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Non-invasive positive pressure ventilation in pneumonia outside Intensive Care Unit: An Italian multicenter observational study

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ABSTRACT

Background and objective: Non-Invasive Ventilation (NIV) represents a standard of care to treat some acute respiratory failure (ARF). Data on its use in pneumonia are lacking, especially in a setting outside the Intensive Care Unit (ICU). The aims of this study were to evaluate the use of NIV in ARF due to pneumonia outside the ICU, and to identify risk factors for in-hospital mortality.

Methods: Prospective, observational study performed in 19 centers in Italy. Patients with ARF due to pneumonia treated outside the ICU with either continuous positive airway pressure (CPAP) or noninvasive positive pressure ventilation (NPPV) were enrolled over a period of at least 3 consecutive months in 2013. Independent factors related to in-hospital mortality were evaluated.

Results: Among the 347 patients enrolled, CPAP was applied as first treatment in 176 (50.7%) patients,NPPV in 171 (49.3%). The NPPV compared with CPAP group showed a significant higher $PaCO_2$ (55 [47–78] vs 37 [32–43] mmHg, $p < 0.001$), a lower arterial pH (7.30 [7.21–7.37] vs 7.43 [7.35–7.47], $p < 0.001$), higher HCO3– (28 [24–33] vs 24 [21–27] mmol/L, $p < 0.001$). *De-novo* ARF was more prevalent in CPAP group than in NPPV group (86/176 vs 31/171 patients,$p < 0.001$). In-hospital mortality was 23% (83/347). Do Not Intubate (DNI) order and Charlson Comorbidity Index (CCI) ≥ 3 were independent risk factors for in-hospital mortality.

Conclusions: Outside ICU setting, CPAP was used mainly for hypoxemic non-hypercapnic ARF, NPPV for hypercapnic ARF. In-hospital mortality was mainly associated to patients' basal status (DNI status, CCI) rather than the baseline degree of ARF.

1. Introduction

Acute respiratory failure (ARF) represents a frequent complication in patients with pneumonia with rates up to 56% [1]. Although oxygen therapy is the cornerstone for ARF treatment, its efficacy might be minimized because of shunt effects due to the presence of pulmonary exudate and atelectasis.To improve oxygenation, alveolar recruitment obtained through the application of either invasive or non-invasive mechanical ventilation (NIV) might be necessary, especially in severe pneumonia [2,3].

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The role of NIV as a tool to treat ARF has dramatically increased over the past decades and its efficacy has been well studied in clinical practice, especially in treating acute cardiogenic pulmonary edema (ACPE) and exacerbation of Chronic Obstructive Pulmonary Disease (COPD). Concerning NIV treatment in ARF patients with pneumonia, its use has been proved to be effective only in patients with COPD [4] and in immunocompromised patients with lung infiltrates [5,6]. The lack of strong evidence in literature led international experts to suggest only cautious trials of NIV in well-selected patients with pneumonia and in trained settings with a clear caveat to avoid a delay in endotracheal intubation [7].

Recent audits reported a use of NIV in patients with ARF due to pneumonia in different settings. According to a recent European survey, up to 17% patients with non-hypercapnic ARF, including those with community-acquired pneumonia (CAP), were treated with NIV [8]. An Italian survey investigated NIV use outside the Intensive Care Unit (ICU) and reported 41% of the participating hospitals using NIV to treat pneumonia in non-immunocompromised patients and 63% pneumonia in immunocompromised patients[9]. Two recent randomized controlled trials (RCTs) also showed the efficacy of Continuous Positive Airway Pressure (CPAP) versus standard oxygen therapy in mild-to-severe pneumonia in a selected population [2,10]. Although supported by limited evidence, the application of NIV in ARF patients with pneumonia seems to be widely applied in clinical practice.

The aims of this study were to evaluate NIV use in “real life” to treat ARF due to pneumonia outside the ICU in Italy, comparing CPAP versus noninvasive positive pressure ventilation (NPPV), and to identify risk factors for in-hospital mortality in these patients.

2. Materialsandmethods

This was a prospective, multi-center, observational study enrolling consecutive patients with ARF due topneumonia admitted to 14 Emergency Departments (ERs) and 5 High Dependent Units (HDU) in Italy during a period of at least three consecutive months between 1st January 2013 to 31st December 2013. The study protocol was approved by the Ethic Committees of all the participating centers and all patients signed an informed consent.

Patients were included in the study if all of the following criteria were met: 1) ≥18 years old; 2) diagnosis of pneumonia; 3) presence of ARF; 4) use of either NPPV or non-invasive CPAP. In order to be more adherent to a real-life situation, patients with a Do-Not Intubated (DNI) order were also included in the analysis.

The exclusion criteria were: 1) patients admitted to ICU 2) patients undergoing invasive mechanical ventilation at the first evaluation.

All patients received antibiotic therapy and the management of pneumonia according to standard operating procedures [7,11,12]. Any physician could set either NPPV or CPAP according to standard operating procedures of its own center. As in the literature is not well known which is superior between CPAP and NPPV in pneumonia, unlike in treatment exacerbation of COPD or ACPE were it is clearly defined, the physician could chose either NPPV or CPAP according to the type of ARF.

2.1. Study definitions

Pneumonia was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization associated with one or more of the following: 1) new or increased cough with/without sputum production; 2) fever (≥37.8 °C) or hypothermia (< 35.6 °C); or 3) abnormal white blood cell count (either leukocytosis or leukopenia), or C-reactive protein values above the local upper limit.

CAP was defined as pneumonia acquired outside the hospital setting. HAP was defined as infections of the pulmonary parenchyma caused by pathogens that are present in hospital settings in patients admitted to the hospital for > 48 h.

ARF was defined as the presence of at least one of the following: PaO2/FiO2 ratio < 250; presence of signs of respiratory distress; respiratory acidosis (pH < 7.35 and paCO2 > 45 mmHg).

NIV included the use of either NPPV or CPAP. NPPV provides two levels of pressures: an inspiratory positive airway pressure (pressure support) and a continuous expiratory positive airway pressure (PEEP). CPAP only provides the continuous PEEP.

“De-novo ARF” was defined by the presence of ARF in a patient without previous history of respiratory or cardiac diseases [13].

Do Not Intubate (DNI) order was defined as the decision of the physician in charge to withheld intubation and to use NIV as “ceiling” treatment considering the characteristics of the patients (e.g. extremely poor functional status prior on admission, very low predicted probability of hospital survival) [14].

Severe sepsis was defined according to the guideline [15].

2.2. Study outcomes and study groups

Two study groups were identified: those treated with NPPV and those receiving CPAP treatment to treatARF due to pneumonia, as first NIV therapy.

In-hospital mortality defined as death for any cause during hospitalization.

2.3. Data collection

Clinical and physiological features, Charlson Comorbidity Index (CCI) [16], type and severity of pneumonia evaluated with the Pneumonia Severity Index (PSI) and the CURB65 score in CAP patients, Kelly Scale and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score were recorded within 24 h after NIV application. Arterial blood gas (ABG) analysis before NIV initiation, the use of CPAP or NPPV, type of interfaces, side effects, criteria for failure and in-hospital mortality were recorded.

2.4. Statistical analysis

The statistical analyses were performed using SPSS (version 20.0) for Mac (IBM, Armonk, NY, USA).The categorical data were presented as the number (percentage).The normally distributed data were presented as the mean (± SD) (or as median and interquartile range [IQR] for non-normally distributed data). Characteristics of patients treated with either CPAP or NPPV were compared. Categorical variables were compared with Chi-square and Fisher's exact tests. Quantitative continuous variables were compared using the Student *t*-test or the Mann-Whitney test for the normally and non-normally distributed variables, respectively.Independent risk factors for in-hospital mortality were analyzed with a logistic regression analysis.A two-sided p-value of 0.05 or less was considered statistically significant.

3. Results

3.1. General description of the population

A total of 347 patients (median age: 77 [IQR 66–85] years old, 57% men) with ARF due to pneumonia who were treated with either CPAP or NPPV were enrolled across 19 hospitals during the study period (Table 1).

Two hundred and ninety-six patients (85.4%) had CAP, while 51 patients (14.6%) had hospital acquired pneumonia (HAP). A microbiological diagnosis of pneumonia was obtained in 20% of the patients.

CPAP was applied in 176 (50.7%) and NPPV in 171 (49.3%) patients. NIV treatment was started in the ER in 268 (77%) patients and in HDU in 79 patients (23%). Patients' characteristics before NIV treatment are reported in Tables 1 and 2.

No significant differences were detected between CPAP and NIV

Table 1
General characteristics of the population.

	Total population (n = 347)	CPAP (n = 176, 50.7%)	NPPV (n = 171, 49.3%)	p	Missing
Age, mean (± SD) median [IQR]	73.78 (± 14) 77 [66–85]	72.42 (± 15) 76 [64–84]	75.18 (± 12) 79 [68–85]	0.072	0
Men	201 (57.9)	108 (61.4)	93 (54.4)	0.188	0
Type of pneumonia					
CAP	296 (85.4)	148 (84.1)	148 (86.5)	0.518	0
HAP	51 (14.6)	28 (15.3)	23 (12.9)	0.664	0
Bilateral pneumonia	103 (31)	62 (35)	41 (26)	0.057	0
Interstitial pneumonia	58 (17)	28 (16)	30 (19)	0.490	0
Severity					
CURB65 ≥ 3[b]	139/275 (50)	73/142 (64)	66/137 (48)	0.199	21
PSI ≥ 4[b]	242/282 (85)	111/140 (79)	131/142 (92)	0.006	14
APACHEII	18.45 (± 5.7)	16.9 (± 5.9)	19.98 (± 5.3)	0.000	10
Shock index ≥0.8	116 (39.7)	65 (43.9)	51 (35.4)	0.152	5
Severe sepsis	255 (74)	130 (75)	125 (74)	0.802	5
Comorbidities					
COPD	159 (45.8)	55 (31.3)	104 (60.8)	< 0.001	0
Congestive heart failure	79 (22.8)	26 (14.8)	53 (31)	< 0.001	0
Chronic kidney disease	89 (25.6)	46 (26.1)	43 (25.1)	0.833	0
Obesity	60 (17.3)	24 (13.6)	36 (21.1)	0.068	0
Neoplastic disease	74 (21.3)	40 (22.7)	34 (19.8)	0.510	0
Charlson Comorbidity Index	204 (58.8)	111 (63.1)	93 (54.4)	0.150	0
< 3	104 (30)	50 (28.4)	54 (31.6)		
3–4	39 (11.2)	15 (8.5)	24 (14)		
≥ 5					
Do not intubation order (DNI)	103 (29.7)	49 (27.8)	54 (31.6)	0.446	0
de novo ARF[a]	117 (33.7)	86 (48.9)	31 (18.1)	< 0.001	0

Values are given as number (%), unless otherwise stated.
[b] Only in patients with CAP.
[a] ARF de novo included patients without previous history of congestive heart failure and/or chronic respiratory diseases. CAP: Community-acquired pneumonia; HAP: hospitalized acquired pneumonia.

group in terms of age, gender, and comorbidities, although the prevalence of COPD and heart failure was significantly higher in the NPPV group. The presence of a *de-novo* ARF was higher in the CPAP group.

The two groups did not differ in terms of vital signs and laboratory analysis at the time of NIV initiation, although NPPV patients showed a significantly lower level of C-reactive protein than patients treated with CPAP (11 vs 17 mg/dL, p = 0.014, respectively). Patients in the NPPV group also showed significant higher $PaCO_2$ levels (55 [47–78] vs 37 [32–43] mmHg, p < 0.001), lower arterial pH (7.30 [7.21–7.37] vs 7.43 [7.35–7.47] p < 0.001), and higher HCO3- (28 [24–33] vs 24 [21–27] mmol/L, p < 0.001) compared with the CPAP group (Table 2). Among patients in the CPAP group, stand-alone CPAP generators were used in 130 (74%) patients, ventilators using CPAP modality in 17 (10%) patients and other devices in 29 (16%) patients. All the patients treated with NPPV used specifically designed ventilators for acute NIV.The interfaces used in CPAP group included helmet in 82 patients (46%), oro-nasal mask in 75 patients (43%), and total-face mask in 20 patients (11%). Interfaces used in NPPV group included: oro-nasal mask in 90 patients (53%), total-face mask in 75 (44%) and helmet in 6 (4%) patients. In the CPAP group, the mean PEEP value was 8 ± 2 cmH_2O, whereas in the NPPV group, the mean PEEP was 6.25 ± 2 cmH_2O and mean PS above PEEP was 16 ± 15 cmH_2O. Duration of CPAP and NPPV treatment was comparable between groups (mean 3.5 ± 2.6 and 3.6 ± 2.6 days, respectively).

3.2. Side effects associated to ventilation

Forty-one of 176 patients (23%) complained of discomfort due to

Table 2
Clinical characteristics of the population.

	Total population (n = 347)	CPAP (n = 176)	NIV (n = 171)	p	Missing
Vital signs					
Respiratory rate, per min	28 [20 − 32]	28 [22–35]	26 [20 − 30]	0.089	5
Heart rate, beats per min	100 [84–112]	100 [84–113]	100 [84–111]	0.753	5
Systolic blood pressure, mmHg	130 [110–150]	130 [110–150]	130 [110–150]	0.822	5
Diastolic blood pressure, mmHg	70 [60–80]	70 [60–80]	70 [60–80]	0.583	5
Kelly scale > 2, number (%)	60 (17.2)	21 (13)	39 (28)	0.001	5
Laboratory findings					
Leukocyte, cells/mm^3	11,780 [7885–16,472]	11.975 [7947–17,612]	11,620 [7822–15,507]	0.578	15
C-reactive protein, mg/dl	14 [4–31]	17 [5–32]	11 [2–27]	0.014	15
Platelets, cell/mm^3	234 [177–311]	233 [170–308]	237 [183–313]	0.572	15
Hemoglobin, mg/dl	12.2 [10.8–13.7]	11.9 [10.6–13.6]	12.6 [11.1–13.7]	0.105	15
Creatinine, mg/dl	1.18 [0.79–1.80]	1.17 [0.79–1.74]	1.18 [0.80–1.98]	0.806	15
PaO_2/FiO_2 ratio	176 [116–225]	171 [112 − 223]	178 [117–228]	0.527	10
$PaCO_2$, mmHg	44 [35–67]	37 [32–43]	55 [47–78]	< 0.001	10
Arterial pH	7.36 [7.26–7.45]	7.43 [7.35–7.47]	7.30 [7.21–7.37]	< 0.001	10
HCO3-, mmol/L	25 [22 − 30]	24 [21–27]	28 [24–33]	< 0.001	10
Lactate, mmol/L	2.7 [2.6–3.2]	2.7 [2.5–3.3]	2.7 [2.5–3.3]	0.900	10

Values are given as median [IQR], unless otherwise stated.

interface in the CPAP group and 49/171 patients (28%) in NPPV group.

Discomfort was responsible for the interruption of ventilation in 11/176 patients (6%) in the CPAP group; among these, 6 were treated with NPPV and 3 eventually died.

In 12/171 patients (7%),NPPVwas interrupted because of discomfort, and 2 died.

Overall, intolerance was responsible of clinical failure and death in 5/60 cases (8%). This means that in our series intolerance does not seem to play a major role in clinical failure and death.

Four of 82 (5%) patients treated with helmet CPAP developed upper limbs edema. Decubitus ulcers appeared in 4/176 patients (2%) of CPAP group and in 16/171 patients (9%) of NPPV group. New onset supraventricular arrhythmias were detected in 6/176 patients (5.2%) in CPAP group and in 7/171 patients (3.9%) in NPPV group. Myocardial ischemia was reported in 2/176 patients (1.8%) of CPAP group and in 1/171 (0.6%) patient in the NPPV group.

3.3. In hospital mortality

Overall, in-hospital mortality was 24% (83/347 patients), with a mortality of 24% (43/176) among patients treated with CPAP, and 23% (40/171) among patients treated with NPPV, p = 0.82. Thirteen patients among CPAP group and 10 among NPPV group (total 23 patients, 27%)died after resolution of ARF, because of other causes different than ARF (advanced neoplastic disease, cardiovascular event, pulmonary thromboembolism, liver cirrhosis).

Among the 83 patients who died, in 50 patients (60.2%) a DNI status was stated before NIV start.

Among the others 33 patients, 19 (23%) were intubated before death.

In the CPAP group 19/176 (11%) were intubated and 9 died after ETI; among these, 7 patients were switched from CPAP to NPPV before ETI. In the NPPV group 22/171 (13%) underwent ETI and 10 died.

In the CPAP group, 34 patients were switched from CPAP to NPPV, 6 because of intolerance and 28 because of inefficacy; among these, 19/34 survived (56%).

In Fig. 1 NIV failure and mortality has been reported in details.

The most significant variables associated with in-hospital mortality were showed in the Table 3. Risk factors independently associated with in-hospital mortality at the multivariate analysis were a CCI ≥ 3 (OR 2.79, 95%CI 1.36–5.7, p = 0.005) and DNI status (OR 6.61, 95%CI 3.4–12.85, p < 0.001).

3.4. On line supplement

The study centers are reported in Supplementary Table S1 and the main pathogen isolated is described in Supplementary Table S2.

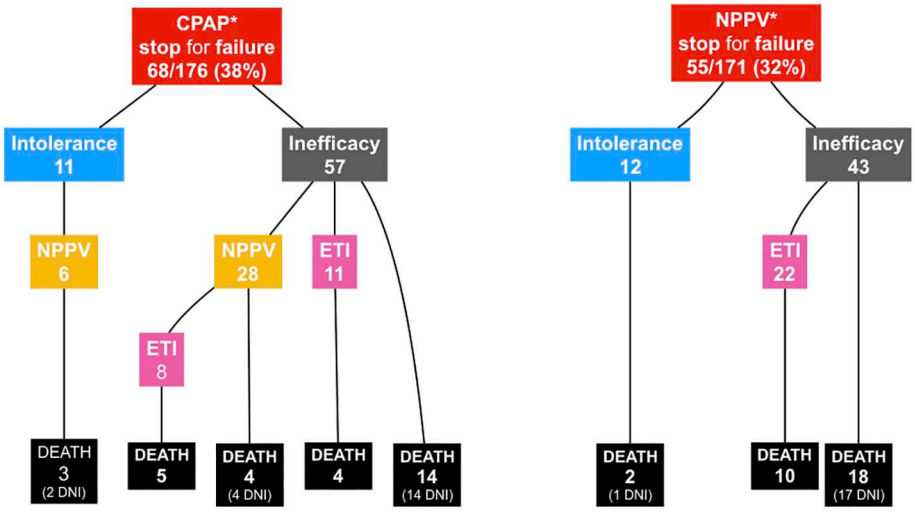
4. Discussion

The main findings of our study were: a) CPAP was used mainly in patients with hypoxemic not-hypercapnic ARF and in the de novo ARF, in line with previous European literature [2,10] b) NPPV was preferred in patients with acute on chronic respiratory failure c) CPAP was applied mainly with high-flow stand-alone generators rather than ventilators and the helmet was the most used interface d) in-hospital mortality are mainly associated to global severity of patients (DNI status, CCI) rather than the baseline degree of ARF.

Despite the literature about the use of NIV in treating ARF in pneumonia is scant and only few RCTs studies have been published to date [4,5,10,17], our data show that NIV is used in the treatment of pneumonia related ARF across many Italian hospitals. As previously described in the survey by Crimi et al. [8], NIV is widely adopted since the 80's in Europe and especially in France and Italy.In our real-life, observational study, the in-hospital mortality was 23%, similar to the in-hospital mortality detected in RCTs with selected population 25% reported by Confalonieri et al. [4], 18% by Ferrer et al [17], and 20% by *Brambilla* et al [10].

Compared to other non-Italian retrospective studies evaluated NIV in pneumonia, our patients seemed to be less severely compromised at the time of NIV initiation. Our population had a mean APACHE II of 18, compared to patients observed by *Carrillo* et al. where SAPS II was 42 [13] or Murad et al. where APACHE II was 23 [18]. Similarly, the impact of gas exchange reported in our paper showing a mean PaO_2/FiO_2 ratio of 176 was higher compared to previous studies by Carrillo and Murad who had a mean PaO_2/FiO_2 ratio in their population of 127 and 108, respectively [13,18]. We might speculate that NIV treatment in our population was started in an earlier stage of ARF, with patients enrolled before their admission to ICU.

In their retrospective study performed in three ICUs and evaluated the use of NIV in pneumonia, Murad et al [18] observed a failure rate outreaching 70%. The authors speculate that their patients received



DNI: do not intubate state; ETI: Endo-Tracheal Intubation
**13 patients in CPAP group and 10 patients in NPPV group died for other causes, after ARF resolution*

Fig. 1. NIV treatment failure and outcome.

Table 3
Risk factors for in-hospital mortality.

	Survivors (n = 264)	Not survivors (n = 83)	p	Missing
Age	76 [63–84]	80 [73–85]	0.002	0
Female, mean (± SD)	117 (44)	29 (35)	0.161	0
CPAP initial treatment	133 (50)	43 (52)	0.820	0
NIV initial treatment	131 (50)	40 (48)	0.820	0
COPD	124 (47)	35 (42)	0.444	0
Chronic Kidney disease	62 (23)	27 (32)	0.100	0
Obesity	54 (20)	6 (7)	0.005	0
Neoplastic disease	42 (15.9)	32 (38.5)	0.001	0
Charlson Comorbidity Index ≥3	94 (35.6)	49 (59)	0.001	0
De-novo ARF	89 (34)	28 (34)	0.997	0
Severe sepsis	187 (72)	68 (82)	0.077	5
DNI status	53 (20)	50 (60)	< 0.001	0
Systolic blood pressure mmHg, median [IQR]	130 [110–150]	130 [110–150]	0.813	5
Diastolic blood pressure mmHg, median [IQR]	70 [60–80]	70 [60–80]	0.460	5
Heart rate, mean (± SD)	100 ± 22	97 ± 23	0.489	5
pH, median [IQR]	7.35 [7.26–7.45]	7.38 [7.29–7.46]	0.228	10
$PaCO_2$ mmHg, median [IQR]	44 [35–68]	45 [34–60]	0.488	10
PaO_2/FiO_2 ratio, median [IQR]	179 [124–233]	161 [107–218]	0.087	10
Lactates > 2 mmol/L	82 (34.9)	36 (50)	0.027	10
Hb g/dL. median [IQR]	12.5 [11.0–13.9]	11.5 [10.3–13.0]	0.001	15
Platelets cell/mm^3, median [IQR]	231 [177–302]	242 [177–336]	0.397	15
Creatinine mg/dl, median [IQR]	1.11 [0.78–1.66]	1.50 [0.93–2.12]	0.002	15
C-reactive protein mg/dl, median [IQR]	13.3 [3.8–29.6]	17 [4.4–37]	0.132	15
HAP	33 (12)	18 (22)	0.041	0
CURB65 ≥ 3[a]	96/215 (45)	43/60 (72)	0.001	21
PSI ≥ 4[a]	182/222 (82)	60/60 (100)	0.000	14
APACHE II. mean (± SD)	18.02 (± 5.83)	19.87 (± 5.25)	0.01	10
Shock index ≥0.8	90 (39)	26 (40)	0.959	5
Kelly > 2	41 (18)	19 (27.1)	0.12	5

Values are given as number (%), unless otherwise stated.
[a] Score calculated only for CAP.

NIV at a later stage in their illness and as an alternative to intubation. Conversely, in another study performed in Italy in 4 Respiratory ICUs where NIV was applied in 126 pneumonia patients, the mortality rate was 24%. Patients' characteristics in terms of respiratory and circulatory compromise were comparable to our population, confirming that patient selection seems to be crucial for NIV success [19].

In our study, in-hospital mortality was independently associated with both the DNI status and the burden of comorbidities. Several elderly or neoplastic patients are usually considered as DNI and are managed outside the ICU. In study, patients with ARF and a DNI order were offered NIV as a “ceiling treatment” [20]. Recent data reported the usefulness of NIV as palliative care in patients with “end-stage” solid tumors and ARF [21,22] and in elderly population, for whom invasive therapy is controversial [23]. It is obvious that in case of failure the mortality of these patients is higher than the rest of the population, as previous reported from Schettino et al. [24] since none of these patients undergo ETI.

We found that mortality was not associated to the severity of ARF, particularly if we consider the level of PaCO2 and PaO_2/FiO_2 ratio. These data are consistent with several studies on risk factors for NIV failure [13]. In contrast to other studies [13,25], *de-novo* ARF and severe sepsis were not associated to mortality, although patients with *de-novo* ARF were treated more frequently with CPAP than with NPPV, probably because of their “non-chronic” status.

These findings, together with the lack of association between initial respiratory compromise and failure, suggest that the global severity of patients and the early NIV application rather than the initial hypoxemia conditioned the final outcome.

Sixty-eight patients failed CPAP treatment; among these, 34 were switched to NPPV, and 19 survivedwithout the need of endotracheal intubation (56%).This may suggest that in case of CPAP failure, NPPV may have a role as rescue treatment.

We observed a low rate of side effects (7%), mainly related to skin irritation, perhaps because of the high percentage of helmet use and full-face mask, conversely to other study [13] where main interfaces were oro-nasal masks carrying a high number of side effect.

Nevertheless, as this is an observational study we are not able to describe the efficacy of the NIV treatment.

The strengths of the study can be summarized as follow: this is the first observational national study investigating the use of both CPAP and NPPV in the treatment of pneumonia outside ICU. It is a multicenter study that included many hospitals across the entire without strict inclusion/exclusion criteria which ensured the generalizability of our results. The limitations of our study are linked to its observational design and the fact that it was conducted in centers with long-term experience in the use of NIV.

In conclusion, in real life setting outside ICU, CPAP seems to be mainly used on pneumonia patients withhypoxemic non-hypercapnic ARF while NPPV among those with hypercapnic ARF. In-hospital mortality seems to be mainly related to the patients' basal status (DNI status, CCI) rather than ARF severity, suggesting that the selection of the appropriate patient may predict NIV success or avoid NIV failure.

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Competing interests

Authors have no conflict of interests to disclose.

Data accessibility

Data are available by writing to corrisponding author.

Declarations of interest

none.

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Appendix A. 3P study group authors

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.09.025.

References

[1] Aliberti S, Brambilla AM, Chalmers JD, et al. Phenotyping community-acquired pneumonia according to the presence of acute respiratory failure and severe sepsis. Respir Res 2014; Mar. 4;15:27.
[2] Cosentini R, Brambilla AM, Aliberti S, et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. Chest 2010;138(1):114–20.
[3] L'Her E, Deye N, Lellouche F, et al. Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med 2005;172:1112–8.
[4] Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA. Umberto MeAcute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. duri G. Am J Respir Crit Care Med 1999;160(5):1585–91. Pt 1.
[5] Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 2001;344:481–7.
[6] Squadrone V, Massaia M, Bruno B, Marmont F, Falda M, Bagna C, et al. (2010) Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. Intensive Care Med 2010;36(10):1666–74.
[7] Mandell LA, Wunderink RG, Anzueto A, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl. 2):S27–72.
[8] Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J 2010;36(2):362–9.
[9] Cabrini L, Esquinas A, Pasin L, et al. An international survey on noninvasive ventilation use for acute respiratory failure in general non-monitored wards. Respir Care 2015;60(4):586–92.
[10] Brambilla AM, Aliberti S, Prina E, et al. Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. Intensive Care Med 2014;40(7):942–9.
[11] Lim WS, Baudouin SV, George RC, et al. Pneumonia guidelines committee of the BTS standards of care committee. Thorax 2009;64(Suppl. 3):iii1–55.
[12] Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005;26(6):1138–80.
[13] Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A, Llamas N, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. Intensive Care Med 2012;38:458–66.
[14] Corral-Gudino L, Jorge-Sánchez RJ, García-Aparicio J, et al. Use of noninvasive ventilation on internal wards for elderly patients with limitations to respiratory care: a cohort study. Eur J Clin Invest 2011;41(1):59–69.
[15] Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580–637.
[16] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.
[17] Ferrer M, Esquinas A, Leon M, et al. Non invasive ventilation in severe hypoxemic respi- ratory failure. A randomized clinical trial. Am J Respir Crit Care Med 2003;168:1438–44.
[18] Murad A, Li PZ, Dial S, Shahin J. The role of noninvasive positive pressure ventilation in community-acquired pneumonia. J Crit Care 2015;30:49–54.
[19] Nicolini A, Ferraioli G, Ferrari-Bravo M, Barlascini C, Santo M, Ferrera L. Early noninvasive ventilation treatment for respiratory failure due to severe community-acquired pneumonia. Clin Respir J 2016;10:98–103.
[20] Curtis JR, Cook DJ, Sinuff T, White DB, Hill N, Keenan SP, et al. The society of critical care medicine palliative noninvasive positive pressure ventilation task force. Noninvasive positive pressure ventilation in critical and palliative care settings: Understanding the goals of therapy. Crit Care Med 2007;35(3):932–9.
[21] Scala R, Nava S. NIV and palliative care. Eur Respir Mon 2008;41:287–306.
[22] Nava S, Ferrer M, Esquinas A, Scala R, Groff P, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. Lancet Oncol 2013;14:219–27.
[23] Scala R. Challenges on non-invasive ventilation to treat acute respiratory failure in the elderly. BMC Pulm Med 2016;16:150.
[24] Schettino G, Altobelli N, Kacmarek RM. Noninvasive positive pressure ventilation reverses acute respiratory failure in select “do-not-intubate” patients. Crit Care Med 2005;33(9):1976–82.
[25] Demoule A, Girou E, Richard JC, Taille S, Brochard L. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med 2006;32(11):1756–65.