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RESEARCH ARTICLE

Parameters predicting non-invasive ventilation failure in COVID-19 patients

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ABSTRACT

Introduction. During COVID-19 pandemic, non-invasive ventilation (NIV) was widely used during COVID-19 Pandemic. The factors predicting NIV failure in COVID-19 patients remain debatable. The goal of this research is to identify the parameters that may correlate NIV failure.

Materials and methods. A retrospective analysis of COVID-19 patients' data, who were admitted to ICU of the Institute of Emergency Medicine, Chisinau, during July-October 2020 and connected to NIV. The study analyzed the demographics, laboratory and respiratory parameters (at admission, at NIV initiation, 24-48h and 72-96h of NIV) and their relation with NIV failure. **.** For continuous variables, the established confidence interval was 95%. The Kruskal-Wallis H test was used for continuous variables and the Fisher's exact test or chi-squared test was used for category data.

Results. In study were included 154 patients. NIV failed in 52 patients. In NIV failure group were registered a higher rate of hypertension (88% vs 74%, p = 0.033), delirium (60% vs 20%, p=0.001) and need for sedation (83% vs 48, p=0.001). The urea levels were lower in NIV success group at admission, at NIV initiation and at 24-48h of NIV. The neutrophil/lymphocyte ratio was higher in NIV failure group at NIV initiation; at 24-48h and 72-96h of NIV. NIV failure group had a higher level of WBC count and C-reactive protein at 24-48h and 72-96h as well as D-dimer at 72-96h of NIV. The ROX index was higher in NIV success group from NIV initiation and through 72h of NIV.

Conclusions. The presence of abnormal values of neutrophil/lymphocyte ratio, urea, lymphocytes, WBC count, C-reactive protein, D-dimer and ROX index during non-invasive ventilation, as well as association of delirium and need for sedation, can be suggestive and informative for high risk of NIV failure in COVID-19 patients. Continuous measurement of these parameters may help the clinicians to decide the optimal timing of conversion to invasive ventilation.

Keywords: non-invasive ventilation, Covid-19, ROX index, failure predictors, hypoxemic respiratory failure.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Currently, there is no consensus about the optimal timing for conversion from non-invasive ventilation to mechanical ventilation in COVID-19 critical ill patients. The identification of the appropriate time of conversion may reduce the morbidity and mortality rate in this category of patients in ICU

The research hypothesis

The demographic, clinical, laboratory and respiratory parameters, closely associated with severity, morbidity and mortality in

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COVID-19 disease, can be associated with non-invasive ventilation failure.

The novelty added by manuscript to the already published scientific literature

Optimization in evaluation of the ricks for non-invasive ventilation failure and improving in respiratory management in COVID-19 patients.

Introduction

The Novel Coronavirus Disease (COVID-19) is an infectious illness that has a pandemic spread since December 2019, infecting over 543,200,000 of the world's population with a 1% of current mortality rate [1].

From the total number of cases, those with asymptomatic, mild, and moderate manifestations represent approximately 80% and the rest of them get severe and critical forms. The rate of Intensive Care Unit (ICU) admission of COVID-19 patients is 11% of the total number of confirmed cases [2]. In patients who have severe and critical manifestation predominates the phenotype of a systemic inflammation, which leads to damage of target organs with tropism for SARS-COV-2 virus (lungs, heart, arterial vascular system, kidneys, ileum and bladder) and The Multiple Organ Dysfunction Syndrome [3, 4].

The Risk factors for severe evolution of COVID-19 are: comorbidities, age older than 65 years, low lymphocytes number, high neutrophil-lymphocyte ratio, high level of D-Dimers, urea, C-Reactive Protein (CRP), ALT, AST and procalcitonin, as well as low PaO2/FiO2 ratio and platelets count etc. [5].

Of the total number of hospitalized COVID-19 non-ICU patients, 33% develop acute respiratory distress syndrome (ARDS), and 26% of them require transfer to ICU. From the total number of COVID-19 ICU-hospitalized patients, 63% are on mechanical ventilation (MV) and approx. 75% are confirmed with ARDS with a mortality rate of up to 93% [6]. This high incidence of ARDS and mortality rate make the pulmonary manifestation of COVID-19 the greatest therapeutic and respiratory support challenge.

The average rate of non-invasive ventilation (NIV) used as respiratory support in COVID-19 is 25.5% [7]. Unfortunately, the predictors of NIV failure as well as clear indications of MV remain debatable. In this context, it is very important to highlight the factors that correlate with NIV failure and would predict the optimal timing for conversion to MV.

Materials and methods

Study population. Was performed the retrospective analysis of COVID-19 patients with acute respiratory failure admitted to the ICU of the Institute of Emergency Medicine, Chisinau, Republic of Moldova, between July 2020 and October 2020 who were connected to NIV. The Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine approved the study and Pharmacy of the Republic of Moldova (minutes No.4 from 07.07.2021).

The inclusion study criteria was need for non-invasive ventilation (BiPAP or PSV) with a duration of more than 24 hours from the initiation. NIV was used more than 20h out of 24h and with application of facemask Criteria for non-invasive ventilation were lack of response to conventional oxygen therapy, absence of tachypnea more than 30-35 respiration/min, absence of severe acidosis or hypercapnia, cooperative patient. Patients in whom non-invasive ventilation was used as a post-extubation support method, or CPAP mode, or were connected to mechanical ventilation in less than 24h after NIV initiation, were excluded from the study. Eligible patients were divided in 2 groups: *NIV success* – patients who were weaned from non-invasive support with respiratory improvement and *NIV failure* – patients who were connected to mechanical ventilation after more than 24h of non-invasive ventilation.

All patients received standard treatment according to the institutional protocol (corticosteroids (methylprednisolone 1mg/kg/day), vitamin therapy, anticoagulants (LMWH or intravenous unfractionated heparin), and antibiotic therapy if necessary. The intubation criteria were based on local institutional practice, including disorder of consciousness, respiratory decompensation (respiratory rate > 30- 35 r/min, participation of auxiliary muscles in the respiratory act) and severe hypoxemia (SpO2 < 85% on maximal non-invasive support).

Data collection. All information was collected from the SiaamS Electronic Medical Record database used in the Institute of Emergency Medicine, Chisinau.

The study was based on the analysis of the following parameters:

Demographic: age, sex, comorbidities (hypertension, diabetes mellitus, obesity), ISARIC (International Acute Respiratory Infection Consortium) score at admission in ICU;

Laboratory: neutrophil-lymphocyte ratio (N/L ratio), lymphocytes count, platelet count, WBC count, urea, creatinine, CRP, D-Dimers level. All parameters were evaluated at admission, at the initiation of NIV, at 24h-48h of NIV and at 72-96h of NIV. In case of multiple samples extraction in these periods, the worse values of these parameters were selected.

Respiratory: the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate (ROX index) was evaluated at the initiation of NIV and then every 12 hours up to 76 hours of NIV.

Outcomes: There were considered as outcomes the duration of NIV, association of delirium (according to the DSM-5 criteria) [8], need for sedation, ICU and hospital length of stay, NIV success or failure, survival.

Statistical analysis. For continuous variables, the established confidence interval was 95%, all other data has been presented as percentage, median and interquartile range. Category variables were reported as number or percentage. Because of non-parametric distribution, The Kruskal-Wallis H test was used for continuous variables and the Fisher's exact test or chi-squared test was used for category data. The diagnostic predictive ability was calculated by statistical analysis of receiver operating curves (ROC). Statistical significance was assigned to the data with a $p < 0.05$. SPSS version 26.0 was used to analyze the data (IBM Corp, Armonk, NY, USA).

Results

A total of 482 patients with severe or critical form of COVID-19 were admitted to ICU, and 154 were enrolled (Figure 1). Demographic and clinical data of the patients are reported in Table 1.

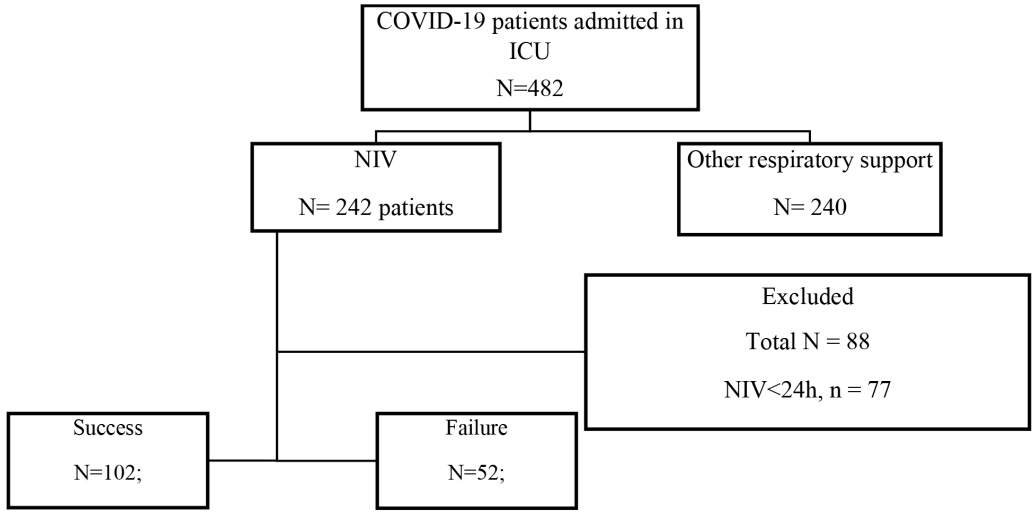

Fig. 1 Study flow chart. ICU - Intensive Care Unit; NIV - non-invasive ventilation; ID - incomplete data.

Table 1. Demographic and clinical data.

Variable	NIV success group (n=102) (66%), Median (IQR)	NIV failure group (n=52) (34%)	*p* value
Age, years	61.5 (54-69.25)	67.5 (60.25-73)	0.02
Male, n (%)	43 (42%)	27 (52 %)	0.25
Hypertension, n (%)	75 (74%)	46 (88%)	0.033
Diabetes mellitus, n (%)	35 (34%)	16 (31%)	0.65
Obesity, n (%)	36 (35%)	21 (40%)	0.53
Day of illness at admission	7 (6-9)	7 (4-9.25)	0.086
ISARIC mortality score points	10 (8-12)	12 (10-14)	0.001
ISARIC mortality score, %	23 (14-33)	33 (23-45)	0.001
ISARIC deterioration score points	615 (544.5-680.5)	673.5 (580-802.5)	0.03
ISARIC deterioration score, %	69 (57.75-78)	77 (63.75-89)	0.03
Outcome			
NIV duration, days	5 (4-7)	6 (4-9)	0.46
Delirium, n (%)	20 (20%)	31 (60%)	<0.001
Need for sedation, n (%)	49 (48%)	43 (83%)	<0.001
ICU stay, days	7 (6-10)	14 (10-17)	<0.001
Hospitalization, days	16.5 (13-23)	14 (10-18.75)	<0.001
In-hospital mortality, n (%)	3 (0.3%)	50 (96%)	<0.001

Note: *ISARIC- International Severe Acute Respiratory Infection Consortium score; ICU - Intensive Care Unit; NIV - non-invasive ventilation. Data are presented as median (interquartile rage IQR)*

Patients in the NIV success group were younger: 61.5 (IQR 54-69.25) vs 67.5 (IQR 60.25-73), (p=0.02). The percentage of male patients was 52% in the NIV failure group vs 42% in the NIV success group (p=0.25). The rate of hypertension was higher in patients who failed the NIV: 88% vs 74% (p=0.033), which represents the risk for NIV failure, OR = 1.203 (CI 95% 1.033-1.401, p=0.0033). The incidence of diabetes mellitus and obesity did not register significant differences between groups. The ISARIC score for deterioration and mortality measured at ICU admission was higher in patients with NIV failure: ISARIC Deterioration score (points/%): 673.5 (77%) vs 615 (69%), (p=0.03) and ISARIC Mortality score (points/%): 12 (33%) vs 10 (23 %), (p=0.001). ICU length of stay (days) was twice shorter in NIV success group, but with longer time of hospitalization. Association of delirium was registered in 20% of cases in NIV success group vs 60% in NIV failure group, (p=0.001). Patients in the NIV success group had less need for sedation 48 % vs 83%, (p=0.001). The presence of delirium and the need for sedation are related to the risk of NIV failure: OR=3.04 (CI 95%, 1.934 - 4.779, p=0.001) for delirium and OR=1.721 (CI 95%, 1.358-2.182 p=0.001) for the need for sedation. Only two patients survived in the NIV failure group, corresponding with 96% of mortality in case of failure. In the NIV success group 3 patients died due to documented pulmonary embolism

after successfully weaning from non-invasive support and discharge from ICU. The Table 2 presents the laboratory parameters of both groups.

Table 2. Patients' baseline laboratory characteristics with statically significance

Variable	NIV success group (n=102) (66%)	NIV failure group (n=52) (34%)	*p* Value
At admission			
Urea, mmol/l	6.7 (5.25-8.3)	8.3 (6.22-11.6)	0.001
At NIV initiation			
N/L ratio	9 (5-13)	10 (6-18.25)	0.047
Urea, mmol/l	6.7 (5.45-8.3)	8.05 (6.37-10.55)	0.003
24-48h of NIV			
N/L ratio	8 (6-15)	15 (8-24)	0.001
Leucocytes, 10^9/l	9.4 (7.5-11.8)	11.3 (8.3-14.9)	0.007
Urea, mmol/l	6.7 (5.45-8.7)	8.25 (6.23-10.9)	0.016
CRP, mg/l	37.7 (18.5-82.7)	69.6 (24-126.25)	0.032
72-96h of NIV			
N/L ratio	11 (5-15)	18 (9-30)	0.001
Lymphocyte,10^9/l	0.86 (0.5-1.38)	0.69 (0.36-0.94)	0.019
Leucocytes, 10^9/l	9.2 (7.4-11.5)	12 (8.8-14.8)	0.001
CRP, mg/l	31.25 (15.32-63.75)	74 (24-138.2)	0.002
D-dimer, mg/l	1.44 (0.58-4.67)	4.4 (1.67-7.62)	0.026

Note: *N/L ratio: neutrophil-lymphocyte ratio; CRP, C-reactive protein; NIV: non-invasive ventilation.*
Data are presented as median (interquartile rage IQR)

The patients with success of NIV, had lower levels of urea (mmol/l) during the hospitalization: at admission to 24-48h of non-invasive ventilation. The neutrophil/lymphocyte ratio recorded statistically significant difference between groups from the start of NIV ventilation and during the 96h of NIV. In the group with NIV failure, the value of C - reactive protein (mg/l) was two-fold higher: 69.6 (IQR 24-126.25) vs 37.7 (IQR 18.5-82.7), p=0.032) at 24-48h and 74 (IQR 24-138.2) vs 31.25 (IQR 15.32-63.75) at 72-96h of NIV. The notable difference between the two groups was found in D-dimer (mg/l) values at 72-96h of NIV: 1.44 (IQR 0.58 - 4.67) *(NIV suc*cess) vs 4.4 (IQR 1.67-7.62) (*NIV failure*), p=0.026 and in lymphocytes number (10^9/l): 0.86 (IQR 0.5-1.38) *(NIV suc*cess) vs 0.69 (IQR 0.36-0.94) (*NIV failure*), p=0.019. WBC count was higher in the NIV failure group at 24-48h and 72-96h of NIV. It was not registered the statistically significant difference in platelets count values during the non-invasive ventilation. Table 3 shows the relationship between different parameters and risk for NIV failure.

The variables that presented the difference in values between the two groups were stratified. Were identified the association between NIV failure and the following parameters: age > 60 years; N/L ratio more than 9.8 at 24-48h and 72-96h of NIV; Leucocytes count > 10x10^9/l at 24-48h, and 72-96h of NIV; Urea > 7.5 mmol/l at admission, NIV initiation and 24h-48h of NIV; D-dimer > 1.5 mg/l at 72-96h of NIV. Values of CRP more than 36 mg/l were correlated with NIV failure only at 72-96h of non-invasive ventilation.

Table 3. Association between demographic characteristics, outcomes, laboratory parameters and risk of NIV failure

Variable	OR (CI 95%)	p-value
Hypertension	1.203 (1.033-1.401)	0.033
Delirium	3.04 (1.934-4.779)	0.0001
Need for sedation	1.721 (1.358-2.182)	0.0001
Age, > 60	1.436 (1.146-1.799)	0.004
N/L ratio, > 9.8 at 24-48h of NIV	1.607 (1.171-2.205)	0.005
N/L ratio, > 9.8 at 72-96h of NIV	1.396 (1.082-1.800)	0.016
Leucocytes, >10x10^9/l at 24-48h of NIV	1.545 (1.130-2.114)	0.009
Leucocytes, >10x10^9/l at 72-96h of NIV	1.667 (1.218-2.280)	0.002
CRP, > 36 mg/l at 24-48h of NIV	1.242 (0.893-1.727)	0.213
CPR, >36 mg/l at 72-96h of NIV	1.512 (1.099-2.082)	0.018
Urea, >7.5 mmol/l at admission	1.527 (1.108-2.104)	0.013
Urea, >7.5 mmol at NIV initiation	1.459 (1.032-2.061)	0.038
Urea, >7.5 mmol/l at 24-48h of NIV	1.471 (1.052-2.058)	0.029
D-dimer, > 1.5 mg/l at 72-96h of NIV	1.545 (1.093-2.185)	0.028

Note*: N/L – neutrophil/lymphocyte ratio; NIV – non-invasive ventilation; CRP – "C" reactive protein.*

Table 4. ROX index values measured dynamically during NIV

Variable	**NIV success group (n=102) (66%)**	**NIV failure group (n=52) (34%)**	***p* Value**
ROX index at NIV initiation	6.03 (5.5-6.5)	5.21 (4.57-6.08)	<0.001
ROX index at 12h of NIV	6.17 (5.65-6.73)	5.48 (4.89-6.13)	<0.001
ROX index at 24h of NIV	6.22 (5.77-6.72)	5.49 (5.01-6.13)	<0.001
ROX index at 36h of NIV	6.23 (5.81-6.78)	5.52 (4.86- 6.07)	<0.001
ROX index at 48h of NIV	6.23 (5.9-6.72)	5.35 (4.85-5.67)	<0.001
ROX index at 60h of NIV	6.23 (5.9-6.72)	5.48 (4.95-5.71)	<0.001
ROX index at 72h of NIV	6.39 (6.02-7.05)	5.41 (4.88-5.71)	<0.001

Note: ROX index: ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate; NIV: non-invasive ventilation.
Data are presented as median (interquartile rage IQR)

The ROX index (Table 4) values was higher in the NIV success group from the NIV initiation until 72h of NIV.

ROC curves of the ROX index predictive model for NIV failure is presented in Table 5. The moderate accuracy in prediction of NIV ventilation failure represents ROX index at NIV initiation (cut-off value: 5.65) with an AUC of 0.696 (p=0.001), sensibility of 70% and specificity of 59.6%. ROX index values from 12 to 36h of NIV demonstrate good accuracy in prediction, with cut-off value of 5.68, AUC 0.708 (p=0.001), a sensibility 74.5% and specificity 59.6% for ROX index at 12h of NIV; cut-off value of 5.86, AUC 0.718 (p=0.001), sensibility 73.5% and specificity 65.4% for ROX index at 24h of NIV and cut-off value 5.68, AUC 0.745 (p=0.001), sensibility 74.5% and specificity 71.1% for ROX index at 36h of NIV. From 48h to 72h of NIV, ROX index

demonstrates a very good predictive model. Its values are: for ROX index at 48h of NIV sensibility 85.3% and specificity 80% at cut-off value 5.71, AUC 0.812, p=0.001, for ROX index at 60h of NIV sensibility 85.3% and specificity 79.2 % at cut-off value 5.74, AUC 0.800, p=0.001 and for ROX index at 72h of NIV sensibility 88.1% and specificity 80% at cut-off value 5.74, AUC 0.841, p=0.001 (Figure 2).

Table 5. ROC curve of the ROX index predictive model for NIV failure.

Variable	Sensitivity (%)	Specificity (%)	Cut-Off Value	AUC (95% CI)	*p*-Value
ROX index at NIV initiation	70	59.6	5.65	0.696 (0.599-0.792)	<0.001
ROX index at 12h of NIV	74.5	59.6	5.68	0.708 (0.612-0.804)	<0.001
ROX index at 24h of NIV	73.5	65.4	5.86	0.718 (0.621-0.815)	<0.001
ROX index at 36h of NIV	74.5	71.2	5.86	0.745 (0.649-0.841)	<0.001
ROX index at 48h of NIV	85.3	80	5.71	0.812 (0.727-0.897)	<0.001
ROX index at 60h of NIV	85.3	79.2	5.74	0.800 (0.713-0.888)	<0.001
ROX index 72h of NIV	88.1	80	5.74	0.841 (0.763-0.919)	<0.001

Note: *AUC - area under the ROC curve; CI - confidence interval; NIV - non-invasive ventilation; ROX index - ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate.*

Discussion

The respiratory support in COVID-19 is dependent on the severity of the disease and can be provided by using nasal cannulas, oxygen masks, high-flow nasal cannulas (HFNC), non-invasive positive pressure ventilation (NIPPV) (CPAP, Bi-PAP, PSV) and MV. During the pandemic, a lot of clinical researches regarding non-invasive support applicability and influence on outcome in COVID-19 patients were performed and different results were registered. More of them encourage the use of non-invasive ventilation support [9].

The successful early NIV was evaluated in the Recovery-RS Clinical Trial, which demonstrated a decrease in mortality when using CPAP therapy as an initial respiratory support strategy compared to conventional oxygen therapy [10].

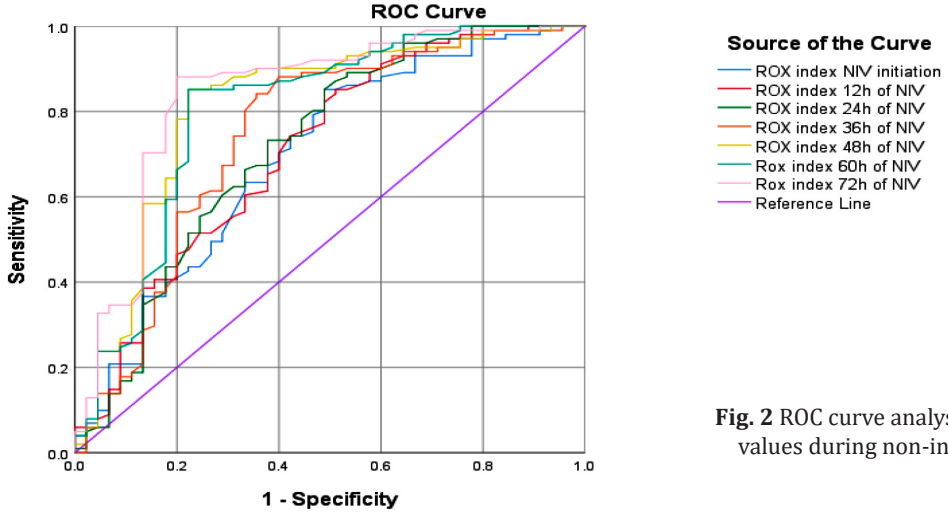

Fig. 2 ROC curve analysis for the ROX index values during non-invasive ventilation.

Overall, the rate of NIV use in COVID 19 patients is 25.5% - 46%, with a failure rate between 30 and 88%. The registered mortality rate in non-success cases is around 59.8% [11-13]. Among the factors that may influence the negative result of non-invasive ventilation are: age > 60 years, comorbidities, low PaO2 / FiO2 ratio, low basal PaO2, CRP value, platelet count, respiratory rate, minute volume, ventilator ratio, D-Dimers level [12]. In this study, the risk for NIV failure was associated with age > 60 years, presence of hypertension, association of delirium and need for sedation during NIV. One of the factors that must be considered in COVID-19 patients at hospital admission is ISARIC score, which was developed, validated, and applied in 9 regions of the United Kingdom. This score evaluates 11 parameters at hospital admission or at first contact with patient. These are the number of comorbidities, age, and sex, presence of pulmonary infiltrates, urea level, respiratory rate, CRP, lymphocyte number, and oxygen saturation [14]. In the presented research, the patients with higher ISARIC mortality and deterioration score were more exposed to NIV failure.

The risk factors and laboratory parameters that influence the result of non-invasive ventilation that have been identified in our study are neutrophil/lymphocyte ratio during non-invasive support, lymphocyte count at 72-96h of NIV, leukocyte count at 24-48h and 72-96h of NIV, urea level during hospitalization, CRP at 24-48h of 72-96h of NIV, D-dimers level at 72-96h of NIV. All these factors, with varying degrees and according to different sources, reflect the clinical evolution, outcome, and prognosis of COVID-19. According to the previous publications, lymphopenia indicates a severe course of COVID-19 disease, due to increased viremia and consumption of immune cells, where the net number of lymphocytes is inversely proportional to the severity of the disease [15].

The previous publication highlighted that the neutrophil-lymphocyte ratio at a value higher than 9.8, indicates the high incidence of ARDS and the need for non-invasive or invasive ventilatory support [16]. The data recorded in this study suggest that neutrophil/lymphocyte ratio (at NIV initiation, at 24-48h of NIV and at 72-96h NIV) and values > 9.8 of N/L ratio represent the risk for NIV failure.

C-reactive protein is the inflammatory marker of the acute phase, and is produced by hepatocytes following stimulation by interleukin-6 and is used as an indicator of the severity of both inflammatory and infectious processes [17]. In the case of patients with COVID-19, it not only directly correlates with the degree and extent of pulmonary damage in the initial stage and the early pulmonary phase [18] but also suggests the possibility of poor prognosis and a four-fold higher rate of negative outcome and respiratory worsening at values more than 10 mg/l [19]. Our data identified increased values of CPR in the NIV failure group at 24-48h and 72-96h and the presence of values > 36mg/l were associated NIV failure.

The presented study showed two-fold values of neutrophil/lymphocyte ratio in dynamics and CRP at 24-48h and 72-96h were identified in the group of patients with NIV failure. This suggests, that increased values of the neutrophil/lymphocyte ratio, CRP and the low number of lymphocytes during NIV indicate the lack of regression of the hyper-inflammatory process, whose evolution is closely correlated with the success of NIV.

The identified high levels of leukocytes in the group of patients with NIV failure suggest an association of bacterial superinfection in this group of patients, which has a rate of 24% in COVID-19 patients, and 41% in case of patients in ICU. The most commonly cultivated germs are Acinetobacter spp. (22.0%), Pseudomonas (10.8%), and Escherichia coli (6.9%) [20]. The presence of bacterial superinfection in patients with COVID-19 disease is an unfavorable prognostic factor, associated with an increased risk of mortality [20].

Because of renal tropism of SARS-COV-2 virus [21], acute kidney injury is recorded at approx. 20% COVID-19 patients, with a mortality rate of approx. 55% in case of its association [22].

Urea values higher than 6.5 mmol/l indicate bad evolution and prognosis and a greater risk of developing the severe and critical form of the illness [23]. The urea values that were related to the risk of NIV failure in this investigation were > 7.5 mmol/l at admission, NIV initiation, and 24-48h of NIV.

Now, there is no consensus on the decision about conversion to mechanical ventilation, this action depends on national or local protocols and tactics, with a lack of global consensus on early or late intubation. These controversies are based on the lack of correlation between the clinical presentation, imaging and the PaO2 / FiO2 ratio used to stratify the severity degree of classic ARDS. For this reason, it has been proposed to manage these patients based on their clinical phenotype [24, 25]. At the same time, the difference in mortality depending on the timing of the intubation has not been proven yet. This justifies the continued application of the wait-and-see approach in some of the clinics [26].

In COVID-19 patients, remain uncertain the criteria and indications for the initiation of mechanical ventilation are. In more of the cases, they are progression of respiratory distress with signs of tissue hypoxia, PaO2 value <50 mmHg, severe acidosis pH <7.25, work of breathing and delirium [27]. Nevertheless, on the other hand, the wait-and-see approach has led to appearance of multiple discussions around the phenomenon of P-SILI (patient self-inflicted long injury) in which lung injury is induced by the patient's own respiratory effort [28].

One of the predictors of non-invasive support techniques failure is ROX Index, which is used for the prediction of the HFNC failure in patients with COVID-19 ARF [29]. Dynamically evaluated every 12 hours, ROX index indicates a high risk of failure of non-invasive ventilation, the need for intubation and mechanical ventilation when its value decrease below 5.99 (more specifically for COVID-19 patients) or 4.88 (in non-covid-19 patients) [30]. The ROX index values that were recorded in this survey were predictive from NIV initiation and during 72h of NIV and may warn about respiratory worsening and the need to discuss the conversion to mechanical ventilation when evaluated in dynamics every 12 hours.

In presented research the reported mortality rate in case of NIV failure was 96%. This may be related to the fact that the study included patients from the first period of the pandemic, this being associated with the lack of experience in medical management and respiratory support.

Conclusions

The abnormal values during continuous measurement of laboratory parameters such as neutrophil/lymphocyte ration, urea level, lymphocyte count, increase in WBC count and maintaining of high values of CPR and D-dimer, as well as association of delirium and need for sedation during NIV, can alert and inform clinicians about the risks of NIV failure in COVID-19 patients with acute respiratory failure. ROX index follow-up every 12h from NIV initiation and through 72h of NIV may predict respiratory worsening in non-invasive ventilated patient. Continuous measurement of these parameters may help the clinicians to decide the optimal timing of conversion to invasive ventilation.

Competing interests

None declared.

Authors' contribution

The authors contributed equally to the research of the scientific literature, the selection of the bibliography, the reading, and analysis of biographical references, the writing of the manuscript and its peer review. All authors have read and approved the final version of the article.

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Patient consent

Obtained.

Ethics approval

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes No.4 from 07.07.2021).

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