Respiratory predictors of NIV failure in moderate-to-severe COVID-19-associated ARDS after deterioration of respiratory failure outside ICU: the COVID-NIV observational study

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Introduction: Observational studies and meta-analysis of these studies have shown very high efficacy of the CPAP therapy in COVID-19-associated acute respiratory failure (ARF) outside ICU. The efficacy of non-invasive ventilation (NIV) after deterioration of respiratory failure in patients who already received conventional oxygen or CPAP is less evident. The goal of the study was to find predictors of non-invasive ventilation failure in patients who didn't respond to the combination of glucocorticoids+tocilizumab/olocizumab with conventional oxygen or CPAP outside ICU, and progressed to moderate-to severe COVID-19 ARDS, based on gas exchange and respiratory physiology.

Methods: This was a prospective observational clinical study (ClinicalTrials.gov NCT04667923) conducted in the COVID-Intensive Care Unit (ICU) of Sechenov University (Moscow, Russia) from October 1, 2020, to May 31, 2021. Patients with COVID-19-associated acute respiratory failure receiving oxygen therapy (<15 l/min on the non-rebreather mask) or continuous positive airway pressure (CPAP)-therapy by CPAP-machines with oxygen flow <15 l/min were daily screened for eligibility. We included screened patients with at least one of the following criteria: fatigue, Patrick scale 5 points, SpO_2<92%. Before the entry to the study, we switched oxygen or CPAP therapy to non-invasive ventilation using NIV ventilator (Trilogy 202, Philips Respironics, USA) using an oro-nasal face mask for at least 2 hours to assess patients' tolerance and need for urgent intubation (CPAP 8 (8-8) cmH_2O plus Pressure Support 10 (8-12) cm H_2O, FiO_2 85 (70-100)% to achieve the following: SpO_2 92-96%, exhaled tidal volume <10 ml/kg of predicted body weight (PBW), decrease in respiratory rate, and visible work of accessory respiratory muscles. We consecutively assessed for eligibility 684 and enrolled 80 patients.

If the patient tolerated NIV and did not have signs of deterioration after 2 hours of NIV, we readjusted FiO_2 to reach target SpO_2, set Pressure support level to achieve Vte<8

ml/kg IBW and the Tobin index < 70, and performed the following measurements for 10 minutes of observation (Day 1): mean respiratory rate (RR), air leak, minimum and maximum exhaled tidal volume (Vte), mean peak inspiratory flow (PIF), minimum and maximum inspiratory time (Ti), mean pressure swing during triggering, SpO_2 with the ROX index calculation, and work of accessory respiratory muscles by Patrick scale. After that, we placed a mainstream capnograph between the mask and ventilatory circuit and asked the patient to make deep exhalation until the alveolar plateau was reached, and measured end-tidal carbon dioxide ($P_{ET}CO_2$). After respiratory measurements, arterial blood gases were tested and arterial partial oxygen tension to inspiratory oxygen fraction (PaO_2/FiO_2) ratio, alveolar dead space (VDalv/VT) according to Bohr-Enghoff equation, and ventilatory ratio (VR) were calculated. All measurements were repeated on days 3, 5, 7, 10, 14, and 21.

Results: Overall, combined success rate outside ICU for conventional oxygen and CPAP was 78.6% (440 of 560 patients). Non-invasive ventilation failure rate in ICU after deterioration of respiratory failure outside ICU was 71.3% (n=57). Patients with the subsequent NIV failure were older at inclusion, more frequently frail, had longer duration of disease before ICU admission, higher rate of CPAP-therapy outside ICU, and longer duration of CPAP outside ICU (**Table 1**)**.** Our data and ROC-analysis showed that respiratory parameters on Day 3 (approximately 48 hours after inclusion) can be used as a predictors of NIV failure in moderate-to-severe COVID-19-associated ARDS. Patients with NIV success showed significant increase PaO_2/FiO_2, SpO_2/FiO_2, ROX index, and decrease in respiratory rate and Patrick score on Day 3, while alveolar dead space in this subgroup remained stable (**Fig.1**). On the opposite, in NIV failure group PaO_2/FiO_2, SpO_2/FiO_2, ROX index didn't improved, respiratory rate even increased, and Patrick scale showed visible work of the accessory respiratory muscles (**Fig.1**). ROC-analysis revealed that gas exchange parameters, and accessory respiratory muscles involvement (Patrick score) on Day 3 can be used as a prognostic tool for NIV failure in moderate-to-severe COVID-19-associated ARDS: PaO_2/FiO_2 <112 mmHg (Se 85%, Sp 83%, AUROC 0.90 (0.93-0.97), p<0.0001); $P_{ET}CO_2$ <19,5 mmHg (Se 68%, Sp 83%, AUROC 0.84 (0.73-0.94), p<0.0001); VDalv/VT > 0.43 (Se 70%, Sp 70%, AUROC 0.78 (0.68-0.90), p<0.0001); ROX-index < 5.02 (Se 78%, Sp 83%, AUROC 0.89 (0.81-0.97), p<0.0001); Patrick score > 2 points (Se 71%, Sp 90%, AUROC 0.87 (0.78-0.96), p=0.006).

Conclusion: In patients who didn't respond to the combination of glucocorticoids+tocilizumab/olocizumab with conventional oxygen or CPAP outside ICU, and progressed to moderate-to severe COVID-19 ARDS, escalation of the respiratory

support to noninvasive ventilation had about 1/3 probability of the NIV success. prediction of the NIV failure can be made after 48 hours based on respiratory physiological parameters such as the ROX index<5.02, PaO_2/FiO_2<112 mmHg, $P_{ET}CO2$<19.5 mmHg, and Patrick score >=2.

Table 1. Patient's demographic characteristics, comorbidities, medications and laboratory values at the first day of NIV

	Overall (n=80)	**NIV success (n=23)**	**NIV failure (n=57)**	**p**
Demographics				
Age, years	71.5 [62.0-80.0]	62.0 [58.0-71.0]	73.0 [66.5-81.5]	0.005
Males, n (%)	54 (56.3)	12 (52.2)	33 (57.9)	0.412
BMI, kg/m^2	30.1 [26.9-33.5]	31.1 [26.9-35.3]	30.1 [27.0-33.2]	0.404
Clinical Frailty Score, points	4 (3-4)	3 (3-4)	4 (4-4)	0.001
Days from disease onset, days	14.0 [9.3-18.0]	11.0 [8.0-14.0]	15.0 [10.5-20.0]	0.005
Days from hospital admission to ICU-NIV, days	6.0 [2.0-12.0]	4.0 [1.0-6.0]	8.5 [4.0-13.0]	0.007

CPAP outside ICU before ICU-NIV, n (%)	24 (30.0)	2 (8.7)	22 (38.6)	0.008
CPAP duration outside ICU before ICU-NIV, days	6.0 [3.3-11.0]	4.0 [3.0-4.0]	7.0 [3.8-11.5]	0.304
SOFA score	4 [3-4]	3 [2-4]	4 [3-4]	**0.001**
Lung CT				
Lung involvement, %	84.5 (74.0-90.0)	75.0 (70.0-86.0)	86.0 (76.5-91.5)	**0.003**
Lung consolidation, %	6.0 (4.0-8.0)	4.0 (3.0-8.0)	7.0 (5.0-8.0)	0.072
Treatment, n (%)				
Dexamethasone 16 mg/day or methylprednisolone 1 mg/kg/day	80 (100.0)	23 (100.0)	57 (100.0)	1.000
Enoxiparine 1 mg/kg/day	80 (100.0)	23 (100.0)	57 (100.0)	1.000
Anticytokine therapy				
Tocilizumab	67 (83.8)	19 (82.6)	45 (78.9)	0.356
Olokizumab	13 (16.2)	4 (17.4)	12 (21.1)	
Laboratory values				

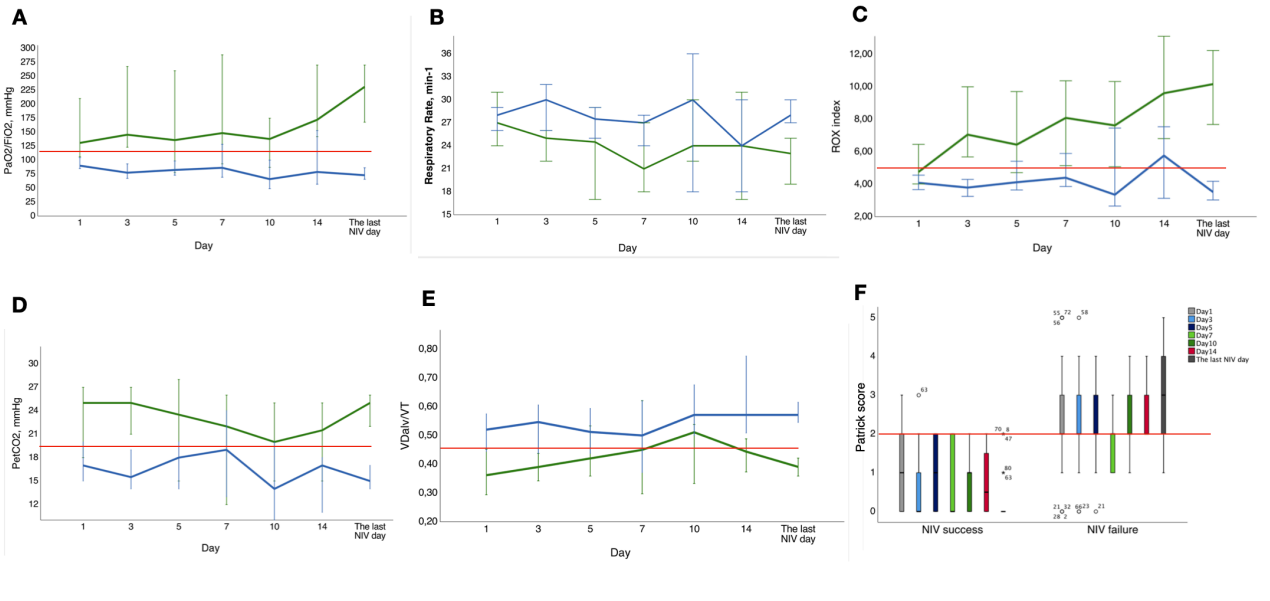
WBC, 10^9/l	11.2 [6.8-14.1]	9.3 [5.8-13.9]	11.7 [8.4-14.8]	0.260
Lymphocytes, 10^9/l	0.5 [0.3-0.7]	0.7 [0.5-0.8]	0.4 [0.2-0.7]	**0.008**
D-dimer, mcg/ml	1281 [446-2147]	1070 [529-1910]	1367 [412-2593]	0.658
Fibrinogen, g/l	5.2 [3.8-7.7]	5.1 [3.5-7.0]	5.6 [4.2-7.9]	0.483
Creatinine, mcg/l	85.8 [72.7-104.5]	75.3 [68.8-89.0]	92.2 [80.4-112.1]	**0.002**
LDH, U/l	1082 [780-1537]	819 [703-1310]	1207 [875-1597]	0.116
CRP, mg/l	37.0 [12.1-92.4]	32.2 [12.3-135.7]	42.0 [11.9-92.4]	0.807

Data presented as medians [interquartile range] or n (%) where appropriate. Differences between groups: Mann-Whitney U-test, Chi-square or Fisher exact test where appropriate. p-value: comparison between survivors and non-survivors.

Lung involvement is defined as the proportion of the lung infiltrates including ground-glass opacities, crazy paving, and consolidation on high-resolution CT scan to whole lung volume. Lung consolidation is defined as the proportion of the lung consolidation volume to lung infiltrates volume. We used medications included in «Prophylaxis, Diagnostics, and Treatment of patients with COVID-19. Temporary Clinical Guideline» issued by the Russian Ministry of Health for that time (versions 5-8)

Abbreviations: BMI: body mass index; CPAP: constant positive airway pressure; ICU: intensive care unit; NIV: noninvasive ventilation; SOFA: sequential organ failure assessment; CT: computed tomography; UFH: unfractionated heparin; LWH: low weight heparin; WBC: white blood cells; LDH: lactate dehydrogenase; CRP: C-reactive protein.

Figure 1. Gas exchange and respiratory monitoring parameters during noninvasive ventilation (NIV) in NIV success and NIV failure groups


A
PaO2/FiO2, mmHg
300
275
250
225
200
175
150
125
100
75
50
25
0
1
3
5
7
10
14
The last NIV day
Day
B
Respiratory Rate, min-1
36
33
30
27
24
21
18
15
1
3
5
7
10
14
The last NIV day
Day
C
ROX index
12,00
10,00
8,00
6,00
4,00
2,00
1
3
5
7
10
14
The last NIV day
Day
D
PetCO2, mmHg
30
27
24
21
18
15
12
1
3
5
7
10
14
The last NIV day
Day
E
VDalv/VT
0,80
0,70
0,60
0,50
0,40
0,30
0,20
1
3
5
7
10
14
The last NIV day
Day
F
Patrick score
5
4
3
2
1
0
NIV success
NIV failure
Day1
Day3
Day5
Day7
Day10
Day14
The last NIV day