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Roberto Cosentini
Stefano Aliberti
Angelo Bignamini
Federico Piffer
Anna Maria Brambilla

Mortality in acute cardiogenic pulmonary edema treated with continuous positive airway pressure

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R. Cosentini (✉) · F. Piffer ·
A. M. Brambilla
Emergency Medicine Department,
Ospedale Maggiore, IRCCS Fondazione
Policlinico-Mangiagalli-Regina Elena,
Via F. Sforza 35, 20122 Milan, Italy
e-mail: roberto.cosentini@policlinico.mi.it
Tel.: +39-02-55033602
Fax: +39-02-55033600

S. Aliberti
Institute of Respiratory Diseases,
University of Milan, Ospedale Maggiore,
IRCCS Fondazione Policlinico-
Mangiagalli-Regina Elena,
via F. Sforza 35, 20122 Milan, Italy

A. Bignamini
School of Specialization in Hospital
Pharmacy, University of Milan,
Viale Abruzzi 42, Milan, Italy

Abstract *Objective:* To investigate mortality in acute cardiogenic pulmonary edema (ACPE) patients treated with continuous positive airway pressure (CPAP) and to identify clinical and laboratory characteristics associated with mortality. *Design:* Observational, retrospective study. *Setting:* Emergency Medicine Department. *Patients and participants:* A total of 454 consecutive ACPE patients treated with CPAP. *Measurements and results:* Demographics, past medical history, clinical characteristics, laboratory evaluation, in-hospital mortality data were collected. Potential predictors of in-hospital mortality that were considered of clinical relevance and immediately accessible on admission were investigated by multivariable logistic regression. ACPE-related mortality rate was 3.8% (17/452 patients) and the in-hospital mortality rate was 11.4% (50/440 patients). Significant independent predictors of increased risk of in-hospital mortality were: advanced age ($P = 0.012$), normal-to-low blood pressure ($P < 0.001$), low PaO_2/FiO_2 ratio ($P = 0.020$), hypocapnia ($P = 0.009$) and anemia ($P = 0.05$). *Conclusions:* Values recorded within few minutes from arrival to the hospital can predict mortality in ACPE patients treated with CPAP who has been tested, for the first time, in a real life study. This can allow physicians to quickly recognize more severe ACPE patients treated with CPAP and plan for aggressive monitoring and treatment and for deciding the better site of care.

Keywords Mortality · Pulmonary · Edema · CPAP · Predictor · NIV

Introduction

Acute cardiogenic pulmonary edema (ACPE) is a life-threatening medical emergency for which non-invasive positive airway pressure, either continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV), in addition to standard medical therapy, is considered a safe and effective treatment [1]. Although administration and effects of medical therapy for ACPE often require time, the physiological advantages resulting from the application of a positive end-expiratory pressure have shown to be prompt and efficacious.

Several randomized controlled trials have clearly proven that, when compared to standard medical therapy alone, the addition of CPAP or NIV in ACPE patients significantly reduces mortality and decreases the need for invasive ventilation and the length of hospitalization [2–4]. For this reason, the use of non-invasive positive airway pressure as a first line intervention in ACPE patients is now becoming mandatory. Different guidelines

produced by the efforts of respiratory, critical care and cardiologic societies strongly recommend the use of CPAP in patients with acute cardiogenic pulmonary edema [1, 5, 6]. When compared to other techniques of non-invasive ventilation requiring use of a ventilator, CPAP has proven not only to be easier to use and quicker to implement in clinical practice, but also to carry smaller associated costs [7]. The use of CPAP in ACPE has also been suggested in settings other than the Intensive Care Unit (ICU) or Emergency Department (ED), as general ward or pre-hospital care [8–11].

The rate of mortality in ACPE patients treated with CPAP and enrolled in different randomized control studies seems to range around 13% [2, 3]. However, since CPAP has been widely adopted into clinical practice, no data on mortality in ACPE patients treated with CPAP are available in a real life study. Moreover, although different predictors of failure of non-invasive ventilation in acute respiratory failure have been previously studied [12, 13], predictors of mortality in ACPE patients undergoing CPAP treatment are needed, to identify those more likely to carry a poor prognosis.

The aims of this study were to investigate mortality and to study clinical and laboratory characteristics upon ED admission associated with mortality in ACPE patients treated with CPAP.

Methods

Setting and participants

This was a retrospective, observational study of consecutive patients admitted with a diagnosis of ACPE to the Emergency Department of IRCCS Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy (an university tertiary care hospital receiving approximately 50,000 visits annually) between 1 January 2003 and 31 December 2006.

All subjects, regardless of age, who satisfied the criteria for ACPE and who were treated with CPAP on admission were enrolled in the study. The diagnosis of ACPE was established on the basis of medical history (acute severe dyspnea) and typical physical findings (widespread pulmonary rales), with chest radiography confirming pulmonary vascular congestion. Criteria for application of CPAP included at least one of the following: (1) severe acute respiratory failure (PaO_2/FiO_2 ratio less than 300); (2) respiratory rate exceeding 30 breaths/min or use of accessory respiratory muscles or paradoxical abdominal motion; (3) respiratory acidosis ($pH < 7.35$, $PaCO_2 \geq 45$ mmHg). CPAP was not applied in ACPE patients if any among the following findings was present: (1) immediate need for endotracheal intubation; (2) severely altered consciousness; (3) shock; (4) need for thrombolysis or angioplasty for acute myocardial infarction; (5) pneumothorax. Criteria for discontinuation from CPAP included all of the following: (1) absence of respiratory distress; (2) respiratory rate < 25 bpm; (3) hemodynamic stability; (4) $pH > 7.35$; (5) PaO_2/FiO_2 ratio > 300 or $SpO_2 \geq 95\%$. All patients enrolled in the study underwent high-flow CPAP (VitalSigns inc., Totowa, USA; 90–140 l/min) as first choice of treatment, in addition to oxygen therapy and medical treatment. Interfaces used were facemask (VitalSigns, USA) or helmet (StarMed, Italy) with a PEEP valve (VitalSigns, USA). CPAP was applied in ACPE patients with an initial PEEP of 10 cmH_2O with a FiO_2 of 0.5. The above criteria for the application of CPAP in ACPE patients as well as the protocol of medical treatment were applied according to local standard operating procedures. No subjects receiving invasive or non-invasive pressure support ventilation before CPAP treatment were included in this study.

Study design

Records of all the enrolled patients were carefully reviewed. Data on admission, before CPAP treatment, were collected and included the following: (1) demographic information and past medical history; (2) clinical characteristics, including systolic and diastolic blood pressure, heart and respiratory rates; (3) laboratory evaluation performed on venous (creatinine, hemoglobin) and arterial sample (arterial blood gas); (4) information needed to derive the Simplified Acute Physiology Score II [14]. A group of investigators of the Emergency Department, Fondazione Policlinico Hospital, Milan, Italy validated the quality of data by checking for discrepancies and inconsistencies before cases were entered into a database. Local institutional review board for human studies approval was obtained.

Acute myocardial infarction (AMI) was defined as typical rise and gradual fall of troponin I with at least one of the following: (1) ischemic symptoms; (2) development of pathologic Q-waves on the ECG; (3) ECG changes indicative of ischemia (ST-segment elevation or depression $\geq$ 1 mm in contiguous limb leads or $\geq$2 mm in precordial leads); (4) new symmetric T-wave inversion in two or more contiguous leads; (5) $R > S$ in V1 or ST depression > 1 mm in V1 that suggest TPI (mirror changes). In-hospital mortality was defined as death by any cause occurring during hospitalization. ACPE-related mortality was defined as death occurring during the episode of ACPE. Late mortality was defined as death occurring after the resolution of the episode of ACPE. Local standard operating procedures of our institution define an episode of ACPE as being resolved when all the criteria for discontinuation of CPAP mentioned above are reached. To study potential predictors of mortality, clinical and laboratory data that are considered of clinical

relevance in patients with ACPE and immediately accessible after admission to the Emergency Room were investigated.

Statistical analysis

All data were statistically analyzed with SPSS (version 13.0, Chicago, IL) for Windows. A descriptive statistic at baseline was performed. Descriptive results are reported as mean (±SD), proportions with 95% confidence interval. Mortality was estimated as absolute risk with 95% confidence interval according to Brown et al. [15]. Potential predictors of in-hospital mortality were investigated with the multivariable binomial logistic regression analysis. A P value <0.05 was considered statistically significant.

Results

Continuous positive airway pressure was first choice treatment, in addition to oxygen and standard medical therapy, in 454 patients admitted to the Emergency Department of Policlinico Hospital with a diagnosis of ACPE during the four full calendar years. Profile of this sample on ED admission and before CPAP treatment is shown in Tables 1, 2, and 3.

The study flowchart is presented in Fig. 1. Among the 454 patients, 2 were transferred to other facilities while ACPE was still in progress and no information is available regarding their outcome. A total of 17 patients died during the acute phase within few hours after admission (median 116 min; range interquartile 71–247 min). Among the survivors, 12 were transferred to other hospitals and no information concerning their in-hospital mortality is available. Among the 423 patients monitored during the post-acute phase, 33 patients died after a median of 7 days (range interquartile 4–13 days). Thus, the ACPE-related mortality rate was 3.8% (17/452 patients) and the in-hospital mortality rate was 11.4% (50/440 patients). Patients transferred to other facilities after the acute phase were not included in the analysis of the in-hospital mortality. Causes of ACPE-related mortality and late mortality are depicted in Table 4.

Among the 376 patients with appropriate troponin I determinations, a total of 36 patients (9.6%) had a diagnosis of AMI. In-hospital mortality was not significantly different in patients with AMI compared to patients without AMI (2/36, 5.6% vs. 33/340, 9.7%, $P = 0.556$).

In-hospital mortality was fitted in a univariate logistic regression model detailed in Fig. 2, evaluating the association of the most relevant demographic, clinical and laboratory data. In-hospital mortality was fitted in a multivariable logistic regression model detailed in Fig. 3. Age and PaO_2/FiO_2 ratio were used as continuous predictors. Respiratory rate values were not considered because too many cases had no information recorded. A sufficiently well-fitted multivariable logistic model was

Table 1 Demographics, comorbidities, clinical data and severity of the disease upon arrival to ED of the study population

Variable	Value	Missing
Total monitored patients	454	
Demographics		
Age, years (mean ± SD)	79.5 ± 10.1	0
Range	39–102	0
<75 (no, %)	121 (26.7)	0
75–84 (no, %)	180 (39.6)	0
≥85 (no, %)	153 (33.7)	0
Male (no, %)	210 (46.3)	0
Comorbidities		
Chronic obstructive pulmonary disease (no, %)	115 (25.4)	2
Essential hypertension (no, %)	242 (53.5)	2
Diabetes mellitus (no, %)	110 (24.3)	2
Coronary artery disease (no, %)	254 (56.2)	2
Chronic renal failure (no, %)	102 (22.6)	2
Physical findings		
Systolic BP, mmHg (mean ± SD)	168.3 ± 33.7	7
Diastolic BP, mmHg (mean ± SD)	96.0 ± 21.2	12
Systolic BP < 140 mmHg and diastolic BP < 90 mmHg (no, %)	68 (15.3)	9
Heart rate, beats/min (mean ± SD)	114.8 ± 22.6	12
Heart rate > 100 beats/min (no, %)	302 (68.3)	12
Respiratory rate, breaths/min (mean ± SD)	40.4 ± 6.8	167
Respiratory rate ≥ 40 breaths/min (no, %)	185 (64.5)	167
SpO_2 (%) (mean ± SD)	87 ± 10	155
SAPS II (mean ± SD)	42.3 ± 8.3	66

BP blood pressure; *SAPS II* Simplified Acute Physiologic Score II

Table 2 Arterial blood gas data upon arrival to ED of the study population

Variable	Value	Missing
Total monitored patients	454	
Arterial blood gas analysis		
pH (mean ± SD)	7.26 ± 0.13	24
$PaCO_2$, mmHg (mean ± SD)	49.8 ± 18.2	22
≤35 (no, %)	81 (18.8)	
≥45 (no, %)	225 (52.1)	
Bicarbonates, mmol/l (mean ± SD)	21.9 ± 4.9	25
<22 (no, %)	227 (52.9)	
>26 (no, %)	66 (15.4)	
PaO_2/FiO_2 ratio (mean ± SD)	184.2 ± 91.6	32
<200 (no, %)	250 (59.2)	
Acid-base status		
Respiratory acidosis (no, %)	135 (31.5)	26
Metabolic acidosis (no, %)	92 (21.5)	26
Respiratory alkalosis (no, %)	14 (3.3)	26
Non-attributable (no, %)	187 (43.7)	26

Table 3 Laboratory data upon arrival to ED and duration of CPAP treatment of the study population

Variable	Value	Missing
Total monitored patients	454	
Laboratory values		
Hemoglobin (g/dl)		
Men (mean ± SD)	13.7 ± 2.0	37
Women (mean ± SD)	12.8 ± 2.1	40
Anemia[a] (no, %)	146 (38.7)	77
I-Troponin (ng/ml)		
>0.15[b] (no, %)	110 (24.2)	101
Creatinine (mg/dl) (mean ± SD)	1.73 ± 1.30	67
>1.3 (no, %)	202 (52.2)	
Duration of CPAP (min) (mean ± SD)	314 ± 442	21

[a] Hemoglobin <12 g/dl for women; <13.5 g/dl for men
[b] I-Troponin >0.15 is the local cutoff

Table 4 Causes of ACPE-related and late mortality in the study population

ACPE-related mortality $n = 17$		Late mortality $n = 33$	
Cardiogenic shock	16	Severe sepsis	10
Respiratory arrest	1	Cardiogenic shock	8
		Pneumonia	3
		Cerebrovascular accident	2
		AECB	1
		Pulmonary embolism	1
		Acute pancreatitis	1
		Other causes	2
		Unknown	5

ACPE acute cardiogenic pulmonary edema; *AECB* acute exacerbation chronic bronchitis

obtained (Nagelkerke R^2: 0.300; Hosmer–Lemeshow test: 0.658; $N = 349$). Independent predictors of increased risk of in-hospital mortality were: age ($P = 0.012$), normal-to-low blood pressure ($P < 0.001$), low PaO_2/FiO_2 ratio ($P = 0.020$), hypocapnia ($P = 0.009$), anemia ($P = 0.05$). Mean (±SD) HCO_3 values on admission were 18 (±4.1) mEq/l among hypocapnic patients and 22.7 ± 4.6 mEq/l among the rest of the study population ($P < 0.001$). Furthermore a HCO_3 level on admission lower than 22 mEq/l was present in 86% (66/77) of the hypocapnic patients and in the 46% (161/352) among the rest of the population ($P < 0.001$).

Discussion

The main finding of this study is the identification of an in-hospital mortality in ACPE patients treated with CPAP of 11% and an ACPE-related mortality of 3.8%. Moreover, advanced age, hypocapnia, normal-to-low blood pressure, low PaO_2/FiO_2 ratio and anemia recorded on admission have been identified as independent risk factors for in-hospital mortality in ACPE patients treated with CPAP.

For the first time in literature, we analyzed an in-hospital mortality among ACPE patients treated with CPAP in a "real-life" study. A recent meta-analysis performed by Peter et al. [2] included 17 different RCTs considering 410 ACPE patients treated with CPAP and reported a mortality rate of 12.9%. The number of patients enrolled in our study is higher than the cumulative number of ACPE patients treated with CPAP included in the above meta-analysis. A large RCT recently performed by Gray et al. [16] (3CPO trial) has shown a 30-day mortality for acidotic ACPE patients treated with CPAP of 15.4% and a 30-day mortality for ACPE patients treated with standard medical therapy (SMT) of 16.4%. Based on these results the authors suggested that NIV cannot improve mortality in ACPE patients. However, the population analyzed by Gray and coworkers was composed only by acidotic patients that accounts of the 61% of our ACPE population. Moreover, the 3CPO trial was performed using a home

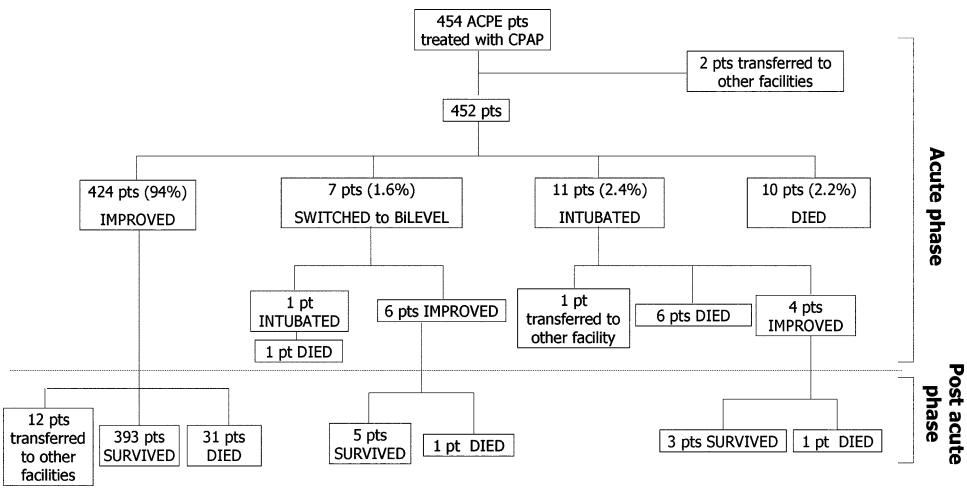

Fig. 1 Flow chart of the study population. *ACPE* Acute cardiogenic pulmonary edema; *pts* patients; *CPAP* continuous positive airway pressure

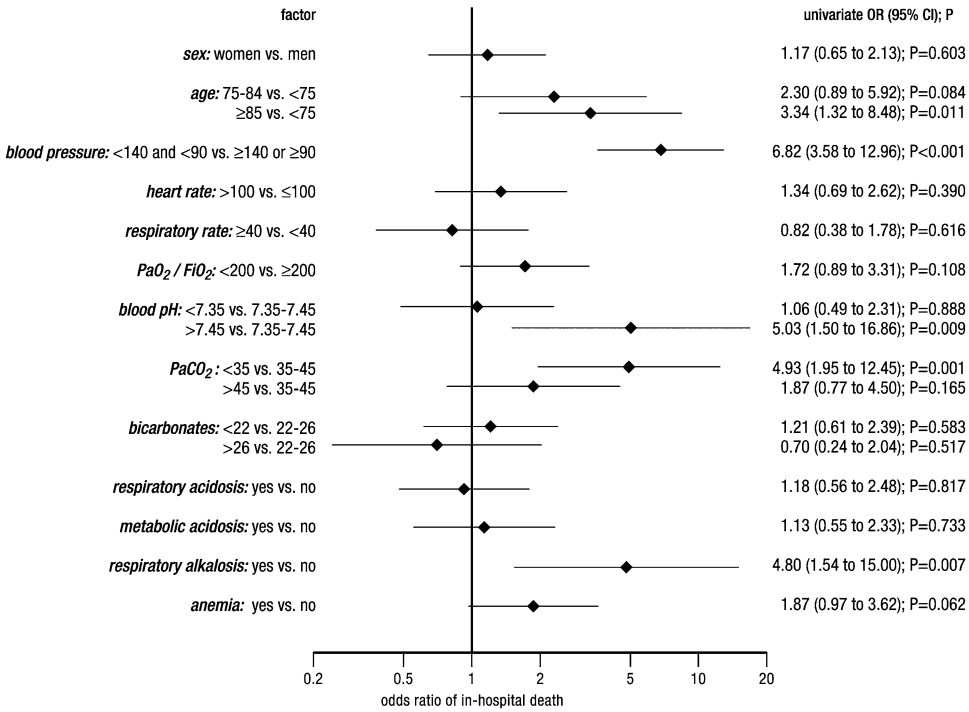

Fig. 2 Univariate logistic regression analysis for in-hospital mortality using demographics, clinical and laboratory data recorded on admission

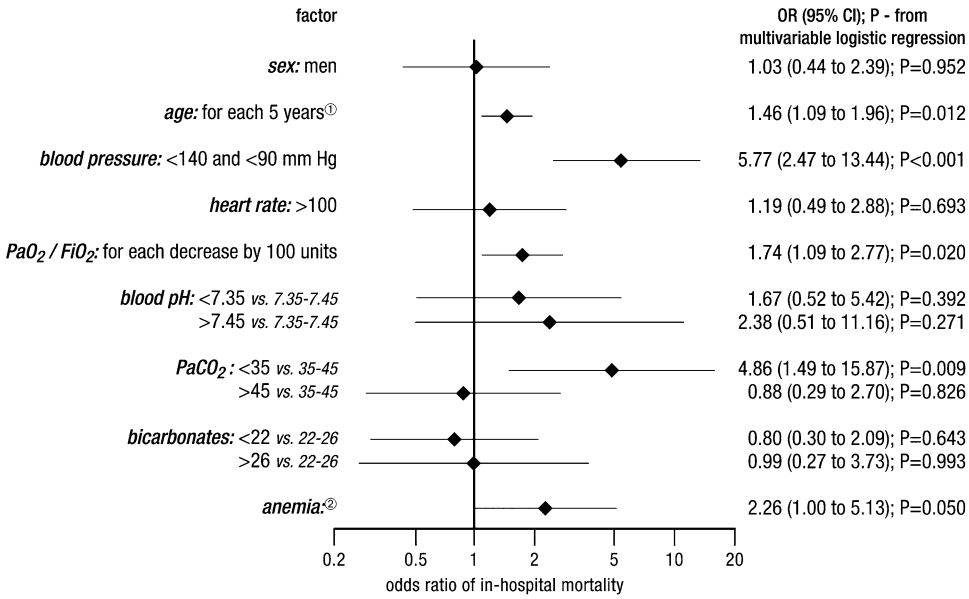

Fig. 3 Multivariable logistic regression analysis for in-hospital mortality using demographics, clinical and laboratory data recorded on admission

① *ages <75 pooled into one group; ages >90 pooled into one group*
② *hemoglobin <12.0 mg/dL in women; <13.5 in men*

ventilator with a low initial PEEP and with a short time of CPAP duration. These limitations could explain why the authors did not find any difference in terms of mortality between the SMT and the CPAP group. On the other hand, in our acidotic ACPE patients treated with a high-flow CPAP for a longer period and in a well-trained setting the mortality was less than a half (7.4%).

Several of the RCTs analyzed by Peter et al. [2] were carried out in an ICU setting, focusing on patients with more severe ACPE. Our study was designed to evaluate mortality in ACPE patients treated with CPAP in an Emergency Department. This setting is representative because patients with ACPE are primarily treated by emergency physicians and then transferred to other

departments after stabilization. Previous experiences have already shown CPAP to be successfully used in an ED setting [17]. We designed a study to consider a heterogeneous population of patients, avoiding strict exclusion criteria as those used in the above RCTs and, thus, increasing generalizability.

Since ours was a large sample size, we were able to define a mortality rate directly related to the acute episode of pulmonary edema in patients treated with CPAP. The ACPE-related mortality rate was 3.8%, corresponding to one-third of the total in-hospital mortality. Therefore, CPAP seems to support patients through the acute event, but nonetheless deterioration of the baseline clinical status after ACPE leads to high in-hospital mortality. L'Her et al. [18] evaluated CPAP in elderly patients with ACPE and reported a mortality of 7% occurred within the first 48 h after admission. When ACPE-related mortality was evaluated in our study, we considered a heterogeneous population and we used an accurate definition, based on the clinical resolution of the acute event and not on a time-related cutoff.

A risk factor associated to in-hospital mortality in our population was advanced age, and this finding could be likely explained with the high number of comorbidities affecting elderly people. Previous studies reported age as an independent factor for mortality in ACPE patients treated with CPAP [19].

A normal-to-low blood pressure on admission has been shown to be associated to in-hospital mortality in our population. Normal-to-low systolic blood pressure on admission has been previously found as predictive factor for mortality and for need of intubation in ACPE patients treated with invasive mechanical ventilation [20–22] and non-invasive bilevel ventilation [22, 23]. In comparison to these studies, our data include an evaluation of both systolic and diastolic blood pressure values and consider ACPE patients undergoing CPAP. One explanation for the increased mortality in ACPE patients with normal-to-low blood pressure on admission could be the increase of intrathoracic pressure due to either invasive or non-invasive application of a positive pressure. This might lead to a decrease in cardiac output and worsen the outcome of ACPE patients with normal-to-low blood pressure. However, past literature has proven a strong association of normal-to-low systolic blood pressure on admission and both mortality or need of intubation also in ACPE patients treated with standard medical therapy alone [24]. Normal-to-low blood pressure on admission seems, thus, to be associated to a poor outcome in ACPE patients, regardless of the application of a positive pressure. Because of this and considering the respiratory benefits of CPAP in ACPE patients, the use of CPAP in normotensive patients seems to be safe and efficacious.

We found hypocapnia on admission to be another factor strongly associated to in-hospital mortality. Two previous small studies enrolling ACPE patients treated with NIV reported hypocapnia to be associated with mortality and failure [25, 26]. In patients with ACPE, hypocapnia could be related to hyperventilation due to anxiety or discomfort, although in our patients the mean respiratory rate was similar in both hypocapnic and normo-hypercapnic patients. We also found that hypocapnia seems to be more frequently associated with metabolic acidosis rather than normo-hypercapnia, because of both the significantly lower mean HCO_3 levels and the significantly greater proportion of low HCO_3 subjects among these patients. Another reasonable explanation of a hypocapnic status could be related to the role played by the cardiovascular impairment in decreasing CO_2 production in tissues and CO_2 transportation. The interaction between hypotension and hypocapnia may, thus, sustain a vicious circle in ACPE patients treated with CPAP.

Recent literature considers low levels of hemoglobin to be associated with a worse outcome in patients with congestive heart failure (CHF) [27, 28]. We found that anemia on admission is a predictor of mortality in ACPE patients treated with CPAP. During a high-oxygen-demand status as an episode of ACPE, a low level of hemoglobin can significantly decrease the amount of oxygen delivered to tissues and worsen the outcome [27]. Furthermore, some literature showed that anemia can clearly define the degree of severity of comorbidities in CHF population [28].

Due to its retrospective design, a weakness of our study is a deficiency in accurately collecting some history and clinical information. This study is strengthened by the large sample size of consecutive ACPE patients treated with CPAP. To our knowledge, this is the first study evaluating risk factors for in-hospital mortality in this population and the first that can allow a clinical distinction between ACPE-related and in-hospital mortality. Our findings are representative of an unselected population and our conclusions, thus, can be easily generalized.

In conclusion, in our real life study the in-hospital mortality in ACPE patients treated with CPAP ranges around 11% and values recorded within minutes from ACPE patient arrival to the hospital can predict it. Particularly, advanced age, normal-to-low blood pressure, hypocapnia, anemia and low PaO_2/FiO_2 ratio are independent predictors for in-hospital mortality. This approach can allow physicians to quickly recognize more severe ACPE patients treated with CPAP, to aggressively monitor and treat them, and to better define the site of care. Future research is needed to study more risk factors associated to in-hospital and ACPE-related mortality in this population.

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