Incidence, Characteristics and Outcomes of Delirium in Patients With Noninvasive Ventilation: A Prospective Observational Study

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Research article

Keywords: Delirium, Noninvasive ventilation, Risk factor

Posted Date: August 27th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-60456/v1>

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Abstract

Background: Knowledge of delirium in noninvasive ventilation (NIV) is lacking. We aimed to report the incidence, characteristics and outcomes of delirium in NIV patients.

Methods: A prospective observational study was performed in an intensive care unit (ICU) of a teaching hospital. Patients who used NIV as a first-line intervention were enrolled. During NIV intervention, delirium was screened using Confusion Assessment Method for the ICU every day.

Results: We enrolled 1083 patients. Of them, 196 patients (18.1%) experienced delirium during NIV intervention. Patients with delirium had higher NIV failure rates (37.8% vs. 21.0%, $p \leq 0.01$), higher ICU mortality (33.2% vs. 14.3%, $p \leq 0.01$) and higher hospital mortality (37.2% vs. 17.0%, $p \leq 0.01$) than the subjects without delirium. They also spent longer time on NIV (median 6.3 vs. 3.7 days, $p \leq 0.01$), and stayed longer in ICU (median 9.0 vs. 6.0 days, $p \leq 0.01$) and hospital (median 14.5 vs. 11.0 days, $p \leq 0.01$). Furthermore, delirium was independently associated with NIV failure, ICU mortality and hospital mortality (OR = 1.97, 2.58 and 2.55, respectively; all p values ≤ 0.01). These results were confirmed in COPD and non-COPD cohorts. Compared with hyperactive delirium patients, the NIV days was longer in hypoactive delirium patients and much longer in mixed delirium patients (median 3.4 vs. 6.5 vs. 10.1 days, $p \leq 0.01$). Similar outcomes were found in the length of stay in ICU and hospital. However, the NIV failure, ICU mortality and hospital mortality did not differ between three subtypes of delirium.

Conclusions: Delirium increases the NIV failure rates, elevates the ICU and hospital mortality, prolongs the NIV days, and lengthens the ICU and hospital stay. Mixed delirium patients use more ICU resources than hypoactive delirium patients and much more than hyperactive delirium patients.

Background

Delirium is a manifestation characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness [1]. Hyperactive, hypoactive and mixed types of delirium are the three subtypes [2]. It frequently occurs in critically ill patients due to various reasons such as pain, stress, anxiety, sleep deprivation, sedation, analgesia and antimicrobial exposure [3–7]. A systematic review and meta-analysis has reported that the pooled incidence of delirium is 31.8% in critically ill patients [8]. And it is much higher (up to 80%) in mechanically ventilated patients [9]. Delirium prolonged the length of stay (LOS) in ICU and hospital, increased hospital mortality and elevated hospital costs [8, 10–12]. Many strategies to prevent delirium have been widely investigated [13–15]. However, these studies mainly focused on mechanically ventilated or surgical patients. The knowledge on delirium in patients who received noninvasive ventilation (NIV) is lacking.

The aim of this study was to describe the incidence, clinical characteristics and outcomes of delirium in NIV patients, and further investigate the distribution of delirium in different subtypes. We also aimed to explore the association between delirium and NIV failure.

Methods

This was a prospective observational study performed in an intensive care unit (ICU) of a teaching hospital from 2016 to 2018. The study protocol was approved by local institutional review board. As the observational nature of this study, the informed consent was waived. Patients who admitted to ICU for NIV as a first-line intervention were enrolled. However, patients less than 18 years old were excluded.

NIV (BiPAP Vision or V60; Philips Respironics, Carlsbad, CA) was initiated by the attending physicians based on the indications described previously [16, 17]. In patients with chronic obstructive pulmonary disease (COPD), the indications for NIV were respiratory rate more than 25 breaths/min, PaCO_2 more than 45 mmHg, pH less than 7.35, $\text{PaO}_2/\text{FiO}_2$ less than 200 mmHg, and vigorous activity of accessory respiratory muscles. In patients with hypoxemic respiratory failure, the indications for NIV were clinical presentation of respiratory distress at rest (such as active contraction of the accessory inspiratory muscles or paradoxical abdominal motion), and $\text{PaO}_2/\text{FiO}_2$ less than 300 mmHg.

Face mask (ZS-MZ-A Face Mask, Shanghai Zhongshan Medical Technology Co., Shanghai, China) was the first choice to connect the patient and the ventilator. The size of the mask was fitted to the patients' face type. The S/T mode was used in COPD patients or other patients with labored breathing. The initial inspiratory positive airway pressure was 8–10 cmH_2O and then it was gradually increased to reach the tidal volume of 6–8 ml/kg or the maximal tolerated level. The initial expiratory positive airway pressure was 4 cmH_2O . And then we gradually increased to counterbalance intrinsic positive end expiratory pressure in COPD patients. In hypoxemic respiratory failure patients, it was increased to maintain the alveoli patency and elevate the end expiratory lung volume. In patients with heart failure, the continuous positive airway pressure was used. The fractional concentration of oxygen was set to achieve peripheral oxygen saturation of > 92%.

At the beginning of treatment, continuous use of NIV was encouraged. Once the patient recovered from respiratory failure, liberation from NIV was considered according to our hospital protocols [18]. However, the intubation was indicated if the respiratory failure progressively deteriorated. The criteria of intubation were listed as follows: respiratory or cardiac arrest, failure to maintain $\text{PaO}_2/\text{FiO}_2$ more than 100, development of conditions necessitating intubation to protect the airway (coma or seizure disorders) or to manage copious tracheal secretions, inability to correct dyspnea, lack of improvement of signs of respiratory muscle fatigue, and hemodynamic instability without response to fluids and vasoactive agents [16, 17]. NIV failure was defined as requirement of intubation.

Delirium was screened using Confusion Assessment Method for the ICU (CAM-ICU) every day [9]. The delirium was assessed based on the following 4 features: (1) fluctuation in mental status, (2) inattention, (3) disorganized thinking, and (4) altered levels of consciousness. Delirium was diagnosed in the presence of features 1 and 2 and either feature 3 or 4. The level of consciousness was assessed by Richmond Agitation-Sedation Scale (RASS) [19]. RASS is a 10-point scale ranging from unarousable (– 5 points) or calm (0 points) to combative (4 points). Three subtypes of delirium were defined as follows

[20]. Hyperactive delirium was defined as present in patients with all positive daily RASS scores (range, 1–4 points) associated with every positive CAM-ICU assessment. Hypoactive delirium was defined as present in patients with all neutral or negative daily RASS scores (range, 0 to – 3 points) associated with every positive CAM-ICU assessment. Mixed delirium was defined as present in patients with daily RASS scores that included both positive values (range, 1–4 points) and neutral or negative values (range, 0 to – 3 points) associated with every positive CAM-ICU assessment.

Statistical analysis

Statistical software (SPSS 17.0; IBM Corp., Armonk, NY) was used to analyze the data. Continuous variables were presented as means with standard deviations or medians and interquartiles (25–75%) when appropriate. Differences between groups were analyzed using Student's t test or Mann–Whitney U test as appropriate. Categorical variables were reported as frequencies and percentages. Differences between groups were analyzed using Chi-squared test or Fisher's exact test. Multivariate logistic regression analysis was used to identify the independent risk factors associated with NIV failure, ICU mortality and hospital mortality. The probability of patients remaining on NIV and in the ICU was analyzed using Kaplan-Meier curves (log-rank test). Statistical significance was considered if a p value was less than 0.05.

Results

We enrolled 1083 patients in this study. Of these, 196 (18.1%) developed delirium during NIV intervention. There were no differences on reasons for NIV, underlying disease, sex, heart rate, respiratory rate, PaCO₂ and PaO₂/FiO₂ between patients with and without delirium (Table 1). However, delirious patients were older than non-delirious ones. They also had higher APACHE II score, lower Glasgow coma scale (GCS), lower mean arterial pressure, and lower pH. Furthermore, delirious patients had higher NIV failure rates, higher ICU mortality, and higher hospital mortality than non-delirious patients. They also spent longer time on NIV and stayed longer in ICU and hospital than non-delirious patients (Supplementary Fig. 1).

Table 1
Comparisons in patients with and without delirium

Variables	No delirium N = 887	Delirium N = 196	<i>p</i>
Age, years	67 ± 14	77 ± 11	≤0.01
Female/Male	261/626	49/147	0.22
APACHE II score	15 ± 4	17 ± 4	≤0.01
Reasons for NIV			
COPD exacerbation	477 (53.8%)	107 (54.6%)	0.67
Pneumonia	184 (20.7%)	48 (24.5%)	
ARDS	63 (7.1%)	11 (5.6%)	
Pulmonary cancer	49 (5.5%)	11 (5.6%)	
Interstitial lung disease	22 (2.5%)	6 (3.1%)	
Asthma	14 (1.6%)	1 (0.5%)	
Heart failure	10 (1.1%)	2 (1.0%)	
OHS	11 (1.2%)	2 (1.0%)	
Pulmonary embolism	15 (1.7%)	0 (0%)	
Others	42 (4.7%)	8 (4.1%)	
Underlying disease			
Hypertension	335 (37.8%)	86 (43.9%)	0.12
Diabetes mellitus	180 (20.3%)	51 (26.0%)	0.08
Chronic heart disease	163 (18.4%)	47 (24.0%)	0.09
Chronic liver disease	36 (4.1%)	4 (2.0%)	0.21
Chronic kidney disease	30 (3.4%)	11 (5.6%)	0.15
Variables collected before NIV			
GCS	14.8 ± 0.8	14.1 ± 1.6	≤0.01
HR, beats/min	111 ± 23	112 ± 22	0.92
RR, breaths/min	31 ± 7	31 ± 7	0.73

NIV = noninvasive ventilation, COPD = chronic obstructive pulmonary disease, ARDS = acute respiratory disease syndrome, OHS = obesity hypoventilation syndrome, GCS = Glasgow coma scale, HR = heart rate, RR = respiratory rate, MAP = mean arterial pressure, LOS = length of stay

Variables	No delirium N = 887	Delirium N = 196	<i>p</i>
MAP, mmHg	100 ± 18	95 ± 17	≤0.01
pH	7.37 ± 0.10	7.34 ± 0.11	≤0.01
PaCO ₂ , mmHg	58 ± 25	61 ± 27	0.16
PaO ₂ /FiO ₂ , mmHg	184 ± 87	190 ± 92	0.45
Outcomes			
NIV failure	186 (21.0%)	74 (37.8%)	≤0.01
NIV duration, days	3.7 (1.7–5.9)	6.3 (2.7–11.0)	≤0.01
ICU LOS, days	6.0 (3.8–9.2)	9.0 (4.8–15.2)	≤0.01
Hospital LOS, days	11.0 (6.8–17.0)	14.5 (7.1–21.1)	≤0.01
ICU mortality	127 (14.3%)	65 (33.2%)	≤0.01
Hospital mortality	151 (17.0%)	73 (37.2%)	≤0.01
NIV = noninvasive ventilation, COPD = chronic obstructive pulmonary disease, ARDS = acute respiratory disease syndrome, OHS = obesity hypoventilation syndrome, GCS = Glasgow coma scale, HR = heart rate, RR = respiratory rate, MAP = mean arterial pressure, LOS = length of stay			

Delirium was independently associated with NIV failure (odds ratio [OR] = 1.97, 95% confidence interval [CI]: 1.34–2.88), ICU mortality (OR = 2.58, 95%CI: 1.74–3.84) and hospital mortality (OR = 2.55, 95%CI: 1.74–3.75) (Table 2). These results were confirmed in patients with and without COPD.

Table 2
Multivariate analysis of risk factors for NIV failure, ICU mortality and hospital mortality

Variables	Overall cohort		COPD cohort		Non-COPD cohort	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
Risk factors for NIV failure						
Delirium	1.97 (1.34–2.88)	≤0.01	2.33 (1.27–4.30)	≤0.01	1.84 (1.13–2.99)	0.02
APACHE II score	1.08 (1.03–1.12)	≤0.01	1.09 (1.02–1.17)	0.02	1.10 (1.05–1.15)	≤0.01
GCS	0.78 (0.66–0.91)	≤0.01	–	–	–	–
RR, breaths/min	1.03 (1.00–1.05)	0.02	–	–	–	–
PaCO ₂ , mmHg	0.975 (0.968–0.982)	≤0.01	–	–	–	–
PaO ₂ /FiO ₂ , mmHg	0.996 (0.993–0.998)	≤0.01	–	–	0.995 (0.992–0.998)	≤0.01
Age, years	–	–	1.04 (1.01–1.08)	≤0.01	–	–
HR, beats/min	–	–	1.01 (1.00–1.03)	0.04	–	–
Diabetes mellitus	–	–	–	–	0.57 (0.36–0.91)	0.02
Risk factors for ICU mortality						
Delirium	2.58 (1.74–3.84)	≤0.01	3.64 (1.89–7.01)	≤0.01	2.16 (1.31–3.56)	≤0.01
APACHE II score	1.06 (1.01–1.11)	0.01	1.18 (1.09–1.28)	≤0.01	1.06 (1.01–1.11)	0.03
GCS	0.77 (0.65–0.91)	≤0.01	–	–	–	–
RR, breaths/min	1.04 (1.01–1.06)	≤0.01	–	–	1.03 (1.00–1.06)	0.03

NIV = noninvasive ventilation, OR = odds ratio, CI = confidence interval, GCS = Glasgow coma scale, HR = heart rate, RR = respiratory rate, COPD = chronic obstructive pulmonary disease

Delirium, sex, age, underlying disease, APACHE II score, GCS, heart rate, respiratory rate, pH, PaCO₂ and PaO₂/FiO₂ were entered into multivariate analysis to identify independent risk factors for NIV failure, ICU mortality and hospital mortality, respectively.

Variables	Overall cohort		COPD cohort		Non-COPD cohort	
PaCO ₂ , mmHg	0.978 (0.970–0.985)	0.01	–	–	–	–
PaO ₂ /FiO ₂	0.998 (0.995–1.000)	0.04	–	–	0.997 (0.994–1.000)	0.04
Age, years	–	–	1.04 (1.01–1.08)	0.03	–	–
Risk factors for hospital mortality						
Delirium	2.55 (1.74–3.75)	0.01	3.34 (1.81–6.18)	0.01	2.11 (1.29–3.45)	0.01
APACHE II score	1.08 (1.03–1.13)	0.01	1.09 (1.02–1.17)	0.02	1.09 (1.04–1.14)	0.01
HR, beats/min	1.01 (1.00–1.02)	0.05	1.02 (1.00–1.03)	0.01	–	–
RR, breaths/min	1.03 (1.00–1.05)	0.03	–	–	1.03 (1.00–1.06)	0.02
GCS	0.82 (0.67–0.97)	0.02	–	–	–	–
PaCO ₂ , mmHg	0.975 (0.968–0.983)	0.01	–	–	–	–
PaO ₂ /FiO ₂	–	–	–	–	0.997 (0.995–1.000)	0.05
Age, years	–	–	1.06 (1.03–1.10)	0.01	–	–
NIV = noninvasive ventilation, OR = odds ratio, CI = confidence interval, GCS = Glasgow coma scale, HR = heart rate, RR = respiratory rate, COPD = chronic obstructive pulmonary disease						
Delirium, sex, age, underlying disease, APACHE II score, GCS, heart rate, respiratory rate, pH, PaCO ₂ and PaO ₂ /FiO ₂ were entered into multivariate analysis to identify independent risk factors for NIV failure, ICU mortality and hospital mortality, respectively.						

Among the delirious patients, 51 (26%) developed hyperactive delirium, 123 (63%) developed hypoactive delirium, and 22 (11%) developed mixed delirium (Table 3). There were no differences in NIV failure, ICU and hospital mortality between three groups. Patients with hyperactive delirium had lowest NIV duration, ICU stay and hospital stay. However, it was higher in patients with hypoactive delirium and much higher in those with mixed delirium (Table 3 and Fig. 1).

Table 3
Subgroup analysis in patients with different subtypes of delirium

Variables	Hyperactive delirium N = 51	Hypoactive delirium N = 123	Mixed delirium N = 22	P
NIV failure	19 (37.3%)	47 (38.2%)	8 (36.4%)	0.98
ICU mortality	16 (31.4%)	41 (33.3%)	8 (36.4%)	0.92
Hospital mortality	17 (33.3%)	47 (38.2%)	9 (40.9%)	0.78
NIV duration, days	3.4 (1.7–8.8)	6.5 (2.9–11.0)	10.1 (6.3–20.5)	0.01
ICU LOS, days	6.8 (3.3–14.1)	8.9 (5.0–15.1)	12.3 (8.1–21.2)	0.01
Hospital LOS, days	12.9 (5.8–19.0)	15.0 (7.9–21.0)	19.5 (9.5–31.0)	0.03
Delirium days	1 (1–2)	1 (1–3)	7 (3–12)	0.01
NIV = noninvasive ventilation, LOS = length of stay				

Age (OR = 1.06, 95%CI: 1.04–1.08) and APACHE II score (OR = 1.07, 95%CI: 1.03–1.13) were risk factors for delirium, and GCS (OR = 0.67, 95%CI: 0.56–0.79) and mean arterial pressure (OR = 0.99, 95%CI: 0.98–1.00) were protective factors (Table 4). However, in patients without COPD, only age and GCS were associated with delirium. The distribution of delirium in different ages and GCS scores were summarized in Fig. 2. Patients with age more than 75 years and GCS less than 14 had the highest incidence of delirium.

Table 4
Multivariate analysis of risk factors for delirium

Variables	Overall cohort		COPD cohort		Non-COPD cohort	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
Age, years	1.06 (1.04–1.08)	≤0.01	1.06 (1.03–1.09)	≤0.01	1.07 (1.05–1.09)	≤0.01
GCS	0.67 (0.56–0.79)	≤0.01	0.74 (0.60–0.92)	≤0.01	0.48 (0.37–0.63)	≤0.01
APACHE II score	1.07 (1.03–1.13)	≤0.01	1.08 (1.00–1.15)	0.04	–	–
MAP	0.99 (0.98–1.00)	0.01	0.98 (0.97–0.99)	≤0.01	–	–
NIV = noninvasive ventilation, OR = odds ratio, CI = confidence interval, GCS = Glasgow coma scale, RR = respiratory rate, MAP = mean arterial pressure, COPD = chronic obstructive pulmonary disease						
Reasons for NIV, sex, age, underlying disease, APACHE II score, GCS, heart rate, respiratory rate, pH, PaCO ₂ and PaO ₂ /FiO ₂ were entered into to multivariate analysis to identify independent risk factors for delirium.						

Discussion

To the best of our knowledge, our study is the largest to explore the incidence, characteristics and outcomes of delirium in NIV patients. A systematic review and meta-analysis has enrolled 239 NIV patients who were assessed the incidence of delirium [21]. The data were extracted from three studies published before 2012 [22–24]. In Rozzini's study, it only enrolled COPD patients ≥65 years old, and failed to report how the delirium was assessed [22]. And in Carlucci's study, the delirium was considered if the moderate or pronounced encephalopathy was diagnosed [23]. Only in Roche Campo's study, the delirium was assessed by CAM-ICU (a recommended tool for diagnosis of delirium), but it only enrolled hypercapnic patients with median age of 82 years old [24]. Therefore, the report of this systematic review is inaccurate. Another study was published at 2016 [25]. It enrolled 153 hypercapnic patients, and only reported the association between delirium and 1-year mortality. As the small sample size, no one reported the situation in different subtypes of delirium [21–25]. However, we enrolled 1083 NIV patients involving different age and diagnosis. The large sample size enabled us to perform stratification analysis based on diagnosis and age, and further explore the situations between patients with different subtypes of delirium.

Hypoactive delirium was the most common subtype reported by Krewulak et al. [2]. In Gual's study, hyperactive delirium was the most common subtype [26]. In our study, the hypoactive delirium was the major subtype, hyperactive delirium was in the middle, and mixed delirium was the lowest one. In addition, the patients with mixed delirium had the longest delirium days and ICU stays. To the best of our

knowledge, this is the first study to report the distribution of subtypes of delirium in NIV patients. Therefore, it adds something new to the field to help the clinical practitioners to manage NIV patients.

Age, level of consciousness and disease severity were risk factors for delirium [27–29]. Our study also demonstrated this issue. However, different with previous studies, we found that mean arterial pressure was a protective factor for delirium. Patients with lower mean arterial pressure were more likely to experience delirium in NIV intervention. The low mean arterial pressure may decrease the cerebral blood flow perfusion and lead to neuropsychic symptom, and subsequently cause delirium. However, this is just a hypothesis, and further exploration is required.

Many studies have reported that disease severity, low level of consciousness, increased respiratory rate and decreased oxygenation were associated with NIV failure [30, 31]. Our study also confirmed this issue. Different with previous studies, we found that delirium was independently associated with NIV failure both in patients with and without COPD. It provides a new insight to clinical practitioners to understand NIV failure.

Delirium was highly associated with ICU and hospital mortality [8, 10–12]. Our study confirmed this point in NIV population. As poor prognosis in delirium patients, prevention of delirium was needed. Pain relief, early mobilization, improvement of sleep quality and minimized noise were the promising methods to reduce delirium in NIV patients [32].

This is a single center observational study performed in an ICU. As we only enrolled medical patients, the incidence of delirium may be skewed. In addition, we only enrolled patients who used NIV as a first-line intervention. Those who used NIV due to postextubation respiratory failure or prevention of extubation failure were excluded since the previous exposure in mechanical ventilation highly associated with delirium. So, the results in our study cannot be extrapolated to the patients who used NIV after extubation.

Conclusions

The incidence of delirium in NIV population is high. The hypoactive delirium is the most common subtype in this population. Delirium increases the NIV failure rates, elevates the ICU and hospital mortality, prolongs the NIV days, and lengthens the ICU and hospital stay.

Abbreviations

NIV = noninvasive ventilation; ICU = intensive care unit; COPD = chronic obstructive pulmonary disease; ARDS = acute respiratory distress syndrome; OHS = obesity hypoventilation syndrome; GCS = Glasgow coma scale; HR = heart rate; RR = respiratory rate; MAP = mean arterial pressure; LOS = length of stay; OR = odds ratio; CI = confidence interval; CAM-ICU= Confusion Assessment Method for the ICU; RASS = Richmond Agitation-Sedation Scale

Declarations

Consent for publication

All authors have reviewed and approved the manuscript for publication.

Availability of data and material

The datasets analyzed during the current study available from the corresponding author on reasonable request.

Ethical approval and consent to participate

The Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University approved the study protocol. Informed consent was waived as the observational nature.

Competing interests

We declare that we have no competing interests.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 81700015) and by Cultivating Fund of the First Affiliated Hospital of Chongqing Medical University (Grant No. PYJJ2017-20)

Authors' contributions

JD conceived the study, joined in study design, study management, data collection, data analysis, and manuscript revision. RZ participated in study design, study management, data collection and drafted the manuscript. LB, XH, SH and LZ participated in study design and data collection, and revised the manuscript. All authors read and approved the final version.

Acknowledgements

We thank all the staffs in ICUs to participate in data collection.

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Figures

Figure 1

Resources use among patients with hyperactive, hypoactive and mixed delirium.

Figure 2

Distributions of delirium in patients with different age and GCS. A1 and A2 indicate the COPD cohort. B1 and B2 indicate the non-COPD cohort.

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