Validity of HACOR score in prediction of non-invasive ventilation outcome in hypoxemic critically ill patients

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Abstract

BackgroundThe use of non-invasive ventilation (NIV) in critically ill patients has dramatically increased [1] as it significantly reduces the work of breathing in patients with acute respiratory failure, thereby reducing the need for intubation [2, 3]. Although NIV is frequently used in patients with hypoxemic respiratory failure, its failure rate remains high (25–59%) [4–9], indicating that not all patients benefit from this treatment.

Previous studies have reported that patients who experience NIV failure have a higher heart rate, lower pH, lower Glasgow Coma Scale (GCS) score, lower oxygenation, and higher respiratory rate than those who experience successful NIV [5, 10–16]. These variables can be used to predict NIV failure. However, the predictive power of NIV failure is low when based only on a single variable. Hypothesizing that a combination of these variables should be potential to increase the predictive power, by combining several variables that are easily obtained by simple bedside measurements in patients with hypoxemic respiratory failure to develop a scale for the prediction of NIV failure.The main objective is to assess the utility of HACOR score to predict NIV failure in patients

with hypoxemic respiratory failure. The secondary objective is to report outcomes in high-risk NIV failure patients who undergo intubation at different time points.

Materials and Methods: This study was a multi-center prospective study, performed in different hospital from February 2017 till October 2018. Our study population included 272 patients divided into 2 groups in relation to successful or failure of NIV weaning: -

 Upon admission they were evaluated by HACOR score at time of admission,1hr,24hrs and 48hrs respectively.

 Also, they were assessed by SOFA, APACHI II scores respectively at same time intervals to assess severity of critical illness

 Those patients were divided into 2 groups in relation to successful or failure of NIV weaning; Failure was identified as need for endotracheal intubation due to inability to maintain patent airway cause of disturbed conscious level and respiratory failure.

1. Group A: describing patients with successful NIV 196 patients.
2. Group B describing patients with failure of NIV 76 patients.

 The study was done in ICU in different hospital

Results: In our study, failure of non-invasive ventilation showed elevated HACOR score, started from time of applying of NIV in ascending way till 48 hours form applying NIV.

There was significant correlation between clinical severity scores and HACOR score where patients with higher clinical severity illness showed higher HACOR scores. Also, there was significant correlation between HACOR and ICU length of stay where patients with higher HACOR scores more likely needed to stay longer in ICU.

Our results showed that Mortality rate was higher in failed NIV groups (64.5%) versus that in successful NIV group (35.5%).

Also, we concluded that Non survivors' group of patients stayed longer duration on every NIV session compared to survivors' patients: (6.4±1.2 vs 4.7±1.3, p-value <0.001).

Non survivors' group of patients stayed longer duration in ICU compared to survivors: (11.5±5.9 vs 9.4 ± 6.4, p-value = 0.001).

On other hand, survived patients had lower mortality rate vs non survivor patients in whole NIV duration (32.8±4.1vs 34.0±7.0, p-value <0.001).

In our study, we discussed HACOR score readings to predict failure of NIV in different pre-determined times 0, 1hr, 24hr and 48hrs which showed that patients with HACOR score at time of admission >6.5 had high risk of NIV failure, patients with HACOR 1h score>5.5 had high risk of NIV failure while patients with HACOR score 24hr from NIV applying >5.5 had high risk of NIV failure.

In our study, successful weaning of NIV shortened length of ICU stay, failed NIV had longer ICU stay with highly significate difference. This might reflect good prognosis, carried by NIV success.

In our study, we could highlight relationship between mortality &HACOR scores. Non-survivors tended to show higher HACOR scores & worsening patterns. HACOR score could provide prognostic information for mortality, as well.

Statistical analysis using ROC curve in our study stated that cut off point for NIV failure using HACOR score at 0,1hr,24hrs then 48hrs were 6.5 ,5.5,5. Respectively showed sensitivity ranged from 60-86.2% and specificity ranged from 62.2-96.9%. With AUC ranged from 0.7 to 0.9.

Keywords: Non-invasive ventilation, NIV failure, Hypoxemic Critically Ill Patients, HACOR Score validity.

Introduction

The use of non-invasive ventilation (NIV) in critically ill patients has dramatically increased [1] as it significantly reduces the work of breathing in patients with acute respiratory failure, thereby reducing the need for intubation [2, 3].

Previous studies have reported that patients who experience NIV failure have a higher heart rate, lower pH, lower Glasgow Coma Scale (GCS) score, lower oxygenation, and higher respiratory rate than those who experience successful NIV [5, 10–16]. These variables can be used to predict NIV failure. However, the predictive power of NIV failure is low when based only on a single variable. Hypothesizing that a combination of these variables should be potential to increase the predictive power, by combining several variables that are easily obtained by simple bedside measurements in patients with hypoxemic respiratory failure to develop a scale for the prediction of NIV failure.

A recent work done by a group of investigators who assessed the validity of a score using simple bedside measurements to predict how successful the NIV therapy would be;

they found that the HACOR score performed well in prediction of NIV failure. Among patients with NIV failure with a HACOR score of > 5 at 1hr of NIV, hospital mortality was lower in those who received intubation at ≤12 h of NIV than in those intubated later. [17].

Patients and Methods

This study was a prospective multi-centre study, performed from February 2017 till October 2018. Our study population included 272 patients who suffered from hypoxemic respiratory failure excluded from the study those who were mentioned in exclusion criteria.

- Upon admission they were evaluated by HACOR score at time of admission,1hr,24hrs and 48hrs respectively.
- Also, they were assessed by SOFA, APACHI II scores respectively at same time intervals to assess severity of critical illness
- Those patients were divided into 2 groups in relation to successful or failure of NIV weaning; Failure was identified as need for endotracheal intubation due to inability to maintain patent airway cause of disturbed conscious level and respiratory failure.

1. Group A: describing patients with successful NIV.
2. Group B describing patients with failure of NIV.

- The study was done in ICU in different hospital.

Population of study & disease condition:

1) Inclusion criteria:

All patients with hypoxemic respiratory failure in whom the use of NIV was deemed appropriate.

2) Exclusion criteria:

a. Severe ARDS with PaO2/fiO2 ≤ 100 mmHg.

b. Multi-organ failure.

c. Do-Not-Intubate scenarios e.g., advanced interstitial lung fibrosis, terminal stage malignancy.

d. Requirement for emergency intubation.

e. Inability to apply a fitted facemask due to facial trauma.

f. Patients who showed marked improvement in respiratory parameters and showed no further need for NIV>24hrs.

g. Inability to protect airways due to disturbed conscious level, aspiration, acute gastric dilatation, upper GIT bleeding, vomiting or copious tracheal secretion.

h. Undrained pneumothorax.

i. NIV intolerance, which is as patient refusal for NIV because of discomfort.

j. Post-cardiac or pulmonary arrest.

k. Recent diagnosis of MI or fatal dysrhythmias.

l. Cardiogenic pulmonary oedema

1) *Methodology in details:*

Each patient was subjected to clinical and radiological assessment as following:

- **Full Clinical assessment:**

1. Full history taking and complete general examination; to determine systemic risk factors.
2. Electrocardiogram (ECG) to exclude recent MI, Arrhythmia.

- **Laboratory Analysis:**

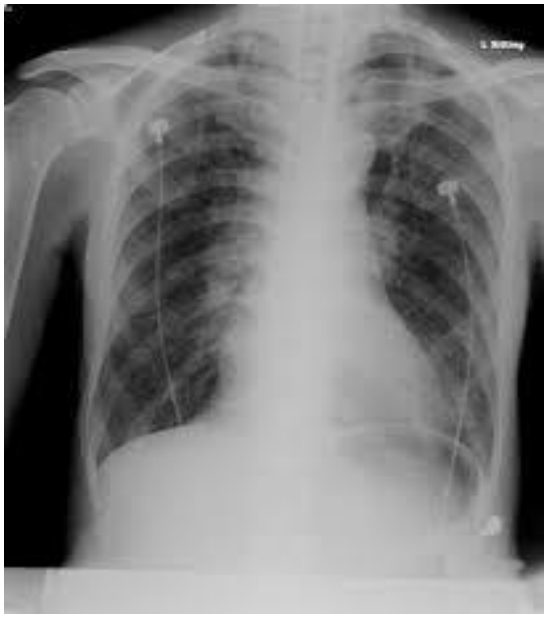
-Routine laboratory investigations including complete blood count, kidney function test, Liver function test, C-reactive protein, serial arterial blood gas to check for any respiratory or metabolic acidosis, Full microbiological cultures including blood, urine and sputum cultures.

- **Imaging analysis:**

- Radiological evaluation including chest X-ray as shown in **fig. (4)** below& CT chest when appropriate.

- Serial ECG and cardiac enzymes to detect myocardial ischemia or arrythmias and sometimes Echocardiography.

- **Fig (4) Chest X-ray of patient with acute exacerbation of COPD**



-Upon admission of the patients, they were evaluated using the SOFA shown in **tab (6)**, APACHI shown in tab (7), Glasgow Coma Scale (GCS) score shown in **tab (8)** and HACOR shown below in **tab (9).**

Table (6) SOFA score

CARDIOVASCULAR	
Mean arterial pressure OR administration of vasopressor	
MAP≥70 mm/Hg	0
MAP<70 mm/Hg	+1
Dopamine ≤ 5µg/kg/min or dobutamine any dose	+2
Dopamine > 5 µg/kg/min OR Epinephrine ≤ 0.1 µg/kg/min OR Norepinephrine >0.1 µg/kg/min	+3
Dopamine > 15 µg/kg/min OR Epinephrine > 0.1 µg/kg/min OR Norepinephrine >0.1 µg/kg/min	+4

KIDNEY SCORE	
Creatinine(mg/dl) (µmol/L) (or urine output) score	
<1.2 (<110)	0
1.2-1.9(110-170)	+1
2.0-3.4(171-299)	+2
3.5-4.9(300-440) (or<500 ml/d)	+3
>5.0 (>440) (or <200 ml/d)	+4

PULMONARY SCORE	
PaO_2/Fio_2(mmHg) SOFA score	
≥400	0
<400	+1
<300	+2
<200 with respiratory support	+3
<100 with respiratory support	+4

NEUROVASCULAR SCORE	
GCS-Glasco Coma Scale SOFA-SCORE	
15	0
13-14	+1
10-12	+2
6-9	+3
<6	+4

COAGULATION	
Plateletsx10^3/µl---SOFA SCORE	
≥150	0
<150	+1
<100	+2

<50	+3
<20	+4

LIVER SCORE	
Bilirubin(mg/dl) SOFA score	
<1.2(<20)	0
1.2-1.9(20-32)	+1
2.0-5.9(33-101)	+2
6.0-11.9(102-204)	+3
>12.0(>204)	+4

Maximum SOFA Score	Mortality
0 to 6	<10%
7 to 9	15-20%
10 to 12	40-50%
13 to 14	50-60%
15	>80%
15 to 24	>90%

Table (7): APACH score

Physiologic value	+4		+3	+2	+1	0	+1	+2	+3	+4
Rectal Temp (^{0}C)	≥ 41		39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
Mean arterial pressure (mmHg)	≥ 160		130-159	110-129		70-109		50-69		≤ 49
Heart Rate	≥ 100		140-179	110-139		70-109		50-69	40-54	≤ 39
Respiratory Rate	≥ 50		35-49		25-34	12-24	10-11	6-9		≤ 5
Oxygenation a) FiO2≥0.5 recorded A-aDO2	a	≥ 500	350-499	200-349		<200				
b) FiO2<0.5 recorded PaO2	b					>70	61-70		55-60	< 55
Arterial PH	≥ 7.7	7.6-7.69			7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
HCO3 (mEq/l)	≥52	41-51.9			32-40.9	22-31.9		18-21.9	15-17.9	< 15
K	≥7	6-6.9			5.5-5.9	3.5-5.4	3.3-4	2.5-2.9		< 2.5
Na	≥100	160-179		155-159	150-154	130-149		120-129	111-119	≤ 110
S. Creat (mqm/dl)	≥3.5	2-3.4		1.5-1.9		0.6-1.4		<0.6		< 20
Hematocrit (%)	≥60			50-59.9	46-49.9	30-45.9		20-29.9		< 20
WBC (103/cc)	≥40			20-39.9	15-19.9	3-14.9		1-2.9		
GCS	Score= 15 minus actual GCS									
A=Total Acute physiology score APS	Sum of the total individual variable points									

B=Age points	C=Chronic Health Points
≤44 years 0 points 45-54 years 2points 55-64 years 3 points 65-74 years 5 points ≥75 years 6 points	If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows: **a.** For nonoperative or emergency postoperative patients -5 points **b.** For elective postoperative patients -2points

APACHE II SCORE =Sum of A (APS points0+B (Age points) +C (Chronic Health points)

Table (8) Glasgow Coma Scale score (GCS).

BEHAVIOR	RESPONSE
Eye opening response	4. spontaneously. 3. to speech 2. to pain 1. No response
Verbal response	5. Oriented to time, person, and place 4. confused 3. inappropriate words 2. Incompressible sounds 1. no response
Motor response	6. obeys commands 5. move to localize pam 4. flex to withdraw pain 3. Abnormal flexion 2. Abnormal extension 1. No response

Tab (9) HACOR score.

Variables	category	Assigned points
Heart rate, beats/min	≤120 ≥121	0 1
PH	≥7.35 7.3-7.34	0 2

	7.25-7.29	3
	<7.25	4
GCS	15	0
	13-14	2
	11-12	5
	≤10	10
PAO2/FIO2	≥201mmHg	0
	176-200 mmHg	2
	151-175 mmHg	3
	126-150 mmHg	4
	101-125 mmHg	5
	≤100 mmHg	6
Respiratory rate, beats/mins	≤30 breaths/min	0
	31-35 breaths/min	1
	36-40 breaths/min	2
	41-45 breaths/min	3
	≥46 breaths/min	4

Protocol of Non-invasive ventilation applying in our study:

The standard NIV interface was used for NIV treatment. Selection of the mask was based on the patient's facial type. The straps of the mask were kept as tight as possible while remaining comfortable to the patient. Patients will be placed in a semi-recumbent position to avoid aspiration, assuming there was no contraindication to this position. Interface NPPV could be administered both with nasal and full-face masks shown below in **fig (5).**

Fig (5) Facemask & nasal mask used for Non-invasive ventilation.

At the beginning of treatment, continuous use of NIV was encouraged. Once the patient recovered from respiratory failure, NIV was used intermittently until the patient could be completely weaned from it. But if the patients were not tolerated using the HACOR score at the determined time 0,1,24hr and 48hrs respectively and clinical conditions of the patients deteriorated we were shifting the patients to invasive ventilation

The positive-end expiratory pressure was maintained at 4–8 cmH_2O. Inspiratory pressure would be initially set at 10 cmH_2O and then increased in increments of 2 cmH2O to achieve the best control of dyspnoea and tolerance of the patient. The fractional concentration of oxygen would be set to achieve peripheral oxygen saturation of >92%.

Patients with hypoxemic failure would be assessed by HACOR score at 0,1hr,24hs then 48hrs from NIV initiation respectively. ***(159)***

<u>Protocol of measuring HACOR score in our study:</u>

The following parameters would be measured at each point determined at time of admission 0,1hr,24hrs then 48hrs; Heart rate, PH (via an arterial blood gases), Glasgow coma scale (GCS), PO2/FO2 ratio, and respiratory rate and each will be given a score described in **tab (9)** showed before.

If the patients failed to maintain oxygenation through using NIV treatment, we shifted them to invasive ventilation and at that time NIV failure reached correlated with HACOR score measured at determined time

NIV failure would be defined as requirement of intubation after NIV intervention based on the following criteria: respiratory or cardiac arrest, failure to maintain a PaO_2/ FiO_2 of >100, development of conditions necessitating intubation to protect the airway (coma or seizure disorders) or to manage copious tracheal secretions, inability to correct dyspnoea, lack of improvement of signs of respiratory muscle fatigue, and hemodynamic instability without response to fluids and vasoactive agents.[(83)]

Outcome:

- Assessment of the utility of HACOR score to predict NIV failure in patients with hypoxemic respiratory failure.
- Assessment of NIV failure and its relation with long duration of ICU stay.
- Failure of NIV and relation to mortality.
- Failure of NIV and its re relation to longer NIV duration.

Statistical methods:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test (Chan, 2003a). For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less

than 5 (Chan, 2003b). Correlations between quantitative variables were done using Spearman correlation coefficient (Chan, 2003c). ROC curve was constructed with area under curve analysis performed to detect best cut-off values of different parameters for detection of mortality and failed NIV. Survival curves were plotted by the Kaplan-Meier method and compared using the log-rank test. HACOR was entered as Independent prognostic factor in COX regression model to estimate Cox proportional hazards ratio (Chan, 2004). P-values less than 0.05 were considered as statistically significant.

Results

This study was a multi-centre prospective study, performed in different hospital from February 2017 till October 2018. Our study population included 272 patients divided into 2 groups in relation to successful or failure of NIV weaning: -

1. Group A: describing patients with successful NIV 196 patients.
2. Group B describing patients with failure of NIV 76 patients.

NIV failure: defined as requirement of intubation after NIV intervention based on the following criteria: respiratory or cardiac arrest, failure to maintain a PaO2/ FiO2 of >100, development of conditions necessitating intubation to protect the airway (coma or seizure disorders) or to manage copious tracheal secretions, inability to correct dyspnoea, lack of improvement of signs of respiratory muscle fatigue, and hemodynamic instability without response to fluids and vasoactive agents.

1. Demographic date:

a) Age:

Analysis of age showed highly significant difference between both groups (61.3 ± 13.0 in group A vs 65.1 ± 16.8 in group B, p-value = 0.001).

Table (10): Age in relation to successful vs failed NIV

	Successful NIV	Failed NIV	P value
Age	61.3±13.0 (60.5)	65.1±16.8(68.0)	0.001

b) Gender:

Analysis of Gender in relation to successful weaning showed no significant difference between both groups.

Table (11): Gender in relation to successful vs failed NIV

Gender	Successful NIV		Failed NIV		P value
Male	125	76.2%	39	23.8%	0.1

	Female	71	65.7%	37	34.3%	

2. Clinical manifestations:

a) Conscious level: -

When analysing conscious level using Glasgow coma scale there is highly significant difference between both groups (14 ±1 in group A vs 13 ± 1 in group B, p-value = 0.001).

Table (12): Conscious level in relation to successful vs failed NIV

	Successful NIV	Failed NIV	P value
Neuro GCS	14±1(15)	13±1(15)	< 0.001

3. Scores for clinical severity assessments:

a) SOFA& APACHE II

NIV failed group persistently showed higher SOFA score and APACHE II:

- Day 0: 5.4 ± 1.7 in group A vs 8.5±1.8 in group B (p-value< 0.001).
- Day 1: 5.3 ± 1.6 in group A vs 8.7 ± 1.7 in group B (p-value< 0.001).
- Day 2: 5.2 ± 1.7 in group A vs 9.0 ± 1.9 in group B (p-value< 0.001).

Comparing APACHI II between both groups showed that APACHE II was 11.2 ± 3.8 in group A vs 17.5±3.8 in group B with significant difference (p-value< 0.001).

Table (13): SOFA& APACHE II in relation to successful vs failed NIV

	Successful NIV	Failed NIV	P value
SOFA Day0	5.4±1.7 (5.0)	8.5±1.6 (8.0)	< 0.001
SOFA Day1	5.3±1.6 (4.0)	8.7±1.7(9.0)	< 0.001
SOFA Day2	5.2±1.7(4.0)	9.0±1.9 (10.0)	< 0.001
APACHE II	11.2±3.8(10.0)	17.5±3.8(16.0)	< 0.001

b) HACOR SCORE:

Comparing HACOR score between both groups showed significant difference HACOR scores were higher in failed NIV group:

- HACOR Day 0: 5.9 ± 1.2 in group A vs 6.9±1.5 in group B (p-value< 0.001).
- HACOR 1hr: 5.1 ± 0.9 in group A vs 5.3 ± 2.5 in group B (p-value< 0.001).
- HACOR Day 1: 4.1 ± 0.9 in group A vs 5.7 ± 1.5 in group B (p-value< 0.001).
- HACOR Day 2: 1.2 ± 0.8 in group A vs 4.8 ± 2.2 in group B (p-value< 0.001).

Table (14): HACOR in relation to successful vs failed NIV

	Successful NIV	Failed NIV	P value
HACOR Day0	5.9±1.2(6.0)	6.9±1.5(7.0)	< 0.001
HACOR 1hour	5.1±0.9(5.0)	5.3±2.5(6.0)	< 0.001

HACOR Day1	4.1±0.9(4.0)	5.7±1.5(6.0)	< 0.001
HACOR Day2	1.2±0.8(1.0)	4.8±2.2(5.0)	< 0.001

4. NIV weaning failure or success and its correlations: -

a) NIV duration:

Analysis of duration of NIV session and whole NIV duration in relation to successful weaning showed highly significant difference between both groups.

Table (15): NIV Duration in relation to successful vs failed NIV

	Successful NIV	Failed NIV	P value
Duration of NIV session	4.7±1.2(4.0)	5.8±1.7(6.0)	< 0.001
Whole NIV duration	34.4±7.0 (35.5)	32.2±5.0 (31.0)	< 0.001

b) ICU length of stay:

Regarding of ICU length of stay in relation to successful weaning of NIV, there is highly significate difference between two groups as: (8.6 ± 3.0 in group A vs 12.9 ± 10.50 in group B, p-value < 0.001).

Table (16): ICU length of stay in relation to successful vs failed NIV

	Successful NIV	Failed NIV	P value
ICU LOS	8.6±3.0 (7.00)	12.9±10.50 (11.00)	< 0.001

c) Change of HACOR score during 48hrs of applying NIV and relation with successful and failure of weaning:

NIV failure group showed incremental changes in sequential HACOR scores, in contrast to NIV successful group.

Table (17): HACOR change in relation to successful vs failed NIV

	Successful NIV	Failed NIV	P value
HACOR change 0>>1	-0.8±0.9(-1.00)	1.6±2.4(-1.00)	0.9
HACOR change 1>>24	-1.0±0.7(-1.00)	0.6 ±1.0(-1.00)	< 0.001
HACOR change 24>>48	-2.9±1.0 (-3.00)	0.8±1.3(-1.00)	< 0.001

d) Diagnosis and relation to NIV weaning:

NIV failure rate in ARDS 59.1%& pneumonia 33.5% & pulmonary oedema 4.7% & COPD 4.3%& while other disease 26.1%.

Table (18): Diagnosis in relation to successful vs failed NIV

		Successful NIV		Failed NIV		P value
Diagnosis	ARDS	9	40.9 %	13	59.1 %	< 0.001
	PNEUMONIA	107	66.5 %	54	33.5 %	
	PULMONARY ODEMA	41	95.3 %	2	4.7%	
	COPD EXERBATION	22	95.7 %	1	4.3%	
	OTHERS	17	73.9 %	6	26.1 %	

e) Clinical diseases and relation to NIV weaning:

NIV failure rates in different medical conditions was recorded: cardiac 23.1%&&Respiratory 28.9% &HAP 42.5%&CAP 31.8% &Renal 36.7%&Hepatic 36.4% and oncology diseases 54.5%.

Table (19): Clinical diseases in relation to successful vs failed NIV

Clinical diseases	Successful NIV		Failed NIV		p-value
Cardiac	133	76.9%	40	23.1%	0.017
Respiratory	64	71.1%	26	28.9%	0.806
HAP	84	57.5%	62	42.5%	<0.001

CAP	122	68.2%	57	31.8%	0.047
Renal	31	63.3%	18	36.7%	0.130
Hepatic	14	63.6%	8	36.4%	0.358
Oncology	15	45.5%	18	54.5%	<0.001

f) Complication and relation to NIV weaning:

Most common complication following NIV failure rate percentages MODS 81.5%%shock 81.5 %& aspiration 19.7%& stress ulcer 15.7% &DVT 2.6% then RRT 2.6%.

Table (20): Complication in relation to successful vs failed NIV

COMPLICATION	Successful NIV		Failed NIV		P value
MODS	62	31.6%	62	81.5%	<0.001
SHOCK	44	22.4%	62	81.5%	<0.001
ASPIRATION	6	3%	15	19.7%	<0.001
STRESS ULCER	5	2.6%	12	15.7%	<0.001
DVT	2	1%	2	2.6%	0.312
RRT	2	1%	2	2.6%	0.312

g) Antibiotics and relation to NIV weaning:

Table (21): Antibiotics relation to successful vs failed NIV

	Successful NIV		Failed NIV		P value
CARBAPENEM	48	48 %	52	52 %	<0.001

QUINOLONES	111	65.3%	59	34.7%	0.001
GM+VE	15	30 %	35	70 %	<0.001
MACROLIDS	34	91.9%	3	8.1 %	0.004
CEPHALOSPORIN&PENCILIN	141	86 %	23	14 %	<0.001
TYGACICLIN& POLYMYXIN	2	15.4%	11	84.6%	<0.001
ANTI-FUNGAL	34	42 %	47	58 %	<0.001

h) Relation between different cultures and NIV weaning:

Table (22): Cultures relation to successful vs failed NIV

	Successful NIV		Failed NIV		
SPUTUM	160	69%	72	31%	0.006
URINE	2	66.7%	1	33.3%	1
BLOOD	194	72.1%	75	27.9%	1

i) Relation between Adequacy of anti-biotic therapy based on C/S and NIV weaning:

Adequacy of empirical anti-biotic therapy was judged according to microbiological data retrospectively, failed NIV in patients who showed adequate regimen of empirical anti-biotics was 16.6% in comparison to those who showed inadequate regimen which was 88.4%, p-value<0.001.

Table (23): Adequacy of anti-biotic therapy based on C/S related successful vs failed NIV

		Failed NIV		Successful NIV		P value
Adequacy of anti-biotic therapy based on C/S	inadequate	38	88.4%	5	11.6%	< 0.001
	adequate	38	16.6 %	191	83.4 %	

j) Relation between using sedation and weaning of NIV:

Using sedation during NIV setting increased failure rate where failure rate in sedated patients was 40.2% versus off sedation group 16.4% with p-value<0.001.

Table (24): Sedation during NIV in relation to successful vs failed NIV

		Failed NIV		Successful NIV		P value
Sedation during NIV	No	23	16.4%	117	83.6%	< 0.001
	Yes	53	40.2 %	79	59.8 %	

5. Mortality prediction and its correlations: -

a. Relation between Mortality and weaning of NIV:

Mortality rate was higher in failed NIV groups (64.5%) versus that in successful NIV group (35.5%) with p-value <0.001.

Table (25): Mortality in relation to successful vs failed NIV

Mortality	Failed NIV		Successful NIV		P value
Died	49	64.5	4	2.1%	< 0.001
Survived	27	35.5%	192	97.9%	

b. Analysis of mortality and relation to HACOR score:

HACOR score were collected for all patients classified according to survival.

Table (26): HACOR in relation to successful vs failed NIV

Mortality	DIED	SURVIVED	P value
HACOR Day0	6.9±1.4(7.00)	6.0±1.3 (6.00)	< 0.001
HACOR 1 hour	6.3±1.4(6.0)	4.8±1.4(5.0)	< 0.001
HACOR Day1	5.7±1.4(6.0)	4.1±1.0(4.0)	< 0.001
HACOR Day2	5.1±2.0(5.0)	1.3±1.2(1.0)	< 0.001

c. Analysis of duration of NIV session &whole NIV duration in relation to mortality:

Non survivors' group of patients stayed longer duration on every NIV session compared to survivors' patients: (6.4±1.2 vs 4.7±1.3, p-value <0.001).

On other hand, survived patients had lower mortality rate vs non survivor patients in whole NIV duration (32.8±4.1vs 34.0±7.0, p-value <0.001).

Table (27): Duration of NIV session in relation to mortality

	DIED	SURVIVED	P value
Duration of NIV session	6.4±1.2 (6.0)	4.7±1.3(4.0)	< 0.001
Whole NIV duration	32.8±4.1(31.0)	34.0±7.0(32.0)	< 0.001

d. ICU length of stay in relation to mortality:

Non survivors' group of patients stayed longer duration of days in ICU compared to survivors: (11.5±5.9 vs 9.4 ± 6.4, p-value = 0.001).

Table (28): ICU length of stay in relation to mortality

Mortality	DIED	SURVIVED	P value
ICU LOS	11.5±5.9(10.001)	9.4±6.4(10.001)	0.001

e. Change of HACOR score during 48hrs of applying NIV and relation with mortality:

Table (29): Change of HACOR score during 48hrs of NIV and relation with mortality.

Mortality	DIED	SURVIVED	P value
HACOR change 0>>1	-0.68±1.4 (0.001)	-1.1±1.53 (-1.0)	0.001
HACOR change 1>>24	-0.65±0.95(-1.0)	-0.93±0.72(-1.0)	0.001
HACOR change 24>>48	-0.65±1.19 (0.001)	-2.80±1.1(-3.0)	≤ 0.001

6. Correlation of HACOR: -

- There was significant correlation between clinical severity scores and HACOR where patients with higher clinical severity illness showed higher HACOR scores.
- Also, there was significant correlation between HACOR and ICU LOS where patients with higher HACOR scores more likely needed to stay longer in ICU.
- Regarding NIV duration we found that there was significant correlation between HACOR and NIV duration with higher HACOR scores more likely to stay shorter duration on NIV.

Table (30): Correlation of HACOR

		APACHE II	SOFA Day0	SOFA Day1	SOFA Day2	Duration of NIV	ICU LOS
HACOR Day0	Correlation Coefficient	0.464	0.347	0.326	0.333	-0.268	0.219
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HACOR 1 hour	Correlation Coefficient	0.315	0.310	0.293	0.322	-0.406	0.149
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	0.014
HACOR Day1	Correlation Coefficient	0.440	0.512	0.497	0.521	-0.390	0.220
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HACOR Day2	Correlation Coefficient	0.563	0.588	0.612	0.611	-0.414	0.223
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

7. ROC curve of HACOR score: -

a) ROC of HACOR scores to predict NIV failure:

-Measuring HACOR score at time of admission had sensitivity of 73.8%, specificity 62.2 % with cut-off point was 6.5. (AUC was 0.699).

-Measuring HACOR score at 1hr from NIV apply had sensitivity of 72.3%, specificity 76.5 % with cut-off point was 5.5. (AUC was 0.784).

-Measuring HACOR score after 24hrs had sensitivity of 60%, specificity 96.9 % with cut-off point was 5.5. (AUC was 0.834).

Fig (6): ROC curve for prediction of failed NIV using HACOR.

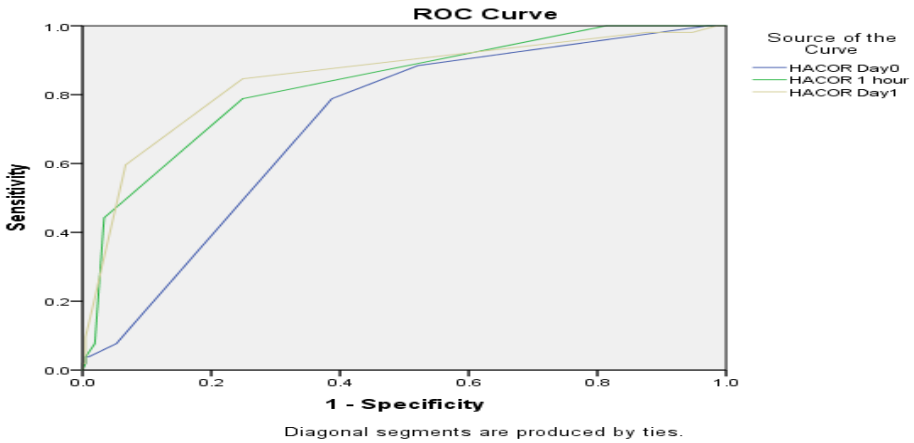


Table (31): Prediction of failed NIV using HACOR

	Area Under the Curve	P value	Cut off	Sensitivity %	Specificity %
HACOR Day0	0.699	< 0.001	6.5	73.8	62.2
HACOR 1 hour	0.784	< 0.001	5.5	72.3	76.5
HACOR Day1	0.834	< 0.001	5.5	60	96.9

b) <u>ROC curve for prediction of Mortality using HACOR:</u>

-Measuring HACOR score at time of admission had sensitivity of 78.8%, specificity 61.2 % with cut-off point was 6.5. (AUC was 0.712).

-Measuring HACOR score at 1hr from NIV apply had sensitivity of 78.8%, specificity 75.1 % with cut-off point was 5.5. (AUC was 0.829).

-Measuring HACOR score after 24hrs had sensitivity of 84.6%, specificity 75.1 % with cut-off point was 4.5. (AUC was 0.848).

-Measuring HACOR score after 48hrs had sensitivity of 86.5%, specificity 93.8 % with cut-off point was 3.5. (AUC was 0.909).

Fig (7): Roc curve for prediction of mortality using HACOR.

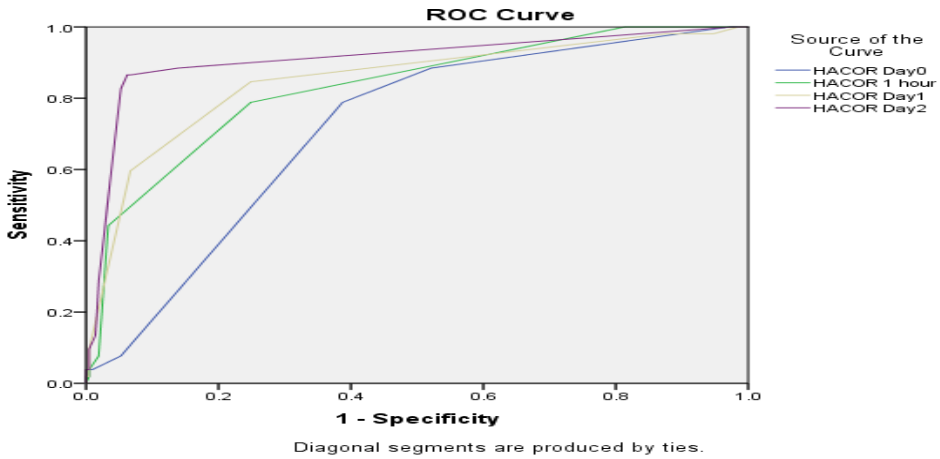


Table (32): Prediction of mortality using HACOR.

	Area Under the Curve	P value	Cut off	Sensitivity %	Specificity %
HACOR Day0	0.712	< 0.001	6.5	78.8	61.2
HACOR 1 hour	0.829	< 0.001	5.5	78.8	75.1
HACOR	0.8	<0.001	4.5	84.6	75.1

Day1	48				
HACOR Day2	0.909	< 0.001	3.5	86.5	93.8

c) ROC curve for prediction of mortality using SOFA and APACHE:

-Measuring SOFA score at time of admission had sensitivity of 86.8%, specificity 75.3 % with cut-off point was 7.5. (AUC was 0.829).

-Measuring SOFA score after 24hr of admission had sensitivity of 90.6%, specificity 74.4 % with cut-off point was 6.5. (AUC was 0.871).

-Measuring SOFA score after 48hr had sensitivity of 90.6%, specificity 78.1 % with cut-off point was 6.5. (AUC was 0.880).

-Measuring APACHII score after 48hr had sensitivity of 86.6%, specificity 74 % with cut-off point was 14.5. (AUC was 0.826).

Fig (8): Roc curve for prediction of mortality using SOFA and APACHE.

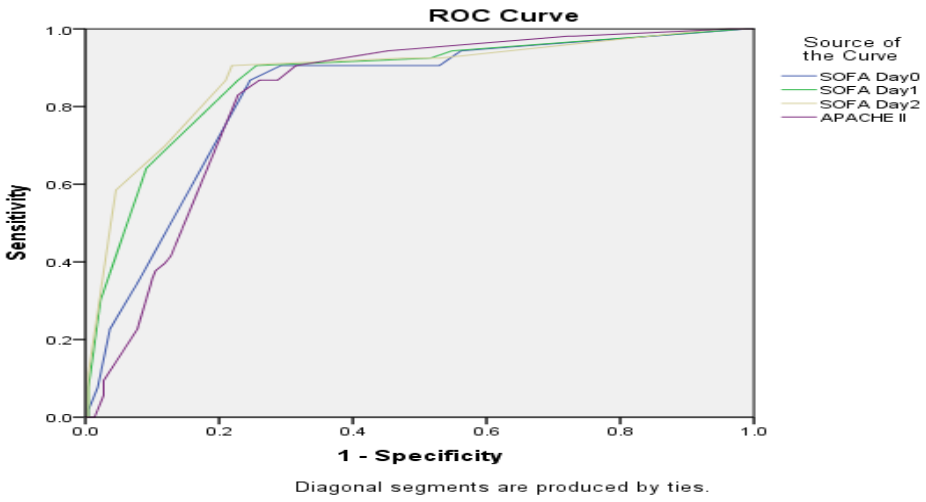


Table (33): Prediction of mortality using SOFA and APACHE II

	Area Under the Curve	P value	Cut off	Sensitivity %	Specificity %
SOFA Day0	0.829	< 0.001	7.5	86.8	75.3
SOFA Day1	0.871	< 0.001	6.5	90.6	74.4
SOFA Day2	0.880	< 0.001	6.5	90.6	78.1
APACHE II	0.826	< 0.001	14.5	86.8	74

8. *Kaplan-Meier of HACOR score*: -

a) Kaplan-Meier for survival in HACOR 0 subgroups:

Cox regression showed that categorization of patients according to HACOR 0 into 2 groups: <6.5vs >6.5 had significance impact on survival (HR =2.280, CI 95% =1.152-4.514, p-value=0.018).

Fig (9) Kaplan-Meier survival in HACOR 0

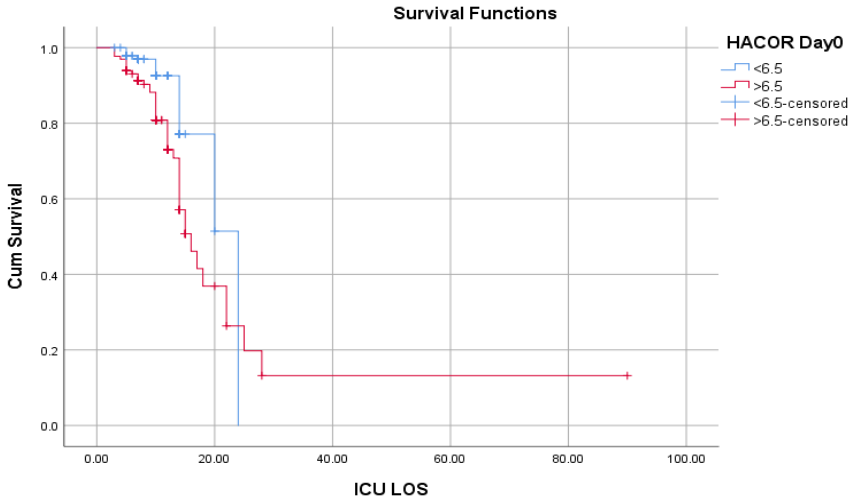


Table (34) Log rank for HACOR 0

Test of equality of survival distributions for the different levels of HACOR Day0.

Overall Comparisons

	Chi-Square	df	P value
Log Rank (Mantel-Cox)	6.201	1	0.013

Tab (35) Cox regression for HACOR 0

	P value	HR	95.0% CI	
			Lower	Upper
HACOR Day 0	0.018	2.280	1.152	4.514

b) <u>Kaplan-Meier for survival in HACOR 1-hour subgroups:</u>

Cox regression showed that categorization of patients according to HACOR 1hr into 2 groups: <5.5 vs >5.5 had significance impact on survival (HR=3.792, CI =95% 1.945-7.392, p-value<0.001).

Fig (10) Kaplan-Meier survival in HACOR 1hr.

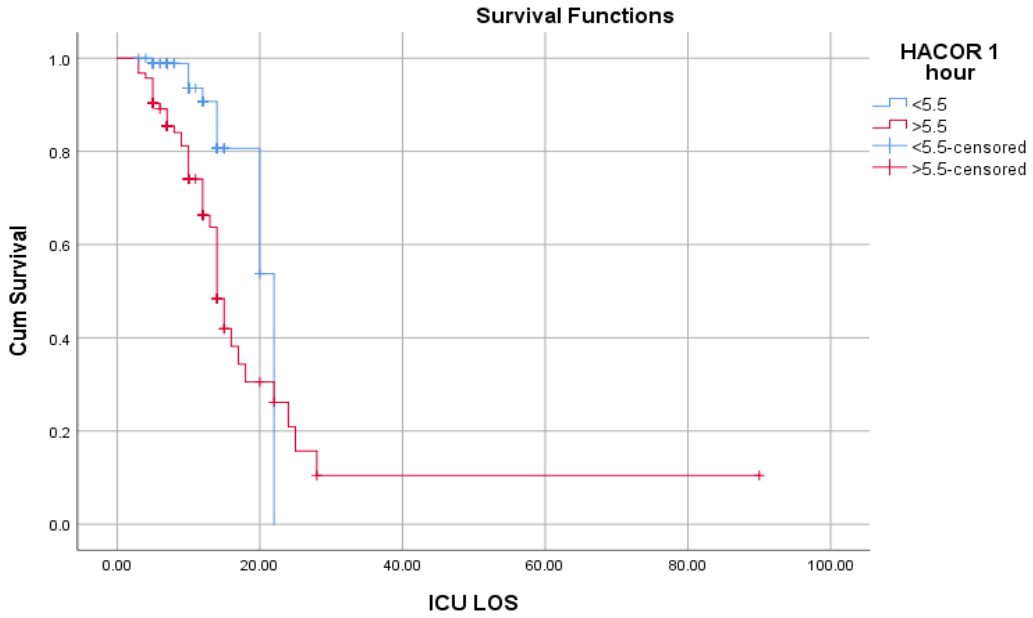


Table (36) Log rank for HACOR1hr.

Overall Comparisons

	Chi-Square	df	P value
Log Rank (Mantel-Cox)	18.341	1	<0.001

Test of equality of survival distributions for the different levels of HACOR 1 hour.

Table (37) Cox regression for HACOR 1hr.

	P value	HR	95.0% CI	
			Lower	Upper
HACOR 1 hour	<0.001	3.792	1.945	7.392

c) <u>Kaplan-Meier for survival in HACOR day 1 subgroups:</u>

Cox regression showed that categorization of patients according to HACOR 24hrs into 2 groups: <4.5 vs >4.5 had significance impact on survival (HR=5.026, CI =95% 2.313-10.919, p-value<0.001).

Fig (11) Kaplan-Meier survival in HACOR 24hrs.

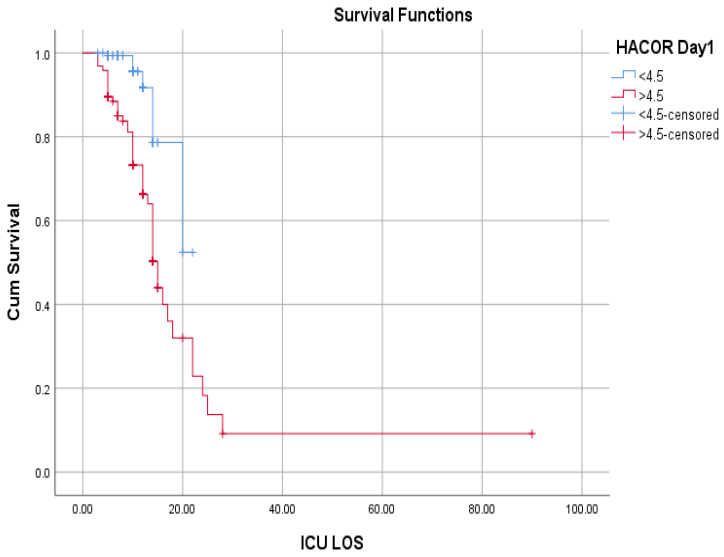


Table (38) Log rank for HACOR 24hrs

Overall Comparisons

	Chi-Square	df	P value
Log Rank (Mantel-Cox)	21.070	1	<0.001

Test of equality of survival distributions for the different levels of HACOR Day1.

Table (39) Cox regression for HACOR 24hrs

	P value	HR	95.0% CI	
			Lower	Upper
HACOR Day1	<0.001	5.026	2.313	10.919

d) <u>Kaplan-Meier for survival in HACOR day 2 subgroups:</u>

Cox regression showed that categorization of patients according to HACOR 48hrs into 2 groups: <3.5 vs >3.5 had significance impact on survival (HR=11.370, CI =95% 5.164-26.648, p-value<0.001).

Fig (12) Kaplan-Meier survival in HACOR 48hrs.

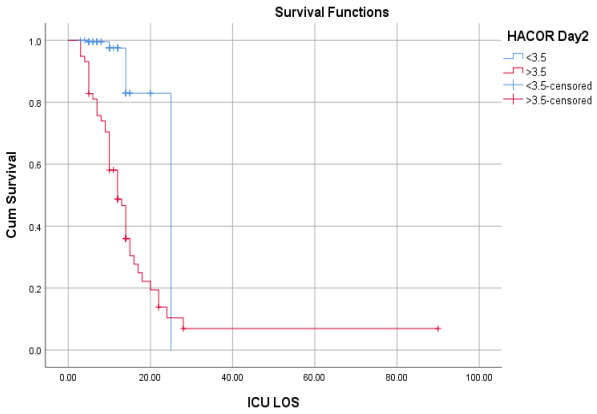


Table (40) Log rank for HACOR 48hrs.

Overall Comparisons

	Chi-Square	df	P value
Log Rank (Mantel-Cox)	53.362	1	<0.001

Test of equality of survival distributions for the different levels of HACOR Day2

Tab (41) Cox regression for HACOR 48hrs

	P value	HR	95.0% CI	
			Lower	Upper
HACOR Day2	<0.001	11.730	5.164	26.648

DISCUSSION

Non-invasive ventilation (NIV) referred to the administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube). The use of non-invasive ventilation has markedly increased over the past two decades, and non-invasive ventilation has now become an integral tool in the management of both acute and chronic respiratory failure, in both the home setting and in the critical care unit. Non-invasive ventilation has been used as a replacement for invasive ventilation, and its flexibility also allows it to be a valuable complement in patient management. Its use in acute respiratory failure is well accepted and widespread.

Our study was a multi-center prospective study, performed in different hospital from February 2017 till October 2018. Our study population included 272 patients divided into 2 groups in relation to failure of NIV.

Failure rate of NIV patients (76 patients) regarding total group of patients (272) in our study was 27.9% and mortality rate was higher in failed NIV groups (64.5%) versus that in successful NIV group (35.5%) with p-value <0.001.

We aimed to validate the use of HACOR score in predicting NIV failure in hypoxemic respiratory failure.

Our study showed that failure of weaning of non-invasive ventilation increased with age as analysis of age showed highly significant difference between successful NIV 61.3±13.0 (60.5) vs failed NIV 65.1±16.8(68.0) as p-value =0. 001. Elderly patients were more likely to experience NIV failure.

It came in accordance with a study done by Ola A, Romah on 60 NIV patients who showed that age showed significant difference between successful &failed groups (56.2±11.6 VS 62.5±8.2, p-value=0.039).

This came in discordance with a study done on 218 patients by Adamantios Chloros (1) who stated that NIV can be applied successfully regardless of patients' age. Although time to NIV success was longer in elders, their mortality was similar to that of younger patients.

Analysis of gender in relation to successful weaning showed no significant difference between successful vs failed NIV group of our study.

This came in accordance with study done by Ola A, Romah who showed also no significance difference between both genders. (2). Also, another study done by Antonello Nicolino on 130 patients showed similar results. (4)

It came with accordance with study done by Kamel A.Aziz who studied 120 mechanically ventilated patients with different causes of respiratory failure, with no significant difference regarding age or gender between patients who were kept on NIV post-extubation versus those kept on simple oxygen mask .(3)

On analyzing conscious level using Glasgow coma scale there was highly significant difference between both successful NIV 15 ± 1 vs failed NIV 14 ± 2 in group B, p-value = 0.001).

This was in accordance with a prospective study done by Pejkovska S on 58 COPD patients, where patients with depressed conscious level showed higher failure rates. (5)

Also, this came in agreement with a study done by Jun Duan on 449 patients with hypoxemia and receiving NIV and showed that NIV failure was related to deterioration of conscious level (successful NIV 14.8 ± 0.8 vs failed NIV 14.4 ± 1.7 with p-value<0.001). (6)

In our study NIV failed group persistently showed higher SOFA score and APACHE II. Increasing severity of illness was related to failure of non-invasive ventilation.

This was in accordance with the study done by Jun Duan who showed that NIV failure was related to increased severity of illness measures by APACHI II score, (failed NIV 19±6 vs successful NIV 16 ± 5 with p-value <0.001).(6) Also another study done by Yang Liu on 1,713 adult patients stated that failure of NIV was significantly related to increased severity of illness demonstrated by elevated SOFA score.(7)Another cross-sectional study done by Umilson Bien on 195 patients agreed that failure of weaning of non-invasive ventilation showed significant correlation with elevated SOFA and APACHE II score. (8)

HACOR score was introduced by Jun Duan for pre-diction of NIV failure in patients with hypoxemic respiratory failure. This took into account heart rate, acidosis, consciousness measured by Glasgow coma scale (GCS), oxygenation measured by ABG, and respiratory rate, variables which were easily obtained by simple bed-side measurements.

In our study, failure of non-invasive ventilation showed elevated HACOR score, started from time of applying of NIV in ascending way till 48 hours form applying NIV.

There was significant correlation between clinical severity scores and HACOR score where patients with higher clinical severity illness showed higher HACOR scores. Also, there was significant correlation between HACOR and ICU length of stay where patients with higher HACOR scores more likely needed to stay longer in ICU.

This came in same way of thinking with study done by Alice Grassi on patients with non-invasive failure showed that NIV failure together with longer duration of ICU stay and higher hospital in-mortality could be predicted by elevated SOFA, APACHI II and HACOR. (9)

That came in accordance with study made by Jun Duan. He demonstrated that NIV failure was related to elevated parameters of HACOR scale. (6)

In our study, we discussed HACOR score readings to predict failure of NIV in different pre-determined times 0, 1hr, 24hr and 48hrs which showed that patients with HACOR score at time of admission >6.5 had high risk of NIV failure, patients with HACOR 1h score>5.5 had high risk of NIV failure while patients with HACOR score 24hr from NIV applying >5.5 had high risk of NIV failure.

This came in accordance with study done by Jun Duan stated that HACOR score readings >5 had high risk of NIV failure but it was different from our study that it measured 0,1hr,12hr,24hr and 48hrs. However, different cut off was set by Jun Duan which might reflect different management policies and to what extent we can accept a deteriorating clinical parameter before deciding invasive ventilation approach. Also, Jun Duan examined HACOR utility in hypoxemic respiratory failure, while we applied HACOR to both hypoxemic and hypercapnic respiratory failure. He excluded COPD patients from recruiting into his study. (6)

Statistical analysis using ROC curve in our study stated that cut off point for NIV failure using HACOR score at 0,1hr,24hrs then 48hrs were 6.5 ,5.5,5. Respectively showed sensitivity ranged from 60-86.2% and specificity ranged from 62.2-96.9%. With AUC ranged from 0.7 to 0.9.

While in the study done by Jun Duan stated that using a HACOR score of 5 as the cut-off value, the diagnostic accuracy for NIV failure assessed at 1h of NIV was 81.8 and 86.0% in the test and validation cohorts, respectively (6).

Our study showed that Failed NIV patients stayed longer duration on every NIV session compared to successful patients: (5.8±1.7 vs 4.7±1.2,

p-value <0.001). However, Failed NIV could not be able to tolerate NIV for longer duration: (32.2±5.0 vs 34.4±7.0, p-value<0.001).

The relation between length of duration of NIV session and failure or success of NIV depend on hemodynamic and conscious level and measured HCOR score at predetermined times 0,1hr 24hr and 48hr.We aimed to increase duration of NIV sessions to benefit from positive pressure ventilation. However, deteriorating clinical parameters did not allow for longer NIV stay.

This came in discordance with study was made by Stefano Nava on 39 patients who showed higher rate of NIV failure related to longer duration of NIV session. (10)

In our study, successful weaning of NIV shortened length of ICU stay, failed NIV had longer ICU stay with highly significate difference. This might reflect good prognosis, carried by NIV success.

Another study agreed that successful NIV shortened the length of ICU stay, this study done by Yang Liu on 963 patents with hypoxemic respiratory failure showed that NIV patients with acute respiratory failure is associated with lower incidence of invasive ventilation and in-ICU mortality rate. (11) Also, another study done by Alexandre Demoule on 554 patients which stated that NIV failure patients have long ICU stay. (12)

In our study, we could highlight relationship between mortality &HACOR scores. Non-survivors tended to show higher HACOR scores & worsening patterns. HACOR score could provide prognostic information for mortality, as well.

Statistical analysis using ROC curve in our using HACOR score and its relation with mortality stated that cut off point for HACOR score 0,1hr,24hrs then 48hrs were 6.5 ,5.5,4.5 then 3.5, could predict mortality with reasonable accuracy.

This came in accordance on study done by Jun Duan showed that non-improvement of HACOR score from 1hour till 48 hours with cut-off point >5 significantly related to failure of NIV and mortality. (6)

There were a number of limitations to our study. The sample size was small in some subgroups, such as pulmonary embolism and heart failure and, consequently, the efficacy of the HACOR scale in these patients may be skewed. In future studies the sample size should be larger to improve the diagnostic power. Second, different protocol for NIV usage in each

hospital center in our study which for sure affected our results. As our study was an observational study, this result should be investigated further in randomized controlled trials.

Conclusion

In our study, we discussed HACOR score readings to predict failure of NIV in different pre-determined times 0, 1hr, 24hr and 48hrs which showed that patients with HACOR score at time of admission >6.5 had high risk of NIV failure, patients with HACOR 1h score>5.5 had high risk of NIV failure while patients with HACOR score 24hr from NIV applying >5.5 had high risk of NIV failure.

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Statistical analysis using ROC curve in our study stated that cut off point for NIV failure using HACOR score at 0,1hr,24hrs then 48hrs were 6.5 ,5.5,5. Respectively showed sensitivity ranged from 60-86.2% and specificity ranged from 62.2-96.9%. With AUC ranged from 0.7 to 0.9.

Statistical analysis using ROC curve in our using HACOR score and its relation with mortality stated that cut off point for HACOR score 0,1hr,24hrs then 48hrs were 6.5 ,5.5,4.5 then 3.5, could predict mortality with reasonable accuracy.

In conclusion, we found that the HACOR score was able to effectively predict NIV failure in patients with hypoxic respiratory failure. Higher HACOR measurements indicated a higher chance of NIV failure. Since the scale was made up of variables that were easily obtained in practice, the HACOR measures could easily be used to evaluate the effectiveness of NIV. Patients with a HACOR score of> 6.5 were at increased risk of NIV failure. In these high-risk patients, early intubation might reduce hospital mortality.

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