Original Article

Investigating Some Effective Factors on the Prediction of Continuous Positive Airway Pressure Failure Rate in COVID-19-Related Hypoxemia

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Abstract

Background: Considering the importance of using Non-Invasive Ventilation (NIV) in COVID-19-related hypoxemia, the present study was conducted to determine the effective factors on Continuous Positive Airway Pressure (CPAP) failure rate in COVID-19-related hypoxemia. **Materials and Methods:** This research was a retrospective cross-sectional study (2021) investigating the records of 200 adult patients with the medical diagnosis of acute respiratory failure (ARF) of COVID-19, admitted to the Intensive Care Unit (ICU) in Shoushtar (southwestern Iran) who underwent CPAP therapy. The Heart rate, Acidosis, Consciousness, Oxygenation, and Respiratory rate (HACOR) scores were measured before the treatment and 1 h after undergoing CPAP treatment. Moreover, patients' demographic and clinical data were recorded. Data were analyzed using the Mann–Whitney, Chi-square, Wilcoxon, and logistic regression tests. The significance level was set at $p \leq 0.05$. **Results:** The mean standard deviation [SD]) age of patients was 63.96 (16.23) years. Among all 200 patients, 78.50% (n = 157) experienced CPAP failure and the remaining 21.50% (n = 43) underwent successful CPAP therapy. Failure chance was 7.10% higher in patients with higher HACOR scores undergoing 1 h CPAP treatment than others. It was also 14.92% higher among patients with diabetes mellitus (DM) than non-DM patients. Additionally, old age (z = 2591.50, p value = 0.02), obesity (z = 2433.00, p value = 0.024), and elevated Blood Urea Nitrogen (BUN) (z = 2620.00, p value = 0.0) impacted CPAP failure rates among patients. **Conclusions:** The HACOR score 1 h after CPAP, DM, old age, obesity, and elevated BUN favor increased CPAP failure rates among patients.

Keywords: *Continuous positive airway pressure, COVID-19, hypoxia*

Introduction

Continuous positive Airway Pressure (CPAP) is one of the methods of Non-Invasive Ventilation (NIV) respiratory support to treat acute hypoxic respiratory failure (hypoxic ARF) associated with coronavirus (COVID-19) pneumonia.[1] According to recent studies, this method has been effective in oxygenation and gas exchange enhancement and has reduced the demand for tracheal intubation.[2] NIV sometimes has been used as ventilator support for patients with spontaneous breathing, hemodynamic stability, and low levels of airway secretions who do not need emergency intubation.[3] A significant number of trials in 2019, USA, indicated the importance of using NIV in patients with COVID-19 with mild to moderate acute respiratory distress syndrome (ARDS), PaO_2 <300 mmHg, and $PaCO_2$ <45 mmHg.[4] ARDS caused by COVID-19 differs substantially from ARDS caused by other diseases and its treatment is dissimilar and challenging.[5] Pneumonia caused by COVID-19 is characterized by unique features that combine the damage by direct cytopathic effects (CPEs) caused by viruses and indirect cytokine storms.[6] NIV refers to administrating respiratory support without endotracheal intubation through a nasal or full-face mask employed in different ARFs. However, in particular, the choice of the interface and the ventilatory setting adopted for NIV play a key role in the success of respiratory assistance. Among the different NIV interfaces, tolerance is the poorest for nasal and oronasal masks, whereas helmets appear to be better tolerated.[7] In this study, an oronasal mask with an appropriate size was used. According to experts, extubation is quite challenging in these patients, and invasive ventilation can result in elevated

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mortality.[8] CPAP may avoid unnecessary endotracheal intubation (ETI) in these patients; however, delaying invasive ventilation may increase the mortality rate.[1] So, early prediction of CPAP failure (including the need to use bilevel (BL) PAP or orotracheal intubation (OTI) and death during ventilation) is crucial to avoid delayed intubation.[5,9]

The Heart rate, Acidosis, Consciousness, Oxygenation, and Respiratory rate (HACOR) score was first developed in 2017 to predict CPAP failure in patients with hypoxemia due to different causes [Table 1].[10] It predicts the early detection of success or failure of CPAP and intubation and can significantly reduce mortality. Studies have confirmed the HACOR score and demonstrated its usefulness in predicting CPAP failure in COVID-19-related hypoxemia.[11,12]

The results of a multicenter study in Italy showed that the failure of CPAP was associated with male sex, polypharmacotherapy (at least three medications), platelet count <180 × 10^9/L, and partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio <240.[5] In another study and during the three Italian pandemic waves, researchers concluded that CPAP success strongly correlated with the worst PaO_2/FiO_2 ratio and D-dimer level at the admission phase.[13] Considering the importance of early detection of factors affecting CPAP failure, preventing intubation delay, and reducing the mortality rate, the limitation of studies in the world and the absence of any studies in the field of effective factors on CPAP failure rate in patients with COVID-19 in the Iranian clinical system, the current study investigated effective factors on CPAP failure rate in COVID-19-related hypoxemia.

Table 1: HACOR[$$] score

Variables	Category	Assigned points
Heart rate (beats/min)*	≤120	0
	≥121	1
PH**	≥7.35	0
	7.30-7.34	2
	7.25-7.29	3
	<7.25	4
GCS***	15	0
	13-14	2
	11-12	5
	≤10	10
PaO_2/FiO_2 ratio****	≥201	0
	176-200	2
	151-175	3
	126-150	4
	101-125	5
	≤100	6
Respiratory rate***** (breaths/min)[$]	≤30	0
	31-35	1
	36-40	2
	41-45	3
	≥46	4

*hbpm: heart beats per minute; **PH: hydrogen ion concentration; ***GCS: Glasgow Coma Scale; ****PaO_2/FiO_2: partial pressure of oxygen in arterial blood/fraction of inspired oxygen; *****RR: respiratory rate; [$]bpm: breaths per minute. Results are presented as absolute value and (percentage), or as means±standard deviation; [$$]Heart rate, Acidosis, Consciousness, Oxygenation, and Respiratory rate

Materials and Methods

This retrospective cross-sectional study was carried out in March–November 2021 using a convenience sampling method on 200 COVID-19 patients' paper medical records with ARF who were admitted to the intensive care unit 3 (ICU) department of Khatam Al Anbia Hospital in Shoushtar City. In this study, according to the ratio formula, as well as the matching paper of Guia *et al*.,[11] the proportion of people who experienced CPAP failure was $p = 0.25$. The error rate ($\alpha = 0.05$) and accuracy ($d = 0.06$) were also considered. Finally, the sample size was estimated to include 200 paper medical records.

The inclusion criteria were patients' medical records, age over 15 years, having PaO_2/FiO_2 ratio less than 300 mmHg, having $PaCO_2$ level less than 45 mmHg in room temperature or oxygen therapy with a FiO_2 value of 28%, having multiple organ system failure (MOSF) scores equal to 2 or 3 due to respiratory failure, using the VELA ventilator model matrix with the same set up in all patients, and using an oronasal mask to provide NIV. In addition, the exclusion criteria were patients' medical records, having sudden cardiorespiratory arrest, failure to protect the airway, having severe hemodynamic instability (medium arterial pressure [MAP] less than 65 mmHg despite vasopressor support), having severe restlessness (Richmond Agitation Sedation Scale [RASS] of over 2, and 5) getting MOSF score more than 3.

The data collection tool included two components: 1- HACOR score designed by Duan *et al*. to predict and evaluate the clinical condition of patients with hypoxemia who had been treated with NIV for various reasons[10] [Table 1]. This scale examines five variables: heart rate, acidosis, consciousness, oxygenation, and respiratory rate. The data required to calculate the HACORE score were extracted from the medical records in two stages before and 1 h after the implementation of CPAP. The highest HACOR score was 25. During the first hour of CPAP therapy, patients with a HACOR score over 5 had a higher risk of failure.[10,11] Moreover, a demographic and clinical characteristics checklist (e.g., age, sex, marital status, underlying disease, body mass index [BMI], smoking, hemoglobin, creatinine, sodium, potassium electrolytes, and blood sugar) was utilized. To collect the data, the medical records of patients with COVID-19 who

used the CPAP mode were checked 40 times; each time, five records were investigated by the researcher. CPAP was initiated at 8 cm H_2O and titrated according to the patient's comfort to improve oxygenation and respiratory pattern. Titrated FiO_2 to maintained SpO_2 >94%. CPAP was applied continuously according to the patient's tolerance. Prone position was performed two to three times a day (each 2 to 3 h) since the admission to the ICU and throughout hospitalization. Proning was only applied after the HACOR evaluation. Data were collected using the HACOR score and demographic checklist. Patients were then assessed based on CPAP results, that is, success or failure. CPAP failure was defined as the demand for intubation or death. Endotracheal intubation (hemodynamic stability/instability), MAP less than 65 mmHg despite using vasopressors, decreased consciousness level of Glasgow Coma Scale (GCS) less than 9, breathing rate more than 40 breaths per minute, respiratory fatigue symptoms, constant PaO_2/FiO_2 ratio of less than 150 mmHg for more than 48 h using the CPAP mode, RASS more than 2, objective criteria, and clinical decision making were considered for intubation.

Data were analyzed in SPSS-24 software using various parametric and non-parametric tools such as Mann–Whitney, Chi-square (Fisher's exact), and Wilcoxon tests. Logistic regression was employed to assess the way the HACOR scale determined the success or failure of the CPAP with other variables. Data were analyzed at a significance level of 0.05.

Ethical considerations

The study was approved by the Ethics Committee of Shoushtar University of Medical Sciences (Ref. no: IR.SHOUSHTAR.REC.1400.017). The confidentiality of all data was ensured by the absence of personally identifiable information (PII).

Results

Considering the demographic and clinical variables, the mean (standard deviation [SD]) age of patients was 63.96 (16.23). Of all patients, 76 (38%) were female, and 190 (95%) were married. Moreover, 55 (27.50%) patients had no underlying disease, 85 (42.50%) had DM, and 70 (35.00%) had hypertension. The CPAP therapy was successful in 43 patients (21.50%) and failed in 157 (78%) patients.

Patients 50 to 60 years old (Z = 2591.50, p value = 0.02) and those with DM (Chi-square = 4.29, p value = 0.039) and higher BMI scores (z = 2433.00, p value = 0.024) showed increased CPAP failure rates. However, there was no significant relationship between CPAP failure and other variables such as gender (Chi-square = 0.89, p value = 0.34), marital status (Chi-square = 0.825, p value = 0.34), and other underlying diseases (Chi-square = 0.70, p value = 0.40), such as HTN (Chi-square = 0.54, p value = 0.45), cardiovascular disease (Chi-square = 0.83, P value = 0.36), hyperlipidemia (Chi-square = 2.52, p value = 0.11), and smoking (Chi-square = 0.01, p value = 0.96). In other words, these factors did not affect the success or failure of CPAP therapy.

Among clinical variables, BUN was the only variable indicating a significant difference with CPAP failure rate (z = 2620.00, p value = 0.0). Patients with higher BUN levels experienced higher CPAP failure rates [Table 2].

There was a significant difference in HACOR scores and its four subscales before and 1 h after starting CPAP titration (z = 3.60, $p < 0.001$). Accordingly, 1 h after CPAP titration, the level of PaO_2/FiO_2 ratio increased (z = 8.74, $p < 0.001$), and tachypnea (z = 5.42, $p < 0.001$, tachycardia (z = 8.61, $p < 0.001$), and GCS (z = 4.87, $p < 0.001$) improved in patients. A HACOR score of over 5, 1 h after CPAP titration, showed increased CPAP failure rates [Tables 2 and 3]. In all mentioned cases, CPAP failure was associated with the need for endotracheal intubation.

The effect of some demographic parameters and underlying diseases on CPAP outcomes was investigated using the logistic regression method in the forward LR manner. The HACOR score, 1 h after CPAP (Wald statistics = 26.67, p value <0.001) and DM (Wald statistics = 9.19, p value = 0.002) (as an underlying disease) influenced the failure of CPAP therapy. According to the Chi-square test, the model had a good fit (Chi-square = 137.14, $p < 0.001$). The HACOR score 1 h after CPAP and DM explained 80% of the variance of CPAP therapy. The CPAP failure chance was 14.92% higher in patients with DM than those without DM. Additionally, the chance of CPAP failure was 7.10% higher in patients with higher HACOR scores 1 h after CPAP [Table 4].

Discussion

This study investigated some of the factors influencing CPAP failure rates in patients with COVID-19 admitted to the ICU for providing respiratory support using CPAP therapy. To date, only a limited number of studies have explored predictors for CPAP failure in patients with COVID-19 pneumonia, which showed inconsistent results. The HACOR score 1 h after CPAP and DM were predictive factors for CPAP failure. Furthermore, old age, obesity, and higher BUN levels influenced CPAP failure rates. Other underlying diseases were not associated with CPAP failure.

Brusasco *et al*. reported that only hypertension independently predicted CPAP failure.[14] However, Cei *et al*. reported that no underlying diseases showed a significant association with CPAP failure.[5]

One key player in COVID-19 is angiotensin-converting enzyme 2 (ACE2), which is essential for the adhesion and uptake of the virus into cells before replication.

Table 2: Comparison of demographic and clinical parameters affecting the success or failure of CPAP[$] therapy

	Mean (SD)/number (%)			Statistics (Mann–Whitney/Chi-square)	*p*
	Total		CPAP failure (*n*=157)		
Age*	63.96 (16.23)	58.48 (15.86)	65.48 (16.06)	2591.50***	0.02[$$]
Gender**					
Female	76 (38.00%)	19 (44.20%)	57 (36.30%)	0.89****	0.346
Male	124 (62.00%)	24 (55.80%)	100 (63.70%)		
Marital status**					
Married	190 (95.00%)	42 (97.70%)	148 (94.30%)	0.825****	0.364
Single	10 (5.00%)	1 (2.30%)	9 (5.70%)		
Smoking**					
Yes	46 (23.00%)	10 (23.30%)	36 (22.90%)	0.01****	0.964
Underlying disease**					
Yes	145 (72.50%)	29 (67.40%)	116 (73.90%)	0.70****	0.402
Diabetes mellitus (DM)**					
Yes	85 (42.50%)	24 (55.80%)	60 (38.20%)	4.29****	0.039[$$]
Hypertension (HTN)**					
Yes	70 (35.00%)	13 (30.20%)	57 (36.30%)	0.54****	0.459
Cardiovascular disease**					
Yes	16 (8.00%)	2 (4.70%)	14 (8.90%)	0.83****	0.361
Hyperlipidemia (HLP)**					
Yes	23 (11.50%)	2 (4.70%)	21 (13.40%)	2.52****	0.112
Body mass index (BMI)**	30.41 (4.33)	29.02 (3.58)	30.70 (4.46)	2433.00***	0.024
HACOR.PRE*	9.13 (3.04)	7.04 (1.86)	9.70 (3.06)	1455.00***	<0.001
HACOR.POST*	8.48 (3.64)	3.50 (1.57)	9.20 (3.04)	210.50***	<0.001
Hemoglobin (HB) *	11.97 (1.63)	11.6 (1.68)	12.07 (1.60)	2906.50***	0.179
Blood urea nitrogen (BUN)*	31.26 (16.76)	24.39 (8.15)	33.15 (18.00)	2620.00***	0.028
Creatinine (Cr) *	1.06 (.71)	0.96 (.50)	1.09 (.76)	2939.00***	0.208
Sodium (Na)	137.57 (4.44)	137.67 (3.68)	137.54 (4.64)	3268.00***	0.796
Potassium (K)	4.13 (.50)	4.06 (0.45)	4.15 (.52)	3232.00***	0.712
Blood sugar (BS)	184.84 (99.37)	187.25 (85.46)	190.61 (96.17)	3244.00***	0.839

*Mean (SD), **Number (%), ***Mann–Whitney, ****Chi-square, ***Mann–Whitney, ****Chi-square. [$]Continuous positive airway pressure

Table 3: Comparison between HACOR[$] variables before and 1 h after starting CPAP[$$] method

	Mean (SD)		*Z* statistics	*p*
	Before CPAP	One-hour after starting the CPAP method		
HACOR	9.13 (3.04)	8.48 (3.64)	3.60	<0.001
Heart rate (HR) Hbpm****	115.64 (17.33)	112.60 (17.16)	8.61	<0.001
Hydrogen ion concentration (PH)	7.35 (0.07)	7.35 (0.08)	0.24	0.786
Glasgow Coma Scale (GCS)	14. 64 (1.03)	14.40 (1.45)	4.87	<0.001
PaO_2/FiO_2 ratio	90.77 (15.47)	114.22 (28.17)	8.74	<0.001
Respiratory rate (RR) bpm*****	33.11 (5.94)	30.18 (5.64)	5.42	<0.001

[$]Heart rate, Acidosis, Consciousness, Oxygenation, and Respiratory rate, [$$]Continuous positive airway pressure, ****hbpm: heart beats per minute; *****bpm: breaths per minute. Values are presented as the mean(SD). The test used Wilcoxon

Changes in the ACE2 expression have been recorded in diabetes.[15] An age-dependent increase in SARS2-CoV-2 receptors (ACE2) in the respiratory epithelium may be responsible for the increased severity of COVID-19 lung disease in elderly patients.[15,16] Thus, the overexpression of ACE2, weak immune system, reduced organ function, or multiple underlying conditions may be found in elderly diabetic patients. These may cause a sharp increase in the risk of CPAP failure rates in these patients.

In the present study, there was no significant association between underlying diseases (e.g. HTN, heart disease, hyperlipidemia) and CPAP failure.

DM is a prevalent underlying disease among ICU-admitted patients with COVID-19. Generally, when patients with DM develop a viral infection, the treatment becomes more challenging due to alterations in blood sugar levels and possibly DM complications. After DM, the infection

Table 4: Effect of some demographic parameters and underlying diseases on CPAP* outcomes

Variable	Coefficients (β)	SE (β)	Wald statistics	*p*	Exp (β)	Log-likelihood	Nagelkerke R^2
Diabetes mellitus (DM)	2.69	0.88	9.19	0.002	14.92	56.70	0.81
Post-CPAP HACOR**	1.96	0.38	26.67	<0.001	7.10		
Constant	9.24	1.80	24.50	<0.001	0.000		

*Continuous positive airway pressure,**Heart rate, Acidosis, Consciousness, Oxygenation, and Respiratory rate

symptoms aggravate, especially in elderly patients with COVID-19 due to impaired cellular and humoral immunity, restricted antibody production against any infection, nutritional deficiencies, potential bacterial colonization in some mucosal surfaces, reduction of body's physiological defense reflexes (e.g., cough and wound healing), and spread of chronic diseases along with infections.[17]

Moreover, according to the results of this study, most patients with COVID-19 had a BMI of greater than 25 Kg/m^2 and faced a higher CPAP failure. Studies showed that obesity is a risk factor for higher COVID-19 severity.[18,19] Obesity is also associated with altered pulmonary mechanics and physiology, increased ACE2 expression, increased viral diversity and titers, and prolonged viral shed, which may further increase the susceptibility to COVID-19 and promote the progression to respiratory failure.[19]

In this study, patients with higher BUN levels experienced higher CPAP failure. The BUN level is a biomarker employed to assess kidney function and hypovolemia. BUN is a parameter of the CURB-65 pneumonia severity scoring system primarily used in pneumonia. Higher levels of BUN in patients with pneumonia, chronic obstructive pulmonary disease (COPD), pancreatitis, acute myocardial infarction (MI), heart failure (HF), sepsis, and elderly patients were associated with a higher mortality rate.[20]

In this study, logistic regression results revealed that the HACOR score 1 h after CPAP could predict CPAP success and failure rate in patients with COVID-19 with hypoxemia admitted to the ICU. This finding confirmed the results reported by Guia *et al*. (2018) on patients with COVID-19 with ARF in terms of determining the benefits of the HACOR score in predicting the CPAP success rate in patients with COVID-19 with hypoxemia. It also confirmed the results reported by Al-Rajhi *et al*. (2018) on patients with acquired pneumonia to examine the results and predict the failure of NIV.[11,21] To investigate the efficacy of this scale in predicting various causes of hypoxemic respiratory failure, Duan *et al*. (2017) designed the HACOR score for respiratory failure for multiple reasons such as bacterial pneumonia, lung cancer, pulmonary embolism, and heart failure. It was found that mechanisms of action were not continuously similar to ARF (pneumonia) caused by SARS-CoV-2.[10] Thereby, the present study investigated this score specifically in patients with COVID-19.

One of the limitations of this study was that only an oronasal mask was utilized to provide NIV because this type of mask was available in our ICUs. However, Coppadoro *et al*. (2021) used head helmets to deliver NIV support. It was concluded that the complication rates of using such masks up to 21% (discomfort, leaks, and skin injuries) mandated close monitoring of the noninvasive positive-pressure ventilation (NPPV) interface; however, helmet therapy could be safely and effectively used to provide NIV during hypoxemic respiratory failure, provide better-improving oxygenation than standard oxygen mask treatment, and possibly would lead to better patient-centered outcomes than other NIV interfaces.[22] Predictive factors in the regression model explained 80% of the changes in the non-invasive method. As the next limitation, the current study only used the considered CPAP titration and did not utilize bilevel positive airway pressure (BIPAP), preventing the comparison between the two methods. Future trials are recommended to compare the efficacy of helmet-CPAP, NIV, CPAP, BIPAP, HFNC, and predictors of each respiratory support technique to provide predictive success/failure scales.

Conclusion

The HACOR score 1 h after the CPAP and DM were predictive factors for CPAP failure. Furthermore, old age, obesity, and higher BUN levels influenced CPAP failure rates. Other underlying diseases were not associated with CPAP failure rates.

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Conflicts of interest

Nothing to declare.

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