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Resource use, characteristics and outcomes of prolonged non-invasive ventilation: a single-centre observational study in China

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ABSTRACT

Objective To report the resource use, characteristics and outcomes of patients with prolonged non-invasive ventilation (NIV).

Design A single-centre observational study.

Setting An intensive care unit of a teaching hospital.

Participants Patients who only received NIV because of acute respiratory failure were enrolled. Prolonged NIV was defined as subjects who received NIV ≥14 days. A total of 1539 subjects were enrolled in this study; 69 (4.5%) underwent prolonged NIV.

Main outcome measures Predictors of prolonged NIV and hospital mortality.

Results The rate of do-not-intubate (DNI) orders was 9.1% (140/1539). At the beginning of NIV, a DNI order (OR 3.95, 95% CI 2.25 to 6.95) and pH ≥7.35 (2.20, 1.27 to 3.82) were independently associated with prolonged NIV. At days 1 and 7 of NIV, heart rate (1.01 (1.00 to 1.03) and 1.02 (1.00 to 1.03], respectively) and PaO_2/FiO_2<150 (2.19 (1.25 to 3.85) and 2.05 (1.04 to 4.04], respectively) were other independent risk factors for prolonged NIV. When patients who died after starting NIV but prior to 14 days were excluded, the association was strengthened. Regarding resource use, 77.1% of subjects received NIV<7 days and only accounted for 47.0% of NIV-days. However, 18.4% of subjects received NIV 7–13.9 days and accounted for 33.4% of NIV-days, 2.9% of subjects received NIV 14–20.9 days and accounted for 9.5% of NIV-days, and 1.6% of subjects received NIV≥21 days and accounted for 10.1% of NIV-days.

Conclusions Our results indicate the resource use, characteristics and outcomes of a prolonged NIV population with a relatively high proportion of DNI orders. Subjects with prolonged NIV make up a high proportion of NIV-days and are at high risk for in-hospital mortality.

Strengths and limitations of this study

- ► This is the first study to report the epidemiological data of patients who required prolonged non-invasive ventilation.
- ► The data of resource use, characteristics and outcomes in patients with prolonged non-invasive ventilation may help the clinical practitioners improve non-invasive ventilation management and serve as a reference for future studies.
- ► Exclusion of patients who have received both invasive and non-invasive ventilation may skew the results.

INTRODUCTION

Non-invasive ventilation (NIV) improves oxygenation and reduces the work of breathing in subjects with hypoxaemia or hypercapnia,[1 2] reduces intubation rates in subjects with acute respiratory failure,[3 4] shortens the duration of invasive mechanical ventilation and reduces ventilator-associated pneumonia when used to facilitate early liberation from invasive mechanical ventilation.[5 6] It also reduces postextubation respiratory failure in subjects at high risk for reintubation.[7 8] A previous study reported that NIV significantly decreased pooled hospital mortality, based on data from 78 randomised controlled trials.[9]

Given the benefits of NIV, its utilisation has dramatically increased in recent years in subjects with hypoxeamic or hypercapnic respiratory failure.[10–12] This in turn has led to a sharp increase in admissions to intensive care units (ICUs) for NIV. This has taxed many ICUs, which have been unable to meet the higher demand for such treatment of critically ill patients.[13] Of subjects who receive invasive mechanical ventilation, 4.4% of them spend more than 21 days on the ventilator but consume 29.1% of ICU beds.[14] In addition, the rate of hospital mortality is high (20%–40%) in patients given long-term mechanical ventilation.[15] The statistical data of prolonged invasive mechanical ventilation may help decision makers and clinicians improve management (eg, in developing prognostic modes and building regional weaning centres).[16 17] However, recent studies have focused only on invasive mechanical ventilation. The resource

Table 1 Demographics

	NIV duration<14 days n=1470 (95.5%)	NIV duration≥14 days n=69 (4.5%)	P value
Age, years	69±14	72±14	0.08
Female/male	418/1052	18/51	0.79
Do-not-intubate order	121 (8.2%)	19 (27.5%)	<0.01
Diagnosis			
AECOPD	848 (57.7%)	34 (49.3%)	0.17
Pneumonia	333 (22.7%)	24 (34.8%)	0.03
ARDS	45 (3.1%)	1 (1.4%)	0.72
Asthma	28 (1.9%)	0 (0%)	0.63
Heart failure	36 (2.4%)	0 (0%)	0.41
Pulmonary cancer	59 (4.0%)	7 (10.1%)	0.03
Others	121 (8.2%)	3 (4.3%)	0.36
Data collected at the beginning of NIV			
APACHE II score	16±4	17±4	0.42
Heart rate, beats/min	112±23	117±26	0.14
Respiratory rate, breaths/min	30±7	30±6	0.91
Systolic blood pressure, mm Hg	137±26	134±23	0.36
Diastolic blood pressure, mm Hg	81±16	80±15	0.59
GCS	14.7±1.0	14.7±0.6	0.78
pH	7.36±0.11	7.40±0.11	0.01
$PaCO_2$, mm Hg	58±25	54±24	0.20
PaO_2/FiO_2	182±89	161±74	0.05
Data collected at day 1 of NIV*			
Heart rate, beats/min	93±20	100±17	0.01
Respiratory rate, breaths/min	24±6	26±6	0.02
Systolic blood pressure, mm Hg	124±20	123±20	0.90
Diastolic blood pressure, mm Hg	71±12	72±12	0.79
GCS	14.8±1.0	14.9±0.3	0.34
pH	7.42±0.07	7.44±0.06	0.04
$PaCO_2$, mm Hg	50±17	48±16	0.30
PaO_2/FiO_2	231±87	203±82	0.01
Data collected at day 7 of NIV†			
Heart rate, beats/min	88±19	94±20	0.01
Respiratory rate, breaths/min	24±5	24±5	0.44
Systolic blood pressure, mm Hg	127±21	127±18	0.94
Diastolic blood pressure, mm Hg	72±12	71±12	0.47
GCS	14.8±0.9	14.7±1.1	0.52
pH	7.42±0.06	7.44±0.06	0.09
$PaCO_2$, mm Hg	50±15	48±15	0.30
PaO_2/FiO_2	228±87	195±72	<0.01

*At day 1 of NIV, only 1158 patients were left in the study.
†At day 7 of NIV, only 343 patients were left in the study (9 patients were excluded because some data were unavailable).
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; GCS, Glasgow Coma Scale; NIV, non-invasive ventilation.

use, characteristics and outcomes of NIV are lacking. Therefore, we investigated these factors.

METHODS

Patient and public involvement

This was a single-centre observational study performed in a respiratory ICU (18 ICU beds, 600–800 admissions per year) of a teaching hospital from May 2011 to July 2017. All subjects who were admitted to our ICU for NIV because of respiratory failure were enrolled. To avoid confounders, we excluded subjects who received both NIV and invasive mechanical ventilation during hospitalisation. We referenced the cut-off value of prolonged mechanical ventilation and defined subjects who used NIV >14 days as prolonged NIV.[18] A do-not-intubate (DNI) order can be made at ICU admission or at NIV as a first-line treatment failure. It was decided by patients themselves or their families.

PROCEDURE

NIV (BiPAP Vision or V60; Philips Respironics, Carlsbad, California, USA) was initiated based on the following criteria, but it was decided by attending physicians at their discretion: PaO_2<60 mm Hg at room air, $PaCO_2$ >45 mm Hg, pH <7.35 and clinical presentation of respiratory distress at rest (such as active contraction of the accessory inspiratory muscles or paradoxical abdominal motion).

NIV was managed as previously described.[19] The use of an oronasal mask (ZS-MZA Face Mask; Shanghai Zhongshan Medical Technology, Shanghai, China) was the first choice for NIV treatment. Mask size was optimised to fit each subject's face. In addition, to balance the trade-off between mask tightness (to minimise air leakage) and the propensity of the mask interface to cause skin lesions, we adjusted the straps to be as tight as comfortably possible while allowing air leaks at <30 L/min. The temperature of the sterile water in the humidifier was monitored and adjusted based on each subject's comfort, tolerance and adherence. Intermittent drinking was administrated if the subject felt thirsty. If there were no contraindications, the head of the bed was elevated to 30–45° to limit aspiration risk. To prevent hospital-acquired infections, a

Table 2 Univariate and multivariate analyses of the risk factors associated with prolonged NIV

	Univariate analyses		Multivariate analyses	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1				
Variables collected at the beginning of NIV				
Age, years	1.02 (1.00 to 1.04)	0.08	–	–
Do-not-intubate order	4.24 (2.42 to 7.42)	<0.01	3.95 (2.25 to 6.95)	<0.01
Heart rate, beats/min	1.01 (1.00 to 1.02)	0.14	–	–
PH≥7.35	2.36 (1.37 to 4.08)	<0.01	2.20 (1.27 to 3.82)	<0.01
$PaCO_2$>45 mm Hg	0.68 (0.42 to 1.09)	0.11	–	–
PaO_2/FiO_2<150	1.35 (0.83 to 2.19)	0.22	–	–
Diagnosis as AECOPD	0.71 (0.44 to 1.16)	0.17	–	–
Diagnosis as pneumonia	1.82 (1.09 to 3.03)	0.02	–	–
Diagnosis as pulmonary cancer	2.70 (1.19 to 6.15)	0.02	–	–
Model 2				
Variables collected at day 1 of NIV				
Heart rate, beats/min	1.02 (1.01 to 1.03)	<0.01	1.01 (1.00 to 1.03)	0.02
Respiratory rate, breaths/min	1.04 (1.01 to 1.08)	0.02	–	–
PH≥7.35	1.02 (0.46 to 2.27)	0.97	–	–
PaO_2/FiO_2<150	2.39 (1.38 to 4.12)	<0.01	2.19 (1.25 to 3.85)	<0.01
Model 3				
Variables collected at day 7 of NIV				
Heart rate, beats/min	1.02 (1.00 to 1.03)	0.01	1.02 (1.00 to 1.03)	0.04
PH≥7.35	1.41 (0.47 to 4.23)	0.54	–	–
PaO_2/FiO_2<150	2.19 (1.14 to 4.19)	0.02	2.05 (1.04 to 4.04)	0.04

Model 1, c-statistic=0.65 (95% CI 0.58 to 0.72).
Model 2, c-statistic=0.66 (95% CI 0.60 to 0.0.72).
Model 3, c-statistic=0.64 (95% CI 0.56 to 0.71).
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; NIV , non-invasive ventilation .

disposable bacterial filter was placed between the circuit and the ventilator. The bacterial filter was changed every day, and the ventilator circuit was changed every 7 days, in line with our hospital protocol.

The attending physicians or respiratory therapists selected the mode of the ventilator (continuous positive airway pressure (CPAP) or spontaneous/time [S/T]). CPAP is usually used in heart failure subjects or hypoxaemic subjects without laboured breathing. S/T, a bilevel positive airway pressure system used in assisted-control mode, is usually applied to hypercapnic subjects or hypoxaemic subjects whose accessory respiratory muscles show vigorous activity. FiO_2 was set to maintain SpO_2>92%. During NIV intervention, if respiratory failure worsened and reached the criteria of intubation, then intubation for invasive mechanical ventilation was performed. Intubation was performed according to previously described criteria.[19] However, in subjects with DNI orders, NIV was continued. If the respiratory failure was reversed, liberation from NIV was performed according to hospital protocol.[20]

Immediately before NIV, we collected data on age, sex, diagnosis, disease severity (assessed by APACHE II score), heart rate, respiratory rate, blood pressure, consciousness (assessed using the Glasgow Coma Scale (GCS)) and arterial blood gas tests. Data on these variables were also collected after 24 hours (day 1) and 7 days of NIV. We also collected information on variables reflecting outcomes such as duration of NIV, duration of ICU stay and hospital mortality.

STATISTICAL ANALYSES

We analysed the data using statistical software (SPSS V.17.0). An unpaired Student's t-test was used to analyse normally distributed continuous variables, and the χ^2 test was used to analyse categorical variables. For abnormally distributed continuous variables, the Mann-Whitney U test was used. At the beginning of NIV, variables with a p value <0.2 in univariate analyses were entered into multivariate analyses (forward stepwise multiple logistic regression analyses) to identify independent risk factors

Table 3 Univariate and multivariate analyses of the risk factors associated with prolonged NIV (patients who died after starting NIV but prior to 14 days were excluded)

	Univariate analyses		Multivariate analyses	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1				
Variables collected at the beginning of NIV				
Age, years	1.02 (1.00 to 1.04)	0.05	1.03 (1.01 to 1.06)	<0.01
APACHE II score	1.04 (0.99 to 1.08)	0.11		
Do-not-intubate order	33.5 (15.9 to 70.7)	<0.01	35.6 (16.0 to 79.1)	<0.01
Heart rate, beats/min	1.01 (1.00 to 1.02)	0.04	–	–
PH≥7.35	2.51 (1.45 to 4.34)	<0.01	2.16 (1.20 to 3.90)	0.01
$PaCO_2$>45 mm Hg	0.57 (0.35 to 0.92)	0.02	–	–
PaO_2/FiO_2<150	1.49 (0.92 to 2.42)	0.11	–	–
Diagnosis as AECOPD	0.61 (0.37 to 0.99)	0.04	–	–
Diagnosis as pneumonia	2.02 (1.21 to 3.78)	<0.01	–	–
Diagnosis as pulmonary cancer	4.04 (1.72 to 9.47)	<0.01	3.53 (1.34 to 9.31)	0.01
Model 2				
Variables collected at day 1 of NIV				
Heart rate, beats/min	1.03 (1.01 to 1.04)	<0.01	1.02 (1.01 to 1.04)	<0.01
Respiratory rate, breaths/min	1.09 (1.04 to 1.13)	<0.01	–	–
PH≥7.35	0.75 (0.33 to 1.69)	0.49	–	–
$PaCO_2$>45 mm Hg	0.61 (0.37 to 0.99)	0.05		
PaO_2/FiO_2<150	3.87 (2.21 to 6.77)	<0.01	3.75 (2.11 to 6.66)	<0.01
Model 3				
Variables collected at day 7 of NIV				
GCS	0.70 (0.48 to 1.02)	0.06		
Heart rate, beats/min	1.03 (1.01 to 1.05)	<0.01	1.03 (1.01 to 1.05)	<0.01
Respiratory rate, breaths/min	1.05 (0.99 to 1.11)	0.08		
PH≥7.35	1.25 (0.41 to 3.84)	0.70	–	–
$PaCO_2$>45 mm Hg	0.64 (0.37 to 1.09)	0.10		
PaO_2/FiO_2<150	3.40 (1.67 to 6.90)	<0.01	3.25 (1.55 to 6.84)	<0.01

Model 1, c-statistic=0.76 (95% CI 0.70 to 0.82).
Model 2, c-statistic=0.70 (95% CI 0.64 to 0.76).
Model 3, c-statistic=0.67 (95% CI 0.60 to 0.75).
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; NIV, non-invasive ventilation.

for prolonged NIV.[21 22] The same method was used at days 1 and 7 to identify independent risk factors for prolonged NIV in subjects who were still on NIV. The c-statistic was used to analyse the predictive power. A p value <0.05 was considered significant.

RESULTS

We enrolled 1539 subjects in this study. The rate of DNI orders was 9.1% (140/1539), the rate of prolonged NIV was 4.5% (69/1539) and hospital mortality was 16.6% (256/1539). At days 1 and 7 of NIV, 1158 and 343 patients were left in the study, respectively. The demographics of patients are summarised in table 1.

Table 2 shows three models developed to identify independent risk factors associated with prolonged NIV. In model 1, a DNI order (OR 3.95, 95% CI 2.25 to 6.95) and pH ≥7.35 (2.20, 1.27 to 3.82) were independently associated with prolonged NIV. The c-statistic was 0.65 (95% CI 0.58 to 0.72) in model 1. At days 1 and 7 of NIV, heart rate (OR 1.01, 95% CI 1.00 to 1.03, and 1.02, 1.00 to 1.03, respectively) and PaO_2/FiO_2<150 (2.19, 1.25 to 3.85, and 2.05, 1.04 to 4.04, respectively) were other independent risk factors for prolonged NIV. The c-statistic was 0.66 (95% CI 0.60 to 0.72) and 0.64 (0.56 to 0.71) in models 2 and 3, respectively. Out of all patients given NIV for <14 days, 220 patients (14.5%) died. When these patients were excluded, the association

Table 4 Outcomes

	NIV duration				
	<7 days n=1187	7–13.9 days n=283	14–20.9 days n=45	≥21 days n=24	P value
Duration of NIV, days	3.0 (1.7–4.0)	9.0 (7.8–10.8)	16.7 (15.1–18.6)	30.0 (23.3–35.2)	<0.01
ICU stay, days	4.7 (2.8–6.6)	10.2 (8.9–13.2)	18.0 (16.1–19.8)	32.7 (25.2–47.3)	<0.01
Hospital stay, days	10.6 (5.9–16.1)	16.8 (12.5–25.9)	21.0 (18.5–28.7)	43.8 (30.8–61.9)	<0.01
Hospital mortality	15.3%	13.4%	51.1%	54.2%	<0.01

As the duration of NIV, ICU stay and hospital stay were not normally distributed variables, they are reported as medians and IQRs.
ICU, intensive care unit; NIV , non-invasive ventilation.

was strengthened (table 3). Furthermore, ICU and hospital stays increased with an increase in NIV days (table 4).

The proportion of subjects who used NIV <7 days was 77.1%, and they accounted for 47.0% of NIV-days (figure 1). In contrast, 18.4%, 2.9% and 1.6% of subjects used NIV 7–14 days, 14–21 days and >21 days but accounted for 33.4%, 9.5% and 10.1% of NIV-days, respectively.

DISCUSSION

In this study, we enrolled a large number of NIV patients, and a small proportion of these patients required prolonged NIV. However, patients with prolonged NIV accounted for a large proportion of NIV-days. At the beginning of NIV, a DNI order and pH ≥7.35 were independent risk factors for prolonged NIV. Tachycardia and low oxygenation were other independent risk factors for prolonged NIV at days 1 and 7 in subjects who were still on NIV.

The use of NIV has sharply increased in recent years.[10 23] However, ICU beds are scarce resources. Refusal of or delayed ICU admission due to a full unit is associated with increased cardiac arrest and mortality.[24–27] Therefore, it is important to reserve ICU beds for patients who require them the most. In the management of patients receiving invasive mechanical ventilation, it is cost-effective to transfer them from the ICU to a regional weaning centre when they reach prolonged ventilation status.[28 29] In this study, we investigated the resource use, characteristics and outcomes of subjects who required prolonged NIV. Generally speaking, patients receiving prolonged NIV are in a less severe state than those who require prolonged mechanical ventilation. Thus, it may be possible to transfer such patients to a regional weaning centre. However, the benefits and risks of doing this require further exploration.

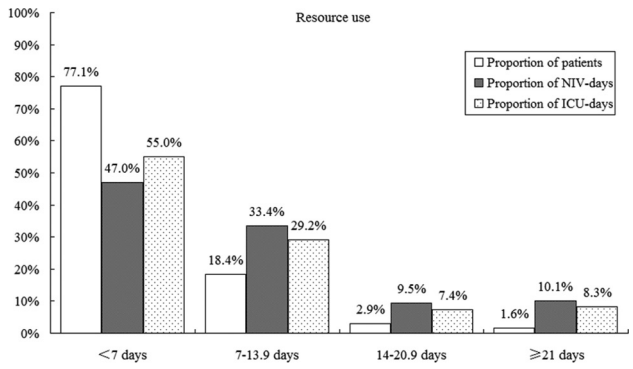

Figure 1 Distribution of resource use classified by duration of non-invasive ventilation (NIV). ICU, intensive care unit.

A multicentre observational study reported that one-fifth of ICU subjects who received NIV in France and Belgium had DNI orders.[30] The hospital mortality of such patients ranged from 44% to 74%, much higher than subjects without a DNI order.[30–32] In our study, a DNI order was an independent risk factor for prolonged NIV. As ICU beds are a scarce resource, it may benefit more patients if NIV is used in subjects without a DNI order. However, cultural norms and ethics differ among different countries. In some countries, NIV may be terminated in palliative care patients with a DNI order when they require intubation; this would lead to a shorter NIV duration. However, in other countries, NIV may be used in palliative care.[33] In the present study, we enrolled patients who received NIV as palliative care with a DNI order. We believe this is valuable to patients and clinical practitioners who use NIV in this situation.

An interesting result of our study is that pH >7.35 at initiation of NIV was an independent risk factor for prolonged NIV; a pH <7.35 indicated acidosis. We speculate that patients with a pH <7.35 are more likely to receive intubation and to die within 14 days of NIV. Other independent risk factors for prolonged NIV were tachycardia and low oxygenation at days 1 and 7 of NIV. It is not surprising that such patients require ventilation support and thus NIV was prolonged.

We also found that the proportion of subjects who required NIV for >14 days was small. However, they accounted for many more NIV-days than other subjects. As ICU space is limited, it is important to appropriately identify which subjects require admission to an ICU. In fact, many studies have reported that use of NIV in the general ward is safe and feasible.[34–36] Thus, it may be a good idea to assign subjects who require prolonged NIV while they are in the general ward. In addition, high-flow nasal oxygen benefits patients with acute respiratory failure in the same as does NIV.[37 38] Hence, it is another

choice for subjects with respiratory failure if NIV is unavailable.

Our study had several limitations. First, we enrolled subjects who used NIV only. As patients who use both NIV and invasive mechanical ventilation may have longer ICU/hospital stays, our study may underestimate the resource use of patients who received NIV. In addition, our selection method may have led to an artificially high number of DNI orders relative to the general population. Thus, whether DNI orders are an independent risk factor for prolonged NIV should be confirmed across all patient groups. Second, this was a single-centre observational study. NIV was managed in the context of the local culture and our hospital protocol. As different centres may have different protocols, extrapolating our results to other centres should be done cautiously. Third, patients who received prolonged NIV had higher rates of pneumonia and pulmonary cancer. When we considered this in multivariate analyses, these patients did not remain in the final model. This indicates that these variables contribute little to the final model.

CONCLUSION

Our data indicate the resource use, characteristics and outcomes of a prolonged NIV population with a relatively high rate of DNI orders. Subjects with prolonged NIV form a small NIV population but account for a high proportion of NIV-days.

Contributors JD designed this study, joined in data collection, analysed the data and prepared the manuscript. LB, LZ and XH joined in data collection, data analysis and manuscript preparation. LJ joined in data analysis, data interpretation and manuscript preparation. SH joined in data interpretation and manuscript revision.

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