

[ ORIGINAL ARTICLE ]

## What Is the Impact of Mildly Altered Consciousness on Acute Hypoxemic Respiratory Failure with Non-invasive Ventilation?

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### Abstract:

**Objective** A severely altered level of consciousness (ALC) is considered to be a possible contraindication to non-invasive ventilation (NIV). We investigated the association between mild ALC and NIV failure in patients with hypoxemic respiratory failure.

**Methods** A retrospective study was conducted by reviewing the medical charts of patients with *de novo* hypoxemic respiratory failure who received NIV treatment. The clinical background and the outcomes of patients with and without ALC were compared.

**Patients** Patients who were admitted to our hospital for acute hypoxemic respiratory failure between July 2011 and May 2015 were included in the present study.

**Results** Sixty-six of the 148 patients had ALC. In comparison to the patients without ALC, the patients with ALC were older (median: 72 vs. 78 years,  $p=0.02$ ), had a higher Acute Physiology and Chronic Health Evaluation II score (18 vs. 19,  $p=0.02$ ), and received a higher level of inspiratory pressure (8 cmH<sub>2</sub>O vs. 8,  $p<0.01$ ). The median Glasgow Coma Scale score of the patients with ALC was 14 (interquartile range, 11-14). There were no significant differences between the groups in the rates of NIV failure (24% vs. 30%,  $p=0.4$ ) and in-hospital mortality (13% vs. 16%,  $p=0.3$ ).

**Conclusion** NIV may be successfully applied to treat acute hypoxemic respiratory failure with mild ALC. NIV may be performed, with careful attention to the appropriate timing for intubation.

**Key words:** acute respiratory failure, critical care medicine, noninvasive ventilation

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### Introduction

Non-invasive ventilation (NIV) is a ventilator technique that is being increasingly adopted for acute and chronic respiratory failure. Many trials have shown the benefits of NIV, including a reduced need for endotracheal intubation and survival benefits (1-3). NIV has been a subject of considerable academic and clinical interest.

The International Consensus Conference on NIV and several reviews have suggested that an altered level of consciousness (ALC) may be a contraindication to NIV in pa-

tients experiencing acute respiratory failure (4-7). ALC is associated with poor cooperation and the risk of aspiration, which can result in NIV failure. Some reports have suggested a significant correlation between ALC and a poor outcome (8, 9).

However, some evidence has suggested the usefulness of NIV for patients with hypercapnia, even those with ALC (10-12). Furthermore, we experience many cases of ALC, including do-not-intubate patients, to whom NIV could be successfully applied. Moreover, most of the studies related to NIV have excluded *a priori* patients with ALC or included different degrees of ALC (from coma to agitation).

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Thus, the application of NIV to patients with ALC, especially those with hypoxemic respiratory failure, remains controversial.

We conducted this study to assess the effectiveness of NIV in the treatment of acute hypoxemic respiratory failure in patients with mild ALC.

## Materials and Methods

### Study design and population

We conducted a historical cohort study. Patients who visited the emergency room (ER) at a community teaching hospital in Japan, from July 2011 to May 2015 were enrolled. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Kobe City Medical Center General Hospital (No. zn170102).

Patients were included if they visited the ER for *de novo* hypoxemic respiratory failure without acute hypercapnic failure ( $\text{pH} < 7.33$  and  $\text{PaCO}_2 > 55$  mmHg) or intracranial disease and received NIV at the ER (12). Patients with respiratory failure caused by an acute exacerbation of underlying respiratory disease, including interstitial pneumonia, chronic obstructive pulmonary disease, group 3 pulmonary hypertension, asthma, and malignancies, were excluded because the outcomes were dependent on the patient's baseline status. The other exclusion criteria were as follows: 1) facial deformity sufficient to affect mask fitting, 2) age  $< 15$  years, or 3) need for urgent endotracheal intubation for various reasons, including a Glasgow Coma Scale (GCS) score of  $\leq 8$  (due to inability to protect the airways).

NIV was considered when patients met one or more of the following criteria: respiratory rate  $> 25$  breaths/min, contraction of accessory inspiratory muscles, paradoxical abdominal motion,  $\text{PaO}_2 < 60$  mmHg while breathing room air, and  $\text{PaO}_2/\text{FiO}_2 < 250$  mmHg while breathing supplemental oxygen. Patients who required urgent intubation because of respiratory arrest, respiratory pauses, severe coma, copious tracheal secretion, or hemodynamic instability were not placed on NIV. NIV was delivered in the continuous positive airway pressure (CPAP) or spontaneous/timed (S/T) mode via a well-fitting full-face mask that was worn constantly until the initiation of the weaning process. The inspiratory positive airway pressure (IPAP) (when applying the S/T mode) and the positive end-expiratory pressure were initially set at 8-12 cmH<sub>2</sub>O and 4-10 cmH<sub>2</sub>O, respectively. These settings were gradually changed depending on the clinical response, as well as the patient's tolerance. The  $\text{FiO}_2$  was adjusted to maintain an  $\text{SpO}_2$  level of at  $\geq 90\%$  with the aim of achieving a satisfactory  $\text{PaO}_2$  level without increasing the degree of hypercapnia. The patients who were included in the present study were classified into two groups, those with a GCS score of 15 (NLC group) and those with a score of 9-14 (ALC group).

We also used the Kelly-Matthay scale, which is used to

assess the level of consciousness of critically ill patients requiring invasive mechanical ventilation. The Kelly-Matthay scale ranges from 1 to 6 (grade 1, alert, follows complex 3-step commands; grade 2, alert, follows simple commands; grade 3, lethargic, but arousable and follows simple commands; grade 4, stuporous, only intermittently follows simple commands even with vigorous attempts at arousal; grade 5, comatose, brain stem intact; grade 6, comatose with brainstem dysfunction) (13).

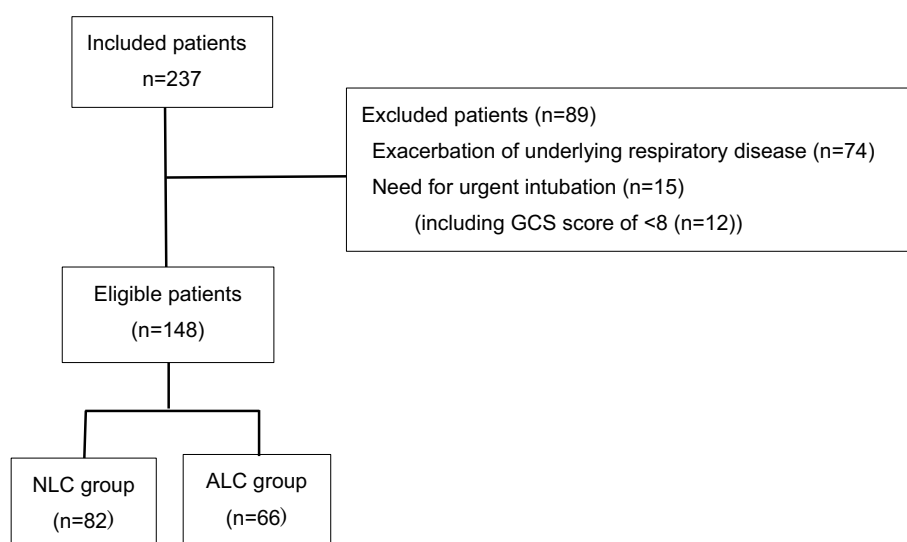
The patients' baseline demographic and physiological characteristics were determined at admission. All data were collected and analysed by the authors of this report.

### Outcome measures

The main outcomes were the rates of NIV failure, death, intubation, and in-hospital mortality. Because the long-term outcome was determined by many other factors (i.e., the cause of respiratory failure and the severity of each disease), we set the outcome as early NIV failure, NIV failure during the first 48 hours after the initiation of NIV, during which consciousness was considered to be an important factor (12, 14-16). NIV was considered to have failed if at least one of the following criteria for endotracheal intubation occurred (12): 1) cardiac arrest or severe haemodynamic instability (difficulty stabilising the peripheral circulation, despite the use of vasoactive agents), 2) respiratory arrest, 3) an increase in  $\text{PaCO}_2$  with the inability to deliver the tidal volume, 4) a pronounced worsening of the signs of respiratory distress with a respiratory rate of  $> 40$  breaths/min under NIV, 5) an  $\text{SpO}_2$  that remained below 90%, despite an  $\text{FiO}_2$  of 1.0, 6) severe difficulty clearing bronchial secretions, 7) mask intolerance with psychomotor agitation requiring sedation, and 8) a worsening level of consciousness (continuously declining GCS score). Patients were considered deceased when they experienced cardiac arrest and failed to be resuscitated. In cases involving patients with a do-not-intubate status, NIV was considered to have failed when the *a priori* criteria for endotracheal intubation were met and the patients were considered deceased at the moment they experienced cardiac arrest. Among the criteria listed for endotracheal intubation, patients were considered to have respiratory and neurogenic failure when they met criteria 2) to 5) and 7) and 8), respectively.

### Statistical analysis

The data are presented as the median and interquartile range (IQR) for continuous variables and the number and percent for categorical variables. We compared the clinical parameters—which were measured at the initiation of NIV—in patients with a normal level of consciousness (NLC) to those in patients with ALC (GCS score of  $\leq 14$ ). Continuous variables were compared using the Wilcoxon rank sum test and categorical variables were compared using the Pearson chi-squared test or Fisher's exact test, as appropriate. Considering the heterogeneity of the diagnoses for admission, pneumonia and heart failure, which were the two largest



**Figure 1.** A flowchart of the patients. NLC: normal level of consciousness, ALC: altered level of consciousness

population subgroups, were assessed.

The time to NIV failure was assessed using the Kaplan-Meier method, and the differences between groups were evaluated with the log-rank test. The endpoint was NIV failure; the results were censored at the time of successful weaning off from NIV. Cox proportional hazard models were constructed to estimate the hazard ratio (HR) of ALC relative to NLC. We constructed a multivariate Cox proportional hazard model to estimate the adjusted HR of ALC with other factors that were considered to be correlated with NIV failure, including age, the PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio, IPAP, and APACHE II score. The cut off values were set at the median value of a parameter (e.g., age >75 years, P/F ratio <150, IPAP >8 cmH<sub>2</sub>O, and APACHE II score >19). The results are expressed as the HR and 95% confidence interval (CI).

Two-tailed p values of <0.05 were considered to indicate statistical significance. All of the statistical analyses were performed using the JMP software program (Ver 8.0 for Windows; SAS Institute, Cary, USA).

## Results

### Patients' characteristics

During the study period, 237 patients received NIV at the ER, 89 of these patients were excluded from the analysis (Fig. 1). The reasons for exclusion were an exacerbation of underlying respiratory disease (n=74) and the need for urgent intubation (n=15), this included 12 patients with GCS scores of ≤8. Among the 148 included patients, 66 had ALC and 82 did not. The patients' clinical features are summarised in Table 1. The patients in the ALC group were older [median: 72 (IQR, 65-82) years vs. 78 (70-84) years, p=0.02], had a higher APACHE II score [18 (13-22) vs. 19 (17-23), p=0.02], and received a higher level of respiratory

support [IPAP: 8 (8-8) vs 8 (8-11) cmH<sub>2</sub>O, p<0.01] in comparison to those in the NLC group. There was variability in the reasons for admission between the two groups. The median GCS score of the ALC group was 14 (IQR, 11-14), of which median scores of the "Eye element", "Verbal element", and "Motor element" were 3 (IQR 3-4), 4 (3-4) and 6 (6-6), respectively. Ten percent of the patients in the ALC group had a Kelly-Matthay scale score of >3.

### The clinical outcomes

There were no significant differences between the groups in the rate of NIV failure [24% (20/82) vs. 30% (20/66), p=0.42] or in-hospital mortality [13% (11/82) vs. 16% (13/66), p=0.3] (Table 2). The patients in the ALC group were divided into those with a GCS score of 14 (n=35) and those with a GCS of ≤13 (n=31). There was also no significant difference in the rate of NIV failure or in-hospital mortality (23% in the GCS=14 group vs. 35% in the GCS≤13 group, p=0.25; 11% vs 29%, p=0.07, respectively). In the ALC group, patients with a Kelly-Matthay scale score of >3 had a higher rate of NIV failure (66% vs. 25%, p=0.03). In the subgroup analyses, the ALC group showed a higher rate of neurological failure (mainly because of the need for sedation) [2% (1/50) vs. 17% (5/29), p=0.01] in comparison to the NLC with heart failure subgroup. ALC was not associated with total NIV failure in the heart failure or pneumonia subgroups.

The Kaplan-Meier curves revealed that the rates of NIV failure in the ALC and NLC groups did not differ to a statistically significant extent (p=0.15, Fig. 2). A total of 41% of the patients in the ALC group and 45% of the patients in the NLC groups were successfully weaned off NIV during the 48 hours after their admission. The multivariate analyses similarly failed to show an association between ALC and NIV failure (p=0.49, Table 3).

**Table 1. Baseline Characteristics of the Patients.**

	NLC group (n=82)	ALC group (n=66)	p value
Male, n (%)	55 (67)	46 (58)	0.29
Age, y median (IQR)	72 (65-82)	78 (70-84)	0.02
APACHE II median (IQR)	18 (13-22)	19 (17-23)	0.02
RR/min median (IQR)	29 (23-32)	30 (24-32)	0.45
PaO <sub>2</sub> /FiO <sub>2</sub> ratio mean (±SD)	178 (±97)	177 (±103)	0.82
Vasoactive agents, n (%)	19 (23)	16 (24)	0.87
HCO <sub>3</sub> , mmol/L mean (±SD)	20 (±5)	21 (±6)	0.73
Reason for admission, n (%)			0.01
Sepsis	4 (5)	6 (9)	
Heart failure	50 (61)	29 (44)	
Pneumonia	18 (22)	28 (42)	
Others	10 (12)	3 (5)	
BMI, m <sup>2</sup> /kg mean (±SD)	22 (±5)	20 (±4)	0.050
GCS score median (IQR)	15 (15-15)	14 (11-14)	<0.01
Eye score median (IQR)	4 (4-4)	3 (3-4)	
Verbal score median (IQR)	5 (5-5)	4 (3-4)	
Motor score median (IQR)	6 (6-6)	6 (6-6)	
Kelly and Matthay scale, n (%)			<0.01
1	82 (100)	0 (0)	
2	0	21 (32)	
3	0	39 (59)	
4	0	3 (5)	
5	0	3 (5)	
6	0	0 (0)	
IPAP, cmH <sub>2</sub> O median (IQR)	8 (8-8)	8 (8-11)	<0.01
EPAP, cmH <sub>2</sub> O median (IQR)	8 (6-8)	8 (5-8)	0.13
CPAP, n (%)	62 (76)	32 (48)	<0.01

NLC: normal level of consciousness, ALC: altered level of consciousness, IQR: interquartile range, GCS: Glasgow Coma Scale, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure

## Discussion

To the best of our knowledge, this is the first study of patients experiencing acute hypoxemic respiratory failure that aimed to investigate the efficacy and safety of NIV in patients with ALC in comparison to fully alert patients. This study showed that mild ALC (defined by a GCS score of 9-14) was not associated with NIV failure and that nearly half of the patients with mild ALC were successfully weaned off ventilator support within 48 hours.

Invasive mechanical ventilation is often an indispensable life-saving measure, but it is also associated with a risk of endotracheal tube- or ventilator-associated pneumonia, which may lead to a poor outcome (17). NIV is an effective method of improving gas change; furthermore, it is less invasive and it is associated with fewer complications, including infections. Successful NIV treatment is associated with a shorter stay in the intensive care unit, a decreased intubation rate and an increased survival benefit (18, 19). Although there is increasing evidence to support the use of other non-invasive devices, including high-flow systems, NIV is still an effective method for managing acute respiratory fail-

ure (20).

The presence of ALC is considered to be a classic contraindication for NIV (4, 5). However, the actual outcomes of patients with mild ALC who have received NIV have not been well studied because they were mostly excluded from randomised, controlled trials. There is increasing evidence to support the safety and efficacy of NIV in the treatment of hypercapnic respiratory failure with ALC (12, 21-23). Scala et al. found that NIV was successful in 75% of patients with mild ALC; however, severe ALC was associated with a high rate of NIV failure (12). They also found that changes in the PaCO<sub>2</sub> level or the degree of acidosis could not fully explain the improvement in the level of consciousness. These authors concluded that other factors, such as non-pulmonary acute organ dysfunction, appeared to play an important role. Although it is difficult to compare the results of the present study to these studies because of differences in the study populations, our study also showed that there was no significant association between ALC and NIV failure. This result suggests that patients with ALC could benefit from NIV with careful management.

The use of non-invasive support for patients with ALC is considered to be minimally effective because of the risk of

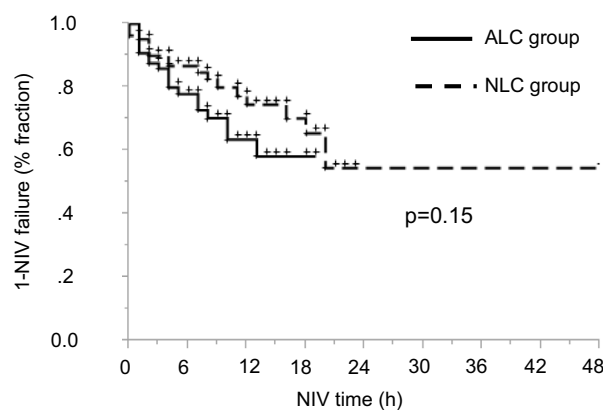
**Table 2. Outcomes in All Patients, and in the Subgroups of Heart Failure and Pneumonia.**

All patients			
	NLC group (n=82) n (%)	ALC group (n=66) n (%)	p value
NIV failure	20 (24)	20 (30)	0.42
Respiratory failure	16 (20)	15 (23)	0.63
Neurological failure	4 (5)	7 (11)	0.34
Death	1 (1)	4 (6)	0.17
Intubated	10 (12)	5 (8)	0.35
In-hospital mortality	11 (13)	13 (16)	0.30
Heart failure			
	NLC group (n=50)	ALC group (n=29)	p value
NIV failure	6 (12)	6 (21)	0.34
Respiratory failure	4 (8)	3 (10)	0.70
Neurological failure	1 (2)	5 (17)	0.02
Death	1 (2)	0 (0)	1.0
Intubated	2 (4)	1 (3)	1.0
Pneumonia			
	NLC group (n=18)	ALC group (n=28)	p value
NIV failure	6 (33)	12 (43)	0.52
Respiratory failure	4 (22)	11 (39)	0.22
Neurological failure	2 (11)	2 (7)	0.55
Death	0 (0)	2 (7)	0.51
Intubated	4 (22)	3 (11)	0.41

NLC: normal level of consciousness, ALC: altered level of consciousness, NIV: noninvasive ventilation

pulmonary aspiration and the patients' inability to cooperate. It is noteworthy that none of the patients in our study developed nosocomial pneumonia. This finding is in accordance with the results of previous studies, which have shown that nosocomial pneumonia was a rare complication in acute respiratory failure patients who received NIV because intubation was avoided (11, 24-27). In this study, none of the patients experienced nosocomial pneumonia. However, the observation period of 48 hours might have been too short to evaluate the true incidence of pneumonia and this might have affected our result. Further studies should be performed to elucidate the actual association between ALC and nosocomial pneumonia.

Our study also showed that the rate of NIV failure in the ALC group (30%) was comparable to that in the NLC group (24%). This finding is similar to previous studies of alert patients receiving NIV for acute hypoxemic respiratory failure (3, 28, 29). This low rate of NIV failure may be attributable to the management of NIV. Corrado et al. demonstrated that a consistent portion of patients could receive non-invasive ventilation using an iron lung in a study that systematically included patients with severe ALC (GCS score of <8). They suggested that, with special care, a non-

**Figure 2. The curves of NIV failure according to the duration of NIV in the ALC and NLC groups. NIV: non-invasive ventilation, ALC: altered level of consciousness, NLC: normal level of consciousness****Table 3. Multivariate Analysis of Factors Related to NIV Failure.**

	HR (95% CI)	p value
ALC	1.28 (0.63-2.61)	0.49
Age >75 vs. ≤75 y	1.89 (0.94-3.88)	0.072
IPAP >8 vs. ≤8 cmH <sub>2</sub> O	1.03 (0.49-2)	0.94
APACHE II score >18 vs. ≤18	1.06 (0.55-2.05)	0.85
PaO <sub>2</sub> /FiO <sub>2</sub> ratio <150	2.44 (1.22-5.17)	0.01

HR: hazard ratio, CI: confidence interval, ALC: altered level of consciousness

invasive ventilation technique could sometimes be applied “beyond” the normal boundaries (30). In our study, NIV was initiated and followed by observation by an ER doctor, intensive care unit doctor, and pulmonologist (who were specialists in respiratory management) until the patients were completely weaned from ventilator support. When patients with respiratory failure receive ventilation, quality management might be important for reducing the rate of NIV failure.

Interestingly, among the heart failure subgroup, the rate of neurological failure in patients with ALC was higher than that in patients with NLC; however, it did not affect the total rate of NIV failure. A possible reason for this finding could be that careful management of the psychological status is required for patients with heart failure because even minor agitation can severely affect the haemodynamic status. Appropriate management, including sedation, may prevent an increase in the incidence of other components of NIV failure, including respiratory failure, intubation, and death.

Among the different scales that assess the level of consciousness, we used the GCS, as it is most commonly used and has been best studied in intensive care settings. Some studies have utilized the Kelly-Matthay scale for critically ill patients requiring ventilation because it is more easily and quickly determined and because it is sensitive to minor changes (12, 13, 31). This scale does not require verbal

evaluation and has started to be used to assess patients receiving mechanical ventilation. However, it is less universally applicable and is not as well studied as the GCS. Furthermore, we could not neglect the effect of the verbal element in patients receiving non-invasive ventilation. It is necessary to develop a neurological score specifically designed for assessing the mental status during both non-invasive and invasive ventilation.

The present study is associated with several limitations. First, our study was retrospective in design, which made it impossible to control the patients' characteristics. Thus, there were differences in the reasons for selecting NIV. We conducted subgroup analyses of patients with heart failure and pneumonia, which were the two largest sub-populations, and found no significant difference in the rate of NIV failure between the ALC and NLC groups. Second, the results should be interpreted with caution because this study was performed at a single centre and included a relatively small number; thus, the statistical power was relatively low.

## Conclusion

With careful monitoring and management NIV may be successfully applied to patients with mild ALC during episodes of acute hypoxemic respiratory failure. However, physicians should be aware that delayed intubation is associated with a poor outcome, and the optimal timing for intubation should not be missed.

**The authors state that they have no Conflict of Interest (COI).**

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