UNIVERSITY OF MEDICINE AND PHARMACY
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DOCTORAL THESIS ABSTRACT

SHORT AND MEDIUM TERM PROGNOSIS IN CARDIOGENIC ACUTE PULMONARY EDEMA

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KEY WORDS

acute pulmonary edema, acute heart failure, vulnerable phase, negative outcomes predictors, risk model, pulmonary hydrostatic pressure, filling pressures, neurohormonal activation, short and medium term prognosis

GENERAL KNOWLEDGE

INTRODUCTION

Acute pulmonary edema (APE) is part of the acute heart failure (AHF) syndromes and is a common medical emergency, characterized by severe shortness of breath (SOB) and pulmonary congestion (1).

The mortality and morbidity in AHF are a serious public health issue (2). More specifically the short and medium term adverse event rate after a hospitalization is particularly high, this is why this is also called the vulnerable phase (3). Prognostic data in the case of APE patients is scarce and is generally limited to the in-hospital phase (4).

PHYSIOPATHOLOGY

The physiopathologic mechanism of APE is movement of fluid from the pulmonary capillary to the interstitial space and finally into the alveoli, causing alveolar edema. This process is determined by the increase in the endothelial filtration rate, which is caused, in the case of cardiogenic APE, by an increase in the intravascular hydrostatic pressure, due to increased filling pressures in the left heart chambers.

EPIDEMIOLOGY

Acute pulmonary edema is the second most common AHF syndrome. The prevalence of APE was reported to be between 13 and 60% in the AHF registries (Table 1). This large difference can be explained by the different inclusion and exclusion criteria. In-hospital mortality was reported to be between 5.6 and 9.1%, and was influenced by parameters such as: admission blood pressure (BP), ejection fraction (EF), renal function and age.

	RO-AHFS (5) Romania n = 3224	EHFS II (6) Europe n = 3580	ATTEND (7) Japan n = 4842	ALARM HF (8) International n = 4953	OFICA (9) France n = 1468	AHEAD (10) Czech R. n = 4153	ESC-HF Pilot (11) Europe n = 1892
APE prevalence (%)	28.7	16.2	60	37	38	18.4	13.3
APE in-hospital mortality (%)	7.4	9.1	-	7.4	7.3	7.1	5.6

Table 1. Acute pulmonary edema prevalence and in-hospital mortality, data from the AHF registries. n = total number of AHF patients.

DIAGNOSIS

The diagnosis is reliant on the patient medical history, physical examination and other specific tests. Most of the time the cause of admission is SOB with orthopnea, but sometimes other symptoms can be present, depending on the underlying cardiac disease. The physical exam is often the most important part of the diagnosis process. Patients can have their general status altered, can be agitated, and are always experiencing severe SOB. The most characteristic auscultation findings are the pulmonary rales or crackles. These are bilateral, starting from the base of the lungs and are present up to at least half of the lung height.

The other diagnostic tests are not necessarily specific to APE and include blood work (preferably arterial gas blood in the acute phase), electrocardiogram (ECG), chest X-ray and transthoracic echocardiogram.

The most important blood tests for diagnosis and prognosis are SaO2, the natriuretic peptides (BNP and NTproBNP), the renal function parameters and the electrolytes levels. Rana *et al.* have shown that a BNP value below 250 pg/ml in not characteristic for cardiogenic APE and should raise the suspicion of noncariogenic APE (12). Regarding the renal function, in the ADHERE registry a blood urea nitrogen (BUN) value of >43 mg/dl was proven to be the strongest predictor of in-hospital mortality, followed by low BP and the admission creatinine level (13).

The chest X-ray is recommended for all APE patients upon admission (14). The most important and characteristic diagnostic element is the presence of pulmonary congestion, which is required for the APE diagnosis.

The transthoracic echocardiography is the most widely use cardiac imaging technique due to its large availability and reduced cost. It can give important information regarding both the structure and the function of the heart. The most commonly use parameter to estimate the cardiac function is the left ventricle ejection fraction (EF). Interestingly enough, the mean EF is about 40% in APE patients, and also about 40% of these patients have normal or just mildly reduced systolic function (Table 2). This finding reinforces the idea that it is not only the systolic impairment that causes APE, but also isolated diastolic dysfunction.

	RO-AHFS (4) Romania n = 924	EHFS II (6) Europe n = 581	ALARM HF (8) International n = 1820	OFICA (9) France n = 631	AHEAD (10) Czech R. n = 748
Mean left ventricle ejection fraction (%)	39.2	40	38.8	42	35

Table 2. Mean left ventricle ejection fraction of APE patients.

MANAGEMENT

The treatment can be classified as pharmacological and non-pharmacological, and also as acute and chronic phase treatment. Since APE is an acute setting syndrome we chose to insist on the acute phase treatment. Also the chronic phase management is not particular to APE, but rather common to all chronic HF patients, depending on the underlying disease, of course.

The non-pharmacological treatment in the acute phase includes oxygen therapy recommended to all patients with SaO2 below 90% or PaO2 below 60 mmHg (14). If the hypoxemia does not improve with oxygen therapy, then mechanical ventilation will be necessary.

The acute phase pharmacological treatment aims to lower the pulmonary artery hydrostatic pressure. The most commonly used drug types are diuretics (loop diuretics like furosemide) and vasodilators. In the RO-AHFS registry iv. furosemide was used in 88.6% of APE patients, and in ALARM-HF in 94.9% of patients (5,8). The mechanism of action of loop diuretics in twofold, stimulating diuresis and thus lowering the blood volume, and also producing vasodilation and thus lowering the afterload. Vasodilators are the second most widely used and recommended medication, being given to between 50 and 73% of APE patients (5,6,8). Vasodilators are recommended to patients that have hypertension and pulmonary congestion, and can even be considered as the first line of therapy, IIa indication (14).

PROGNOSIS

Acute pulmonary edema in-hospital mortality has been reported to be between 5.6 and 7.4%. The only prognostic data specific to APE patients comes from the RO-AHFS and ALARM-HF registries, the rest of the available data deals with AHF patients in general. In RO-AHFS in-hospital was associated with old age, presence of an acute coronary syndrome (ACS), presence of ventricular arrhythmias, elevated BUN, left bundle branch block, inotrope treatment and mechanical ventilation (4). In ALARM-HF the predicting parameters were low BP, creatinine over 1.4 mg/dl and a history of heart disease (8).

The evolution of APE patients after discharge has not been studied specifically, except for the recently published ESC-HF-LT registry. Chioncel *et al.* have reported the APE 1 year all-cause mortality to be 28.1%, any-cause hospitalization to be 39.7%, and HF hospitalization 28.1%. The composite endpoint of 1 year all-cause mortality and HF hospitalization was reached by 40.6% of APE patients (15).

PERSONAL RESEARCH

INTRODUCTION AND RATIONALE

The rationale of the study is based on the personal observation that a large number of patients admitted with AHF had also had previous recent AHF admissions. This observation is corroborated with published data that show the risk of adverse events (death and readmission) being the highest on short and medium term after a hospitalization, in the so called vulnerable phase (3).

Thus was born the idea for a prospective study to analyze AHF patients during hospitalization and then follow them up in order to identify the parameters that would predict short and medium term negative outcomes. We have chosen to study a subgroup of AHF syndromes and not all the AHF patients because this approach allowed us to reduce the study group variability and also to devise a feasible and also detailed study protocol. When it came to choosing which AHF syndrome to study, APE was the obvious choice for us. The main reasons were the fact that APE is quite common and this would allow us to recruit a sufficient number of patients, the fact that the diagnosis is easily established and unambiguous, and also the fact that the rate of post discharge events is high enough to provide statistical power.

METHODS

This was an observational, prospective, cohort study.

The inclusion criteria was based on the European Society of Cardiology APE diagnosis criteria of the (1):

- SOB at rest with orthopnea and tachypnea
- Rales and crackles in at least half of the lung area
- Pulmonary congestion seen on chest X-ray
- Native SaO_2 <90% on pulse oximetry

The exclusion criteria was:

- Noncardiogenic APE
- Presence of an acute myocardial infarction (STEMI or NSTEMI)
- Impossibility to collect the necessary data
- Impossibility to follow-up

All the patients admitted with the diagnosis of cardiogenic APE in between February and May 2016 in the two hospitals were enrolled. The distribution was as follows: 36 patients from the "Bagdasar-Arseni" Emergency Hospital, Bucharest and 34 patients from the Craiova Emergency County Hospital. For every patient a total of more than 100 parameters were collected and analyzed.

RESULTS

DESCRIPTIVE STATISTICS

A total of 70 patients were included in the study. All the patients were followed-up via telephone call at 1 and 6 months. The mean age was 72.1 ± 9.5 years. There were the same number of males and females, 35 each.

The most common preexisting conditions were hypertension, atrial fibrillation, ischemic heart disease and diabetes mellitus (DM). The mean systolic BP on admission was 166.8 mmHg and the mean heart rate was 101.1 bmp. Only 17 patients (24.2%) of patients had leg edema on admission.

Of all blood test variables we will only mention the NTproBNP, which directly reflects the elevated filling pressures. The mean NTproBNP value was 8739.2 pg/ml on admission and 4159.9 on the discharge day.

The echocardiography findings are presented below:

Echocardiography parameter	Mean value	Normal range
LVEF (%)	39.5±11.4	52-72 (M), 54-74 (F)
LV EDV (ml/m^2)	77.7±29.5; 82.3 (M), 73.1 (F)	34-74 (M), 29-61 (F)
IVS (mm)	12.9±2.6; 12.7 (M), 13.2 (F)	6-10 (M), 6-9 (F)
Septal LV S' (cm/s)	4.9±1.2	>6.5
E/e'	18.4±8.1	<14
TAPSE (mm)	18.4±4.3	>17
RV FAC (%)	40.3±7.8	>35
RV free wall S' (cm/s)	10.7±2.5	>9.5
PAPs (mmHg)	40.9±16.7	<37
LA ESV (ml/m^2)	53.7±22	16-34
RA ESV (ml/m^2)	33.6±12.1; 34.6 (M), 32.6 (F)	25±7 (M), 21±6 (F)

Table 3. Mean values and normal ranges of the echocardiographic parameters. M = male; F = female; LVEF = left ventricle ejection fraction; EDV = end-diastolic volume; LV = left ventricle; IVS = interventricular septum; RV = right ventricle; FAC = fractional area change; LA = left atrium; ESV = end-systolic volume; RA = right atrium; PAPs = pulmonary artery pressure. Normal range from: (14,15)

All of the patients had diastolic dysfunction. The most important valve function findings are the facts that 82.8% of patients had moderate or severe mitral regurgitation, that 18.5% had moderate or severe aortic stenosis, and that 65.7% had moderate or severe tricuspid regurgitation.

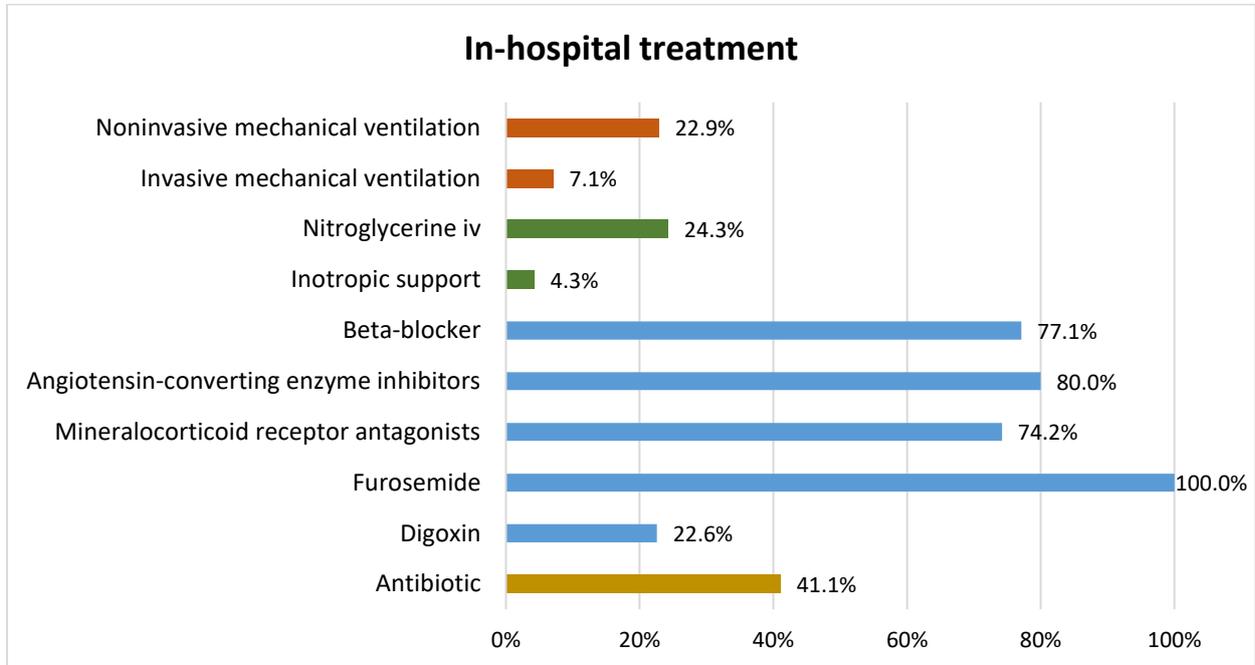In-hospital management is briefly presented in the following figure:

Figure 1. In-hospital treatment for APE patients.

ANALITICAL STATISTICS

The mean hospitalization duration was 7.19 ± 3.33 days. The total number of in-hospital deaths was 3 (4.3%). No patient was lost during follow-up. At 1 months there were 7 deaths and 7 readmissions. At 6 months there were 2 more deaths and 14 more readmissions. By the end of the follow-up a total of 33 patients (47.1%) have reached the combined endpoint of all-cause death and/or HF hospitalization.
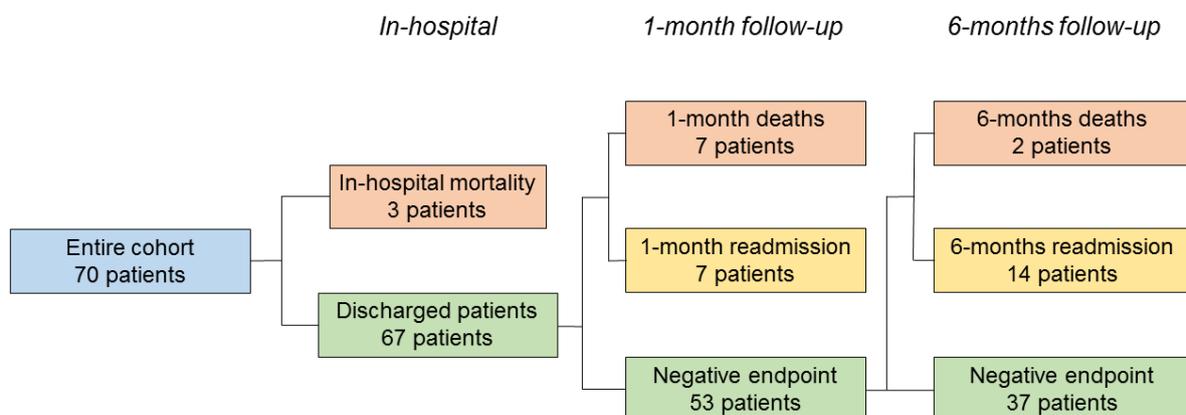

Figure 2. Cohort in-hospital, 1-month and 6-months evolution.

The following table presents some of the parameters studied, more specifically, the ones that had a significant association with the endpoint, and also some that have been shown to have prognostic value in other studies but have not shown significant association with the endpoint in this study.

| Parameter	Positive outcome	Negative outcome	p
Age (years)	69.30	75.24	**0.0079**
Male sex (%)	45.95	54.55	0.4726
Diabetes mellitus (%)	18.92	60.61	**0.0003**
Systolic BP (mmHg)	176.46	159.82	0.0570
Diastolic BP (mmHg)	96.89	86.82	**0.0436**
HR (b/min)	102.86	99.30	0.6501
NTproBNP admission (pg/ml)	7233.56	10371.36	**0.0294**
NTproBNP discharge (pg/ml)	3230.63	5121.31	**0.0129**
Creatinine admission (mg/dl)	0.99	1.26	**0.0003**
Creatinine discharge (mg/dl)	0.99	1.28	**0.0040**
Na$^+$ admission (mmol/l)	139.36	137.79	**0.0361**
Atrial fibrillation (%)	13.52	51.52	**0.0014**
Pleural effusion (%)	10.81	36.36	**0.0110**
Ejection fraction (%)	39.47	39.64	0.9520
RV FAC (%)	45.76	37.66	**0.0001**
RA volume (ml/m2)	49.24	66.97	**0.0435**
CPAP (%)	18.92	2727	0.4060
Iv. nitroglycerine (%)	13.51	26.36	0.1605

Table 4. Mean values of echocardiographic parameters and their predictive value.

In order to estimate the predictive value of each parameter we calculated a regression equation for each individual parameter. After that, in order to develop a prognostic model, we used the forward conditional method and introduced each variable into the model and only kept those that improved its predictive power.

The final result shows that the following parameters have the highest prognostic value: age, diabetes mellitus, admission creatinine, heart rhythm (whether or not it is sinus rhythm), presence of pleural effusion, and RV function (calculated as FAC). The final equation that will determine whether a patient has a high risk over short and medium term is:

Pred(ENDPOINT) = 1 / (1 + exp(-(-9.10806+2.81117* Rhythm+5.32147*DZ+4.40246* Pleural effusion+0.13426*Age+3.19685*Creatinine-0.20627*FAC VD)))

A value over 0.5 is positive, while one under 0.5 is negative. This specific prognostic value has a sensibility of 97.50% and a specificity of 88.89%.
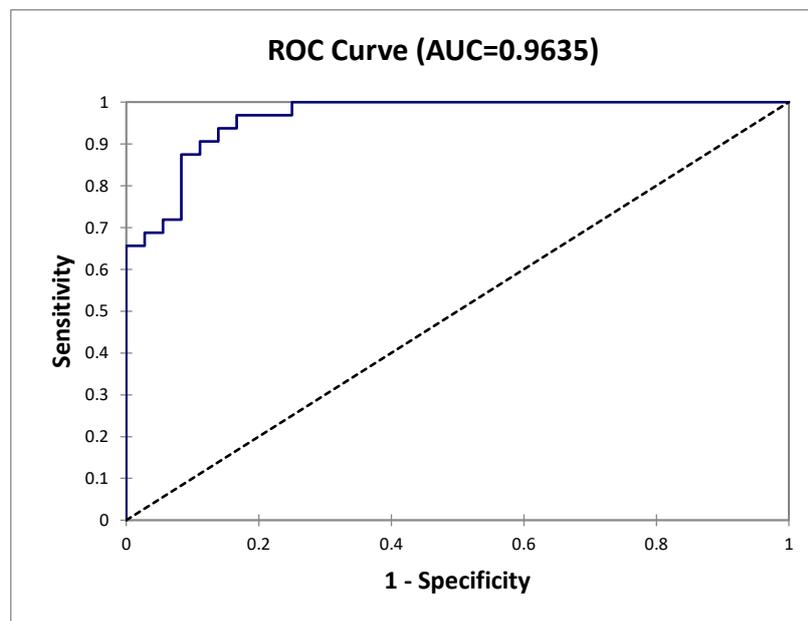
DISCUSSION

The risk score could be calculated before discharge and thus it might aid in tailoring the patient specific treatment and the follow-up plan. Patients who are deemed to have high risk should perhaps be reevaluated in order to see if they are indeed suitable for discharge or if they would benefit from a longer hospitalization. If the latter is true, then it might be necessary to transfer them to a primary or secondary care facility, where there needs be a specific HF department.

After discharge, high risk patients should have a more intensive follow-up plan. Also they should be instructed to recognize early signs of HF decompensation (worsening SOB and leg swelling) and to come in for a visit as soon as these occur.

STUDY LIMITATIONS AND FUTURE RESEARCH

The main limitation of the study is the relatively small number of patients enrolled. Another limitation could be the fact that the patients were recruited from just 2 hospitals, both being emergency university hospitals. Thus it is necessary to test the predictive model in other types of medical institutions that deal with APE patients.

Due to the limitations listed above we consider necessary to further validate the predictive model. This can be the subject of future research projects.

CONCLUSIONS

The demographic data shows an equal distribution between sexes, but women had a higher mean age. Regarding the medical history, about half of the patients had had at least one HF hospitalization in the previous year. The most notable finding of the clinical exam was the high BP value on admission for the majority of patients.

The ECG analysis revealed that atrial fibrillation was the most common arrhythmia, present in about 1/3 of patients. The echocardiography data shows a wide distribution of ejection fraction values in the cohort, ranging from normal to severely reduced, but diastolic dysfunction was present in all the patients.

Almost half of the APE patients experienced a short and medium term adverse event. The parameters that had a stastically significant association with the negative outcome were: age, previous history of HF, blood pressure, leg swelling, pleural effusion, NTproBNP, creatinine, hyponatremia, right ventricle function, left atrium dimensions, diabetes mellitus and atrial fibrillation.

Using some of these parameters a predictive model was developed which has a sensibility of 87.50% and a specificity of 88.89%.

This study proposes the use of a specific prognostic model for APE patients with the purpose of tailoring the management and follow-up plan to the individual risk score. This could aid in the reduction of the high short and medium term adverse event rate.

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