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Impact of prehospital noninvasive mechanical ventilation in acute pulmonary edema: the NIVEMS cohort study

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BACKGROUND. Acute pulmonary edema (APE) is a frequent medical event requiring out-of-hospital attendance of emergency services. Early prehospital noninvasive ventilation (NIV) can improve the clinical course of APE.

OBJECTIVES. To analyze changes in oxygen saturation measured by pulse oximetry (SpO_2) and respiratory frequency (RF) in patients with APE treated with early prehospital NIV vs conventional oxygen therapy.

METHOS. Prospective double-cohort study with data recorded for 433 patients with APE attended by advanced life support units of the emergency medical system of Catalonia from January 1, 2014, to March 31, 2018. Patients were exposed to either prehospital NIV or conventional oxygen therapy. To analyze data we used the Kaplan-Meier method and Cox regression modelin and calculated of adjusted hazard ratios (aHR).

RESULTS. The NIVEMS (Noninvasive Ventilation in Emergency Services) study collected valid data to analyze for 382 patients with a mean (SD) age of 79.7 (9.58) years; 56.3% were women. Prehospital NIV was applied in 44.7% of the cohort. The median time until optimization of SpO_2 to more than 94% was 10 min (95% CI, 8.37-11.63 min) with NIV vs 30 min (95% CI, 19.44-40.56 min) with conventional oxygen therapy. The median time until optimization of RF to fewer than 28 breaths/min was 31 min (95% CI, 24.56-37.44 min) with NIV vs 50 min (95% CI, 38.61-61.39 min) with conventional therapy. NIV favored optimization of SpO_2 (aHR, 4.66; 95% CI, 2.91-7.45) and RF (aHR, 3.24; 95% CI, 1.97-5.31).

CONCLUSION. Prehospital application of NIV in patients with clinically suspected APE is associated with a shorter time to optimization of SpO_2 and RF.

Keywords: Acute pulmonary edema. Noninvasive ventilation. Prehospital emergency care. Respiratory frequency. Oxygen saturation. Conventional oxygen therapy.

Impacto de la aplicación prehospitalaria de ventilación mecánica no invasiva en el edema agudo de pulmón. Estudio NIVEMS

INTRODUCCIÓN. El edema agudo de pulmón (EAP) es un motivo de asistencia frecuente en los servicios de emergencias prehospitalarios. La aplicación de ventilación mecánica no invasiva (VMNI) prehospitalaria puede mejorar la evolución clínica de estos pacientes de manera precoz.

OBJETIVOS. Analizar el impacto de la VMNI sobre los parámetros clínicos en pacientes con EAP a nivel prehospitalario, valorando la evolución de la saturación de oxígeno ($SatO_2$) y la frecuencia respiratoria (FR), comparado con pacientes tratados con oxigenoterapia convencional.

MATERIAL Y MÉTODOS. Estudio prospectivo de doble cohorte de pacientes con EAP atendidos por las unidades de soporte vital avanzado (SVA) del *Sistema d'Emergències Mèdiques* (SEM) de Catalunya, durante el periodo del 1 de enero del 2014 al 31 de marzo del 2018. El criterio de exposición fue la aplicación de VMNI, frente al grupo control, donde se mantuvo la oxigenoterapia convencional. Se realizó análisis de supervivencia mediante Kaplan Meier y regresión de Cox y se calculó la *Hazard ratio* ajustada (HRa).

RESULTADOS. Se reclutaron 382 pacientes, con edad media de 79,7 años (SD 9,58) y 56,3% de mujeres. La VMNI se aplicó en el 44,7% de la cohorte. La mediana de tiempo en optimizar la $SatO_2 > 94\%$ con VMNI fue de 10 minutos (IC 95%: 8,37-11,63), frente a 30 minutos (IC 95%: 19,44-40,56) sin VMNI. La mediana de tiempo en presentar una $FR < 28$ respiraciones por minuto fue con VMNI de 31 minutos (IC 95%: 24,56-37,44), frente a 50 (IC 95%: 38,61-61,39) del grupo sin VMNI. Realizar VMNI mejoró la tasa de optimización de la $SatO_2$ con una HRa de 4,66 (IC 95%: 2,91-7,45) y de la FR con una HRa de 3,24 (IC 95%: 1,97-5,31).

CONCLUSIONES. Aplicar VMNI prehospitalaria a pacientes con sospecha clínica de EAP reduce el tiempo de optimización de parámetros clínicos de saturación de oxígeno y frecuencia respiratoria.

Palabras clave: Edema agudo de pulmón. Ventilación no invasiva. Atención urgente prehospitalaria. Frecuencia respiratoria. Saturación de oxígeno. Oxigenoterapia convencional.

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Introduction

Acute heart failure can present in emergency departments (EDs) in different clinical scenarios, one of which is acute pulmonary edema (APE). APE is characterized by the presence of severe, life-threatening, acute hypoxemic respiratory failure.[1,2] Early initiation of specific treatments in these patients may have short-term benefits. Thus, early administration of vasodilators or diuretics in the prehospital setting appears to improve short-term mortality; although randomized studies are needed to confirm these hypotheses, some observational studies support this notion.[3-7] Currently, noninvasive mechanical ventilation (NIV) is a key element in the management of patients with APE, as its application improves the clinical condition, reduces respiratory effort and dyspnea, lowers the need for orotracheal intubation, decreases the length of the ICU stay, and even hospital mortality, with a high level of supporting evidence.[8-10] Consequently, NIV has become a widely used oxygenation and ventilation therapy in EDs, especially in patients with APE and exacerbations of chronic obstructive pulmonary disease (COPD).[11,12]

Given these beneficial outcomes and the technological evolution of ventilators and consumables, this technique has been widely implemented in prehospital emergency medical services (EMS) in recent years.[13-15] However, its benefits in this setting—particularly concerning short-term mortality—remain debated, as some observational studies have not replicated the consistent in-hospital results. To date, no study has compared prehospital NIV initiation with NIV started in the ED.[13,16]

While mortality reduction is a key goal, achieving rapid clinical improvement is equally important, particularly in APE, which involves a significant adrenergic surge and severe anxiety. The objective of this study was to analyze the short-term impact of NIV on clinical parameters in prehospital patients with APE, assessing changes in oxygen saturation (SpO_2) and respiratory rate (RR) vs patients on conventional oxygen therapy without NIV.

Methods

Design

The NIVEMS study (Non-Invasive Ventilation Emergency Medical Services) was designed as a prospective, dual-cohort study, including consecutive patients with clinical APE attended by advanced life support (ALS) units of the Catalonia EMS. The exposure criterion was the application of NIV, while the control group received conventional oxygen therapy. The study was conducted by the EMS, a public health organization providing prehospital emergency care across Catalonia. In 2012, NIV was progressively incorporated into ALS unit equipment. In 2013, specific NIV training was introduced for all health care personnel (emergency technicians, nurses, and physicians), and a consensus protocol was established for NIV use in APE, allowing its application in other clinical situations at the provider's discretion. The study was conducted in 2 Catalan health care regions—Barcelona City and Metropolitan South, comprising 20 ALS units. Recruitment occurred from January 1st, 2014 through March 31st, 2018. The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committees of the 3 participant hospitals. All patients gave their prior informed consent, initially oral given their acute condition.

Patients and variables

Inclusion and exclusion criteria are shown in Table 1. Once enrolled, pharmacologic treatment followed the European Society of Cardiology recommendations valid at that time.[17] Assignment to the NIV exposure group was based on logistical and training availability—that is, whether the ALS unit was equipped with NIV interfaces and personnel had completed the training. Control group patients were treated by ALS units not yet trained in NIV. In the NIV cohort, treatment was administered concurrently with optimal medical therapy, following the consensus protocol outlined in Table 2. Demographic data, past medical history, acute episode symptoms, initial vital signs, administered pharmacologic therapy, and prehospital NIV parameters were collected.

The primary outcome variables were SpO_2 (measured by noninvasive pulse oximetry) and RR, recorded after first medical contact and every 15 minutes until ED transfer.

Sample size

Sample size was estimated for 2 independent risk groups. Prior EMS data indicated expected optimization rates of SpO_2 > 94% and RR < 28 breaths/min at 60% without NIV and 85% with NIV within the first hour. Assuming a 1:1 group ratio, 85% power, and a two-sided α = 0.05, a minimum of 82 patients per group was required to detect a 25% relative risk difference.

Table 1. Inclusion and exclusion criteria of participants

Inclusion criteria
– Age > 18 years.
– Clinical suspicion of APE based on symptoms and history (orthopnea, diffuse crackles on auscultation, edema, previous APE episodes, etc.) without evidence of pulmonary aspiration or infection.
– Oxygen saturation ≤ 90% after administration of FiO_2 > 0.5.
– Tachypnea > 30 breaths per minute.
– Increased respiratory effort with use of accessory muscles, Patrick Scale > 3.
– Borg dyspnea scale ≥ 5.
– Patient with sufficient level of consciousness to cough and expectorate.
– Adult, cooperative patient.
– Patients attended by ALS units of the Catalonia Emergency Medical System (EMS) in the Barcelona region.
Exclusion criteria
– History of any of the following conditions: chronic obstructive pulmonary disease GOLD stage III or IV, persistent asthma, or severe aortic stenosis.
– Patients with clear contraindications for NIV: hemodynamic instability, inability to maintain airway patency, facial trauma, or tracheostomy.
– Patients showing clear signs of requiring orotracheal intubation: decreased level of consciousness, bradypnea, or hemodynamic instability.
– Patients with ST-segment elevation acute coronary syndrome.
– Lack of hospital confirmation of the diagnosis of APE.
– Interhospital transfers.

APE: acute pulmonary edema; FiO_2: fraction of inspired oxygen; ALS: advanced life support; EMS: Emergency Medical System; NIV: noninvasive ventilation.

Table 2. Protocol for initiation of prehospital noninvasive mechanical ventilation

Initiation and maintenance of NIV in APE
– Begin as early as possible after the initial diagnosis, at the patient's bedside.
– Use a pneumatic transport ventilator not specifically designed for NIV: Oxilog-3000 plus® or Weinmann-Medumat®.
– Select the most appropriate oronasal interface for the patient.
– Prepare the patient: position, explain the technique, and present the interface.
– Place the interface while initiating ventilatory parameters. Check for leaks and readjust the interface if necessary.
– Ventilatory parameters
• Mode: CPAP.
• FiO_2: 1.0.
• Initial PEEP: 5 cm H_2O. After a 5-minute adaptation period, increase in increments of 2 cm H_2O until reaching an average of 10–12 cm H_2O.
• If no improvement is achieved after 15 minutes –> add pressure support over PEEP (CPAP-ASB).
• Initial pressure support: 8 cm H_2O, up to a maximum of 12 cm H_2O.
• Under no circumstances should IPAP exceed 22 cm H_2O.

NIV: noninvasive ventilation; APE: acute pulmonary edema; CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; CPAP-ASB: noninvasive ventilation with pressure support over continuous positive airway pressure; IPAP: inspiratory positive airway pressure.

Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies and the quantitative ones as mean (SD) or median (IQR), depending on distribution. The χ^2 test was used for categorical comparisons and the Student t test for continuous variables. For temporal evolution analysis of dependent variables, Kaplan-Meier survival curves were estimated using the Mantel-Haenszel (Log-Rank) test. Censored (recovered) events were defined as $SpO_2 > 94\%$ and RR < 28 breaths/min. A Cox proportional hazards model was then applied to calculate hazard ratios (HRs) with 95% confidence intervals (CIs), adjusted for variables significant in bivariate analysis. Final optimization rates were also calculated. $P < .05$ or a 95% CI excluding 1 was considered statistically significant. Analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 433 patients initially registered in the NIVEMS trial, 382 (88.2%) were eventually included: 178 (46.6%) in the NIV group and 204 (53.4%) in the control group. Fifty-one patients (11.8%) were excluded—37 for having a non-APE primary diagnosis and 14 due to follow-up loss or incomplete records. Patient characteristics are shown in Table 3. Women comprised 53.4%, with a mean age of 79.1 years (SD, 9.9). A past medical history of heart disease was found in 60.7%, and 14% had previous APE admissions. Nearly all patients presented increased dyspnea, and 43.2% reported palpitations. Physical examination revealed a mean RR of 36 breaths/min and baseline SpO_2 of 72.9%. Most received vasodilators, morphine chloride, and diuretics as initial therapy.

Compared with controls, NIV patients were younger, had fewer previous APE hospitalizations, and were less functionally dependent. However, despite similar symptoms, they presented worse clinical status, with higher systolic blood pressure, tachycardia, and tachypnea. Regarding NIV characteristics (Table 4), 35.4% required pressure support above PEEP, 5.1% showed device intolerance, and 3.4% required intubation; no deaths occurred in either group. Mean NIV duration was 48.2 minutes (SD, 17.2). After NIV initiation, $SpO_2 > 94\%$ was achieved in 91% of patients, vs 69.3% in controls ($P < .001$). The median time to optimization was 10.0 minutes (95% CI, 8.37–11.63) in the NIV group vs 30.0 minutes (95% CI, 19.44–40.56) in controls. The Cox regression model (Figure 1) showed that the application of NIV improved the oxygen saturation (SpO_2) optimization rate, with an adjusted HR of 4.66 (95% CI, 2.91–7.45). Regarding RR, the NIV group achieved an RR < 28 breaths/min in 67.7% of cases vs 51.9% in the oxygen therapy group ($P < .001$). The median time to optimization was also shorter in this group—31 minutes (95% CI, 24.56–37.44) vs 50 minutes (95% CI, 38.61–61.39) in the oxygen therapy group. NIV improved the RR optimization rate (Figure 2), with an adjusted HR of 3.24 (95%CI, 1.97–5.31).

Discussion

The study results show significant improvements in SpO_2 and RR among patients with APE who received prehospital NIV vs those treated with conventional oxygen therapy. Of note, the study was conducted between 2014 and 2018, a period during which scientific evidence supporting the use of NIV—both in hospital and prehospital settings for patients with APE—was steadily increasing.[8,11,12] In our study, we focused on evaluating the short-term clinical improvement associated with NIV use in patients with APE treated at home. For this purpose, we selected 2 key parameters in patients with acute hypoxemic respiratory failure in the clinical context of APE—SpO_2 and RR—since both improve with NIV in prehospital and hospital settings, and these improvements are associated with better clinical outcomes.[18-21]

SpO was measured noninvasively using pulse oximetry, allowing indirect assessment of arterial oxygen partial pressure in these patients.[22,23] In our study, SpO_2 improved significantly and more rapidly in patients receiving NIV. However, we should mention that this parameter primarily reflects alveolar–capillary or gas exchange function and does not always correlate with evident clinical improvement, as tachypnea may persist despite preserved SpO_2.[23]

RR is one of the parameters most closely related to clinical evolution and showed a faster and more significant improvement in patients treated with NIV, suggesting a substantial reduction in dyspnea. In this regard, SpO_2 recovery was much faster than RR normalization. An important finding in our study is that both parameters improved significantly within the first 10 minutes for SpO_2 and 31 minutes for RR, indicating a very early clinical benefit. In most reviewed studies, follow-up periods were longer—up to 10 hours—and improvement was not assessed this early.[8,18] This early clinical benefit is particularly relevant, as it occurs even in patients for whom the prehospital NIV dura-

Table 3. Baseline Characteristics of the NIVEMS cohort and univariate analysis according to prehospital noninvasive mechanical ventilation use

	Total N = 382 n (%)	Without NIV N = 204 n (%)	With NIV N = 178 n (%)	*P* value
Demographic data				
Age (years) [mean (SD)]	79.1 (9.9)	81.4 (9.3)	76.4 (10.1)	< .001
Age > 70 years	302 (79.1)	90 (88.2)	61 (68.5)	.001
Female sex	204 (53.4)	54 (52.9)	44 (53.9)	.891
Medical history				
Hypertension	312 (81.7)	173 (84.8)	139 (78.1)	.092
Diabetes mellitus	149 (39.0)	86 (42.2)	63 (35.4)	.177
Active smoking	36 (9.4)	20 (9.8)	16 (9.0)	.785
CKD	87 (22.8)	49 (24.0)	38 (21.3)	.534
COPD	70 (18.3)	42 (20.6)	28 (15.7)	.222
Stroke	43 (11.3)	26 (12.7)	17 (9.6)	.326
Previous heart disease	232 (60.7)	129 (63.2)	103 (57.9)	.284
Atrial fibrillation	201 (52.6)	105 (51.5)	96 (53.9)	.631
Previous admission for APE	54 (14.1)	38 (18.6)	16 (9.0)	**.008**
Baseline NYHA class III–IV	98 (25.6)	51 (25.0)	47 (26.4)	.797
Barthel index < 60 points	83 (21.7)	53 (26.0)	30 (16.9)	.041
Symptoms				
Increased baseline dyspnea	369 (96.6)	194 (95.1)	175 (98.3)	.099
Paroxysmal nocturnal dyspnea	78 (20.4)	37 (18.1)	41 (23.0)	.237
Orthopnea	172 (45.0)	89 (43.6)	83 (46.6)	.556
Lower limb edema	160 (41.9)	87 (42.6)	73 (41.0)	.746
Palpitations	165 (43.2)	94 (46.1)	71 (39.9)	.223
Poor peripheral perfusion	24 (6.3)	9 (4.4)	15 (8.4)	.112
Body temperature > 37.5°C	15 (3.9)	8 (3.9)	7 (3.9)	.958
Borg dyspnea scale [mean (SD)]	8 (2)	8.2 (2)	7.8 (2)	.892
Initial vital signs [mean (SD)]				
SBP (mmHg)	173.3 (32.9)	167.8 (30.7)	179.2 (34.4)	**.018**
DBP (mmHg)	97.5 (22.9)	95.8 (22.3)	99.5 (25.6)	.284
HR (bpm)	112.2 (22.6)	106.5 (23.3)	118.6 (22.4)	**< .001**
RR (breaths/min)	36.0 (6.4)	34.3 (6.1)	38.8 (6.2)	**< .001**
Baseline SpO_2 (%)	75.9 (10.4)	76.2 (9.9)	74.4 (10.5)	.513
SpO_2 with O_2 at 5 min (%)	90.0 (5.0)	90.6 (4.6)	89.5 (5.4)	.103
Axillary temperature (°C)	36.0 (1.7)	36.1 (1.6)	35.9 (1.7)	.782
$ETCO_2$ (mmHg)	34.5 (8)	34.8 (7)	34.3 (8)	.805
IV pharmacologic treatment				
Morphine chloride	288 (75.4)	146 (71.6)	142 (79.7)	.064
Nitroglycerin	285 (74.6)	148 (72.5)	137 (77.0)	.322
Diuretics	348 (91.1)	189 (92.6)	159 (89.3)	.258
Digoxin	75 (19.6)	35 (17.2)	40 (22.5)	.515
Amiodarone	25 (6.5)	10 (4.9)	15 (8.4)	.170
Methylprednisolone	63 (16.4)	38 (18.6)	25 (14.0)	.230
Other	148 (38.8)	75 (36.8)	73 (41.0)	.396

NIV: noninvasive ventilation; SD: standard deviation; APE: acute pulmonary edema; CKD: chronic kidney disease (Cr > 2 mg/dL); COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm: beats per minute; RR: respiratory rate; SpO_2: oxygen saturation; $ETCO_2$: end-tidal carbon dioxide; IV: intravenous.
Bold values indicate statistical significance ($P < .05$).

Table 4. Characteristics of prehospital noninvasive ventilation

	Total N = 382 n (%)
Exclusive CPAP mode	115 (64.6)
Need for pressure support over PEEP	63 (35.4)
PEEP value (mbar) [mean (SD)]	8 (2)
Pressure support value (mbar) [mean (SD)]	10 (1.5)
Need for orotracheal intubation*	6 (3.4)
Discontinuation of NIV due to intolerance	9 (5.1)
Discontinuation of NIV prehospital due to improvement	15 (8.4)
Continuation of prehospital NIV in the emergency department	130 (73.0)
Total duration of prehospital NIV (min) [mean (SD)]	48 (17.2)

*The need for orotracheal intubation was due to exhaustion, hemodynamic instability, or decreased level of consciousness.
NIV: noninvasive ventilation; CPAP: continuous positive airway pressure; PEEP: positive end-expiratory pressure; SD: standard deviation.

tion is short, supporting its initiation at home.[20,24] The stabilizing effect of NIV at the patient's bedside appears independent of the duration of the intervention and facilitates safer transfer to the hospital.

Regarding the ventilation mode used, in more than half of cases, NIV was performed exclusively with the CPAP (continuous positive airway pressure) mode. Studies comparing different NIV modalities—mainly CPAP vs pressure support ventilation—have not found significant differences in clinical or prognostic outcomes. Therefore, first-line use of the simpler CPAP technique is recommended, with escalation to pressure support if the patient shows signs of ventilatory failure.[10,17,18,22]

This study has several limitations. It was conducted in a prehospital setting, where care and NIV application were performed by heterogeneous clinical teams. To minimize this variability, standardized prior training and strict selection criteria were implemented. NIV tolerance varies depending on patient characteristics, potentially introducing selection bias. Regarding pharmacological treatment, not all patients received vasodilators, which can improve dyspnea and may influence RR outcomes. Additionally, differences in vasodilator dosing could have affected results.

In conclusion, a significant association was observed between prehospital NIV use in APE patients and faster correction of SpO_2 and RR parameters, allowing for optimal and early treatment initiation. NIV should be considered a first-line therapy for APE within emergency medical services, as it requires minimal additional time for trained healthcare teams and provides short-term clinical benefits.

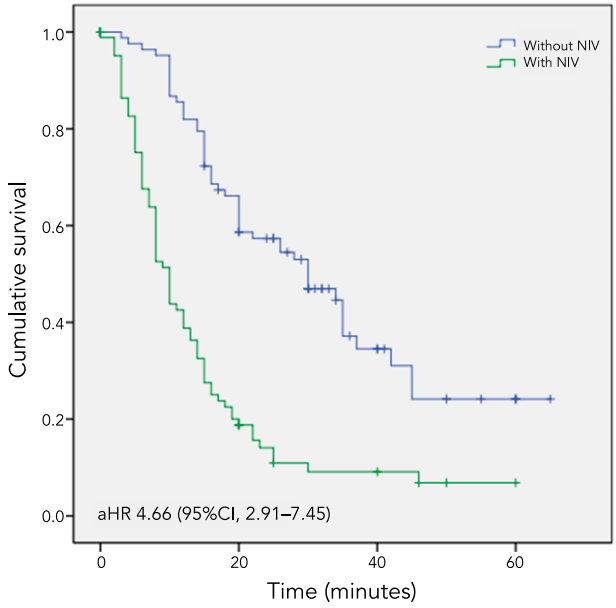

Figure 1. Survival curve for oxygen saturation > 94% in patients with noninvasive ventilation vs the control group.
NIV: noninvasive ventilation.

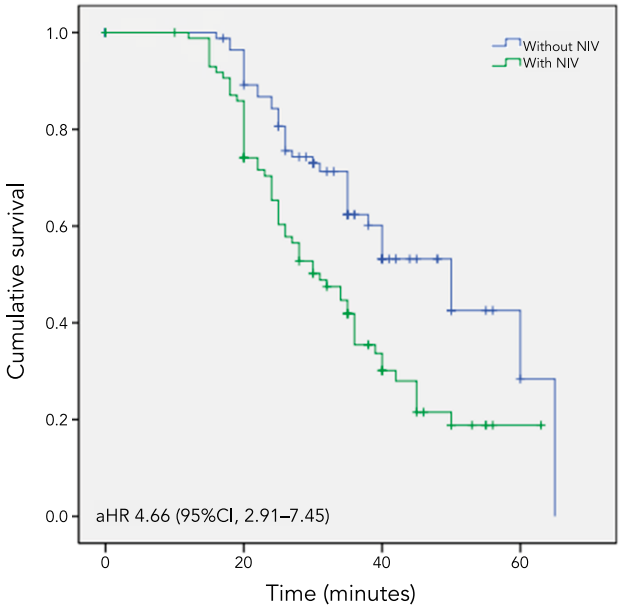

Figure 2. Survival curve for respiratory rate < 28 breaths per minute in patients with noninvasive ventilation vs the control group.
NIV: noninvasive ventilation.

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