Reduced survival in patients with ALS with upper airway obstructive events on non-invasive ventilation


To cite this version:

HAL Id: hal-01325417
https://hal.sorbonne-universite.fr/hal-01325417
Submitted on 2 Jun 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.
Reduced survival in ALS patients

with upper airway obstructive events on noninvasive ventilation

Marjolaine Georges (1,2); Valérie Attali (2,3); Jean Louis Golmard (4); Capucine Morélot-Panzini (1,2); Lise Crevier-Buchman (5); Jean-Marc Collet (3); Anne Tintignac (1); Elise Morawiec (1); Valery Trosini-Desert (1); François Salachas (6); Thomas Similowski (1,2); Jesus Gonzalez-Bermejo (1,2).

1. AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Département “R3S”, Service de Pneumologie et Réanimation Médicale, F-75013, Paris, France

2. Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, Paris, France


4. AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Département de biostatistiques, F-75013, Paris, France

5. AP-HP, Hôpital Européen Georges Pompidou, Unité de la Voix, Service ORL et Chirurgie Cervico-Faciale, Paris, France

5. Université Paris Descartes, CNRS UMR 7018, Paris

6. AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Département de Neurologie et Centre de Référence pour la SLA, F-75013, Paris, France

Running head: Upper airway obstruction on NIV in ALS

Correspondence: jesus.gonzalez@aphp.fr
Abstract: 247 words
Noninvasive ventilation (NIV) is part of standard care in amyotrophic lateral sclerosis (ALS). Intolerance or unavailability of NIV, as well as the quality of correction of nocturnal hypoventilation have a direct impact on prognosis.

Objectives: We describe the importance of NIV failure due to upper airway obstructive events, the clinical characteristics, as well as their impact on the prognosis of ALS.

Methods: Restrospective analysis of the data of 190 patients with ALS and NIV in a single-center for the period 2011 to 2014. 179 patients tolerating NIV for more than 4 hours per night without leaks were analysed.

Results: Among the 179 patients, after correction of leaks, 73 remained inadequately ventilated at night (defined as more of 5% of the night spent at <90% of SpO2), as a result of obstructive events in 67% of cases (n=48). Patients who remained inadequately ventilated after optimal adjustment of ventilator settings presented shorter survival than adequately ventilated patients. Unexpectedly, patients with upper airway obstructive events without nocturnal desaturation and in whom no adjustment of treatment was therefore performed also presented shorter survival. On initiation of NIV, no difference was demonstrated between patients with and without upper airway obstructive events. In all patients, upper airway obstruction was concomitant with reduction of ventilatory drive.

Conclusions: This study shows that upper airway obstruction during NIV occurs in ALS patients and is associated with poorer prognosis. Such events should be indentified as they can be corrected by adjusting ventilator settings.
Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of unknown origin. After onset of the first symptoms, the median survival without respiratory assistance is 19 months\(^1\) and about 7 months in patients with documented diaphragmatic involvement\(^2\). Most deaths are due to respiratory causes\(^3\). For these reasons, noninvasive ventilation (NIV) is now part of standard care of ALS\(^4,5\). By delivering positive pressure ventilatory assistance via a nasal or face mask, NIV relieves dyspnea and improves quality of life\(^6\). The survival benefit of NIV has been reported to range from 7 months\(^7\) to 12 months or more\(^8,9\). Intolerance of NIV or lack of availability of NIV\(^8,9\) is a missed opportunity to improve quality of life and prognosis\(^4\). However, initiation of NIV is more difficult in ALS patients than in patients with other neuromuscular diseases\(^10\), while the quality of correction of nocturnal hypoventilation has a direct impact on prognosis\(^11\). The failure of NIV to maintain satisfactory ventilation at night is related to the presence of leaks in more than one half of cases\(^11\), but other mechanisms, sometimes associated, are also involved, including upper airway obstructive events, central events comprising reduction of the ventilatory drive, and patient-ventilator asynchrony\(^11,12\). When nocturnal hypoventilation persists after correction of leaks, it is recommended to perform respiratory polygraphy during NIV to identify the mechanisms responsible\(^13\). We describe the role of upper airway obstructive events in failure of NIV in patients with ALS, their clinical characteristics, and their intrinsic prognostic impact.
Material and Methods

Background

This single-center observational study was conducted in the Department of Respiratory Medicine and Medical Intensive Care of a 1600-bed university hospital. This department is associated with the rare diseases reference center for ALS in the same hospital. Initiation and surveillance of NIV in ALS patients is performed in an 8-bed day-care unit, according to a recently validated model\textsuperscript{14}, which devotes 80% of its activity to the management of respiratory failure in ALS\textsuperscript{11}.

Patients

Between 2011 and 2012, NIV was initiated in our center in 190 patients with definite or probable ALS according to El Escorial criteria\textsuperscript{15}, and the patients’ outcome was followed until 2014. NIV was well tolerated (NIV > 4 h/24 h) by 179 of these patients\textsuperscript{9} (Figure 1). All these 179 patients were included in the analysis. Analysis of these data was approved by the Institutional Review Board of the Société de Pneumologie de Langue Française (French learned society for respiratory medicine), and all patients provided their written informed consent to the anonymous use of their personal data. All the patients received riluzole, and, as appropriate, secretions management with In/Exsufflator and gastrostomy. The patients and their caregivers all received logistical and psychological support by the Paris ALS Network care\textsuperscript{16}.

Respiratory management and evaluation

The indication for NIV was based on the current consensual criteria\textsuperscript{5}. NIV was initiated according to the current standardized procedure in the department, over a period of 3 to 5 days\textsuperscript{17} (Table 1). During the follow up, the effectiveness of NIV was assessed in terms of symptoms (including NIV-related discomfort), blood gases, the analysis of ventilator-
recorded tracings and nocturnal oximetry. This was performed in all patients in a systematic manner after one month of NIV (M1) and then every three months, as previously described in detail. Patients were considered to be inadequately ventilated (16) at night when they presented nocturnal SpO₂ < 90% for more than 5% of the nocturnal recording time. Built-in monitoring software was used to detect air leaks, which were then corrected. In the absence of leaks, ventilator software were able to detect with good accuracy possible obstructive events (see previously report for details) (Figure 2) and nap polygraphy (or polysomnography for 5 patients) was then performed in all the patients inadequately ventilated and who were suspected to have upper airway obstructive events (Figure 2). An obstructive event on NIV was defined by a ≥ 50% drop in airflow for 10 seconds or longer with no concomitant changes in the amplitude of the pressure signal and was considered to be associated with reduction in ventilatory drive when it occurred in the absence of associated thoracoabdominal paradox. The absence of obstructive events was defined by an obstruction index < 5/h on the ventilator software. All the patients were ventilated with a respiratory backup rate, to provide for central apneas. Pharyngolaryngeal assessment was also performed by nasal endoscopy (Pentax, VNL-1190STK), during spontaneous breathing in 11 patients and noninvasive ventilation in 1 patient (Figure 3 and supplementary video on line).

Interventions in case of inadequate ventilation due to obstructive events

After correction of the leaks, the corrective interventions in patients were, in this order: 1/ step by step increase in expiratory positive airway pressure (EPAP) to a maximum of 10 cmH20 if tolerated; 2/ trial use of self-adapting inspiratory pressure devices (IVAPS mode, Resmed, Sydney, Australia; AutoAdvanced, Philips Respironics, Pensylvania, USA); 3/ switch to volume-controlled mode; 4/ trial of other mechanical treatments (mandibular advancement device, cervical collar).
**Statistical analysis**

Descriptive statistics used numbers and percentages for qualitative variables and Quantitative variables were described in terms of their median and interquartile range because of strong skewness in some distributions. Comparisons between groups of patients used Chi² tests for qualitative variables and Wilcoxon-Mann-Whitney tests for quantitative variables. Prognostic factors were analyzed in the framework of survival analysis. Survival time was defined as the time between first signs of the disease and date of death. Patients alive at the date of analysis were considered to be censored at this date. Survival functions were estimated by the Kaplan-Meier method and between-group comparisons were tested by log-rank tests. All computations were performed by SAS V9.3 (SAS Institute Inc, Cary, NC, USA).

**Results**

After correction of leaks, 106 of the 179 patients evaluated were considered to be adequately ventilated at night (group 1) and 73 remained inadequately ventilated (group 2) (supplementary Table 2 on line and Figure 1).

In group 2, for 49 patients (67% of inadequately ventilated patients), poor ventilation was due to obstructive events (group 2 O +). Correction was obtained in 21 of these 49 patients after adjustment of ventilator settings (Group 2 O +/-) (titration of EPAP up to 10 cm H₂O guided by polygraphy and tolerance, followed, in the case of failure, by a trial of automatic modes (Figure 2) and finally a trial of volume-controlled mode). Obstructive events could not be eliminated in 28 patients despite adjustment of ventilator settings (group 2 O +/-). In this case, ventilator settings were adjusted to ensure the least residual apneas and the best subjective tolerance.

In group 1, 38 patients presented upper airway obstructive events (Group 1 O +). However, in the absence of nocturnal desaturation and symptoms, no change of treatment was proposed in
this group.

Results of pharyngolaryngeal endoscopic assessment in 11 patients are listed in the online supplement (Figure 3 and supplementary video on line).

Patients who remained inadequately ventilated after optimization of NIV settings (to uncorrected obstructions (group 2 O+/+) or other causes (group 2 O-)) presented shorter survival (respectively 14[7-27] months and 12[6-23] months) than ventilated patients without or corrected upper airway obstructive events (group 1 O- and group 2 O+/-) (respectively 26[13-45] months (p=0.04 and 0.03) and 29[20-53] months, (p=0.01 and 0.01))(Figure 4). Unexpectedly, patients with upper airway obstructive events without nocturnal desaturation, in whom no adjustment of treatment was therefore proposed (Group 1 O+), had a shorter survival (13[7-40] months) than that of adequately ventilated patients without upper airway obstructive events after adjustments group 2 O+/- (p=0.026); and a survival that was not significantly different from that of patients considered to be inadequately ventilated.

In the light of these results, we compared patients without and with upper airway obstructive events on the first recording (O-, n=92, i.e. 51% and O+, n=87, i.e. 49%, respectively). No significant difference was demonstrated between O+ and O- patients at the time of initiation of NIV (Table 1), except that Group O- comprised more patients with bulbar onset ALS (24 patients versus 12, p = 0.034), but with no significant difference of the bulbar score at the time of initiation of NIV and that Group O- comprised more patients with gastrostomy (n =21, 23%, vs. n= 9, 10%, in group O+, p = 0.02), without difference in survival in patients with or without gastrostomy in the whole group. In the adequately ventilated patients, the patients with upper airway obstructive events had more desaturations but all less than 5% of the night, and a shorter use of NIV (supplementary Table 3 on line).

In all O+ patients, obstructive events were consistently associated with a reduction of ventilatory drive (Figure 2). In the 20 patients in whom complete PSG was performed,
obstructive events predominantly occurred during REM sleep, but were always associated with loss of accessory respiratory muscle activity.

None of the patients presented hyperventilation on NIV (Table 1), and no significant difference in variations of PaCO₂ without and with NIV were observed between O + patients and O- patients.

The majority of patients were ventilated with a face mask, with no significant difference between the 2 groups.

O + patients presented more criteria of NIV failure: diurnal alveolar hypoventilation was less well controlled by NIV (PaCO₂: 50 [44-55] mmHg versus 43 [41-48] mmHg in O- patients, p<0.001 and 67% of O + patients (n=57) were hypercapnic (PaCO₂ > 45 mmHg) on NIV versus 34% of O- patients (n=37), p< 0.001.

Effective interventions in patients of group 2 O + (n=49) were: 1/ increased expiratory positive airway pressure (EPAP) to the maximum of our protocol (10 cm H₂O) for 18 patients (Figure 2) 2/ use of self-adapting inspiratory pressure devices in 8 patients (IVAPS mode, Resmed, Sydney, Australia or AutoAdvanced mode, Philips Respironics, Pensylvania,USA) for 3 patients, 3/ switch to volume-controlled mode in 1 patient (VT 500ml, Ti1,3 EPAP 4).

Other treatments were tried without success: custom-made mandibular advancement device, as also recently described by Veldhuis et al. ²¹, was tried in addition to NIV in 4 patients, but was discontinued after 3 to 6 months due to poor tolerance. Due to the possible role of the oronasal mask, the oronasal mask was replaced by a nasal mask, which was not supported by the patients concerned due to air leaks. Anterior dislocation of the jaw using a cervical collar was tried, but without success, in 3 patients.

**Discussion**

This study confirms that upper airway obstruction is one of the mechanisms of NIV failure in
ALS\textsuperscript{10,11,21,22}. The prevalence of upper airway obstruction, which has not been previously systematically evaluated, is high (45\% of our patients after correction of leaks). It is noteworthy that NIV-related upper airway obstructive events in ALS patients appear to be mediated by central mechanisms, as obstructive events (defined as cessation or marked decrease of flow with maintained airway pressure) are associated with decreased or abolished thoracoabdominal movements (Figure 2). Finally, obstructive events in this setting are associated with poorer prognosis, even when they do not reduce the efficacy of NIV to correct desaturations (group 1 O-patients) (Figure 4). Correction of obstructive events improves survival (Figure 4).

**Putative mechanisms**

*Abnormal upper airway collapsibility in ALS*

A number of ALS-related factors can theoretically increase upper airway collapsibility. Upper airway involvement has been extensively described in this disease, particularly in the pharynx and larynx\textsuperscript{23,24}, due to degeneration of corticobulbar fibers, with bilateral glossopharyngeal and hypoglossal nerve lesions, responsible for so-called “bulbar” symptoms with impairment of voice and swallowing, atrophy of the tongue with fasciculations and abnormal corticobulbar reflexes\textsuperscript{23,25}. Very heterogeneous appearances in endoscopy were observed, ranging from a completely normal airway to complete collapse of the entire airway (Figure 3 and supplementary video online). However, recent studies in ALS have confirmed that the endoscopic appearance of the pharynx and larynx may be normal despite spontaneous and permanent electromyographic activity of the tongue in a great majority of patients\textsuperscript{26}, although demonstration of fasciculations is limited by the marked difficulty of obtaining complete relaxation of the tongue (only 6\% of patients\textsuperscript{25}). More simply, DePaul et al. demonstrated decreased strength of the tongue in almost all patients, even in patients with no dysarthria or swallowing disorders\textsuperscript{24}. Decreased strength of the tongue would constitute a predisposing
factor to increased upper airway collapsibility and we believe that the prevalence of this abnormality in ALS (with or without an obvious bulbar lesion) is probably severely underestimated. Clinical evaluation (bulbar score) and nasal endoscopy are clearly unable to identify patients at high-risk of upper airway collapse when treated by NIV, indicating the need for a specific diagnostic approach. We did not have enough data to differentiate bulbar and pseudobulbar patients, a differentiation that should be explored in future studies. Finally, other mechanisms, described in different diseases, may also be responsible of upper airway obstruction; these include chronic irritation of the surface of the pharynx, a higher propensity of the airways to collapse at low lung volume or upper airway nocturnal redistribution of interstitial fluid for example.

**NIV-related inhibition of compensatory mechanisms**

ALS-related obstructive events are observed only during sleep and/or NIV, suggesting the existence of wakefulness-related compensatory mechanisms that have been shown to involve cortical processes. A similar finding has been observed in obstructive sleep apnea syndrome (OSAS), in which snoring and obstructive events are not observed during wakefulness despite the fact that the upper airways of OSAS patients present anatomical and functional abnormalities predisposing to airway collapse. These abnormalities are compensated by increased ventilatory drive to upper airway dilator muscles, in which a specific cortical drive participates. NIV could affect this compensation via several mechanisms. Firstly, NIV may reduce PaCO₂, which would decrease global ventilatory drive and which could promote glottal closure phenomena in the same way as induction of hypocapnia in healthy subjects. Secondly NIV could induce mechanical inhibition of ventilatory drive, independent of any variations in CO₂, and related to changes in thoracic afferents and their cortical processing, as NIV abolishes the cortical activity related to breathing that characterizes some ALS patients, which has been interpreted to be a compensatory mechanism. Finally, a third
mechanism could be related to sleep induction, as described in OSAS\textsuperscript{39}.

**Prognostic impact**

In the patients of this series, obstructive events were associated with poorer prognosis, without any obvious confounder for low survival (smoking habits, riluzole use, respiratory secretions management and nutritionnal support). Of note, the presence of a gastrostomy was less often noted in the patients with obstructive events, probably because of the lower number of bulbar patients in this group (Table 1). We did not find any difference in survival between patients with or without gastrostomy, as all the patients received nutritional support. We were surprised to find that a poorer survival was observed not only in patients considered to be inadequately ventilated but also in patients considered to be adequately ventilated, i.e. with no nocturnal desaturations (group 1 O + patients). Nocturnal SpO\textsubscript{2} monitoring is therefore probably not sufficiently precise to detect poor quality sleep in patients with obstructive events or the criteria of nocturnal SpO\textsubscript{2} < 90\% for more than 5\% of the nocturnal recording time\textsuperscript{11} could be too high as suggested in Table 3. However, this is an important point, as correction of obstructive events is associated with improved survival. The present study shows that adjustments of ventilator settings can control obstructive events in 58\% of cases, with no survival difference between patients corrected during treatment and those who were immediately adequately ventilated. The most frequently effective treatment was to try to reduce upper airway collapsibility by increasing EPAP to high levels. Unfortunately, this was not always effective and no therapeutic intervention effective in all patients has yet been identified. Nethertheless, these difference in survival must be analysed with caution in this not controlled, retrospective study and should be confirmed in future controlled studies.

In conclusion, upper airway obstructive events associated with decreased ventilatory drive and promoted by NIV are observed in more than half of ventilated ALS patients. The presence of this phenomenon must be systematically investigated, as it can be corrected by adjusting ventilator settings in the majority of cases. Although the retrospective and single-
center design of this study limits its impact, obstructive events nevertheless appear to be an important phenomenon with an impact on survival.
Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Anthropometric data</th>
<th>n</th>
<th>Group O- (n=92)</th>
<th>n</th>
<th>Group O + (n=87)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>92</td>
<td>64.6 [57.3-71.9]</td>
<td>87</td>
<td>63.6 [57.1-72.1]</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (number of men - %)</td>
<td>40</td>
<td>55 [60%]</td>
<td>41</td>
<td>58 [67%]</td>
<td>NS</td>
</tr>
<tr>
<td>Body Mass Index (kg.m⁻²)</td>
<td>90</td>
<td>23.1 [19.6-25.9]</td>
<td>87</td>
<td>21.8 [19.1-25.0]</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking greater than 20 pack-years (number of patients - %)</td>
<td>38</td>
<td>0 [0-10]</td>
<td>40</td>
<td>0 [0-10]</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Neurological assessment**

| Time from onset to diagnostic (months) | 92 | 9 [5-17] | 86 | 12 [6-16] | NS |
| ALSFRS-R score (/48) | 85 | 40 [35-43] | 85 | 40 [36-43] | NS |
| Bulbar onset (n - %) | 89 | 24 (27) | 86 | 12 (14) | 0.03 |
| Gastrostomy in the follow up (number of patients-%) | 92 | 21 (23%) | 87 | 9 (10%) | 0.02 |

**Respiratory assessment**

| VC sitting/supine (L) | 58/63 | 1.46 [0.92-2.05] | 65/62 | 1.44 [1.12-2.05] | NS |
| Pmax (cmH2O and % predicted) | 66 | 21 [12-31] and 21 [12-34] | 60 | 24 [13-55] and 25 [14-55] | NS |
| SNIP (cm H2O and % predicted) | 68 | 19 [12-26] and 19 [13-28] | 59 | 20 [14-36] and 24 [16-36] | 0.04 |
| Cough peak flow (L/min) | 81 | 160 [10-250] | 66 | 120 [70-200] | NS |
| PacO₂ before NIV/on NIV (mmHg) | 91/87 | 48 [43-52] | 43 [41-48] | 49 [46-55] | NS |
| deltaPaCO₂ (mm Hg) | 86 | 4 [11-10] | 85 | 1 [11-10] | NS |
| PacO₂ before NIV/on NIV (mmHg) | 60/87 | 73 [67-82] | 78 [70-85] | 75 [68-82] | NS |

**Noninvasive ventilation parameters**

| IPAP (cm H₂O) | 92 | 13 [12-14] | 87 | 13 [12-15] | NS |
| EPAP (cm H₂O) | 92 | 4 [4-4] | 87 | 4 [4-6] | 0.01 |
| RR (min⁻¹) | 91 | 16 [14-16] | 86 | 16 [14-16] | NS |
| NIV use (hours per day) | 87 | 10 [8-14] | 84 | 8 [6-10] | <0.001 |
| Estimated Vt ¹ | 86 | 440 [390-510] | 84 | 417 [355-472] | 0.04 |
| Leaks (L.min⁻¹) | 86 | 1 [0-16] | 84 | 1 [0-6] | NS |
| Face mask (n - %) | 91 | 75 [69-82] | 87 | 75 [68-80] | NS |

Results are expressed as median [IQR]
Abbreviations: ALSFRS-R revised Amyotrophic Lateral Sclerosis - Functional Rating Scale, RR back-up respiratory rate, EPAP: expiratory positive airway pressure, IPAP: inspiratory positive airway pressure, NIV: noninvasive ventilation, PaO₂: arterial oxygen tension, PaCO₂: arterial carbon dioxide tension, PiMax: maximal inspiratory mouth pressure (measured from functional residual capacity), SNIP: Sniff Nasal Inspiratory Pressure (measured from functional residual capacity), TS90: time spent with transcutaneous pulsed oxygen saturation less than 90%, VC: vital capacity, Vt: tidal volume. NS : not significant

13
Figure legends

Figure 1: Flowchart of the patients included

Figure 2: Upper part: Example of decreased nocturnal SpO₂ recorded on polysomnography with reduction of flow (arrows) despite effective ventilator pressure, indicating obstruction associated with reduction or even absence of thoracoabdominal muscle movements. This obstructive event was corrected by increasing EPAP (circle).
Lower part: same event recorded by the ventilator built-in monitoring software showing decreased flow rate (arrows) despite effective ventilator pressure (Rescan™, Resmed, Sydney, Australia).

Figure 3: Awake nasopharyngeal fiberoptic endoscopy on spontaneous breathing (upper part) and on NIV (lower part): Immediate obstruction of the upper airway at all the levels, from the tongue to the glottis.

Figure 4: Patient survival, from onset of disease, according to the presence of obstructive events, whether or not they were corrected.
Group 1 O-: Group of patients without obstructive events and immediately adequately ventilated.
Group 1 O +: Group of patients with obstructive events considered to be adequately ventilated.
Group 2 O-: Group of inadequately ventilated patients without leaks or obstructive events.
Group 2 O +/-: Group of patients with obstructive events, inadequately ventilated then adequately ventilated after treatment.
Group 2 O +/+: Group of patients with obstructive events, inadequately ventilated and remaining inadequately ventilated after treatment.
References

Funding statement:
"This work was supported by the program "Investissement d'Avenir ANR-10-AIHU 06 of the French Government »

Competing Interests statement:
The authors have no conflict of interest to declare

Contributorship Statement
1. Conception and design,
2. Acquisition of data
3. Analysis
4. Interpretation of data
5. Drafting the work or revising

Marjolaine Georges (1, 2, 3, 4, 5); Valérie Attali (1, 2, 3, 4, 5); Jean Louis Golmard (1,3,4,5); Capucine Morélot-Panzini (1, 2, 3, 4, 5); Lise Crevier-Buchman (1,2,4,5); Jean-Marc Collet (2,4); Anne Tintignac (1,2,5); Elise Morawiec (1,2,5); Valery Trosini-Desert (1,2,5); François Salachas (1,3,4,5); Thomas Similowski (1, 3, 4, 5); Jesus Gonzalez-Bermejo (1, 2, 3, 4, 5).
190 ALS patients ventilated between 2011 and 2012

179 tolerant to NIV (>4h)

Group 1:
106 patients adequately ventilated

Group 1.O-: 68 patients without obstructive events

Group 1.O+: 38 patients with obstructive events

Group 2:
73 patients inadequately ventilated

Group 2.O-: 24 patients without obstructive events

Group 2.O+: 49 patients with obstructive events

Group 2.O+/+: 28 patients patients with obstructive events despite adjustments

Group 2.O+/-: 21 patients without obstructive events after adjustments

Figure 1
Figure 2
Figure 4

The figure shows a Kaplan-Meier survival curve with different groups labeled:

- Group 2.O+/-
- Group 1.O-
- Group 2.O-
- Group 1.O+
- Group 2.O+/+

The x-axis represents time in months, ranging from 0 to 12. The y-axis represents the percentage of survivors, ranging from 0 to 100.

The table below provides the number of samples (n) for each group at different time points:

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.O+/-</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>1.O-</td>
<td>68</td>
<td>63</td>
<td>60</td>
<td>58</td>
<td>56</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>2.O-</td>
<td>24</td>
<td>22</td>
<td>20</td>
<td>17</td>
<td>13</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>1.O+</td>
<td>38</td>
<td>34</td>
<td>32</td>
<td>28</td>
<td>26</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>2.O+/+</td>
<td>28</td>
<td>24</td>
<td>21</td>
<td>19</td>
<td>18</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

The p-value for the comparison is 0.01, indicating a statistically significant difference between the groups.

The figure also includes notes indicating "NS" for non-significant differences.