitors	9 (5.3)	46 (12)	0.014
Diabetes mellitus	8 (4.7)	54 (14.1)	0.001
COPD	3 (1.8)	55 (14.3)	<0.001
Asthma	6 (3.5)	7 (1.8)	NS
Other respiratory diseases	3 (1.8)	19 (5)	NS
Ischemic heart disease	2 (1.2)	39 (10.2)	<0.001
Active cancer	5 (2.9)	28 (7.3)	NS
Chronic kidney disease	1 (0.6)	45 (11.7)	<0.001
Previous TIA/stroke	4 (2.4)	22 (5.7)	NS
Liver disease	3 (1.8)	19 (5)	NS
Cognitive impairment	0 (0)	72 (18.8)	<0.001
Onset of symptoms, days	7.2 ± 6.3	5.9 ± 4.6	NS
Clinical features at ED admission, n (%)			
Fever	133 (78.2)	328 (85.4)	0.036
Dyspnea	53 (31.2)	156 (40.6)	0.037
Cough	109 (64.1)	206 (53.6)	0.026
Conjunctivitis	6 (3.5)	2 (0.5)	0.012
Rhinorrhea	12 (7.1)	9 (2.3)	0.014
Sore throat	26 (15.3)	13 (3.4)	<0.001
Headache	31 (18.2)	14 (3.7)	<0.001
Asthenia	33 (19.4)	57 (14.8)	NS

Myalgia/Arthralgia	37 (21.8)	30 (7.8)	<0.001
Diarrhea	32 (18.8)	49 (12.8)	NS
Anosmia	21 (12.4)	8 (2.1)	<0.001
Ageusia/Dysgeusia	32 (18.8)	19 (5)	<0.001
Syncope	1 (0.6)	5 (1.3)	NS
Respiratory rate, breaths/min	17 ± 3	21 ± 6	<0.001
Heart rate, beats/min	88 ± 15	91 ± 17	NS
Arterial pressure, systolic – diastolic, mmHg	133 ± 20 – 78 ± 11	125 ± 22 – 74 ± 13	0.001
Body temperature, °C	36.8 ± 0.6	37.3 ± 0.9	<0.001
SpO_2, %	97.8 ± 1.6	94.7 ± 4.3	<0.001

Data are presented as number (n) and percentage (%) for dichotomous values or average and standard deviation for continuous values. RAAS, renin–angiotensin–aldosterone system; ARBS, angiotensin-receptor blockers; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; NS, not significant.

Hospitalized patients were 69.3% (N=384): they were older and had more comorbidities than the other group. Our analysis showed that a ROX index value < 25.7 was reliable in predicting the need of hospitalization with 76.5% sensitivity and 65.6% specificity (AUC=0.737, 95%CI 0.696–0.779, p<0.001). In particular, when population was split based on age, ROX index value was 26 for patients < 65 years old (sensitivity of 71%, specificity of 60%, AUC=0.667, 95%CI 0.607–0.728, p<0.001) and 23.3 for patients ≥ 65 years old (sensitivity of 81%, specificity of 62.4%, AUC=0.764, 95%CI 0.686–0.842, p<0.001). ROC curve is represented in Figure 2A.

The accuracy of NEWS2 and RR in the prediction of hospitalization were also calculated and resulted lower than ROX index. In particular, NEWS2 sensitivity was 66% and specificity 69% (AUROC 0.736; 95%CI 0.688-0.805) whereas concerning RR sensitivity was 71% and specificity 56% (AUROC 0.692; 95%CI 0.649-0.734).

Furthermore, after 30-days follow up, 82 (14.8%) patients died after 10.35 ± 7.21 days; their age was 82.1 ± 9 (56-100), 79 patients were ≥ 65 years and 51 were males (62.2%). ROX index < 22.3 is statistically related with higher 30-days mortality, with a 74.8% sensitivity and 65.9% specificity (AUC= 0.764, 95%CI 0.708-0.820, p<0.001) [Figure 2B].

Moreover, data showed that a ROX index value < 26 was able to identify patients with viral pneumonia, as assessed at CT scan (sensitivity 62.3%, specificity 60%, AUC=0.657, 95%CI 0.595–0.719, p<0.001). Table 4 shows ROC analysis of ROX index.

Table 4. AUROC, 95%CI, P Value, Sensitivity and Specificity derived from ROC analysis of ROX index.

Variable	ROX index	AUROC	95% CI	p value	Sensitivity (%)	Specificity (%)
Hospitalization	25.7	0.737	0.696 – 0.779	<0.001	76.5	65.6
Patients < 65 y.o.	26	0.667	0.607 – 0.728	<0.001	71	60
Patients ≥ 65 y.o.	23.3	0.764	0.686 – 0.842	<0.001	81	62.4
30-days mortality	22.3	0.764	0.708 – 0.820	<0.001	74.8	65.9
Viral pneumonia	26	0.657	0.595 – 0.719	<0.001	62.3	60

During the entire hospitalization, 24 patients (6.25%) underwent endotracheal intubation. Their mean age was 68.7 (56-79) and 58.3% were males. Their mean ROX index just before intubation was 3.8 (range 2.5-5.71). At 30 days follow-up, 16 of them (66.7%) were alive.

Out of 554 patients, 8 patients were discharged but returned in the ED within the following 7 days and were hospitalized. Mean ROX indexes vary as follows: 30.3 (6.2; range 21.9-39.4) at the first assessment and 24.6 (5.5; 14.5-29.5) during the second assessment, p=0.012.

Discussion

In this monocentric study we suggest adding ROX index in the first ED evaluation of COVID-19 patients in order to identify cut off values able to correlate with viral pneumonia on imaging tests (CT or ultrasound). This ability is particularly important when pandemic impacts on limited ED resources, where patients suitable to underwent imaging tests have to be safely selected. In our cohort a ROX index value lower than 26 was associated with imaging findings of viral pneumonia.

Furthermore, we demonstrate that ROX index is also a simple tool able to discriminate, at admission to the ED, patients with COVID-19 infection requiring hospital admission (ROX index lower than 25.7) from those who can be safely discharged. For patients ≥ 65 years old, the cut-off value of ROX index is 23.3.

The decision regarding hospitalization in our cohort of patients was made based on the usual decision-making process used in the acute ED patient (i.e. based on multimodal elements: laboratory and imaging data, respiratory pattern, blood gas analytical data, comorbidity data and patient characteristics). The ROX cut off was then extrapolated on the group of hospitalized patients, being aware that it cannot be the only element to be used, but to be included in a broader reasoning.

Moreover, ROX index shows a good sensitivity even in COVID-19 patients who usually present a dissociation between the severity of hypoxemia and respiratory mechanics [6], often with normal RR. Additionally, ROX index of <22.3, related to 30-days mortality rate, is lower than its values for hospitalization and pneumonia findings, confirming that lower ROX index predicts a higher mortality risk. It is interesting to note that only 8 of the 170 patients discharged returned to the ED and were consequently hospitalized. In this small subset of patients, the reduction of ROX index was an indicator of worsening.

ROX index was firstly described by Roca et al in 2016 [10], in a two centers prospective observational cohort study including 157 patients with pneumonia/ARDS admitted to ICU and treated with HFNC. They showed that a ROX Index < 4.88, measured 12 hours after HFNC onset, was related to a higher risk of intubation (sensitivity of 70.1%, specificity of 72.4%). Same results were found in a following multicenter prospective observational study, built to validate the diagnostic accuracy of the index, that enrolled 191 patients with pneumonia admitted to ICU and treated with HFNC [12]; a second external validation was carried out using the FLORALI cohort study [13]. Beside its initial purpose the ROX Index was also applied as a predictor of successful HFNC weaning (cut off value > 9.2) [14] and as an indicator to titrate FiO_2 and set the optimal flow rates in patients with ARF treated with HFNC [15].

ROX index is an easy-to-use tool that relies on variables directly linked to oxygenation (assessed by SpO_2/FiO_2) placed in the numerator, and to respiratory distress (assessed by RR), potentially leading to pump failure, placed in the denominator, hence obtaining an additive effect, since severe patients are more likely to have lower SpO_2/FiO_2 and higher RR [10]. The variables required are non-invasive, easily and quickly obtained, as well as reproducible. Our study demonstrated the higher accuracy of ROX index compared to RR alone in the prediction of hospitalization. Moreover, we highlighted an accuracy comparable to NEWS2, a well-known score for the identification of the degree of illness in ED that however requires more variables and time to be calculated.

During COVID-19 pandemic, the main challenge has been the evaluation of a huge number of patients suffering from an unknown disease, frequently requiring hospitalization, without a proportional increase of resources and hospital capacity [9].

In this study we suggest the application of ROX index during the first assessment of COVID-19 patients in the ED, as an additional tool to help the emergency physician to evaluate the clinical severity of patients, in order to safely discharge from hospital. Our data confirm that ROX index, together with laboratory, imaging and clinical findings, can be a reliable and useful tool in the emergency setting.

To the best of our knowledge this is the first study with a large population in which ROX index is used in patients with SARS-CoV-2 infection at the admission in the ED. Moreover the majority of our population didn't receive respiratory support and didn't fulfill ARDS criteria [16]. This explains why our ROX index values are different from what Roca et al. [10] defined in the original study.

On the other hand, the main limits of our study are its monocentric design and the nature of the pandemic crisis. Furthermore, our data show that this is a "mild" population, it will be appropriate to evaluate whether the same results can be extended to patient populations with more severe clinical features. Indeed, we did not measure the "true" FiO_2 delivered to patients and we cannot exclude that air entrainment occurred, especially in patients with high respiratory demand. Further studies will be necessary to validate the use of ROX index and its cut-off values, possibly with a multicentric design.

Considering what we previously mentioned, ROX index seems to be a good combination of accuracy, non-invasivity and promptness, especially in those scenarios where the blood gas analyzer is not available. For instance, it could be used by the nursing triage to place patients at adequate priority levels, by the attribution of colors code which are directly related to the waiting time in the ED. For the same reasons we also suggest the application of ROX index in patients with COVID-19 suspicious symptoms prior the admission to the ED, such as territorial health care services, by using pulse oximetry. The expectation is to help general practitioners to better manage outpatients through a common index, especially in the unfortunate hypothesis of a further outbreak.

Declarations

Author contributions: Alice Gianstefani and Gabriele Farina designed the study, reviewed and edited the manuscript; Francesca Alvau, Maria Laura Artesiani, Sara Bonfatti, Francesca Campinoti, Ilaria Caramella, Michele Ciordinik, Andrea Lorusso, Sara Nanni and Daniela Nizza enrolled the patients, reviewed the literature, wrote the manuscript and produced the figures. Veronica Salvatore made a substantial contribution to the statistical analysis. Stefano Nava and Fabrizio Giostra reviewed and edited the manuscript. All authors read and approved the final manuscript in compliance with Ethical Standards.

Conflict of Interest: the authors declare that they have no conflict of interest.

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Ethics approval: approval was obtained from the ethics committee of Bologna (Ethics approval number: 551/2020/Oss/AOUBo). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent: verbal informed consent was obtained prior to the interview.

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Figures

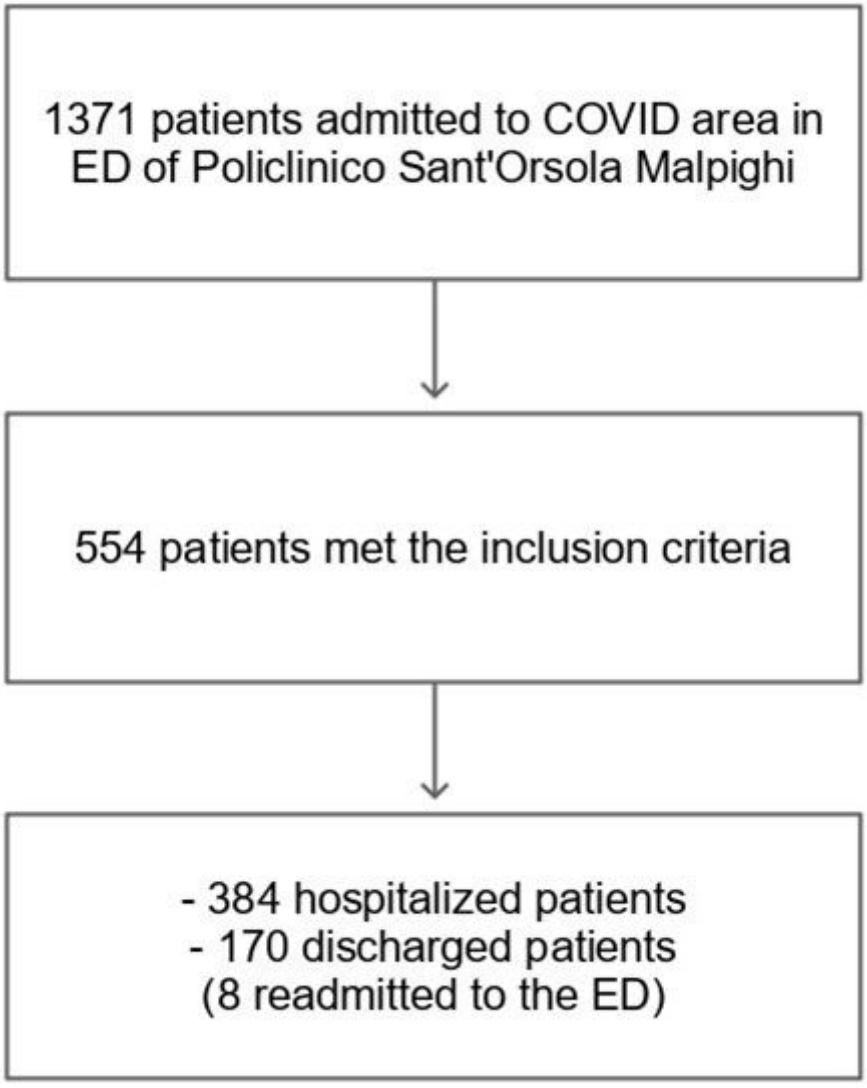

Figure 1

Patient’s enrollment flow chart.

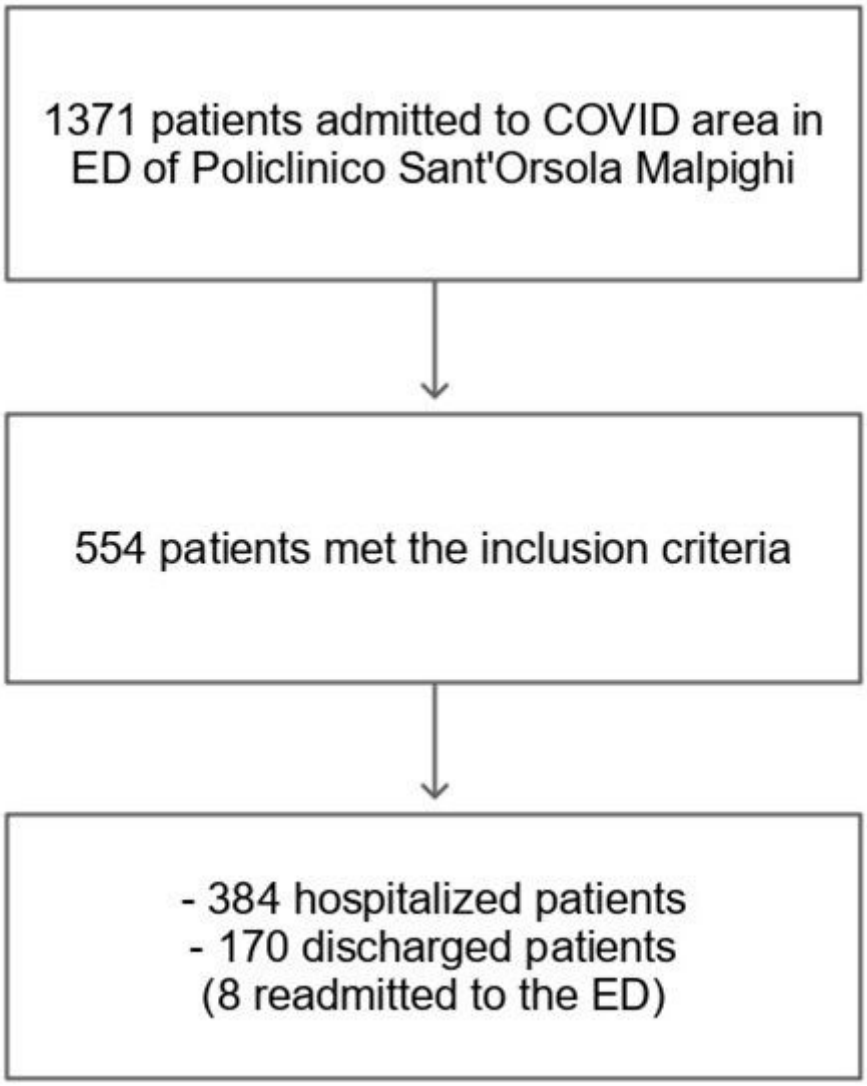

Figure 1

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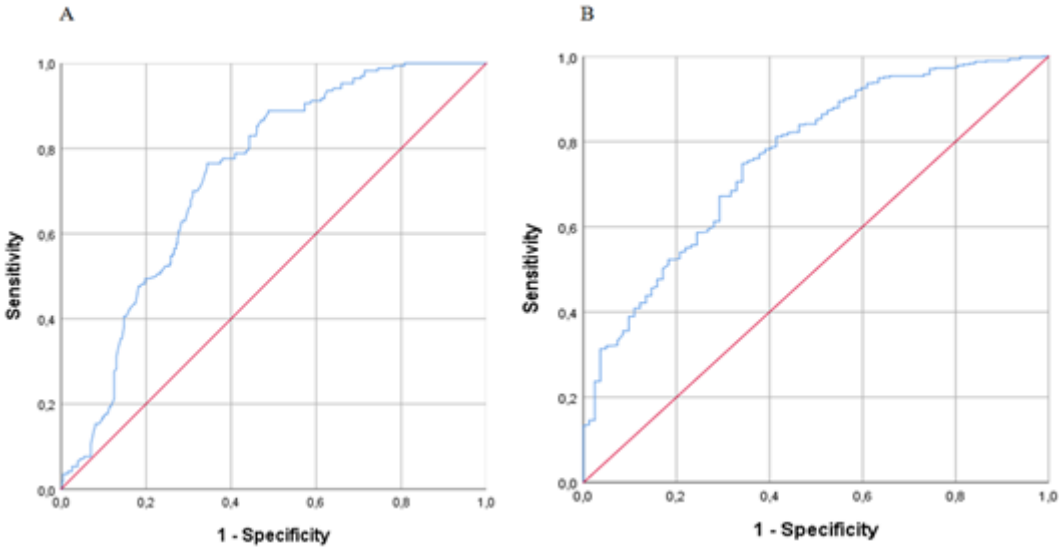
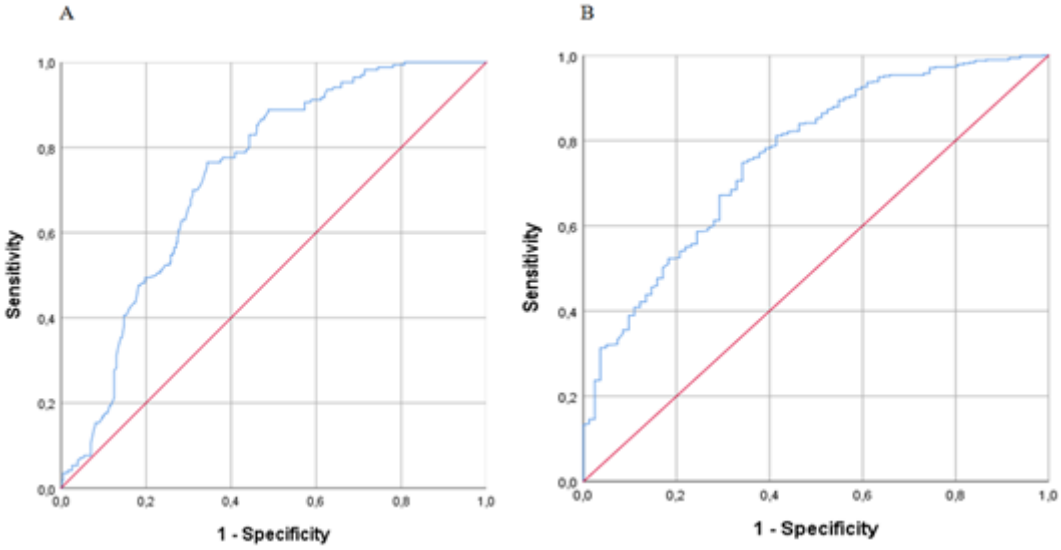


Figure 2

A: Receiver operating characteristic (ROC) analysis of ROX index in predicting hospitalization (AUC 0.737; 95% CI, 0.696 – 0.779; p<0.001). B: Receiver operating characteristic (ROC) analysis of ROX index in predicting 30-days mortality (AUC 0.764; 95% CI, 0.708 – 0.820; p<0.001).



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