Intensive Care Med (2012) 38:458–466
DOI 10.1007/s00134-012-2475-6

ORIGINAL

Andres Carrillo
Gumersindo Gonzalez-Diaz
Miquel Ferrer
Maria Elena Martinez-Quintana
Antonia Lopez-Martinez
Noemi Llamas
Maravillas Alcazar
Antoni Torres

Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure

Received: 22 July 2011
Accepted: 6 January 2012
Published online: 9 February 2012

A. Carrillo · G. Gonzalez-Diaz · M. E. Martinez-Quintana · A. Lopez-Martinez · N. Llamas · M. Alcazar
ICU, Hospital JM Morales Meseguer, Murcia, Spain

M. Ferrer (✉) · A. Torres
UVIIR, Servei de Pneumologia, Institut del Tòrax, Hospital Clinic, IDIBAPS, Universitat de Barcelona, Villarroel 170, 08036 Barcelona, Spain
e-mail: miferrer@clinic.ub.es
Tel.: +34-93-2275549
Fax: +34-93-2275549
URL: http://www.idibapsrespiratoryresearch.org

M. Ferrer · A. Torres
Centro de Investigación Biomedica En Red-Enfermedades Respiratorias (CibeRes, CB06/06/0028)-Instituto de Salud Carlos III, Madrid, Spain

Abstract *Purpose:* The use of non-invasive ventilation (NIV) in severe acute respiratory failure (ARF) due to community-acquired pneumonia (CAP) is controversial, and the risk factors for NIV failure in these patients are not well known. We assessed the characteristics and predictors of outcome of patients with CAP and severe ARF treated with NIV. *Methods:* We prospectively assessed 184 consecutive patients; 102 had "de novo" ARF, and 82 previous cardiac or respiratory disease. We defined successful NIV as avoidance of intubation and intensive care unit (ICU) survival at least 24 h in the ward. We assessed predictors of NIV failure and hospital mortality in multivariate analyses. *Results:* Patients with "de novo" ARF failed NIV more frequently than patients with previous cardiac or respiratory disease (47, 46% versus 21, 26%, $p = 0.007$). Worsening radiologic infiltrate 24 h after admission, maximum Sepsis-Related Organ Failure Assessment (SOFA) score and, after 1 h of NIV, higher heart rate and lower PaO_2/FiO_2 and bicarbonate independently predicted NIV failure. Likewise, maximum SOFA, NIV failure and older age independently predicted hospital mortality. Among intubated patients with "de novo" ARF, NIV duration was shorter in hospital survivors than non-survivors (32 ± 24 versus 78 ± 65 h, $p = 0.014$). In this group, longer duration of NIV before intubation was associated with decreased hospital survival (adjusted odds ratio 0.978, 95% confidence interval 0.962–0.995, $p = 0.012$). This association was not observed in patients with previous cardiac or respiratory disease. *Conclusions:* Successful NIV was strongly associated with better survival. If predictors for NIV failure are present, avoiding delayed intubation of patients with "de novo" ARF would potentially minimise mortality.

Keywords Non-invasive ventilation · BiPAP · Acute respiratory failure · Severe community-acquired pneumonia

Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality [1, 2]. Severe CAP is conceptually pneumonia requiring admission to the intensive care unit (ICU) or carrying a high risk of death [2, 3].

The cornerstone of the treatment of pneumonia is antibiotic therapy, and ventilatory support in patients with severe respiratory failure [4]. Invasive mechanical ventilation presents multiple complications [5, 6]. For this reason non-invasive ventilation (NIV) has been used for acute or acute-on-chronic respiratory failure of diverse

aetiologies [7–9]. The most important rationale for using NIV is to overcome an episode of severe acute respiratory failure (ARF) without the need for endotracheal intubation. However, few studies have assessed specifically the usefulness of NIV in patients with pneumonia [10], and it is even considered controversial due to a major variability in failure rates [10–13], which are generally higher than those observed in chronic obstructive pulmonary disease (COPD) [14] or cardiogenic pulmonary oedema [15]. Moreover, predictive factors for NIV failure have been studied in different aetiologies [13, 14, 16, 17]. A recent study found that lack of improvement in arterial oxygenation was the main predictor of NIV failure in patients with CAP [18]. However, this study assessed a limited number of patients. Therefore, studies assessing factors predicting outcome for NIV in larger populations of CAP with severe ARF are still needed.

In spite of the controversy surrounding the use of NIV out of COPD exacerbations or cardiogenic pulmonary oedema, several observational reports illustrate that hypoxaemic ARF is among the most frequent indications for NIV in real practice [19, 20]. The ICU of our institution has been using NIV for the management of patients with severe ARF secondary to pneumonia who do not need emergency intubation for more than 15 years.

Since the available evidence on the efficacy of NIV in pneumonia is not compelling, appropriate patient selection should be a key point to improve the success of this technique. To determine the clinical results and evolution of patients with CAP and severe ARF treated with NIV at our institution, we assessed the characteristics and outcomes of these patients and determined factors that predict failure of the technique and mortality.

Methods

Patients

We prospectively followed all consecutive patients with severe ARF due to CAP receiving NIV treatment in an 18-bed ICU of Hospital Morales Meseguer, a general university hospital in Murcia, Spain, from January 1997 to December 2008. The study was approved by the Ethics Committee of the institution.

Pneumonia was defined as a new pulmonary infiltrate on the admission chest radiograph and symptoms and signs of lower respiratory tract infection. Exclusion criteria were any degree of immunosuppression and other criteria previously published [21]. All patients received timely empiric antimicrobial therapy according to the local protocols.

All patients received stress ulcer and deep venous thrombosis prophylaxis. Patients with COPD, other chronic respiratory diseases, or in the presence of wheezing received nebulised bronchodilators and systemic steroids. Patients with hypotension received initially intravenous fluid therapy with crystalloids; if haemodynamic instability persisted, norepinephrin was initiated. Patients who responded to vasoactive drugs remained on NIV unless they required intubation for other reasons.

Non-invasive ventilation protocol

The indication for NIV was done by the attending physicians. Patients were continuously monitored with electrocardiogram, pulse oximetry, invasive and/or non-invasive blood pressure, and respiratory rate. The criteria used for implementing NIV were: (1) moderate to severe dyspnoea accompanied by respiratory rate $\geq$30 breaths/min or signs of increased work of breathing such as active contraction of the accessory respiratory muscles, and (2) arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2) ratio <250. Patients in need for emergency intubation at admission (respiratory or cardiac arrest, respiratory pauses with loss of alertness or gasping for air, major agitation inadequately controlled by sedation, signs of exhaustion, massive aspiration, inability to manage respiratory secretions appropriately, and haemodynamic instability without response to fluids and vasoactive agents) [13] were not treated with NIV.

Non-invasive ventilation was applied with specific NIV ventilators (BiPAP ST-D and VISION Ventilator; Respironics, Inc., Murrysville, PA, USA). As previously described [13, 21], patients were ventilated using the bi-level positive airway pressure mode (BiPAP). Face mask was used as first choice, but nasal mask was optionally used if patients did not tolerate face mask. The initial inspiratory positive airway pressure (IPAP) was set at 12 cmH_2O, and levels were raised by 2–3 cmH_2O as tolerated but did not exceed 25 cmH_2O. The initial expiratory positive airway pressure (EPAP) was set at 5 cmH_2O, and the levels were raised by 1–2 cmH_2O if needed to improve hypoxaemia. The FiO_2 was set to achieve SpO_2 >92% or PaO_2 >65 mmHg. Arterial blood gas samples were obtained from each patient before the connection to the ventilator and after 1 h of NIV. Subsequently, samples were obtained as clinically indicated.

Effectiveness of the technique

Non-invasive ventilation was considered successful if a patient avoided endotracheal intubation, was discharged from the ICU and remained alive and conscious for at least 24 h after being transferred to the ward. Failure of NIV therapy occurred when a patient experienced

worsening of gas exchange or respiratory distress leading to intubation or death. If NIV failed, patients who had not declined intubation underwent such procedure according to the criteria stated above [13, 21].

Data collection

At the start of NIV therapy demographic, clinical and laboratory variables were collected. The variables specifically related to pneumonia were the presence of unilateral or bilateral involvement, involvement of one or more pulmonary lobes, and pleural effusion on chest radiography, and the presence of aetiologic pathogens in diagnostic samples. Worsening pulmonary infiltrate was considered when a chest radiography done in the first 24 h of ventilation therapy showed an increase in pulmonary involvement for at least one lobe compared with the previous radiography. Patients' degree of severity and organ failure were estimated with the Simplified Acute Physiology Score (SAPS)-II [22], the Acute Physiology and Chronic Health Evaluation (APACHE)-II [23] and Confusion, Elevated Blood Urea Nitrogen, Respiratory Rate and Blood Pressure plus Age ≥65 years (CURB65) score [24] calculated at admission, and the Sepsis-Related Organ Failure Assessment (SOFA) [25] score calculated daily. Septic shock [26] at admission was also noted.

Acute respiratory failure was considered "de novo" in patients without previous cardiac or respiratory disease [19].

Statistical analysis

Qualitative or categorical variables, expressed as number and percentages, were compared with the χ^2 or Fisher's exact tests. Continuous variables were expressed as mean ± standard deviation (SD), and compared between groups using the Student t test for independent data, and with Pearson's correlation between two continuous variables. All the analyses were two-tailed, and p values <0.05 were considered significant.

The variables identified as predictors of NIV failure and hospital mortality on univariate analysis were included in a multivariate logistic regression with a conditional stepwise forward model ($p_{in} < 0.10$, $p_{out} < 0.05$) to correct for co-linearity. Adjusted odds ratios and 95% confidence intervals were computed for variables independently associated with NIV failure or hospital mortality. The predictive capacity for NIV failure or hospital mortality of quantitative variables were assessed with receiver-operating characteristic (ROC) curves; the area under the curve (AUC), optimal cut-off values, sensitivity, specificity and positive and negative likelihood ratio [27] were calculated. Data were processed with SPSS 16.0.

Results

Patients

During the study period 250 patients were admitted to the ICU with primary diagnosis of CAP; 50 (20%) received oxygen therapy, 16 (6%) were intubated at ICU admission, and 184 (74%) received NIV. Patients received NIV for 44 ± 33 h (mean ± SD) along 2.8 ± 1.9 days. During NIV treatment the maximal inspiratory and expiratory positive airway pressure were 19 ± 3 and 9 ± 1 cmH_2O, respectively.

Non-invasive ventilation was successful in 116 patients (63%). Among patients with NIV failure, 59 were intubated (32%), and the remaining 9 patients died without intubation after a do-not-intubate order. The main reason for intubation was worsening of respiratory insufficiency in 39 patients, uncontrolled shock in 17, and intolerance to NIV in 3 cases.

Patients with "de novo" ARF and previous cardiac or respiratory disease (Table 1)

Acute respiratory failure was considered "de novo" in 102 (55%) patients, whereas the remaining had history of cardiac or respiratory disease. Patients with previous cardiac or respiratory disease failed NIV less frequently than patients with "de novo" ARF. They were older and more frequently males. At admission they had higher $PaCO_2$ and bicarbonate, lower arterial pH and respiratory rate, and more frequently decreased consciousness.

Complications related with non-invasive ventilation

Sixty-nine (38%) patients had at least one complication related with NIV. The most common complications were skin lesions, from erythema to skin ulceration (57, 31%), eye irritation (24, 13%), claustrophobia (15, 8%), and gastric distension (6, 3%). The duration of NIV was longer in those who presented skin lesions (69 ± 38 versus 32 ± 23 h, respectively, $p < 0.001$), without differences between the two groups. Serious complications were three cases of total intolerance, one of nosocomial pneumonia during NIV, one pneumothorax, one patient with vomiting and bronchial aspiration and two cases with mucus plugs detected on intubation.

Prediction of non-invasive ventilation failure (Table 2)

In both groups, patients with successful NIV treatment were less severe, assessed by less need for vasoactive

Table 1 Clinical and ventilatory characteristics of patients with "de novo" acute respiratory failure and with previous cardiac or respiratory disease

	"De novo" ARF ($n = 102$)	Previous CR disease[a] ($n = 82$)	p value
Age (years)	62 ± 18	72 ± 11	<0.001
Sex, male/female	60/42	63/19	0.015
NIV success, *n* (%)	55 (54%)	61 (74%)	0.007
SAPS-II	42 ± 14	46 ± 14	0.078
CURB65	2.5 ± 1.0	2.7 ± 0.9	0.097
Maximum SOFA score			
During NIV	7.0 ± 3.8	6.3 ± 3.2	0.16
During ICU stay	8.2 ± 4.9	7.0 ± 4.2	0.064
Vasoactive drugs at onset of NIV, *n* (%)	31 (30%)	19 (23%)	0.35
ARDS criteria, *n* (%)	35 (34%)	15 (18%)	0.024
Glasgow Coma Score ≤12, *n* (%)	8 (8%)	20 (24%)	0.004
Respiratory rate (breaths/min)	37 ± 7	34 ± 7	0.003
Heart rate (beats/min)	108 ± 20	105 ± 20	0.28
PaO_2/FiO_2 ratio (mmHg)	127 ± 34	136 ± 37	0.084
$PaCO_2$ (mmHg)	42 ± 14	60 ± 22	<0.001
Arterial pH	7.37 ± 0.08	7.27 ± 0.12	<0.001
HCO_3 (mEq/L)	21.3 ± 2.8	30.1 ± 6.2	<0.001
ICU stay (days)	10 ± 12	7 ± 7	0.089
Hospital stay (days)	20 ± 16	20 ± 18	0.87
ICU mortality, *n* (%)	22 (22%)	12 (15%)	0.31
Hospital mortality, *n* (%)	28 (28%)	19 (23%)	0.63

Values are given as mean ± SD or *n* (%)

ARF acute respiratory failure, *CR* cardiac or respiratory, *NIV* non-invasive ventilation, *SAPS* Simplified Acute Physiology Score, *CURB65* Confusion, Elevated Blood Urea Nitrogen, Respiratory Rate and Blood Pressure plus Age ≥65 years, *SOFA* Sepsis-Related Organ Failure Assessment, *ICU* intensive care unit

[a] Among patients with previous cardiac or respiratory disease, 67 patients had COPD, associated with a chronic heart disease in 15 cases, with morbid obesity in 6, and with chest wall deformity in 1 case. Overall, 14 patients had morbid obesity associated with hypoventilation, and 3 patients had a chest wall deformity. In this group, 22 patients had chronic heart disease, including 15 cases associated with COPD and 2 with obesity associated with hypoventilation

drugs at onset of NIV, severity scores and acidosis, had less extensive radiologic findings, less acute respiratory distress syndrome (ARDS) criteria, and lower respiratory and heart rate and better oxygenation after 1 h of NIV. In patients with "de novo" ARF, successful NIV was also associated with lower respiratory rate and better oxygenation at onset of NIV. In patients with previous cardiac or respiratory disease, successful NIV was also associated with lower heart rate at onset of NIV and higher arterial pH and better level of consciousness after 1 h of NIV. Age, sex and $PaCO_2$ were not related with NIV outcome in both groups.

The ICU stay was shorter, and mortality lower in patients with successful treatment with NIV.

Since the variables significantly associated with NIV outcome were essentially the same for patients with "de novo" ARF and previous cardiac or respiratory disease (Table 2), the multivariate analysis of predictors of NIV outcome was performed in the overall population. The variables independently associated with NIV failure were worsening of radiological infiltrate 24 h after admission, maximum SOFA score during NIV, and higher heart rate, lower PaO_2/FiO_2 ratio and lower bicarbonate after 1 h of NIV (Table 3). Except for heart rate, these variables were highly accurate in predicting NIV failure, as shown in this table.

Analyses of survival (Table 4)

Hospital survivors from both groups were younger, less severe, assessed by severity scores and acidosis, had failed NIV less frequently, and had lower respiratory rate after 1 h of NIV. In patients with "de novo" ARF, survival was also associated with less worsening of pulmonary infiltrate 24 h after the onset of NIV and better oxygenation. In patients with previous cardiac or respiratory disease, survival was also associated with bilateral radiologic involvement and ARDS criteria, and need for vasoactive drugs at onset of NIV. As for NIV outcome, sex and $PaCO_2$ were not related with survival in both groups.

In the overall population, the multivariate analysis identified maximum SOFA score during the ICU stay, NIV failure and older age as independent predictors of hospital mortality (Table 5). Maximum SOFA score and NIV failure were the most accurate variables in predicting NIV failure, as shown in this table.

Delayed intubation and hospital mortality

Among intubated patients with "de novo" ARF, the duration of NIV in hospital survivors was shorter than that

Table 2 Variables associated with successful and unsuccessful treatment with non-invasive ventilation in patients with "de novo" ARF and previous cardiac or respiratory disease

	"De novo" ARF			Previous cardiac or respiratory disease		
	NIV success ($n = 55$)	NIV failure ($n = 47$)	p value	NIV success ($n = 61$)	NIV failure ($n = 21$)	p value
SAPS-II	38 ± 11	47 ± 15	<0.001	42 ± 11	58 ± 16	<0.001
CURB65	2.3 ± 0.9	2.7 ± 1.1	0.077	2.5 ± 0.8	3.4 ± 0.9	<0.001
Maximum SOFA score during NIV	5.0 ± 2.5	9.3 ± 3.8	<0.001	5.1 ± 2.2	9.6 ± 3.6	<0.001
Radiologic findings, *n* (%)						
Bilateral involvement	10 (18%)	27 (57%)	<0.001	6 (10%)	9 (53%)	0.002
Worsening pulmonary infiltrate 24 h after onset of NIV	4 (10%)	37 (90%)	<0.001	12 (20%)	13 (52%)	<0.001
ARDS criteria, *n* (%)	10 (18%)	25 (71%)	<0.001	6 (10%)	9 (43%)	0.002
Vasoactive drugs at onset of NIV, *n* (%)	8 (26%)	23 (74%)	<0.001	6 (10%)	13 (62%)	<0.001
Glasgow Coma Score ≤12, *n* (%)						
After 1 h of NIV	1 (2%)	4 (9%)	0.18	6 (10%)	7 (33%)	0.018
Respiratory rate (breaths/min)						
At onset of NIV	35 ± 6	39 ± 9	0.013	33 ± 7	35 ± 8	0.31
After 1 h of NIV	30 ± 5	37 ± 9	<0.001	29 ± 3	32 ± 6	0.018
Heart rate (beats/min)						
At onset of NIV	106 ± 22	110 ± 17	0.36	101 ± 19	116 ± 18	0.002
After 1 h of NIV	101 ± 19	110 ± 18	0.029	98 ± 17	116 ± 20	<0.001
PaO_2/FiO_2 ratio (mmHg)						
At onset of NIV	135 ± 30	116 ± 35	0.004	139 ± 31	127 ± 50	0.21
After 1 h of NIV	178 ± 32	139 ± 39	<0.001	181 ± 35	158 ± 57	0.028
Arterial pH						
At onset of NIV	7.38 ± 0.08	7.36 ± 0.11	0.44	7.28 ± 0.12	7.24 ± 0.12	0.19
After 1 h of NIV	7.37 ± 0.05	7.36 ± 0.10	0.32	7.31 ± 0.08	7.25 ± 0.11	0.005
HCO_3 (mEq/L)						
At onset of NIV	22.2 ± 2.3	20.2 ± 3.0	0.001	31.0 ± 3.4	27.4 ± 5.8	0.012
After 1 h of NIV	22.3 ± 2.8	19.3 ± 3.7	<0.001	32.0 ± 3.8	25.1 ± 8.6	0.002
ICU stay (days)	6 ± 4	15 ± 16	0.001	5 ± 3	13 ± 13	0.010
Hospital stay (days)	19 ± 14	21 ± 18	0.51	18 ± 14	24 ± 26	0.32
Among survivors	19 ± 14	26 ± 10	0.055	18 ± 14	28 ± 27	0.099
ICU mortality, *n* (%)	0 (0%)	34 (50%)	<0.001	0 (0%)	12 (57%)	<0.001
Hospital mortality, *n* (%)	5 (9%)	23 (49%)	<0.001	5 (8%)	14 (67%)	<0.001
Among intubated patients, *n* (%)[a]	–	16 (40%)	–	–	12 (63%)	–

Values are given as mean ± SD or *n* (%)

ARF acute respiratory failure, *NIV* non-invasive ventilation, *SAPS* Simplified Acute Physiology Score, *CURB65* Confusion, Elevated Blood Urea Nitrogen, Respiratory Rate and Blood Pressure plus Age ≥65 years, *SOFA* Sepsis-Related Organ Failure Assessment, *ICU* intensive care unit, *ARDS* acute respiratory distress syndrome

[a] The remaining nine patients died without intubation after a do-not-intubate order

Table 3 Multivariate analysis of variables independently associated with non-invasive ventilation failure in the overall population

	Adj. OR	95% CI	p value	AUC	Optimal cut-off	Sensitivity (%)	Specificity (%)	Likelihood ratio	
								Positive	Negative
Maximum SOFA during NIV	1.442	1.187–1.753	<0.001	0.86	≥7	81	80	4.08	0.24
Worsening X-ray infiltrate 24 h after onset of NIV	84.23	16.74–423.8	<0.001	–	–	77	86	5.58	0.27
Heart rate 1 h after NIV onset, min^{-1}	1.064	1.029–1.100	<0.002	0.68	≥104	63	67	1.93	0.55
PaO_2/FiO_2 ratio 1 h after NIV onset, mmHg	0.980	0.965–0.996	0.012	0.78	<144	53	91	5.58	0.52
HCO_3 1 h after NIV onset, mEq/L	0.802	0.711–0.905	<0.001	0.77	<23	67	68	2.72	0.48

Adj. OR adjusted odds ratio, *CI* confidence interval, *SOFA* Sepsis-Related Organ Failure Assessment, *AUC* area under the ROC curve

of non-survivors (32 ± 24 versus 78 ± 65 h, $p = 0.014$, Fig. 1 left panel), with an AUC of 0.70 for predicting hospital mortality. The duration of NIV before intubation that best predicted mortality was ≥53 h, with sensitivity of 69% and specificity of 83%. The SAPS-II, CURB65 and SOFA scores at admission did not correlate with the

Table 4 Variables associated with hospital mortality in patients with "de novo" ARF and previous cardiac or respiratory disease

	"De novo" ARF			Previous cardiac or respiratory disease		
	Alive ($n = 74$)	Dead ($n = 28$)	p value	Alive ($n = 63$)	Dead ($n = 19$)	p value
Age (years)	58 ± 19	73 ± 11	<0.001	71 ± 11	76 ± 7	0.024
SAPS-II	39 ± 12	50 ± 15	<0.001	43 ± 12	57 ± 17	<0.001
CURB65	2.2 ± 0.9	3.1 ± 1.1	<0.001	2.5 ± 0.8	3.5 ± 0.9	<0.001
Maximum SOFA score during ICU stay	6.3 ± 3.2	13.3 ± 4.9	<0.001	5.5 ± 2.3	11.9 ± 5.3	<0.001
NIV failure, *n* (%)	24 (32%)	23 (82%)	<0.001	7 (11%)	14 (74%)	<0.001
Radiologic findings, *n* (%)						
Bilateral involvement	24 (32%)	13 (46%)	0.28	8 (13%)	7 (37%)	0.037
Worsening pulmonary infiltrate 24 h after onset of NIV	23 (31%)	18 (44%)	0.003	17 (27%)	8 (47%)	0.20
ARDS criteria, *n* (%)	22 (30%)	13 (46%)	0.18	8 (13%)	7 (37%)	0.037
Vasoactive drugs at onset of NIV, *n* (%)	20 (27%)	11 (39%)	0.34	8 (13%)	11 (58%)	<0.001
Glasgow Coma Score ≤12: *n* (%)						
At onset of NIV	3 (4%)	5 (18%)	0.034	13 (21%)	7 (37%)	0.22
After 1 h of NIV	2 (3%)	3 (11%)	0.13	8 (13%)	5 (26%)	0.17
Respiratory rate, breaths/min after 1 h of NIV	31 ± 7	33 ± 5	0.026	29 ± 3	32 ± 5	0.054
PaO_2/FiO_2 (mmHg)						
At onset of NIV	132 ± 33	112 ± 32	0.006	134 ± 30	143 ± 54	0.49
After 1 h of NIV	167 ± 41	144 ± 35	0.011	175 ± 33	176 ± 66	0.95
Arterial pH						
At onset of NIV	7.38 ± 0.09	7.34 ± 0.12	0.080	7.28 ± 0.11	7.24 ± 0.13	0.32
After 1 h of NIV	7.38 ± 0.06	7.34 ± 0.10	0.11	7.30 ± 0.09	7.28 ± 0.10	0.27
HCO_3 (mEq/L)						
At onset of NIV	22 ± 3	20 ± 3	0.053	31 ± 3	28 ± 6	0.058
After 1 h of NIV	22 ± 3	19 ± 4	0.003	32 ± 4	25 ± 9	0.002

Values are given as mean ± SD or *n* (%). Variables with $p < 0.10$ are shown in this table

NIV non-invasive ventilation, *SAPS* Simplified Acute Physiology Score, *APACHE* Acute Physiology and Chronic Health Evaluation, *CURB65* Confusion, Elevated Blood Urea Nitrogen, Respiratory Rate and Blood Pressure plus Age ≥65 years, *SOFA* Sepsis-Related Organ Failure Assessment, *ICU* intensive care unit, *ARDS* acute respiratory distress syndrome

Table 5 Multivariate analysis of variables independently associated with hospital mortality in the overall population

	Adj. OR	95% CI	p value	AUC	Optimal cut-off	Sensitivity (%)	Specificity (%)	Likelihood ratio	
								Positive	Positive
Maximum SOFA during ICU stay	1.342	1.158–1.556	<0.001	0.86	≥12	68	95	13.3	0.34
NIV failure	6.78	1.65–27.95	0.008	–	–	79	77	3.48	0.27
Older age (years)	1.118	1.056–1.185	<0.001	0.68	≥72	72	57	1.68	0.49

Adj. OR adjusted odds ratio, *CI* confidence interval, *SOFA* Sepsis-Related Organ Failure Assessment, *AUC* area under the ROC curve, *NIV* non-invasive ventilation

duration of NIV in these patients, indicating that patients with longer time on NIV before intubation were not more severely ill at admission. Moreover, the need for vasoactive drugs at onset of NIV was associated with shorter duration of NIV before intubation (31 ± 40 versus 65 ± 52 h, respectively, $p = 0.030$), indicating that patients treated with vasoactive drugs who need intubation fail earlier than those without these drugs. After adjusting for these variables, increased duration of NIV before intubation in hours was significantly associated with decreased hospital survival (adjusted odds ratio 0.978, 95% confidence interval 0.962–0.995, $p = 0.012$).

By contrast, no relationship was found between duration of NIV before intubation and mortality in patients with previous cardiac or respiratory disease (Fig. 1, right panel).

Discussion

Patients with CAP and previous cardiac or respiratory disease responded better to NIV than those with "de novo" ARF, as expected from previous studies [10, 19]. Successful NIV treatment strongly predicted

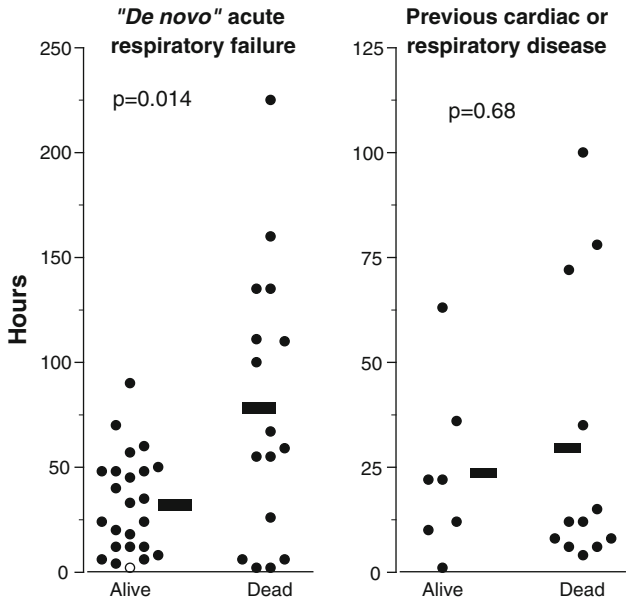

Fig. 1 Duration of non-invasive ventilation in patients who needed intubation and survived or died in the hospital. *Left panel* patients with "de novo" acute respiratory failure. *Right panel* patients with previous cardiac or respiratory disease. *Horizontal bars* represent mean values of survivors and non-survivors for intubated patients from each group

survival. We have also found a consistent association between delayed intubation and decreased survival in patients with "de novo" ARF.

The only randomised clinical trial that assessed the efficacy of NIV in patients with CAP and severe ARF showed that the benefits of NIV in terms of less need for intubation and better survival were restricted to patients with COPD and hypercapnic respiratory failure only [10]. More recently, NIV was effective in decreasing the rates of intubation and mortality in severely hypoxaemic patients with pneumonia, compared with high-concentration oxygen therapy, with faster improvement of hypoxaemia and tachypnoea [13]. Although those results were promising, routine use of NIV in patients with CAP and without COPD is not clearly recommended by recent guidelines [1, 28].

Patients with CAP are among those with the highest rate of NIV failure, either in COPD patients [29] or those with hypoxaemic ARF [11, 12, 17]. The rate of NIV failure in patients with pneumonia is widely variable, being lower in controlled clinical trials (21–26%) [10, 13, 30] than observational studies (33–66%) [11, 12, 17, 18, 31], possibly due to selection criteria of patients. We found similar rates of NIV failure in our population.

The risk factors for NIV failure have been studied in mixed patients with hypoxaemic ARF [17, 32, 33]. In specific populations with severe CAP treated with helmet NIV, a 56% failure rate was reported [18]. Higher severity of patients, worse oxygenation, lower pH, and less improvement of blood gases after ventilatory support were related with NIV failure on univariate analysis. This study, however, was restricted to patients with "de novo" ARF, and did not consider variables other than general severity scores and ventilatory and respiratory parameters.

Studies on NIV often include pneumonia as a cause of "de novo" or hypoxaemic ARF only. However, the great proportion of previous cardiac or respiratory disease in our patients is not surprising, since large published series of hospitalised patients with CAP report high rates of chronic respiratory or cardiac co-morbidities [34, 35]. Hence, the outcome of NIV in patients with CAP from studies that have excluded COPD or hypercapnic patients [11, 12, 17, 18] should not be extrapolated to general CAP populations treated with NIV.

Similarly to previous reports [17–19, 21, 33], severity scores at admission and worse respiratory and cardiovascular function were associated with NIV failure. Variables related with initial severity and worse clinical evolution in pneumonia, such as the need for vasoactive drugs, organ system dysfunction [28, 36], and extension and worsening of radiological infiltrates, were also associated with failure. These variables had not been assessed in previous reports.

Higher organ system failure during NIV treatment, including metabolic acidosis, and variables related with worse initial response to the empiric treatment and NIV support were independently associated with NIV failure on multivariate analysis. These results indicate that the optimal management of these patients seems not restricted to appropriate support with NIV but should also include general support measures and effective empiric treatment.

Concerns have been raised due to the high mortality rate of patients who fail NIV treatment, particularly in "de novo" ARF, and the possibility that unnecessary delay of intubation results in excess mortality [19, 32]. Particularly, an actual mortality of patients intubated after NIV failure higher than mortality predicted by severity scores has been reported [32]. However, these comparisons may be misleading, since severity scores often underestimate hospital mortality in ICU patients [37, 38]. To our knowledge, this is the first time a consistent association between delayed intubation and increased mortality in patients with CAP and "de novo" ARF has been shown. Longer duration of NIV before intubation was not related with severity of patients at admission. Moreover, patients with vasoactive drugs who needed intubation failed NIV earlier than those without. Therefore, this excess of mortality should be attributed to delayed intubation rather than a more severely ill selected population.

Several variables independently associated with NIV failure, such as higher SOFA score, worsening of radiologic infiltrate and low oxygenation after 1 h of NIV, were highly predictive of this event (Table 3). In patients

with "de novo" ARF, we strongly advise careful management in order to avoid potential harm related to excessive delay in intubation when the response to NIV is not positive, particularly when they require vasoactive drugs, a condition particularly associated with NIV failure in patients with acute lung injury [32], as well as in those patients who do not achieve those PaO_2/FiO_2 cut-offs after 1 h of NIV treatment, as previously described [17, 33]. By contrast, this recommendation cannot apply for patients with previous cardiac or respiratory disease.

In the overall population, older age, NIV failure and higher organ system failure were independently associated with hospital mortality. Thus, further improvement of survival could be potentially achieved by combining adequate support against organ system dysfunction and optimal NIV management of these patients.

The present study has several limitations. First, the effectiveness of any treatment must be determined by a randomised controlled trial. In the absence of a control group, definitive conclusions cannot be drawn. Second, the study was conducted in a centre with major experience in the use of NIV, and therefore these results cannot be extrapolated to less trained and equipped hospitals.

In conclusion, successful treatment with NIV, which is strongly related with less organ system failure of patients and a good initial response to the antimicrobial treatment and NIV support, was strongly associated with better survival. In presence of predictors for NIV failure, avoiding delayed intubation of patients with "de novo" ARF is strongly advised in order to potentially minimise mortality.

Acknowledgment Funded by CibeRes (CB06/06/0028)-ISCiii, 2009 SGR 911, IDIBAPS.

References

1. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG (2007) Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(Suppl 2):S27–S72
2. Restrepo MI, Anzueto A (2009) Severe community-acquired pneumonia. Infect Dis Clin North Am 23:503–520
3. Oosterheert JJ, Bonten MJ, Hak E, Schneider MM, Hoepelman AI (2003) Severe community-acquired pneumonia: what's in a name? Curr Opin Infect Dis 16:153–159
4. Pierson DJ (2002) Indications for mechanical ventilation in adults with acute respiratory failure. Respir Care 47:249–262
5. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903
6. Pinhu L, Whitehead T, Evans T, Griffiths M (2003) Ventilator-associated lung injury. Lancet 361:332–340
7. Mehta S, Hill NS (2001) Noninvasive ventilation (State of the Art). Am J Respir Crit Care Med 163:540–577
8. (2001) International consensus conferences in intensive care medicine: noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 163:283–291
9. Nava S, Hill N (2009) Non-invasive ventilation in acute respiratory failure. Lancet 374:250–259
10. Confalonieri M, Potena A, Carbone G, Della Porta R, Tolley E, Meduri G (1999) Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med 160:1585–1591
11. Jolliet P, Abajo B, Pasquina P, Chevrolet JC (2001) Non-invasive pressure support ventilation in severe community-acquired pneumonia. Intensive Care Med 27:812–821
12. Domenighetti G, Gayer R, Gentilini R (2002) Noninvasive pressure support ventilation in non-COPD patients with acute cardiogenic pulmonary edema and severe community-acquired pneumonia: acute effects and outcome. Intensive Care Med 28:1226–1232
13. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A (2003) Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 168:1438–1444
14. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS (2003) Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: cochrane systematic review and meta-analysis. BMJ 326:185–189
15. Weng CL, Zhao YT, Liu QH, Fu CJ, Sun F, Ma YL, Chen YW, He QY (2010) Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. Ann Intern Med 152:590–600
16. Rodriguez ML, Carrillo AA, Melgarejo MA, Renedo VA, Parraga RM, Jara PP, Millan MJ, Gonzalez DG (2005) Predictive factors related to success of non invasive ventilation and mortality in the treatment of acute cardiogenic pulmonary edema. Med Clin (Barc) 124:126–131
17. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, Pelaia P, Principi T, Gregoretti C, Beltrame F, Pennisi MA, Arcangeli A, Proietti R, Passariello M, Meduri GU (2001) Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med 27:1718–1728
18. Carron M, Freo U, Zorzi M, Ori C (2010) Predictors of failure of noninvasive ventilation in patients with severe community-acquired pneumonia. J Crit Care 25:514–540
19. Demoule A, Girou E, Richard JC, Taille S, Brochard L (2006) Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med 32:1756–1765
20. Schettino G, Altobelli N, Kacmarek RM (2008) Noninvasive positive-pressure ventilation in acute respiratory failure outside clinical trials: experience at the Massachusetts General Hospital. Crit Care Med 36:441–447

21. Gonzalez Diaz G, Carrillo Alcaraz A, Pardo Talavera JC, Jara Perez P, Esquinas Rodriguez A, Garcia Cordoba F, Hill NS (2005) Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. Chest 127:952–960
22. Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II a severity of disease classification system. Crit Care Med 13:818–829
24. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT (2003) Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 58:377–382
25. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710
26. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM (2004) Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32:858–873
27. Fischer JE, Bachmann LM, Jaeschke R (2003) A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. Intensive Care Med 29:1043–1051
28. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le JI, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA (2009) BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 64 (Suppl 3):iii1–iii55
29. Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, Vitacca M (1995) Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax 50:755–757
30. Antonelli M, Conti G, Rocco M, Bufi M, Deblasi RA, Vivino G, Gasparetto A, Meduri GU (1998) A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 339:429–435
31. Cheung MT, Yam LY, Lau CW, Ching CK, Lee CH (2000) Use of non-invasive positive-pressure ventilation for acute respiratory failure: prospective study. Hong Kong Med J 6:361–367
32. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O (2006) Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. Crit Care 10:R79
33. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, Rocco M, Maviglia R, Pennisi MA, Gonzalez-Diaz G, Meduri GU (2007) A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 35:18–25
34. Liapikou A, Ferrer M, Polverino E, Balasso V, Esperatti M, Piner R, Mensa J, Luque N, Ewig S, Menendez R, Niederman MS, Torres A (2009) Severe community-acquired pneumonia: Validation of the Infectious Diseases Society of America/American Thoracic Society Guidelines to Predict an Intensive Care Unit Admission. Clin Infect Dis 48:377–385
35. Aliberti S, Amir A, Peyrani P, Mirsaeidi M, Allen M, Moffett BK, Myers J, Shaib F, Cirino M, Bordon J, Blasi F, Ramirez JA (2008) Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. Chest 134:955–962
36. Lisboa T, Blot S, Waterer GW, Canalis E, de MD, Rodriguez A, Rello J (2009) Radiologic progression of pulmonary infiltrates predicts a worse prognosis in severe community-acquired pneumonia than bacteremia. Chest 135:165–172
37. Goldhill DR, Sumner A (1998) Outcome of intensive care patients in a group of British intensive care units. Crit Care Med 26:1337–1345
38. Goldhill DR, Withington PS (1996) The effect of casemix adjustment on mortality as predicted by APACHE II. Intensive Care Med 22:415–419