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HACOR Score in Predicting Non-invasive Ventilation Failure in Acute Decompensated Heart Failure and AECOAD Patients

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Abstract

Aim: To compare the diagnostic accuracy of HACOR score in predicting non-invasive ventilation (NIV) failure among acute exacerbation of chronic obstructive airway disease and acute decompensated heart failure patients, and study the correlation of HACOR score with a length of stay and hospital mortality rate.

Materials and Methods: A prospective observational study was conducted in the Emergency Department of Hospital Melaka. We enrolled patients who presented with acute respiratory distress and started them with NIV. The efficacy of the HACOR score is evaluated at several interval time points, before NIV initiation, 1 h, 2 h post NIV initiation.

Results: HACOR score is much lower in NIV success subgroups and 100% NIV failure rate for the HACOR score more than 7 at 1 h and 2 h of NIV. With a cut-off value of more than 5 in 1 h of NIV, the diagnostic power is 86.27% with a sensitivity of 62.50% and specificity of 90.70%. While at 2 h of NIV the HACOR score of more than 5, its diagnostic power is 87.50% a sensitivity of 50% and specificity of 95%. In 0-2 hours of NIV, area under the curve for predicting NIV failure was 0.788, 0.868 and 0.925, respectively.

Conclusion: The HACOR has good diagnostic accuracy when it is assessed at 1-2 h of NIV. It is convenient to use it to assess the efficacy of NIV especially for heart failure patients. However, HACOR score was a weak predictor of mortality in our study. The length of hospital stay was also found to be longer for those who failed to respond to NIV in our study.

Keywords: HACOR score, acute exacerbation of chronic obstructive airway disease, acute respiratory failure, chronic obstructive pulmonary disease, acute decompensated heart failure, non-invasive ventilation

Introduction

Non-invasive ventilation (NIV) is the delivery of assisted mechanical ventilation to the lungs without the need of endotracheal intubation. It represents a standard of care for treating acute exacerbation of chronic obstructive airway disease (AECOAD) and acute decompensated heart failure (ADHF) (1). NIV has also been a promising option for palliative care patients who have a "do not intubate" status, this would also be expected to favor the usage of NIV in the elderly (2,3). To date, the use of NIV in other causes of acute respiratory failure (ARF) has not shown much success and generally delay in providing the definitive treatment. In contrast to invasive mechanical ventilation through endotracheal intubation, NIV offers a range of advantages like minimizing the risk ventilator-associated pneumonia and the need for sedation. It also preserves airway clearance and swallowing, allows oral patency and intermittent ventilation so that normal eating, drinking and communication are permitted (1,4,5). However, for some emergency conditions (e.g. cardiorespiratory arrest, extreme psychomotor agitation, severe haemodynamic instability, non-hypercapnic coma and multiple organ failure) must be considered absolute contraindications for NIV and require prompt intubation (1,6). NIV should not cause any delay in intubation if patients fail to respond to NIV as well. Thus, early identification of NIV failure is reducing morbidity and mortality. For this, HACOR score has been developed and has shown to predict NIV failure accurately in patients with ARF.

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In the current emergency setting, risk scoring for NIV failure is not routinely practice. In contrast to patients who have received invasive mechanical ventilation upon presentation to the emergency department (ED), those who received NIV initially but subsequently experience NIV failure and then receive intubation are associated with a higher risk of hospital mortality (7-9). Thus, identifying the predictors of NIV failure has attracted significant interest because of the strong link between failure and poor outcomes.

Researchers used stepwise multivariable regression analysis to identify parameters measured 1 h after initiation of NIV that predicted NIV failure. Each of the five parameters identified - **H**eart rate, **A**cidosis, **C**onsciousness, **O**xygenation, and **R**espiratory rate (HACOR) was assigned points such that the combined HACOR score ranged from 0 to 25 points with higher scores indicating higher likelihood of NIV failure (10). The HACOR scale variables are easily available at the bedside and easy to apply. It is a reasonable tool to use and would benefit the patient for early identification of those who are in high risk of requiring early intubation rather than trial of NIV.

Operational Term Definition

ADHF

- ADHF is defined as a sudden worsening of HF symptoms and is usually caused by cardiogenic pulmonary edema with rapid fluid accumulation in the lungs, although it can occur without pulmonary edema (11).

AECOAD

- An AECOAD is a clinical diagnosis made when a patient with COAD experiences a sustained (eg, 24-48 h) increase in cough, sputum production, and/or dyspnea. AECOAD has clinical consequences ranging from a self-limited illness to progressive respiratory failure (12-14).

Materials and Methods

Study Design and Setting

This study was a prospective observational study conducted in the Emergency Department of Hospital Melaka, Malaysia from 1st August 2020-30th July 2021 after receiving approval from the medical research and ethics committee, Ministry of health Malaysia (study code: NMRR-20-1066-55129 S1 R3, date 2.7.2020).

Population and Sample Size

The study enrolled all patients who presented to the Emergency Department of Hospital Melaka, Malaysia with acute respiratory distress and started with NIV within the study period. We used availability (simple convenience sampling), those who fulfill the inclusion criteria were enrolled into the study whilst that fall into exclusion criteria were excluded. Demographic and clinical data were collected from each participant as well.

The estimated sample size is calculated based on α precision of 0.05, effect size 0.15, power of 0.80, number of predictors 20, a two-sided test and an assumption of a moderate effect. Our power calculation was performed using G-Power Software Windows version 3.2. The statistical test was set to linear multiple regression. The calculated sample size was 56. With a 10% drop out rate, the final calculated sample size was 62.

Inclusion Criteria

1. The patient aged 18 years or older.
2. Patients with ARF (AECOAD and ADHF) who started on NIV in the Emergency Department of Hospital Melaka.

Exclusion Criteria

1. Patients who required urgent intubation and the criteria(s) as listed below:

Decreased consciousness and loss of airway reflexes, as follows:

- Failure to protect the airway against aspiration - decreased consciousness that leads to regurgitation of vomit, secretions, or blood.

Failure to ventilate, as follows:

- Result of failure to maintain and protect the airway.
- Prolonged respiratory effort that results in fatigue or failure, as in status asthmaticus or severe COAD.

Failure to oxygenate (ie, transport oxygen to pulmonary capillary blood), as follows:

- Result of failure to maintain and protect the airway or failure to ventilate.
- Acute respiratory distress syndrome.
- Large pneumonia or air-space disease.

The anticipated clinical course or deterioration (eg, need for situation control, tests, procedures), as follows:

- Septic shock with high minute-ventilation and poor peripheral perfusion (Rapid Sequence Intubation: Background, Indications, Contraindications).

1. With intolerance to NIV, the subject refuses to receive it because of discomfort, even after intermittent use has been attempted.
2. Patients and their relatives who refused to participate in this study.

3. Patients who were started on NIV in other healthcare centers and subsequently transferred to the Emergency Department of Hospital Melaka.

Materials and Procedures

Patients with ARF who have started on NIV are enrolled. However, patients who require urgent intubation or intolerance to NIV have been excluded. NIV intolerance is defined as the termination of NIV due to the subject's refusal to receive it because of discomfort, even after intermittent use has been attempted.

The decision to initiate NIV is chosen by the attending physicians based on either the common clinical presentation of acute respiratory distress (use of accessory inspiratory muscles, paradoxical abdominal motion, respiratory rate >30 breaths/min) or arterial blood gas revealing PaO_2 <70 mmHg, $PaCO_2$ more than 45 mmHg or a PaO_2/FiO_2 ratio of <300 with supplemental oxygen.

The NIV has been managed according to the protocol of ED and intensive care unit (ICU). The face mask is the first choice of interface to connect the ventilator to the patients. The size of the face mask is properly chosen to fit the patient's face with the strap applied to minimize air leaking. The initial modes are CPAP or spontaneous/time mode. For subjects with hypoxemia or heart failure only, the initial mode is set as CPAP. For subjects with hypercapnia or vigorous activity of accessory respiratory muscles, spontaneous/time mode has been used Jinhua et al. (15). The positive end-expiratory pressure is started at 5-10 cmH_2O and titrated to a maximum pressure of 15 cmH_2O according to the clinical response and tolerance of the patient. The fractional concentration of oxygen was set to achieve peripheral oxygen saturation of >92%. Apart from NIV, medical therapies, which include intravenous antibiotics, isosorbide dinitrate, aminophylline, magnesium sulfate are initiated based on the nature of presenting illness.

The efficacy of the HACOR score is evaluated at several interval time points, before NIV initiation, 1 h, 2 h post NIV initiation. The arterial blood pH, PaO_2, $PaCO_2$, PaO_2/FiO_2, Glasgow Coma Scale (GCS), respiratory rate, and heart rate are recorded as per parameters in the HACOR score. Arterial blood gases are usually monitored in the ED for patient(s) presenting with acute respiratory distress during the presentation, one hour after airway intervention (either started on NIV or intubation) to adjust settings on a ventilator, two hours post airway management to decide the effectiveness of treatment and decide on further plan.

If subjects feel any discomfort during NIV at any point of interval, physicians, respiratory therapists, or nurses will check the parameters, circuit, humidification, air leak, straps, etc. ensure maximum comfort. If subjects have NIV intolerance despite the above methods, NIV will be terminated. There has been no delay in the intubation. Intubation will be performed on subjects who meet the criteria for intubation while subjects who do not meet the criteria(s) for intubation will receive appropriate oxygen therapy. Whereas for subjects who responded well to NIV, they will eventually be weaned from NIV once respiratory failure relieved.

The criteria for intubation include persistent respiratory distress with a respiratory rate of more than 35 breaths/min, failure to maintain a PaO_2/FiO_2 above 100 mmHg, inability to correct respiratory acidosis, development of conditions necessitating intubation to protect the airway (coma or unable to maintain airway), hemodynamic instability without response to fluids and vasoactive agents, and respiratory or cardiac arrest. Once respiratory failure is relieved, subjects will be eventually weaned from NIV totally.

Outcomes, which include the duration of NIV and length of hospital stay, are collected when subjects are discharged or died. For subject(s) who ended up with intubation, the time and date of initiation of invasive mechanical ventilation has been recorded as well.

Data Collection and Outcomes

The primary outcomes were NIV success, which defined as avoidance of intubation or death during use of NIV or the subsequent 48 h, early or late NIV failure and in-hospital mortality rates per age group. Other secondary outcomes include subject characteristics (age, gender, ethnic, underlying risk factors, type and cause of respiratory failure, CXR finding) and physiologic variables (temperature, heart rate, GCS, oxygen saturation, pH, PaO_2, FiO_2, respiratory rate), duration of mechanical ventilation use, and length of stay in the hospital.

Statistical Analysis

Data were collected manually with a data collection sheet. All statistical analysis for the study was performed using statistical software Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM SPSS Statistics 2017). A p-value of <0.05 is considered statistically significant.

Continuous variables are presented as mean±standard deviation. Categorical variables are reported as numbers and percentages, and the differences among groups were analyzed using the chi-square tests. The differences between pairs of groups were analyzed using the unpaired Student's t-test. The differences among the three groups were analyzed using one-way ANOVA.

We have also performed multivariate analysis fitting forward stepwise binary logistic regression to identify potential predictors of NIV failure, calculating the odds ratios, with their corresponding 95% confidence intervals. The variables selected for the model are those corresponding to p-values of less than 0.05 in the univariate analysis or which have been found to be significant in the previous literature. The diagnostic accuracy of NIV failure is analyzed using the area under the receiver operating characteristic curves (AUC).

Results

Sixty two patients are included in our study, 52 patients are in ADHF subgroup and the remaining 10 are in the AECOAD subgroup. ARF patients, particularly those with underlying congestive heart failure, are more likely to respond well to NIV, on the other hand those with type 2 respiratory failure are at risk of NIV failure. Both GCS and heart rate are the powerful predictors of NIV failure in the HACOR scale (Table 1). In the derivation, HACOR scores are much lower in the NIV success patients and 100% NIV failure rate for the HACOR score ≥7 at 1 h and 2 h of NIV (Figure 1).

In the derivation cohort, we have found 6 variables collected at the initiation of NIV are highly associated with NIV failure in univariate analyses, which are the heart rate, GCS, PaO_2/FiO_2, respiratory rate, HACOR score >5 and patient with COPD (Table 2). However, all these variables are independently associated with NIV failure except for GCS and patients with underlying COPD. The variable of pH is less associated with NIV failure. NIV failure is associated with increased hospital mortality and length of hospital stay.

A different cut-off value of HACOR score was been tested to determine its diagnostic accuracy in predicting NIV failure upon patient presentation, 1 h and 2 h post NIV application. A cut-off value of ≥5 in 1 h of NIV, the diagnostic power is 86.27% with the sensitivity of 62.50% and specificity of 90.70%. Whereas in 2 hours of NIV with the HACOR score of ≥5, its diagnostic power is 87.50% with the sensitivity of 50% and specificity of 95%. In 0-2 hours of NIV, AUC for predicting NIV failure is 0.788, 0.868 and 0.925 (Table 3).

In a comparison of diagnostic accuracy between AECOAD and ADHF subgroups, the latter was shown to be more accurate in the prediction of NIV failure with a diagnostic accuracy of 59.62% and sensitivity of 80% and 54.76% specificity (Table 4).

The mortality rate is high for patients who proceed with intubation following NIV failure, 50% for immediate failure and 71.43% for early failure following NIV failure (Table 5). Length of hospital stay was also found to be longer for those who failed to respond to NIV in our study (Table 6).

Discussion

NIV has gained acceptance worldwide over the past decade and is now considered the first choice for the ventilation modality for patients with ARF especially those related to exacerbation of obstructive airway disease and acute decompensated heart failure. It is now commonly used in the ED. Many studies have shown that the early initiation of NIV is strongly encouraged in the ED for these patients, it lowers morbidity and mortality and when used appropriately, it can even shorten hospital stay (16).

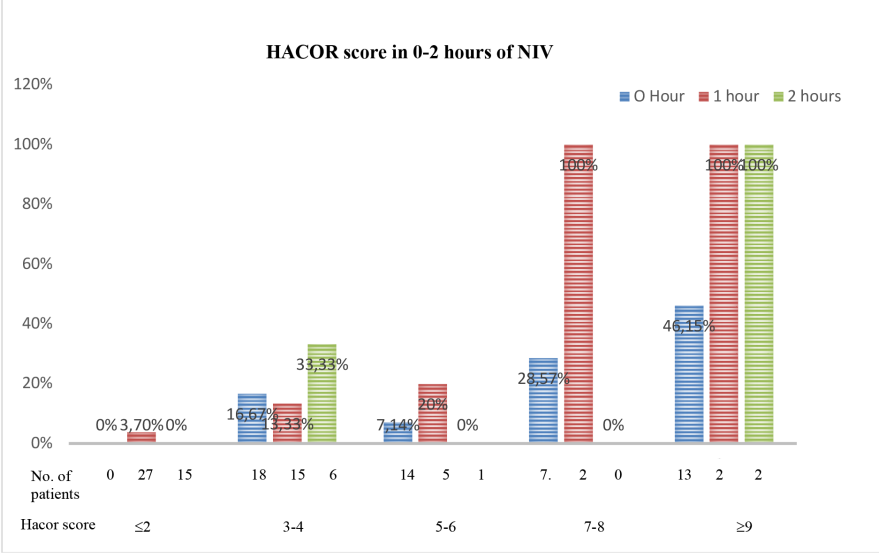

Figure 1. NIV failure rates in patients with different HACOR scores

NIV: Non-invasive ventilation, HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate

ARF in the setting of AECOAD is characterized by worsening hypoxemia and often presents with a certain degree of carbon dioxide retention and respiratory acidosis. Hypoxaemia probably results from worsening ventilation-perfusion (V/Q) mismatching, often with modest increases in the shunt fraction (14). There is evidence that suggests that worsening of V/Q mismatch with the loss of central drive to breathe is a result of loss of hypoxic vasoconstriction and loss of hypoxaemic ventilatory drive, although the mechanism is much debated (17,18). The presence of decompensated hypercarbia during an acute exacerbation is an important prognostic consideration and correlates with the risk of both short-and long term mortality (19). NIV when used in the setting of AECOAD, improves gas exchange during COAD exacerbations, with an increase in PaO_2, a decrease in $PA\text{-}aO_2$,

Table 1. Demographic and clinical characteristics comparison between patients that success or fail treatment with non-invasive positive pressure ventilation

	Total population n=62	NIV success n=50	NIV failure n=12	p value
Mean age±SD, years	59.82±11.42	61.40±10.90	53.25±11.64	0.881[a]
Gender, n (%)				
Male	32 (51.6)	25 (50.00)	7 (58.33)	
Female	30 (48.4)	25 (50.00)	5 (41.67)	0.443[b]
Race, n (%)				
Malay	37 (59.68)	28 (56.00)	9 (75.00)	
Chinese	20 (32.26)	18 (36.00)	2 (16.67)	
Indian	5 (8.06)	4 (8.00)	1 (8.33)	0.863[b]
Diagnosis, n (%)				
Acute decompensated heart failure	52 (83.87)	42 (84.00)	10 (83.33)	
AECOAD	10 (16.13)	8 (16.00)	2 (16.67)	0.955[b]
Co-morbidities, n (%)				
Diabetes mellitus	38 (61.29)	28 (56.00)	10 (83.33)	0.815[b]
Hypertension	51 (82.26)	41 (82.00)	10 (83.33)	0.814[b]
Dyslipidemia	14 (22.58)	12 (24.00)	2 (16.67)	0.823[b]
Congestive heart failure	10 (16.13)	10 (20.00)	0 (0)	0.016[b]*
Chronic kidney disease	22 (35.48)	17 (34.00)	5 (41.67)	0.242[b]
Chronic obstructive airway disease	3 (4.84)	0 (0)	3 (25.00)	0.53[b]
The type of respiratory failure n (%)				
Type 1	53 (85.48)	42 (84.00)	11 (91.67)	
Type 2	9 (14.52)	8 (16.00)	1 (8.33)	0.039[b]*
Data collected with NIV Mean±SD				
Heart rate, beats/min	116.35±7.15	115.8±6.43	118.67±9.59	0.008[a]*
pH	7.31±0.84	7.32±0.82	7.28±0.90	0.957[a]
GCS	14.79±0.87	14.94±0.24	14.17±1.85	<0.001[a]*
PaO_2/FiO_2, mmHg	180.26±54.89	186.56±53.57	154±54.68	0.671[a]
Respiratory rate, breaths/min	33.71±3.96	33.32±3.69	35.3±4.77	0.122[a]
Total HACOR scores	5.55±3.79	4.74±2.97	8.92±4.98	0.215[a]
Hospital mortality	8 (12.90)	6 (12.00)	4 (33.33)	0.071[b]
Length of hospital stay Mean±SD	8.05±8.82	7.94±7.95	8.50±12.22	0.02[a]*

[a]Independent samples t-test, [b]chi-square test, *p values <0.05.
Variables are presented as mean±SD. Categorical variables are reported as numbers and percentages.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, SD: Standard deviation, AECOAD: Acute exacerbation of chronic obstructive airway disease, GCS: Glasgow Coma Scale

Table 2. Univariate and multivariate analyses for risk factors associated with NIV failure				
	Univariate analysis OR (95% CI)	p value[a]	Multivariate analyses OR (95% CI)	p value[b]
Mean age ≤50	0.326 (0.077-1.377)	0.115	0.132 (0.009-1.999)	--
Male	1.400 (0.391-5.008)	0.604	7.50 (0.458-122.70)	0.158
Diagnosis				
Acute decompensated heart failure	0.952 (0.175-5.193)	0.955	--	--
AECOAD	1.050 (0.193-5.725)	0.955	--	--
Co-morbidities				
Diabetes mellitus	3.93 (0.779-19.804)	0.081	--	--
Hypertension	0.952 (0.175-5.193)	0.955	--	--
Dyslipidemia	0.633 (0.121-3.301)	0.585	--	--
Congestive heart failure	1.316 (1.126-1.538)	0.05*	--	--
Chronic kidney disease	0.647 (0.155-2.708)	0.549	--	--
Chronic obstructive airway disease	6.56 (3.593-11.962)	<0.001*	0.000 (0.000-0.000)	<0.001*
The type of respiratory failure				
Type 1	2.1 (0.236-18.577)	0.498	--	--
Type 2	0.48 (0.054-4.232)	0.498	--	--
Data collected with NIV				
Heart rate (>121 beats/min)	5.5 (2.209-14.879)	<0.001*	2.854 (0.845-9.635)	0.091
pH (≤7.25)	0.817 (0.273-2.448)	0.718	1.234 (0.297-5.126)	0.772
GCS (≤15)	0.157 (0.106-0.232)	<0.001*	0.000 (0.000-0.000)	<0.001*
PaO_2/FiO_2 (≤150)	0.265 (0.102-0.689)	0.005*	0.459 (0.122-1.724)	0.249
Respiratory rate, breaths/min	7.33 (1.524-35.282)	0.005*	2.651 (0.417-16.84)	0.301
Total HACOR score ≤5	4.409 (1.75-11.106)	0.001*	1.982 (0.535-7.339)	0.306
Hospital mortality	68.6 (6.958-676.36)	<0.001*	0.000 (0.000-0.000)	<0.001*
Length of hospital stay	7.313 (1.046-51.1)	0.025*	--	--

[a]Chi-square test, [b]multinomial logistic regression analysis, *p values <0.05.
OR: Odds ratio, CI: Confidence interval, AECOAD: Acute exacerbation of chronic obstructive airway disease, GCS: Glasgow Coma Scale, HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, PaO_2/FiO_2: Arterial partial pressure of oxygen to fraction of inspired oxygen ratio

and a reduction in $PaCO_2$. This is largely mediated by the increase in alveolar ventilation by an increase in tidal volume, it also assists in the reducing of the work of breathing by offloading the inspiratory muscle (16). The causes of ARF due to an exacerbation of COPD are more complex and more heterogeneous, the key to successfully managing this group of patient lie in the early recognition of key variables associated with failure and acting on them in a timely fashion to avoid delaying intubation (20).

However, ARF in the setting of decompensated heart failure, NIV may improve cardiac and respiratory performances in this group of patients by increasing the functional residual capacity, opening collapsed and under ventilated alveoli, thus decreasing right-to-left intrapulmonary shunt, reducing the pulmonary oedema, improving oxygenation by the mean of alveolar recruitment and lung compliance, with clear benefits in functional capacity, it also indirectly improve cardiac output with the application of PEEP by reducing the left ventricular afterload. By all these means, the result of NIV may decrease the resting heart rate and the systolic blood pressure (21). Thus, the rate of NIV failure in acute pulmonary oedema is found to be very low as well. Many studies have shown good outcomes, and some even report the successful rate up to 96% (22). In this group of patients, the severity of hypoxemia, acidosis and their initial responses to NIV are found to be strong predictors of NIV outcomes (23).

Numerous studies have been conducted to identify the variables and numerators associated with NIV failure. Many variables associated with NIV failure when treating ARF have been studied but assessing risk of NIV failure with only a few variables may not have predictive power (10). Some of these variables are simple bedside assessments and handy to use such as cough integrity, respiratory rate, arousability. Others may require more thorough evaluation and calculation based on the laboratory results and clinical assessment, such as Acute Physiology and Chronic Health Evaluation 2. When a quick decision is needed especially in the

Table 3. Diagnostic accuracy of different cuts of points of HACOR scale in predicting NIV failure at different time frames

HACOR score ≥4										
Hour of NIV	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
0	0.788 (0.656-0.921)	100.00	44.00	30.00	100.00	-	1.79	0.00	54.84	0.002*
1	0.868 (0.731-1.000)	75.00	69.77	31.58	93.75	6.92	2.48	0.36	70.59	0.001*
2	0.925 (0.809-1.000)	75.00	85.00	50.00	94.44	17.00	5.00	0.29	83.33	0.008*
HACOR score ≥5										
Hour of NIV	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
0	0.788 (0.656-0.921)	75.00	50.00	26.47	89.29	3.00	1.50	0.50	54.84	0.002*
1	0.868 (0.731-1.000)	62.50	90.70	55.56	92.86	16.25	6.72	0.41	86.27	0.001*
2	0.925 (0.809-1.000)	50.00	95.00	66.67	90.48	19.00	10.00	0.53	87.50	0.008*
HACOR score ≥6										
Hour of NIV	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
0	0.788 (0.656-0.921)	75.00	68.00	36.00	91.89	6.38	2.34	0.37	69.35	0.002*
1	0.868 (0.731-1.000)	62.50	95.35	71.43	93.18	34.17	13.44	0.39	90.20	0.001*
2	0.925 (0.809-1.000)	50.00	100.00	100.00	90.91	-	-	0.50	91.67	0.008*

*p values <0.05.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, AUC: Area under the curve of receiver operating characteristics, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

hectic environment of the majority of emergency setting, simple bedside observations and rapidly available laboratory results are preferable to estimate the risk of those patients who are at risk of NIV failure. From a pragmatic perspective, the HACOR score reliably serves the need for prediction of NIV failure. The study by Duan et al. (10), 2017 tested the hypothesis that combining several variables into a score could increase the predictive power, thus a scoring system called HACOR has been created using several variables. The HACOR risk scoring system uses the scale of heart rate, acidosis, consciousness level, PaO_2/FiO_2, respiratory rate, which are easily available bedside. In the study by Duan et al. (10), 2017, HACOR score >5 at 1 h of NIV has diagnostic accuracy for predicting NIV failure of 81.8% in the test group and 86.0% in the validation group. When combining all the subjects, those with a HACOR score ≤5 at 1 hour of NIV has a failure rate of 18.4% with hospital mortality of 21.6%, and subjects with a HACOR score more than 5 in 1 h of NIV has a failure rate of 87.1% with hospital mortality of 65.2%. For subjects who had an HACOR score of more than 5, early intubation resulted in significantly lower mortality than late intubation. Limitations of the study include the limitation of comparing the predictive power of HACOR score in different subgroups of patient, which is generally used generally for all acute hypoxemia respiratory failure patients.

In our study, the HACOR score has good diagnostic accuracy for NIV failure when it is assessed at 1-2 h of NIV. Six variables collected at the initiation of NIV are highly associated with NIV failure in univariate analyses, which are the heart rate, GCS, PaO_2/FiO_2, respiratory rate, HACOR score >5 and patient with underlying COPD. Heart rate and GCS are the most powerful predictors in terms of predicting NIV failure, whereas pH is less relevant in predicting NIV failure. HACOR score was found be more accurate in predicting NIV failure in the ADHF subgroup.

Table 4. Diagnostic accuracy of HACOR score ≥5 at 0 H (AECOAD vs acute decompensated heart failure)

Diagnosis	AUC (95% CI)	Sensitivity, %	Specificity, %	PPV (%)	NPV (%)	Odds ratio	Positive likelihood ratio	Negative likelihood ratio	Diagnostic accuracy (%)	p value
AECOAD (n=10)	0.594 (0.071-1.000)	50.00	25.00	14.29	66.67	0.333	0.67	2.00	30.00	0.695
Acute decompensated heart failure (n=52)	0.811 (0.680-0.941)	80.00	54.76	29.63	92.00	4.842	1.77	0.37	59.62	0.002*

*p values <0.05.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, AUC: Area under the curve of receiver operating characteristics, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, AECOAD: Acute exacerbation of chronic obstructive airway disease

Table 5. Predictors of mortality

No.	Predictor	Mortality (n)	p value	OR (95% CI)
1.	HACOR score (at 0 h) HACOR score ≥5 (n=34) HACOR score <5 (n=28) HACOR score (at 1 h) HACOR score ≥5 (n=9) HACOR score <5 (n=42) HACOR score (at 2 h) HACOR score ≥5 (n=3) HACOR score <5 (n=21)	 5 3 2 4 0 1	 0.641[a] 0.283[a] 0.699[a]	 0.696 (0.151-3.208) 0.368 (0.056-2.412) 1.050 (0.954-1.155)
2.	NIV outcome NIV failure (n=12) NIV success (n=50)	 2 6	 0.665[a]	 0.682 (0.120-3.890)
3.	Intubation timing Immediate (≤1 h) (n=4) Early (1-48 hours) (n=7) Late (≥48 h) (n=1)	 2 5 0	 0.006[b] <0.001[b] -	 0.020 (0.001-0.331) 0.008 (0.001-0.107) -

[a]Pearson chi-square test, [b]Multinomial logistic regression analysis.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, OR: Odds ratio, CI: Confidence interval

HACOR scores are much lower in the NIV success subgroup and 100% NIV failure rate for the HACOR score ≥7 at 1 h and 2 h of NIV. NIV failure is also associated increase hospital mortality, 33% compare 12% of those responded well NIV. NIV failure indirectly increase the length of hospital stay.

Apart from clinical parameters and laboratory results used for the risk assessment of NIV failure; skill, experience and enthusiasm of the medical personnel who manage NIV also play a crucial role in NIV success rate. Several studies have shown that NIV success rate remained steady despite an increasing severity of illness of patients treated with NIV (24), the improved outcomes are also indirectly attributed to the "learning effect" of the medical personnel with the routine use of NIV (4). However, up to date, most of the published papers do not distinguish between whether NIV failure is due to intolerance of the technique and when NIV could be applied appropriately; but despite this, the patient still deteriorated. It is possible that the outcomes in these two situations might be different. In one case, the failure is of the application of assisted ventilation, whereas in the second it is failure of assisted ventilation to improve gas exchange, etc.

Patient tolerance is another critical factor for NIV success. Indirect evidence suggests that fighting with the machine which result in asynchrony, could result in immediate NIV failure. Thus, strategies which include optimization of the ventilator setting by adjusting the trigger sensitivity, appropriate PEEP level and minimizing leak can avoid such undesirable events (25). In our study, we have excluded these factors in correlation with NIV failure, however there is a noticeable favorable outcome if NIV is applied and monitored by experience medical personnel and during the shift, whereby the patient load is manageable in the critical resuscitation zone. Further studies are needed in future research to look into these indirect factors with NIV success rate in correlation with HACOR score.

Table 6. Predictors of the length of hospital stay			
No.	**Predictor**	**Duration, days Mean±SD**	**p value**
1.	HACOR score (at 0 h) HACOR score ≥5 (n=34) HACOR score <5 (n=28) HACOR score (at 1 h) HACOR score ≥5 (n=9) HACOR score <5 (n=42) HACOR score (at 2 h) HACOR score ≥5 (n=3) HACOR score <5 (n=21)	 9.85±10.16 9.32±7.32 12.50±9.48 7.27±6.71 17.00±12.12 6.94±7.17	 0.295[a] 0.137[a] 0.162[a]
2.	NIV outcome NIV failure (n=12) NIV success (n=50)	 8.50±12.22 7.94±7.95	 0.020[a]
3.	Intubation timing Immediate (≤1 h) (n=4) Early (1-48 hours) (n=7) Late (≥48 h) (n=1)	 10.75±16.07 5.00±9.33 24±12.22	 0.345[b]

[a]Independent samples t-test, [b]One-Way ANOVA test.
HACOR: Heart rate, acidosis, consciousness, oxygenation, and respiratory rate, NIV: Non-invasive ventilation, SD: Standard deviation

NIV may be useful for the avoidance of intubation or death in patients with acute respiratory distress. some initial responders, despite an initial brief improvement with NIV, they may later deteriorate and to the extent of late intubation and die. Most studies report a substantial percentage of late NIV failure (26) suggesting that initial improvement of arterial blood gases and clinical parameters do not guaranteed a successful outcome. This is true and has been observed for both type 1 and type 2 respiratory failure patients in our study.

GCS and heart rate are found to be very powerful predictors for predicting NIV failure when used to assess the HACOR score upon patient's arrival. Same reported by Duan et al. (10), the consciousness was the most relevant variable in predicting NIV failure in our study. A drop in GCS even with 14 out of 15 upon application of NIV tends to have a higher failure rate. This is followed by heart rate in our study, which is otherwise found less relevant in the Duan et al. (10) study. Many studies have found that the application of NIV has shown improvement in beneficial effects on the control of blood pressure in association with an increase in cardiac parasympathetic modulation of heart rate especially in acute exacerbation of COAD and in pulmonary oedema patients, these effects are due to the increase in baroreflex sensitivity of heart rate and thus reset the operating point for baroreflex sensitivity to a lower blood pressure, indicating improvements in the neural control of heart HR (27).

Many studies compare various age groups, their characteristics with regard to the outcome of NIV. Majority studies reported that NIV is most often used in older patients particularly age 65 and above (20). This phenomenon is probably explained by the greater prevalence of chronic lung or heart disorders in the older age group. Additionally, do-not- intubate status is observed more frequently with aging, also contributing to greater use of NIV in the elderly and aged. In our study, the mean age for the NIV success group is 61.40±10.90 while the failure group is 53.25±11.64. There was no significant difference in the rate of NIV failure in terms of the age group in our study and the outcome in our study is similar to the majority of the studies. Interestingly neither the Acute Physiology and Chronic Health Evaluation 2 (APACHE) score nor age are predictive of failure (28).

The mortality rate in NIV failure patients is 16.67% and the mortality rate is high if the patient proceeds with intubation following NIV failure. By using a cut-off point of 5 for the HACOR scale, it is a weak predictor of mortality upon presentation, 1 h and 2 h post NIV intervention. The length of hospital stay was found to be longer for those who failed to respond to NIV in our study. Most of these patients who failed to respond to NIV ended up with endotracheal intubation and thus increased the length of stay in critical units.

Study Limitations

To limit the burden of investigators, data are collected as often as possible, as long as patients remained in the emergency department, the hours of duration on NIV are collected from the presentation up to two hours post NIV. Patients are then followed up in critical unit or general ward for their clinical progress throughout the admission. The drawback of this approach is the failure to determine the diagnostic power of NIV after certain hours. Patients treated with NIV for a shorter period and subsequently intubated are considered early or late failure depending of the timing of intubation after an initial favorable respond to NIV. In these patients, it seems likely that the impact of intubation would have a predominant effect on patient outcome. Furthermore, we have not collected data on the seniority of medical personnel who handle the NIV in ARF patients, the type of interface they applied (facemask/helmet), or the setting on the ventilator. We cannot exclude the possibility of clinicians may having a lack of experience in adjusting the proper setting for NIV or their preference to intubate the patient based on personal's risk taking/experience.

Moreover, we have not collected patient's severity scores such as the APACHE score and thus external validation cannot be done. The correlation of the parenteral medications like antibiotics, frusemide, aminophylline with the patient's outcome also not established. Finally, the number of subjects enrolled is lower than what we have expected due to the unforeseen Coronavirus disease-2019 pandemic, we are also limited by small numbers of subjects in our AECOAD subgroup.

Firstly, the small sample size and enrollment from a single centre may limit generalizability. A larger prospective multi-centre study may provide a clearer paradigmatic of the Malaysian population as a whole. Second, more AECOAD subgroup sample should be recruited to prevent the skew of data in the analysis and comparison of diagnostic accuracy between AECOAD and heart failure subgroups. More variables mentioned in the limitations chapter, staff's details, which include their seniority and skills, should be collected to verify the reliability of the HACOR score in predicting NIV failure.

Conclusion

NIV can reduce the need of endotracheal intubation, improving the outcome of patients. When successful, it can be associated with a reduction in the duration of ICU and hospital stay, which may have important economic implications. The HACOR was developed for predicting NIV failure, it has good diagnostic accuracy when it is assessed at 1-2 h of NIV. Higher scores indicated higher chances of NIV failure. It is convenient to use it to assess the efficacy of NIV especially in heart failure patients. However, HACOR score was a weak predictor of mortality in our study.

Ethics

Ethics Committee Approval: This study was been approved by the Malaysia Medical Research and Ethics Committee (MREC) through the National Medical Research Register (ID: NMRR-20-1066-55129 S1) on 02.07.2020.

Informed Consent: Written consent was obtained from the participants who fulfilled the inclusion criteria.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.H.T., Concept: Y.H.T., M.Z.A.M.N., A.M.N.A., R.M.A., Design: Y.H.T., M.Z.A.M.N., A.M.N.A., R.M.A., Data Collection or Processing: Y.H.T., Analysis or Interpretation: Y.H.T., M.Z.A.M.N., A.M.N.A., R.M.A., Literature Search: Y.H.T., Writing: Y.H.T.

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