ORIGINAL ARTICLE

Predictive factors for noninvasive mechanical ventilation failure among COVID-19 critically ill patients - a retrospective cohort study

Mirza Kovačević, Nermina Rizvanović, Adisa Šabanović Adilović

Department of Anaesthesiology and Intensive Care Unit, Cantonal Hospital Zenica; Bosnia and Herzegovina

ABSTRACT

Aim To identify predictive factors related with noninvasive ventilation (NIV) failure that are not based on the patient's respiratory status or acid base gas analyses in COVID-19 critically ill patients, and to create a predictive model of NIV failure.

Methods A total of 73 COVID-19 critically ill patients who developed acute respiratory failure and underwent NIV were divided into two groups: Group 1, patients who required endotracheal intubation and invasive mechanical ventilation after NIV and Group 2, patients with successful weaning from NIV. Demographic data, clinical symptoms and signs, clinical index and scores, duration indicators and laboratory data were analysed. Predictive factors of NIV failure were assessed using univariate and multivariate regression analyses followed by the receiver operating characteristic (ROC) curve.

Results In the Group 1 (NIV failure) there were 54 (73.97%) patients. Predictive factors for NIV failure were: the presence of dyspnoea on the day of admission at hospital ($p<0.05$; sensitivity 44.40%; specificity 84.20%), higher radiographic assessment of lung oedema score (RALES) on the day of starting NIV ($p<0.009$; sensitivity 70.40%; specificity 73.75%), higher length of NIV ($p<0.014$; sensitivity 48%; specificity 84.10%) and higher urea on the day of starting NIV ($p<0.004$; sensitivity 70.44%; specificity 73.72%)

Conclusion NIV treatment in COVID-19 critically ill patients has a high failure rate. In addition to respiratory parameters, dyspnoea, higher RALES, higher length of NIV and increased urea value could predict NIV failure. These factors should be considered in treatment decision making.

Key words: acute respiratory failure, dyspnoea, RALES, urea

Corresponding author:
Mirza Kovačević
Department of Anaesthesiology and Intensive Care Unit,
Cantonal Hospital Zenica
Crkvice 67, 72 000 Zenica,
Bosnia and Herzegovina
Phone: +387 32 447 000;
Fax: +387 32 226 576;
E-mail: kovacevic.mirza@hotmail.com
ORCID ID: https://orcid.org/0000-0002-3492-4100

Original submission:
06 April 2021;
Revised submission:
17 May 2021;
Accepted:
25 May 2021
doi: 10.17392/1385-21

Med Glas (Zenica) 2021; 18(2):362-369

INTRODUCTION

COVID-19 virus is a new, predominantly respiratory virus, first recognized in China, in December 2019 and has spread all over the world. Severe clinical condition with acute respiratory failure (ARF) caused by COVID-19 virus poses a serious threat to citizens and healthcare systems or professionals (1,2). About 15-30% of patients with COVID-19 viral infection deteriorate to acute respiratory distress syndrome (ARDS) within the first two days of hospital admission and require some type of respiratory support (3). Conventional oxygen therapy by face mask, high-flow nasal oxygen, NIV or invasive mechanical ventilation (IMV) are used in the treatment of hypoxemic ARF observed in COVID-19 viral infection. The IMV requires endotracheal intubation, which is associated with major medical complications, and which leads to significant medical costs. Indications for endotracheal intubation of patients with COVID-19 are strictly defined and based on the severity of hypoxemia, clinical respiratory variables, or ventilation variables. These indications should be limited to: airway protection (disorder of consciousness), severe decompensated acidosis (pH <7.20-7.25), severe hypoxemia (PaO_2 <50 mmHg or SaO_2 <90% -92%), signs and symptoms of tissue hypoxia (4).

The NIV is one of the first-line therapies in order to avoid endotracheal intubation in patients with ARDS (5). Limited data described a high rate of NIV failure in a previously reported ARF caused by other types of coronavirus infections, such as Middle East respiratory syndrome corona virus (MERS-CoV) or severe acute respiratory syndrome corona virus (SARS-CoV) (6). The patients with COVID-19 treated with NIV are admitted to intensive care units (ICU) under the constant supervision of experienced medical staff, capable of endotracheal intubation (7).

Related factors that may impair ventilation and respiratory mechanics in NIV-treated patients and contribute to endotracheal intubation have not been precisely identified. Some studies have described risk factors for the requirement for NIV support in critically ill COVID-19 patients (8,9), but predictive factors for NIV failure are not sufficiently investigated. There is no consensus among anaesthesiologists on acceptable predictors for NIV failure.

The aim of this study was to define predictive factors for NIV failure and the necessity of endotracheal intubation among COVID-19 critically ill patients, regardless of the severity of hypoxemia, clinical respiratory variables, or ventilation variables. We evaluated the predictive value of demographic parameters, clinical signs and symptoms, clinical index and scores, duration indicators, laboratory and radiological findings and created a corresponding model for prediction of NIV failure.

PATIENTS AND METHODS

Patients and study design

This single centered retrospective cohort study was conducted over the period of seven months, between July 2020 and February 2021, in the Department of Anaesthesiology and Intensive Care Unit at the Cantonal Hospital in Zenica, Bosnia and Herzegovina. During the observed period, 186 patients were admitted to the ICU with COVID-19 ARF. After obtaining the Ethical Committee's approval and a written informed patient consent, 73 adult patients fulfilled the study criteria and were included in the study. Inclusion criteria were patients with a positive reverse transcription-polymerase chain reaction of nasopharyngeal swab samples for SARS-CoV-2, admitted to the ICU, presented with hypoxemic ARF and treated with NIV. Electronic data from the ICU medical reports were used.

The patients were divided into two groups: Group 1 (54 patients, negative NIV outcome), patients whose ICU treatment started with NIV but required endotracheal intubation and invasive mechanical ventilation and Group 2 (19 patients, positive NIV outcome), patients whose ICU treatment started with NIV and finished successful weaning from NIV.

One hundred and thirteen patients were excluded from the study due to non-fulfilment of the study criteria. Exclusion criteria were: the patients treated with conventional oxygen therapy by face mask, the patients treated with NIV less than 24 hours, the patients with severe ARDS who required immediate endotracheal intubation, uncon-

scious patients and other contraindications for NIV such as facial abnormalities, fixed obstruction of the upper airways and vomiting (Figure 1).

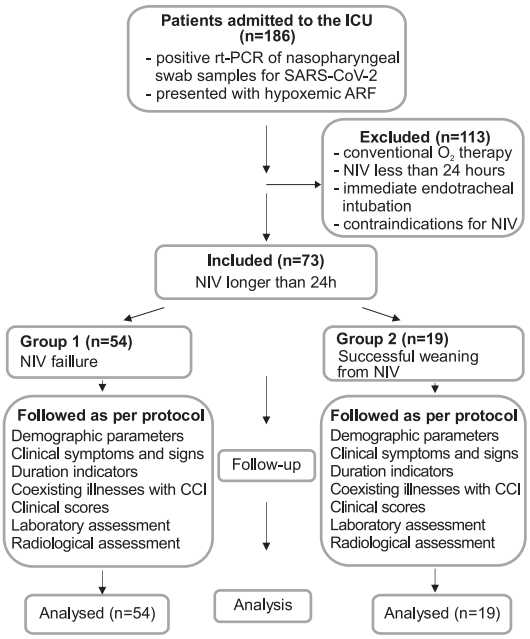

Fig.1. Flow diagram of the study protocol

Methods

Ventilation strategy. After the admission to the ICU, the patients were selected for NIV by an anaesthesiologist, according to the already established protocol at the ICU. Indications for the use of NIV were as follows: moderate to severe dyspnoea with tachypnea (≥25 breaths/min), use of accessory muscles, acid-base disturbance (pH <7.30; $PaCO_2$ >45 mmHg; PaO_2 <45 mmHg), SpO_2 <85% with FiO_2 0.5 (10). Initial continuous positive airway pressure (CPAP) was delivered to the patient using an NIV mask with pressure values of 5-10 cmH_2O. If hypoxemia (PaO_2 <50 mmHg**)** or desaturation (SpO_2<80%) persisted after NIV administration, the positive end-expiratory pressure (PEEP) was increased for 1-2 cmH_2O, or inspiratory pressure was increased for 2-3 cmH_2O to receive an inspiratory volume of 6-8 mL/kg. In the case of further exacerbation, when patients met the criteria for endotracheal intubation (severe acidosis pH <7.25; severe hypoxemia PaO_2 <50 mmHg or impaired consciousness), IMV was used as the main ventilatory support. In contrast, successful respiratory support with NIV was based on improving general clinical condition of the patient, respiratory and heart rate, mental state and improving the gas exchange index (11).

Pharmaceutical strategy. All patients were treated according to the diagnosis and treatment protocol of the new coronavirus infection (12). The therapy included corticosteroids, anticoagulants, proton pump inhibitors, and vitamin supportive therapy. Antiviral medications, antibiotics and immunomodulatory therapy were administrated in consultation with an infectologist, according to clinical status and laboratory findings.

Patients variables. The following variables were considered as possible predictors of NIV failure and involved in the regression analysis: demographic parameters, clinical symptoms and signs, clinical index and scores, duration indicators and laboratory data.

Demographic parameters involved age and gender. Clinical symptoms and signs were recorded on the day of admission at hospital, marked with YES or NO and included: fever, cough, dyspnoea, chest pain, weakness, abdominal pain, diarrhoea, nausea, vomiting, headache, anosmia, myalgia, anorexia, heart rate, mean arterial pressure (MAP) and temperature.

Clinical index and scores were recorded on the day of admission to the ICU: Charlson Comorbidity Index (CCI) (13), Simplified Acute Physiology Score II (SAPS II) and Acute Physiology and Chronic Health Evaluation II (APACHE II) (14). Radiographic Assessment of Lung Edema Score (RALES) (15) was performed in two following time: T1- on the day of admission to the ICU and T2- on the day of starting NIV.

Evaluated duration indicators were measured in days: length of symptoms to the day of hospitalization, length from admission day to starting of NIV, length of NIV and overall length of hospitalization.

Laboratory data consisted of blood count, biochemistry and immunology data. Blood samples for blood count (white blood cells, platelets, neutrophils, lymphocytes) and biochemistry parameters (urea, creatinine, sodium and potassium) were taken in three following time periods: T1- on the day of admission at ICU, T2- on the day of starting NIV and T3- on the day of endotracheal intubation for Group 1 or on the day of successful weaning from NIV for Group 2. Blood samples for analysis of immunological parameters C-reactive protein (CRP) and procalcitonin (PCT) were taken in two following time periods: T1- on the day of admission at ICU and T2- on the day of starting NIV.

Statistical analysis

Categorical variables were presented as frequencies and percentages and analysed using $\chi 2$ test. The Kolmogorov-Smirnov test was used to examine the normality of the distribution. Continuous variables were presented as means and standard deviation (SD) and analysed using Student's t test. All collected data were compared to identify the differences between the two groups. Statistical significance was considered as $p< 0.05$. Due to the dichotomous nature of the dependent variable (NIV failure), the logistic regression method was used for further statistical analysis. An univariate logistic regression analysis was used to calculate the independent association of each observed variable with NIV failure. Multivariate stepwise logistic regression was used to estimate the predictive model of NIV failure. Adjusted odds ratios (OR) and 95% confidence interval (CI) were calculated for potential predictors. Predictive ability of variables in the NIV failure model was evaluated by the receiver operating curves (ROC); area under the curve (AUC), optimal cut-off, sensitivity and specificity were calculated.

RESULTS

A total of 73 patients were included in the study. There were statistically significantly more males versus females, 49 (67.1%) and 24 (32.9%), respectively ($p<0.01$). The mean age of the patients was 65.3 (±9.81) years. There were 54 patients in the Group 1 (negative NIV outcome) and 19 patients in the Group 2 (positive NIV outcome). The NIV was applied with an overall success rate of 26%.

There were no statistically significant differences in gender and age between the groups. The presence of dyspnoea, anorexia and increased MAP on the day of admission at hospital, higher RALES on the day of starting NIV and higher length of NIV showed a statistically significant predictive value for NIV failure ($p<0.05$). The CCI score was statistically significantly higher in the Group 1 than in the Group 2 (3.37% versus 1.68%; $p<0.045$), but a predictive value for NIV failure was not recorded ($p=0.114$) (Table 1).

Table 1. Demographic data, clinical symptoms and sings, clinical index and scores and duration indicators according to the groups

Parameter	Patients group		p	Univariate analysis		p
	Group 1 (n=54)	**Group 2** (n=19)		**OR**	**95% CI**	
Age (years) (Mean±SD)	65.23 ±8.73	65.49 ±11.31	0.367	0.99	0.94-1.04	0.690
Male/Female (No, %)	36/18 (49.3/24.7)	13/6 (17.8/8.2)	0.889	1.08	0.35-3.32	0.889
Clinical symptoms and sings (YES/NO)						
No (%)						
Fever	42/12 (77.8/22.2)	16/3 (84.2/15.8)	0.551	1.52	0.16-2.63	0.553
Cough	36/18 (66.7/33.3)	16/3 (84.2/15.8)	0.146	0.37	0.09-1.45	0.157
Dyspnoea	30/24 (55.6/44.4)	3/16 (15.8/84.2)	0.026	0.23	0.06-0.89	0.034
Chest pain	6/48 (11.1/88.9)	17/2 (10.5/89.5)	0.944	1.06	0.19-5.77	0.944
Weakness	40/14 (74.1/25.9)	12/7 (63.2/36.8)	0.366	1.66	0.54-5.07	0.368
Abdominal pain	3/51 (5.6/94.4)	17/2 (10.5/89.5)	0.461	0.50	0.07-3.24	0.468
Diarrhoea	6/48 (13.0/87.0)	1/18 (5.3/94.7)	0.594	2.68	0.30-23.35	0.372
Nausea	7/47 (11.1/88.9)	3/16 (15.8/84/2)	0.355	0.66	0.14-2.9	0.596
Vomiting	5/49 (9.3/90.7)	1/18 (5.3/94.7)	0.585	1.83	0.20-16.80	0.590
Headache	2/52 (3.7/96.3)	1/18 (5.3/94.7)	0.768	0.69	0.05-8.90	0.769
Anosmia	10/44 (18.5/81.5)	1/18 (5.3/94.7)	0.165	4.09	0.48-34.33	0.194
Myalgia	14/40 (25.9/74.1)	17/2 (10.5/89.5)	0.163	2.97	0.60-14.53	0.178
Anorexia	21/33 (38.9/61.1)	2/17 (89.5/10.5)	0.022	5.40	1.13-1.09	0.034
Mean±SD						
HR (beat/min)	101.69±18.83	104.21 ±18.48	0.616	0.99	0.96-1.02	0.610
MAP (mmHg)	100.11±14.42	90.61 ±12.92	0.013	1.05	1.00-1.09	0.019
Temperature (°C)	37.14±0.93	37.25 ±1.09	0.66	0.88	0.51-1.51	0.655
Clinical index and scores (%) (Mean±SD)						
CCI	3.37±4.31	1.68±2.66	0.045	1.14	0.96-1.36	0.114
SAPS II	6.56±4.60	5.45±2.87	0.226	1.07	0.93-1.24	0.326
APACHE	22.9±9.15	20±6.87	0.264	1.04	0.97-1.11	0.265
RALES T1	30.85±10.10	26±11.70	0.88	1.04	0.99-1.09	0.093
T2	36.59±8.29	29.47±10.56	0.013	1.08	1.02-1.15	0.007
Duration indicators (days) (Mean±SD)						
LSH	6.39±3.03	7.47±2.72	0.173	0.88	0.74-1.05	0.178
LANIV	3.19±3.01	2.84±2.61	0.66	1.04	0.86-1.26	0.656
LNIV	3±1.48	4±1.76	0.019	0.69	0.50-0.95	0.026
LOH	9.63±5.1	11.89±5.23	0.102	0.92	0.83-1.01	0.113

Group 1, patients whose treatment started with noninvasive ventilation but required endotracheal intubation; Group 2, patients whose treatment finished successful weaning from noninvasive ventilation;

OR, odds ratio; CI, confidence interval; SD, standard deviation; HR, heart rate; MAP, mean arterial pressure; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; APACHE II, Acute Physiology and Chronic Health Evaluation II; RALES, Radiological Assessment Lung Edema Score; T1, on the day of admission to the ICU; T2, on the day of starting noninvasive ventilation; LSH, length of symptoms to the hospitalization, LANIV, length from admission to starting of noninvasive ventilation; LNIV, length of noninvasive ventilation; LOH, length of overall hospitalization

Table 2. Laboratory data according to the groups

Parameter (reference) (Mean±SD)	Time	Patients group		p	Univariate analysis		p
		Group 1 (n=54)	Group 2 (n=19)		OR	95% CI	
WBC (3.4-10x109/L)	T1	10.95±6.48	10.40±4.77	0.735	1.01	0.92-1.11	0.731
	T2	13.40±7.32	13.68±5.89	0.882	0.99	0.92-1.07	0.880
	T3	16.28±7.79	14.55±7.83	0.409	1.03	0.96-1.10	0.404
Platelets (150-400x109/L)	T1	232.24±97.93	227.36±83.6	0.847	1.00	0.99-1.00	0.845
	T2	252.90±109.58	244.57±82.66	0.764	1.00	0.99-1.00	0.760
	T3	245.74±121.02	251.84±108.28	0.847	1.00	0.99-1.00	0.844
Neutrophils (0.40-0.70 x109/L)	T1	1.52±2.56	2.00±3.47	0.530	0.94	0.79-1.12	0.530
	T2	9.68±8.06	7.11±5.67	0.205	1.05	0.97-1.14	0.204
	T3	9.79±8.16	7.01±3.02	0.199	1.19	0.94-1.11	0.258
Lymphocytes (0.40-0.70 x109/L)	T1	0.20±0.32	0.13±0.20	0.379	2.88	0.25-32.36	0.390
	T2	0.63±0.56	0.48±0.40	0.349	1.93	0.59-6.29	0.276
	T3	0.52±0.45	0.47±0.37	0.426	1.04	0.51-6.10	0.291
Urea (1.7-8.3 mmol/L)	T1	9.07±5.86	7.86±4.30	0.412	1.04	0.93-1.16	0.409
	T2	14.84±9.13	9.77±3.87	0.038	6.65	2.05-21.06	0.002
	T3	12.10±11.38	8.00±6.68	0.738	1.07	0.97-1.19	0.155
Creatinine (44-84 mmol/L)	T1	96.92±80.21	80.52±49.05	0.406	1.00	0.99-1.01	0.419
	T2	110.87±128.44	63.68±33.97	0.016	2.99	1.12-7.93	0.028
	T3	140.40±158.03	87.47±75.37	0.007	3.05	1.33-6.99	0.008
Sodium (136-146 mmol/L)	T1	137.57±4.14	137.36±3.85	0.843	1.01	0.88-1.16	0.840
	T2	139.01±5.22	140.36±5.38	0.351	0.95	0.86-1.05	0.347
	T3	141.35±7.03	139.10±5.32	0.209	1.05	0.96-1.15	0.209
Potassium (3.6-5.4mmol/L)	T1	4.04±0.68	4.14±0.74	0.540	0.76	0.33-1.75	0.534
	T2	4.14±0.79	4.11±0.68	0.883	1.05	0.52-2.11	0.881
	T3	4.47±0.92	4.26±0.79	0.250	1.44	0.77-2.69	0.249
CRP (0.5-10 g/L)	T1	83.03±29.32	83.15±15.29	0.990	1.03	0.98-1.02	0.986
	T2	100.97±125.72	91.36±44.54	0.746	1.00	0.99-1.00	0.748
PCT (0-0.046ng/mL)	T1	0.56±1.01	3.60±12.39	0.074	1.33	0.51-1.33	0.439
	T2	2.64±4.17	3.47±7.75	0.563	1.06	0.88-1.06	0.562

Group 1, patients whose treatment started with noninvasive ventilation but required endotracheal intubation; Group 2, patients whose treatment finished successful weaning from noninvasive ventilation; OR, odds ratio; CI, confidence interval; SD, standard deviation; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; T1, on the day of admission to the ICU; T2, on the day of starting noninvasive ventilation; T3, on the day of endotracheal intubation for Group 1 and on the day of successful weaning from noninvasive ventilation for Group 2

Higher mean value of urea and creatinine were recorded in the Group 1 compared with the Group 2 (14.84 versus 9.77 and 110.87 versus 63.68, respectively) on the day of starting NIV as well as higher mean value of creatinine (140.40 versus 87.47) on the day of starting IMV. Increased mean value of urea and creatinine on the day of starting NIV as well as increased mean value of the creatinine on the day of starting IMV showed statistically significant predictive value for NIV failure ($p<0.05$) (Table 2).

After multivariate stepwise logistic regression analysis of the parameters independently associated with NIV failure, the presence of dyspnoea on the day of admission to hospital ($p<0.004$), the RALES on the day of starting NIV ($p<0.001$), the length of NIV ($p<0.025$) and the mean value of urea on the day of starting NIV ($p<0.004$) were included in the predictive model of NIV failure (Table 3).

The most important predictive factor in the proposed model of NIV failure was increased mean value of urea on the day of starting NIV (sensitivity 70.44%, specificity 73.72%; $p<0.004$) (Table 4).

Table 3. Multivariate analysis of the parameters independently associated with noninvasive ventilation failure

Parameter	Multivariate analysis			
	p	OR	95% CI	
			Lower	Upper
Dyspnoea	0.004	0.08	0.00	0.91
Anorexia	0.356	2.52	0.34	18.76
MAP	0.067	1.48	0.98	2.28
RALES T2	0.001	1.18	1.06	1.30
LNIV	0.025	0.54	0.31	0.92
Urea T2	0.004	0.09	0.01	0.47
Creatinine T2	0.597	0.61	0.10	3.77
Creatinine T3	0.698	1.46	0.21	10.07

OR, odds ratio; CI, confidence interval; MAP, mean arterial pressure; RALES T2, Radiological Assessment Lung Edema Score on the day of starting noninvasive ventilation; LNIV, length of noninvasive ventilation; urea T2, mean value of urea on the day of starting noninvasive ventilation; creatinine T2, mean value of creatinine on the day of starting noninvasive ventilation; creatinine T3, mean value of creatinine on the day of endotracheal intubation

Table 4. The receiver operating characteristic (ROC) curve data of predictive model for noninvasive ventilation failure

Parameters	AUC	Sensitivity (%)	Specificity (%)	Cut off	p	95% CI	
						Lower	Upper
Dyspnea	0.64	44.40	84.20	0.50	0.05	0.50	0.79
RALES T2	0.70	70.40	73.75	31	0.009	0.56	0.84
LNIV	0.69	48.25	84.10	2.5	0.014	0.54	0.83
Urea T2	0.72	70.44	73.72	1.5	0.004	0.58	0.85

AUC, area under the curve; CI, confidence interval; RALES T2, Radiological Assessment Lung Edema Score on the day of starting noninvasive ventilation; LNIV, length of noninvasive ventilation; urea T2, mean value of urea on the day of starting noninvasive ventilation

DISCUSSION

This single centered retrospective cohort study investigated predictive factors for NIV failure among COVID-19 respiratory critically ill patients, that are not based on patient's respiratory status or acid-base gas analyses. Demographic parameters, clinical signs and symptoms, clinical scores, coexisting illnesses, radiological and laboratory findings were compared between patients who underwent IMV or NIV. The results of this study suggest that the presence of dyspnoea on the day of admission at hospital, higher RALES score on the day of starting NIV, higher length of NIV and increased value of urea on the day of starting NIV are included in the predictive model of NIV failure.

In the presented study, of a total of 74 patients with NIV support, 54 patients required IMV. The NIV failure rate was 73.97%. Our results confirmed previous NIV failure rate data of 56-76% (16). These results could be explained by a poorer response to NIV in patients with ARF due to COVID-19 infection compared to patients with ARF due to community-acquired pneumonia, a heterogeneity of the criteria for respiratory support measures or leakage of objectivity in the clinical studies (17).

Dyspnoea has been reported in more than 50% of patients with COVID-19 (18) and a significantly higher incidence has been found in patients in need of ICU care (19). In this study, the presence of dyspnoea was a predictive factor for NIV failure, recorded in 55.6% patients with negative NIV outcome. Dyspnoea develops due to worsening of hypoxia, increased respiratory effort and the use of accessory muscles and tachypnea (20).

Malnourished patients have decreased immunity and bone marrow function, pancytopenia and increased risk of severe morbidity (21). In the presented study, anorexia was more common in the NIV failure group (38.9% patients) but not showed a statistically significant value to be included in the predictive model. A severe form of COVID-19 infection in patients with anorexia could be explained by disruption of the angiotensin-converting enzyme 2 cell receptor function in the small intestine (22).

In our study hemodynamic instability, increased MAP and heart rate, recorded in the group with the negative NIV outcome was supported by hypoxia. The predictive value of the MAP for NIV failure was not found. In the multicenter observational study, Liu et al. did not determine the statistical significance of MAP for predicting NIV failure. The reported NIV failure rate was 81% versus 76% in our study (23).

In our research, the mean CCI was 3.37 in the group with a negative NIV outcome, but the CCI was not independently associated with NIV failure. Other authors found CCI median 2 (1–3) in the NIV + IMV group (24). The RALES system is often used to quantify the progression of lung involvement in patients with COVID-19 (25). Our study showed the RALES on the day of starting NIV of 25-50% lung involvement (four points) in the group with a negative NIV outcome; it was strongly associated with NIV failure with a value of area under the curve or diagnostic accuracy of tests of 0.70, a sensitivity 70.40% and a specificity 73.75%. The RALES on the day of starting NIV is the second most significant factor in our predictive model of NIV failure. Burns et al. concluded that the only statistical significance for NIV success was lower level of the X-ray imaging score (26).

The length of NIV of six days in our study showed a predictive value for negative NIV outcome; in the group with the positive NIV outcome, the length of NIV was four days. Similar results were reported by Mukhtara et al., the duration of successful NIV treatment was two to five days (27).

No statistically significant difference between the groups in terms of white blood cells count, platelets, neutrophils, lymphocytes, CRP and procalcitonin was found in our study. Contrary, Guan et al. (1099 patients) recorded an increase of CRP in 91.1% and lymphocytopenia in 92.6% of patients requiring IMV (28). Opposite results could have been caused by a large difference in the number of involved patients between the two studies.

Urea and creatinine values did not differ statistically significantly in patients with COVID-19 treated with a high-flow nasal cannula compared with NIV (29). The results of our study showed mean urea and creatinine values higher in the group with NIV failure; creatinine value did not show predictive significance for NIV outcome although higher urea value on the day of starting NIV proved to be the most significant factor in

the predictive model of NIV failure. This result indicates accurate monitoring of the urea value in the patients treated with NIV.

There are some limitations of the study. The single centered, retrospective nature, without a control group and small number of patients could influence failure to achieve excellent prognostic accuracy of factors. A number of important laboratory data were not monitored due to collection inconsistencies. For better insight into the predictors of NIV failure, future studies are needed, with more laboratory data (transaminases, immunological and coagulation data).

In conclusion, the use of NIV remains a significant alternative to avoid IMV, during the COVID-19 pandemic. The predictive model developed in this study showed that the presence of dyspnoea on the day of admission at hospital, higher RALES score on the day of starting NIV, higher length of NIV and increased value of urea on the day of starting NIV are strongly related with NIV failure. In addition to respiratory parameters, this predictive model should be accurately monitored and considered in making timely therapeutic and diagnostic decisions.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interest: None to declare.

REFERENCES

1. Chakraborty C, Sharma AR, Sharma G, Bhattacharya M, Lee SS. SARS-CoV-2 causing pneumonia-associated respiratory disorder (COVID-19): diagnostic and proposed therapeutic options. Eur Rev Med Pharmacol Sci 2020; 24:4016-26.
2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single centered, retrospective, observational study. Lancet Respir Med 2020; 8:475–81.
3. Xia J, Zhang Y, Ni L, Chen L, Zhou C, Gao C, Wu X, Duan J, Xie J, Guo Q, Zhao J, Hu Y, Cheng Z, Zhan Q. High-flow nasal oxygen in coronavirus disease 2019 patients with acute hypoxemic respiratory failure: a multicenter, retrospective cohort study. Crit Care Med 2020; 48:1709-86.
4. Pisano A, Yavorovskiy A, Verniero L, Landoni G. Indications for tracheal intubation in patients with coronavirus disease 2019 (COVID-19). J Cardiothorac Vasc Anesth 2020; 35:1276-80.
5. Luo J, Wang MJ, Zhu H, Liang B, Liu D, Peng X, Wang R, Li C, He C, Liang Z. Can non-invasive positive pressure ventilation prevent endotracheal intubation in acute lung injury/acute respiratory distress syndrome? A meta analysis. Respirology 2014; 19:1149-57.
6. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, Hawa H, Alothman A, Khaldi A, Raiyet BA. Clinical course and outcomes of critically ill patients with middle east respiratory syndrome coronavirus infection. Ann Intern Med 2014; 160:389-97.
7. Gundem TM, Olasveengen TM, Hovda KE, Gaustad K, Schondorf C, Rostrup M, Froyshov S, Undseth O, Tonby K, Holten AR, Sunde K. Ventilatory support for hypoxaemic intensive care patients with COVID-19. Tidsskr Nor Legeforen 2020; 140.
8. Suardi LR, Pallotto C, Esperti S, Tazzioli E, Baragli F, Salomoni E, Botta A, Frigieri FC, Pazzi M, Stera C, Carlucci M, Papa R, Meconi T, Pavoni V, Blanc P. Risk factors for non-invasive/invasive ventilatory support in patients with COVID-19 pneumonia: a retrospective study within a multidisciplinary approach. Int J Infect Dis 2020; 100:258–63.
9. Di Domenico SL, Coen D, Bergamaschi M, Albertini V, Ghezzi L, Cazzaniga MM, Tombini V, Colombo R, Capsoni N, Coen T, Cazzola KB, Di Fiore M, Angaroni L, Strozzi MA. Clinical characteristics and respiratory support of 310 COVID19 patients, diagnosed at the emergency room: a singlecenter retrospective study. Intern Emerg Med 2020.
10. Chawla R, Dixit SB, Zirpe KG, Chaudhry D, Khilnani GC, Mehta Y, Khatib KI, Jagiasi BG, Chanchalani G, Mishra RC, Samavedam S, Govil D, Gupta S, Prayag S, Ramasubban S, Dobariya J, Marwah V, Sehgal I, Jog SA, Kulkarni AP. ISCCM guidelines for the use of non-invasive ventilation in acute respiratory failure in adult ICUs. Indian J Crit Care Med 2020; 24:61-81.
11. Khilnani GC, Jain N. Do we need a protocol for weaning patients from noninvasive ventilation? Indian J Crit Care Med 2014; 18:775–7.
12. Jamshaid H, Zahid F, Din IU, Zeb A, Choi HG, Khan GM, Din FU. Diagnostic and treatment strategies for COVID-19. AAPS Pharm Sci Tech 2020; 21:222.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373-83.
14. Salluh JI, Soares M. ICU severity of illness scores: APACHE, SAPS and MPM. Curr Opin Crit Care 2014; 20:557-65.
15. Warren MA, Zhao Z, Koyama T, Bastarache JA, Shaver CM, Semler MW, Rice TW, Matthay MA, Calfee CS, Ware LB. Severity scoring of lung oedema on the chestradiograph is associated with clinical outcomes in ARDS. Thorax 2018; 73:840-6.

16. Faraone A, Beltrame C, Crociani A, Carrai P, Lovicu E, Filetti S, Sbaragli S, Alessi C, Smith MC, Angotti C, Fortini A. Efectiveness and safety of noninvasive positive pressure ventilation in the treatment of COVID19associated acute hypoxemic respiratory failure: a single center, nonICU setting experience. Intern Emerg Med 2020.
17. Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A, Llamas N, Alcazar M, Torres A. Non-invasive ventilation (NIV) in community-acquired pneumonia (CAP) and severe acute respiratory failure (ARF): effectiveness and risk factors for failure and mortality. Intensive Care Med 2012; 38:458-66.
18. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med 2020; 35:1545–9.
19. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Z, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323:1061-9.
20. Carter C, Aedy H, Notter J. COVID-19 disease: noninvasive ventilation and high frequency nasal oxygenation. Clinics In Integrated Care 2020; 1:100006.
21. Walsh O, McNicholas F. Assesment and management of anorexia nervosa during COVID-19. Ir J Psychol Med 2020; 37:187-91.
22. Lee I, Huo T, Huang Y. Gastrointestinal and liver manifestations in patients with COVID-19. J Chin Med Assoc 2020; 83:521-3.
23. Liu L, Xie J, Wu W, Chen H, Li S, He H, Yu Y, Hu M, Li J, Zheng R, Li X, Qiu H, Tong Z, Du B, Fan E, Yang Y, Slutsky AS. A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study. Lancet Digit Health 2021; 3.
24. Sivaloganathan AA, Nasim-Mohi M, Brown MM, Abdul N, Jackson A, Fletcher SV, Gupta S, Grocott MPW, Dushianthan A. Noninvasive ventilation for COVID-19-associated acute hypoxaemic respiratory failure: experience from a single centre. BJA 2020; 125:368-71.
25. Borghesi A, Maroldi R. COVID19 outbreak in Italy: experimental chest Xray scoring system for quantifying and monitoring disease progression. Radiol Med 2020; 1:1–5.
26. Burns GP, Lane ND, Tedd HM, Deutsch E, Douglas F, West SD, Macfarlane JG, Wiscombe S, Funston W. Improved survival following ward-based non-invasive pressure support for severe hypoxia in a cohort of frail patients with COVID-19: retrospective analysis from a UK teaching hospital. BMJ Open Resp Res 2020; 7:e000621.
27. Mukhtara A, Lotfya A, Hasanina A, El-Hefnawyb I, El Adawy A. Outcome of non-invasive ventilation in COVID-19 critically ill patients: a retrospective observational study. Letter to the Editor. Anaesth Crit Care Pain Med 2020; 39:579–80.
28. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng G, Yuen KY, Chen R, Tang C, Wang T, Chen P, Xiang J, Li S, Wang J, Liang Z, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Wang J, Liu J, Chen Z, Li G, Zheng Z, Qiu S, Luo J, Ye C, Zhu S, Zhong N. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382:1708-20.
29. Duan J, Chen B, Liu X, Shu W, Zhao W, Li J, Li Y, Hong Y, Pan L, Wang K. Use of high-flow nasal cannula and noninvasive ventilation in patients with COVID-19: a multicenter observational study. Am J Emerg Med 2020; S0735-6757(20)30666-5.