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Early assessment of the efficacy of noninvasive ventilation tested by HACOR score to avoid delayed intubation in patients with moderate to severe ARDS

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Abstract

Background: Use of noninvasive ventilation (NIV) in patients with moderate to severe ARDS is controversial. We aimed to use HACOR (combination of heart rate, acidosis, consciousness, oxygenation and respiratory rate) score to comprehensively assess the efficacy of NIV in ARDS patients with $PaO_2/FiO_2 \leqslant 150$ mmHg.

Methods: Secondary analysis was performed using the data collected from two databases. We screened the ARDS patients who used NIV as a first-line therapy. Patients with $PaO_2/FiO_2 \leqslant 150$ mmHg were enrolled. NIV failure was defined as requirement of intubation.

Results: A total of 224 moderate to severe ARDS patients who used NIV as a first-line therapy were enrolled. Of them, 125 patients (56%) experienced NIV failure and received intubation. Among the intubated patients, the survivor had shorter time from initiation of NIV to intubation than nonsurvivors (median 10 vs 22 h, $p < 0.01$). The median differences of HACOR score before and 1–2 h of NIV were 1 point (interquartile range: 0–3). We defined the patients with $\triangle$HACOR >1 as responders (n = 102) and the rest to non-responders (n = 122). Compared to non-responders, the responders had higher HACOR score before NIV. However, the HACOR score was lower in the responders than non-responders after 1–2 h, 12 h, and 24 h of NIV. The responders also had lower NIV failure rate (36% vs 72%, $p < 0.01$) and lower 28-day mortality (32% vs 47%, $p = 0.04$) than non-responders.

Conclusions: NIV failure was high among patients with moderate to severe ARDS. Delayed intubation is associated with increased mortality. The reduction of HACOR score after 1–2 h of NIV can identify the patients who respond well to NIV.

Keywords: ARDS, mechanical ventilation, noninvasive ventilation

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Background

Acute respiratory distress syndrome (ARDS) is characterized by rapid-onset respiratory failure caused by a variety of direct and indirect insults to the parenchyma or vasculature of the lungs.[1] Oxygen therapy is the main intervention for ARDS to reverse hypoxemia including high-flow nasal cannula, noninvasive ventilation (NIV) and invasive mechanical ventilation. Among the ARDS population, NIV has been used as a first-line therapy in 15.5% of cases.[2] It can improve the PaO_2/FiO_2 and reduce the work of breathing.[3] Therefore, NIV reduces the incidence of endotracheal intubation and hospital mortality.[4]

Although the benefits got from NIV, NIV failure is associated with increased mortality.[5] $PaO_2/FiO_2 \leqslant 150$ mmHg is associated with NIV failure.[6,7] A large epidemiologic study showed that patients who received NIV as a first-line therapy were more likely

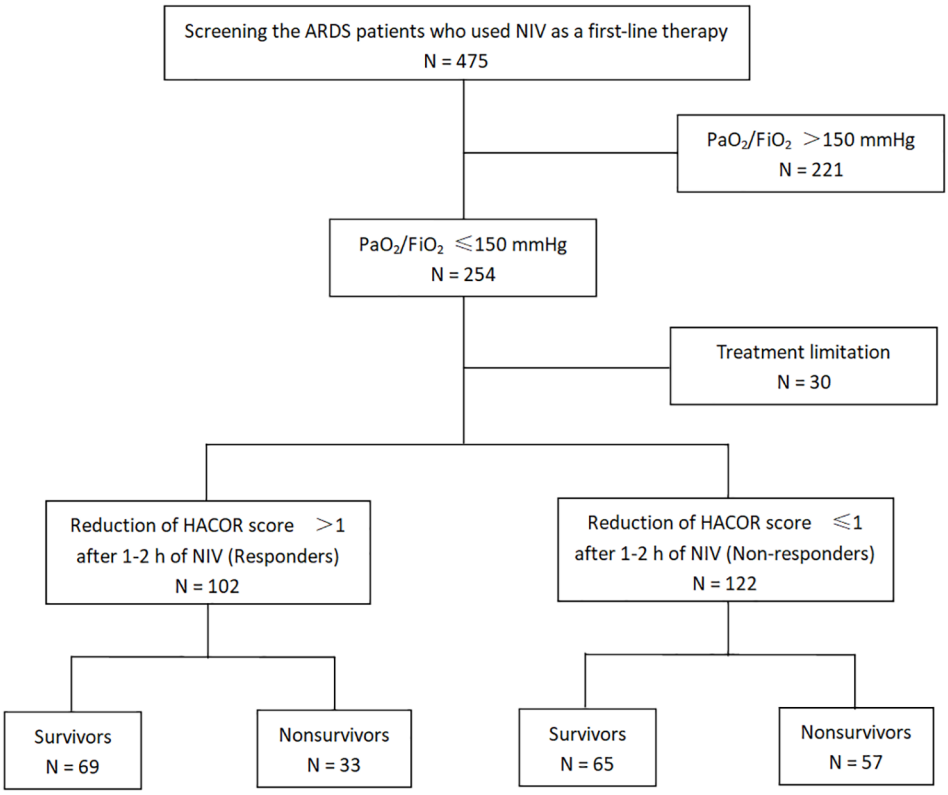

Figure 1. Flowchart of patient screening.

to die than those who directly received invasive mechanical ventilation among the cases with $PaO_2/FiO_2 \leqslant 150$ mmHg.[2] However, not all the ARDS patients with $PaO_2/FiO_2 \leqslant 150$ mmHg require intubation. Assessment of the patients who respond well to NIV can reduce unnecessary intubation and ventilator-associated complications.

The HACOR (assessed by heart rate, acidosis, consciousness, oxygenation and respiratory rate) score has high predictive power to distinguish NIV success and failure among patients with acute respiratory failure.[8–10] However, the impact of HACOR score on NIV outcomes in ARDS patients with $PaO_2/FiO_2 \leqslant 150$ mmHg is unclear. Here, we aimed to assess the moderate to severe ARDS patients who respond well to NIV with the use of HACOR score.

Methods

This was a secondary analysis of the data came from two previous published articles.[8,11] In Duan *et al*'.s[8] study, the data were prospectively collected from June 2011 to June 2016 in a respiratory intensive care unit (ICU). A total of 807 patients with hypoxemic respiratory failure received NIV as a first-line therapy. Of them, 130 cases were diagnosed as ARDS and considered to be eligible in current study. In Shu *et al*'.s[11] study, the data were prospectively collected from September 2017 to December 2019 in 17 ICUs in China. A total of 3754 patients were screened, and 345 ARDS patients who received NIV as a first-line therapy were candidates. As the aim of current study is focused on ARDS patients with $PaO_2/FiO_2 \leqslant 150$ mmHg, 221 cases with mild to moderate ARDS were excluded (Figure 1). Another 30 cases with treatment limitation were also excluded. Therefore, a total of 224 patients were enrolled to final analyses. The study protocol was approved by the local ethics committee and institutional review board (the First Affiliated Hospital of Chongqing Medical University, NO. 2021-414). As this was a secondary analysis, the informed consent was waived.

The management of NIV has been described in previously published articles.[8,11] The attending physicians initiated the use of NIV based on the

following criteria: clinical presentation of respiratory distress at rest (such as active contraction of the accessory inspiratory muscles, paradoxical abdominal motion, or respiratory rate more than 25 breaths/min), $PaO_2 < 60$ mmHg at room air or $PaO_2/FiO_2 < 300$ mmHg with supplemental oxygen. The face mask as the first choice was used to connect the patient to the ventilator. The positive-end expiratory pressure (PEEP) was maintained at 4–8 cmH_2O and inspiratory pressure was maintained around 15 cmH_2O. If the patient failed to tolerate the pressure of 15 cmH_2O, it was decreased. The lowest pressure of 8 cmH_2O was allowed. The fraction of inspiration oxygen was set to achieve peripheral oxygen saturation more than 92%. The upper limit of saturation was not predetermined. But it was limited no more than 98% in most of the participated centers. If the respiratory failure was reversed, the weaning from NIV was performed. However, if the respiratory failure was worsened, the intubation for invasive mechanical ventilation was considered. The NIV failure was defined as requirement of intubation. The criteria of intubation were referenced previous standards.[8,11]

The HACOR score was assessed before, and after 1–2 h, 12 h and 24 h of NIV.[8] It included five variables (heart rate, acidosis, consciousness, oxygenation and respiratory rate). The acidosis was assessed by pH, the consciousness was assessed by Glasgow Coma Scale (GCS), and the oxygenation was assessed by PaO_2/FiO_2. Supplementary table 1 summarized the points in each variable. Higher points indicate a higher risk of NIV failure.

Statistical analysis

For continuous variables, we reported median value with interquartile range (IQR) or mean value and standard deviation (SD) when appropriate. For categorical variables, we reported numbers and percentage. Unpaired Student's t test was used to analyze the normally distributed continuous variables and Mann–Whitney U test was used to analyze the non-normally distributed continuous variables. Chi-square test or Fisher's exact test was used to analyze the categorical variables when appropriate.

To assess the efficacy of NIV, the differences of HACOR score before and 1–2 h of NIV were calculated. Given the previous study used the increase of oxygenation more than the median value after prone position to define the response to prone position in ARDS patients, we classified the patients with ΔHACOR larger than the median value to responsible group and the rest to non-responsible group.[12] The Kaplan-Meier curve was used to analyze the cumulative 28-day survival probability and the difference between two groups was analyzed by log-rank test. A p value less than 0.05 was considered to be statistical significance.

Results

Association between delayed intubation and poor outcomes

Among the 224 moderate to severe ARDS patients, NIV failure occurred in 125 cases (56%). All the patients with NIV failure received intubation for invasive mechanical ventilation. Among the intubated patients, we recorded 43 survivors and 82 non-survivors at 28 days (Table 1). There were no differences in age, sex and APACHE II score between survivors and nonsurvivors. The vital signs, arterial blood gas tests and HACOR score collected before and after 1–2 h of NIV were also no differences between the two groups. The survivors only had lower proportion of pulmonary ARDS (70% vs 90%, $p < 0.01$) on the terms of demographics.

The time from NIV initiation to intubation was median 10 h (IQR: 2-22) in survivors (Figure 2). However, it increased to 22 h (IQR: 5-77) in non-survivors. The crude odds ratio (OR) of death at 28 days was 1.015 per one hour delayed intubation (95% confidence interval (CI): 1.004-1.026). When the OR was adjusted by age, sex, disease severity, origin of ARDS, comorbid conditions, vital signs, arterial blood gas tests, ventilator parameters and HACOR score, it was 1.015 (95%CI: 1.001-1.029).

Outcomes between responders and non-responders

The differences of HACOR score before and after 1-2 h of NIV were summarized in supplementary Figure 1. The median value was 1 (IQR: 0-3). In the total cohort, patients with ΔHACOR >1 were defined as responders (n = 102) and those with ΔHACOR ⩽ 1 as non-responders (n = 122). The responders had lower proportion of pulmonary ARDS (63% vs 84%, $p < 0.01$) than non-responders (Table 2). Before NIV, the HACOR score was higher (7.7 ± 2.7 vs 6.7 ± 2.0, $p < 0.01$)

Table 1. Demographics.

Variables	Overall cohort			Intubated cohort		*p*
	Success *N* = 99	Failure *N* = 125	*p*	Survivors *N* = 43	Nonsurvivors *N* = 82	
Age, years	56 ± 17	58 ± 18	0.41	56 ± 18	59 ± 17	0.28
Male gender, (%)	61 (62%)	93 (74%)	0.04	32 (74%)	61 (74%)	>0.99
APACHE II score	15 ± 5	16 ± 6	0.03	16 ± 6	17 ± 6	0.95
Pulmonary ARDS	62 (63%)	104 (83%)	< 0.01	30 (70%)	74 (90%)	< 0.01
Comorbid conditions						
Hypertension	33 (33%)	36 (29%)	0.47	8 (19%)	28 (34%)	0.10
Diabetes mellitus	14 (14%)	26 (21%)	0.22	8 (19%)	18 (22%)	0.82
Solid tumor	4 (4%)	7 (6%)	0.76	1 (2%)	6 (7%)	0.42
Chronic kidney disease	9 (9%)	7 (6%)	0.43	3 (7%)	4 (5%)	0.69
Chronic liver disease	5 (5%)	7 (6%)	> 0.99	0 (0%)	7 (9%)	0.09
Chronic heart disease	6 (6%)	12 (10%)	0.46	6 (14%)	6 (7%)	0.34
Chronic lung disease	9 (9%)	12 (10%)	> 0.99	4 (9%)	8 (10%)	> 0.99
Data collected before NIV						
Systolic blood pressure, mmHg	131 ± 22	128 ± 25	0.34	129 ± 28	127 ± 23	0.55
Diastolic blood pressure, mmHg	77 ± 15	77 ± 14	0.72	78 ± 17	76 ± 12	0.29
Heart rate, beats/min	114 ± 24	117 ± 24	0.48	118 ± 22	116 ± 24	0.65
Respiratory rate, breaths/min	31 ± 7	34 ± 8	< 0.01	35 ± 9	34 ± 7	0.58
pH	7.46 ± 0.08	7.43 ± 0.08	< 0.01	7.44 ± 0.08	7.42 ± 0.09	0.36
$PaCO_2$, mmHg	32 (28-37)	33 (29-38)	0.44	32 (26-37)	34 (28-39)	0.25
PaO_2/FiO_2	119 ± 21	107 ± 26	< 0.01	110 ± 24	106 ± 26	0.32
GCS = 15	90 (91%)	110 (88%)	0.52	37 (86%)	73 (89%)	0.77
HACOR score	6.4 ± 2.0	7.8 ± 2.5	< 0.01	7.8 ± 2.3	7.7 ± 2.5	0.92
Data collected after 1-2 h of NIV						
Systolic blood pressure, mmHg	125 ± 18	122 ± 21	0.26	124 ± 22	121 ± 21	0.37
Diastolic blood pressure, mmHg	75 ± 12	73 ± 13	0.27	74 ± 13	73 ± 12	0.46
Heart rate, beats/min	106 ± 23	113 ± 25	0.03	116 ± 23	111 ± 25	0.30
Respiratory rate, breaths/min	27 ± 6	33 ± 8	< 0.01	34 ± 8	33 ± 9	0.61
pH	7.46 ± 0.05	7.42 ± 0.09	< 0.01	7.41 ± 0.11	7.42 ± 0.08	0.47
$PaCO_2$, mmHg	33 (29-38)	33 (30-39)	0.39	33 (29-37)	33 (30-39)	0.54
PaO_2/FiO_2	175 ± 67	116 ± 49	< 0.01	117 ± 44	116 ± 52	0.98
GCS = 15	93 (94%)	107 (86%)	0.05	37 (86%)	70 (85%)	>0.99
Inspiratory pressure, cmH_2O	13 (11-15)	14 (11-16)	0.08	14 (11-16)	14 (12-16)	0.98
PEEP, cmH_2O	6 (5-8)	6 (5-7)	0.03	6 (5-8)	6 (5-6)	0.12
HACOR score	3.6 ± 2.2	7.3 ± 3.2	< 0.01	7.9 ± 3.0	7.0 ± 3.2	0.17

ARDS, acute respiratory distress syndrome; GCS, Glasgow Coma Scale; HACOR, heart rate, acidosis, consciousness, oxygenation and respiratory rate; NIV, noninvasive ventilation; PEEP, positive-end expiratory pressure.

in responders than that in non-responders (Figure 3). However, the HACOR score was lower in responders after 1-2 h, 12 h, and 24 h of NIV (3.7 ± 2.8 vs 7.3 ± 2.9, $p < 0.01$; 3.4 ± 2.5 vs 5.5 ± 2.4 $p < 0.01$; and 2.6 ± 2.7 vs 5.2 ± 2.8, $p < 0.01$, respectively).

The reduction of respiratory rate and heart rate after 1-2 h, 12 h and 24 h of NIV was faster in responders than that in non-responders (Figure 4). The PaO_2/FiO_2 in responders was also improved faster. The NIV failure rate was 36% in responders, which was much lower than non-responders (72%). The 28-day mortality was also lower in responders (32% vs 47%, $p = 0.04$).

Discussion

Current study shows that 56% of ARDS patients with PaO_2/FiO_2 less than 150 mm Hg experienced NIV failure. Delayed intubation is associated with increased mortality. After 1-2 h of NIV, 46% of patients respond well to NIV assessed by HACOR score. The responders were associated with decreased NIV failure and 28-day mortality.

Previous studies have reported that delayed intubation leads to increase in mortality.[13–16] Among the patients who received high-flow nasal cannula,

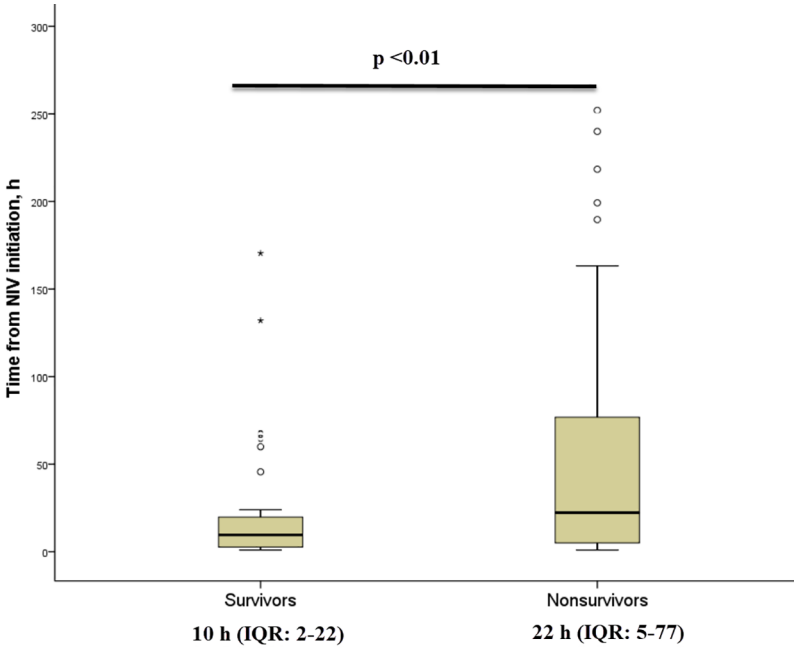

Figure 2. Time from NIV initiation to intubation among patients who experienced NIV failure.

ICU mortality was 39.2% in patients who experienced intubation less than 48 h; however, it increased to 66.7% in those beyond 48 h.[15] Among the patients who received NIV due to de

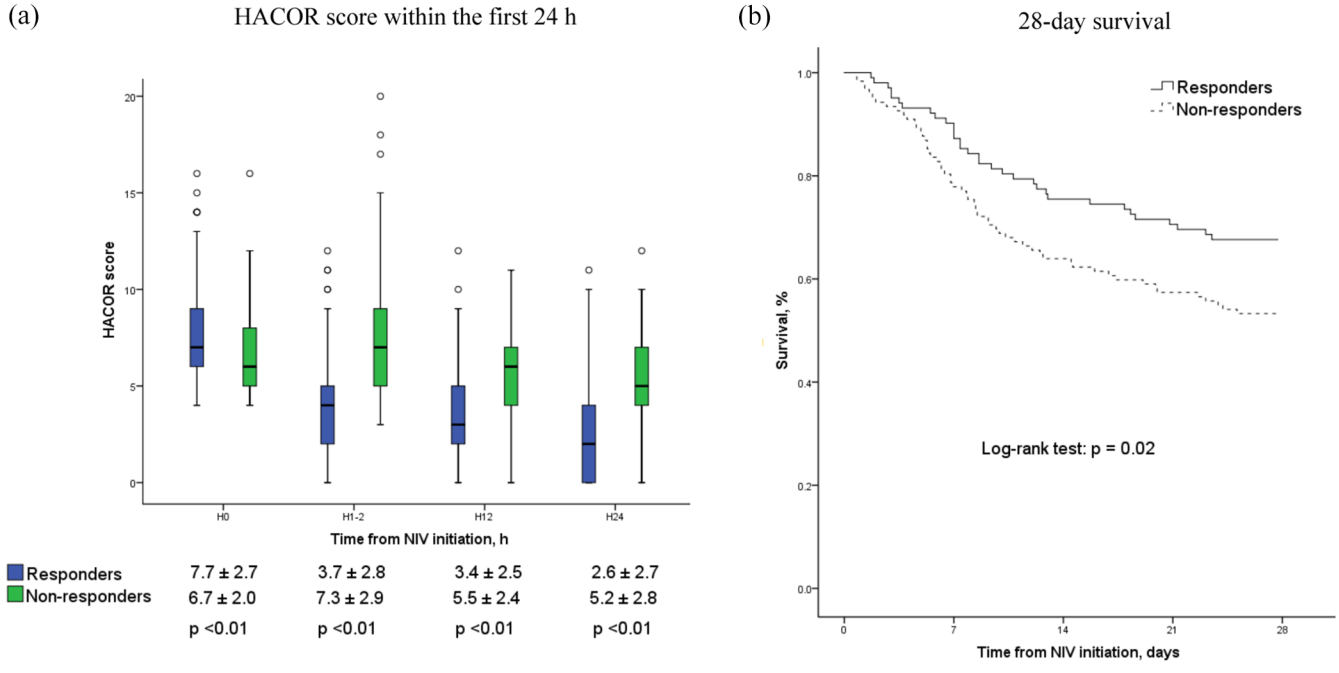

Figure 3. The HACOR score from initiation to 24 h of NIV and 28-day survival in patients who responded well and badly to NIV: (a) describes the HACOR score within 24 h of NIV between responders and non-responders and (b) describes 28-day mortality between responders and non-responders..

Table 2. Comparisons between the patients who respond well and badly to NIV.

Variables	Responders $N = 102$	Non-responders $N = 122$	p
Age, years	56 ± 18	58 ± 17	0.29
Male gender, (%)	69 (68%)	85 (70%)	0.77
APACHE II score	16 ± 5	16 ± 6	0.62
Pulmonary ARDS	64 (63%)	102 (84%)	< 0.01
Comorbid conditions			
Hypertension	31 (30%)	38 (31%)	> 0.99
Diabetes mellitus	14 (14%)	26 (21%)	0.16
Solid tumor	4 (4%)	7 (6%)	0.76
Chronic kidney disease	7 (7%)	9 (7%)	> 0.99
Chronic liver disease	8 (8%)	4 (3%)	0.15
Chronic heart disease	8 (8%)	10 (8%)	> 0.99
Chronic lung disease	9 (9%)	12 (10%)	0.82
Data collected before NIV			
Systolic blood pressure, mmHg	130 ± 23	128 ± 24	0.55
Diastolic blood pressure, mmHg	77 ± 15	77 ± 14	0.84
Heart rate, beats/min	120 ± 24	112 ± 23	0.02
Respiratory rate, breaths/min	34 ± 8	32 ± 7	0.13
pH	7.43 ± 0.10	7.44 ± 0.07	0.34
$PaCO_2$, mmHg	32 (28-37)	33 (27-37)	0.86
PaO_2/FiO_2	115 ± 22	111 ± 26	0.18
GCS = 15	84 (82%)	116 (95%)	< 0.01
HACOR score	7.7 ± 2.7	6.7 ± 2.0	< 0.01
Data collected after 1-2 h of NIV			
Systolic blood pressure, mmHg	123 ± 19	124 ± 21	0.63
Diastolic blood pressure, mmHg	74 ± 13	74 ± 12	0.91
Heart rate, beats/min	110 ± 24	109 ± 24	0.80
Respiratory rate, breaths/min	29 ± 8	32 ± 8	< 0.01
pH	7.44 ± 0.07	7.43 ± 0.09	0.31
$PaCO_2$, mmHg	33 (29-38)	34 (30-39)	0.25
PaO_2/FiO_2	185 ± 69	107 ± 32	< 0.01
GCS = 15	88 (86%)	112 (92%)	0.20
Inspiratory pressure, cmH_2O	12 (11-15)	14 (12-16)	0.07
PEEP, cmH_2O	6 (5-8)	6 (5-8)	0.75
HACOR score	3.7 ± 2.8	7.3 ± 2.9	< 0.01
Outcomes			
Intubation	37 (36%)	88 (72%)	< 0.01
28-day mortality	33 (32%)	57 (47%)	0.04

ARDS, acute respiratory distress syndrome; GCS, Glasgow Coma Scale; HACOR, heart rate, acidosis, consciousness, oxygenation and respiratory rate; NIV, noninvasive ventilation; PEEP, positive-end expiratory pressure.

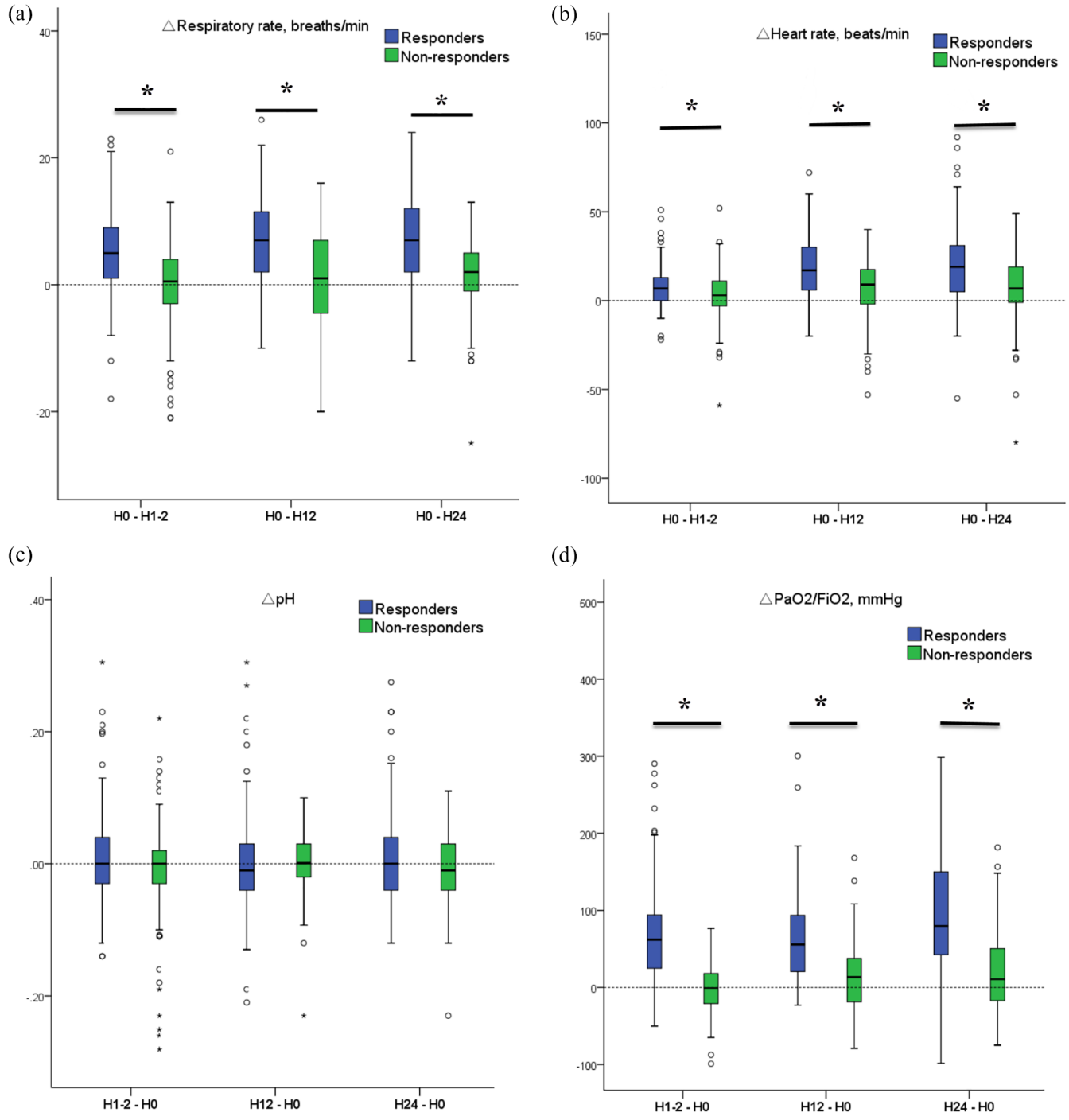

Figure 4. The changes of respiratory rate, heart rate, pH, and PaO_2/FiO_2 within 24 h of NIV in patients who responded well and badly to NIV: (a) describes the changes of respiratory rate from initiation to 24 h of NIV in responders and non-responders, (b) describes the changes of heart rate from initiation to 24 h of NIV in responders and non-responders, (c) describes the changes of pH from initiation to 24 h of NIV in responders and non-responders, and (d) describes the changes of PaO2/FiO2 from initiation to 24 h of NIV in responders and non-responders.

novo acute respiratory failure, the time from NIV initiation to intubation was 32 h in survivors, but it increased to 78 h in nonsurvivors.[16] In our study, we also found that the survivors were received intubation earlier than nonsurvivors among the patients who experienced NIV failure. Per one

hour delayed intubation was associated with 1.019-fold increase in 28-day mortality. These results validate the viewpoint that delayed intubation is associated with increased mortality. Early intubation is a potential strategy to reduce mortality.

Noninvasive strategies appear safe and effective in patient with $PaO_2/FiO_2 > 150$ mmHg, while they can yield delayed intubation with increased mortality in a significant proportion of cases with $PaO_2/FiO_2 \leqslant 150$ mmHg.[17] However, in clinical practices, the use of NIV in ARDS patients with $PaO_2/FiO_2 \leqslant 150$ mmHg is not rare. Among the ARDS patients who received NIV as a first-line therapy, the proportion of $PaO_2/FiO_2 \leqslant 150$ mmHg was 49.29%.[2] Among the moderate to severe ARDS patients, the mortality was higher in the cases who received NIV as a first-line therapy than those who directly received invasive mechanical ventilation. The most likely reason for increased mortality is delayed intubation. Early identification of the patients who respond well to NIV is crucial. Current study used the HACOR score to assess the efficacy of NIV in moderate to severe ARDS patients and found that reduction of HACOR score more than 1 point after 1-2 h of NIV had the ability to identify the patients who responded well or badly to NIV. Among the non-responders, early termination of NIV and performance of intubation is potential to reduce mortality.

In clinical practices, it is common to assess the efficacy of NIV by several clinical variables, e.g. respiratory rate, heart rate, oxygenation *et al.*[8,18] However, how to comprehensively assess the efficacy of NIV is lacking. The HACOR was scored by five easily obtained variables (heart rate, acidosis, consciousness, oxygenation, and respiratory rate), and the importance of each variable was ranked by the weights.[8] Therefore, it has the potential to assess the efficacy of NIV. Current study shows the benefits on reduction of NIV failure and 28-day mortality among patients who respond well to NIV assessed by HACOR score after 1-2 h of NIV. It indicates that the HACOR score is a promising scale to manage NIV patients with moderate to severe ARDS.

This study has several limitations. First, this is a secondary analysis of previous collected data. The performance of intubation was decided by the attending physician's discretions. Delayed intubation is inevitable. Second, we only reported how to assess the efficacy of NIV using HACOR score after 1-2 h of intervention. The efficacy beyond 2 h of NIV is unclear. Third, the risk of NIV failure is high in moderate to severe ARDS patients. The reduction of HACOR score only reflects a relatively lower risk of NIV failure. Combination of other variables to assess the efficacy of NIV is required.

Conclusions

Although the use of NIV in ARDS patients with $PaO_2/FiO_2 \leqslant 150$ mmHg is not encouraged, the proportion reaches 50% in the whole ARDS patients who used NIV as a first-line therapy. Delayed intubation is associated with 28-day mortality. Reduction of HACOR scores more than 1 point after 1-2 h of NIV can assess the patients who respond well to NIV. The responders are associated with a reduction of NIV failure and 28-day mortality.

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Author contributions

Linfu Bai: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Yuliang Liu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Jun Duan: Conceptualization; Data curation; Formal analysis; Methodology; Project

administration; Resources; Supervision; Writing – review & editing.

Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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