

In-hospital and short-term prognostic factors in acute pulmonary edema: clinical and morphological features

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Abstract

Introduction: There are extensive records which have included patients with acute heart failure (AHF), but specific studies about prognosis in acute pulmonary edema (PE) are scarce and have enrolled a small number of patients. The objectives of this study were to evaluate the predictive factors of short-term evolution in patients with PE. **Patients, Materials and Methods:** This was a prospective, two-center survey of 70 consecutive patients admitted for acute cardiogenic PE. The follow-up was performed one month after discharge. The composite endpoint was in-hospital death, and death of any cause or readmission for heart failure (HF) at one month after discharge. Heart and lung tissue analysis was performed postmortem to identify morphological features of PE. **Results:** In-hospital mortality was 4.2%, another 14.2% died in the first month, and an additional 10% required rehospitalization for HF. The characteristics significantly associated with end-point occurrence were: history of kidney disease, anemia, diabetes mellitus, lack of prior angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker treatment, lower systolic blood pressure (BP) at admission, lower diastolic BP at admission, creatinine at admission and at discharge, an increase in creatinine during stay, glomerular filtration rate at admission, serum sodium at admission, decrease in serum sodium during hospitalization, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) at discharge, right ventricle fractional area change, left atrium volume index. We created a multiple logistic regression model and identified five prognostic factors: age, diabetes, creatinine, diastolic BP, serum sodium. This model correctly classified 48 (96%) patients without worsening and 13 (65%) patients with worsening, providing an overall accuracy of 87.1%. Necropsy was performed on five patients and fragments of left ventricle myocardium and lung were harvested for histopathological and immunohistochemical studies. The myocardium exhibited fibrosis areas where the myocytes were completely or partially replaced by collagen fibers. Lung tissue analysis revealed some case-to-case differences, but the common finding was alveoli size larger than normal, with the lumen completely or almost completely covered by an eosinophilic liquid. **Conclusions:** The factors that best predicted the short-term outcome in PE were age, diabetes, diastolic BP, creatinine, serum sodium.

Keywords: pulmonary edema, acute heart failure, short-term mortality.

Introduction

Pulmonary edema (PE) is a specific form of acute heart failure (AHF) characterized by a marked increase in pulmonary capillary hydrostatic pressure that determines severe dyspnea accompanied by pulmonary congestion and oxygen desaturation.

There is a multitude of registry data analyzing in-hospital course of patients with PE, with mortality ranging from 5% to 9% and predicting factors including age, acute coronary syndromes, low blood pressure (BP), decreased left ventricular ejection fraction (LVEF), and renal failure [1–8]. There is however very few information available on the post-discharge course of these patients and the predictors of adverse events.

The follow-up data of AHF syndromes suggest mortality rates of 9% and rehospitalization as high as 30% at 90 days. In the OPTIMIZE-HF study, the most important predictors of short- and medium-term negative outcomes were admission serum creatinine and hemoglobin levels,

BP, and pulmonary disease [9]. In another trial, independent predictors of mortality or readmission were not using a beta-blocker, pedal edema, hyponatremia, lower creatinine clearance, and higher brain natriuretic peptide (BNP) [10]. However, because of the heterogeneity of AHF syndromes, it is unclear if these data can be applied to the specific case of PE patients.

The aim of the current study was to evaluate medium-term prognosis of PE patients and identify the predicting factors for rehospitalization and mortality. Furthermore, we intended to develop a negative outcomes-predicting algorithm that would help the clinician identify at-risk patients and tailor a specific post-discharge management plan for them.

Patients, Materials and Methods

This was a prospective, two-center survey of all consecutive patients admitted for acute cardiogenic PE.

Patients were enrolled between February and May 2016 from “Bagdasar-Arseni” Emergency University Hospital, Bucharest (36 patients) and Emergency County Hospital of Craiova, Romania (34 patients).

The diagnosis of acute PE was based on patient's history (acute onset), clinical examination (dyspnea at rest with orthopnea, pulmonary rales/crackles in more than one-third of the lung fields), chest X-ray (alveolar edema), and oxygen desaturation (oxygen saturation <90%).

Study design

Patient history, co-morbidities, precipitating factors, signs and symptoms, medications were recorded on admission. Other data collected included electrocardiogram parameters, laboratory results including N-terminal prohormone of brain natriuretic peptide (NT-proBNP), serum sodium and potassium and creatinine at admission and discharge, medication and other therapies used (e.g., mechanical ventilation). Standard transthoracic echocardiography was performed in all patients within the first three days of admission. In total, more than 100 parameters were recorded for each patient. Follow-up was done one month after discharge by phone, if the patient was not already readmitted in the same Hospital. The composite endpoint was in-hospital death, and death of any cause or readmission for heart failure (HF) at one month after discharge. Rehospitalization for HF was defined according to the *European Society of Cardiology (ESC) Heart Failure Association (HFA)* consensus document, as a hospitalization requiring at least an overnight stay in-hospital caused by worsening of HF symptoms and/or signs requiring new administration of intravenous HF therapy [11].

Statistical analysis

Statistical analysis was performed using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT 2014 add-on for MS Excel (Addinsoft SARL, Paris, France), and IBM Statistical Package for the Social Sciences (SPSS) Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for processing the data. To describe the numerical data used in the present study, we used the classical statistical indicators, arithmetic mean and standard deviation.

To test the normality of the data, we used the Anderson–Darling and Shapiro–Wilk tests. Because the study involved a numerical comparison between two groups of patients that did not have a normal (Gaussian) distribution, the nonparametric Mann–Whitney test was used. To test the dependencies between categorical data and the outcome, we used χ^2 (chi)-square test. After identifying variables that show an influence on the study outcome, we tried to develop a statistical model to predict the outcome of the study. To achieve this, we used logistic regression. In the *logit* model, the *log* odds of the outcome were modeled as a linear combination of the predictor variables. We assessed the likelihood of the model by mean of the Cox & Snell pseudo R^2 , and its corrected version, the Nagelkerke R^2 . We also assessed the model/s “goodness-of-fit” with the Hosmer & Lemeshow test.

Histopathological and immunohistochemical study

Necropsy was performed on five patients, which deceased in hospital (during the initial or ulterior hospitalization in the one-month follow-up), and fragments of left ventricle myocardium and lung were harvested for histopathological and immunohistochemical (IHC) studies. The biological material was fixed in 10% buffered formalin solution (pH 7.4) for 48 hours, after which it was included in paraffin, by using the classical histological technique. On the material included in paraffin, we made sections with a 4- μ m thickness in the Microm HM350 automatic rotary microtome equipped with a water bath section-transfer system (STS, microM). The sections were stained with Hematoxylin–Eosin (HE) and green light trichrome, the Goldner–Szekely (GS) technique, for the histopathological study. Other histological sections were selected for IHC studies. These were collected on poly-L-lysine covered slides and dried in a thermostat, at 37°C, for 24 hours, in order to increase the adherence of sections to the port-object slide. Then, the sections followed the classical protocol of IHC processing: deparaffinization, section hydration, antigen recovery (the slides were boiled in a sodium citrate solution, pH 6, for 21 minutes, in a microwave oven), blocking of endogenous peroxidase (by incubating the biological material into 3% oxygenated water, at room temperature), blocking non-specific sites (the sections were included into 2% skimmed milk for 30 minutes). Prepared as such, the sections were incubated with primary antibodies for 18 hours (overnight), in a refrigerator, at 4°C, and the next day was applied the biotinylated secondary antibody for 30 minutes, at room temperature, after which was applied Streptavidin–Horse-radish peroxidase (HRP) for 30 minutes, followed by slide washing in 1% PBS 3x5 minutes. The signal was detected by using 3,3'-Diaminobenzidine (DAB) (Dako). Finally, followed the contrasting with Mayer's Hematoxylin, alcohol dehydration, xylene clarification and slide fixing using the DPX environment (Fluka).

For the IHC study, we used the following antibodies: anti-human CD3 (clone F7.2.38, Dako, 1:100 dilution), anti-human CD20cy (clone L26, Dako, 1:100 dilution), anti-human CD68 (clone KP1, Dako, 1:200 dilution), anti-human CD79- α (clone JCB117, Dako, 1:50 dilution), and anti-human CD34 (clone QBEnd10, Dako, 1:100 dilution), for highlighting a possible inflammatory reaction that sometimes appears in PE and alterations of pulmonary microvascularization.

Results

Our study included 70 patients, of which 20 (28.57%) reached the negative outcome composite endpoint (in-hospital death, death or hospitalization for HF at one month after discharge). In-hospital mortality was 4.28% (three patients), another 14.28% (10 patients) died in the first month, and an additional seven patients required re-hospitalization for HF. No patients were lost to follow-up.

Mean age was 72.1 years and exactly 50% of patients were male. Most of the patients had a history of HF (84.29%) and about half of them (51.42%) having had a previous hospitalization due to HF. Furthermore, of these latter patients, half had had a previous episode of acute PE (25.71% of the total number of patients). Another interesting finding was the fact that 32 (45.71%) patients had been hospitalized for HF in the previous year.

Patients' characteristics according to outcome are presented in Tables 1 and 2.

Table 1 – Patients characteristics according to outcome (categorical variables)

Parameter	Not worsening (50 patients)	Worsening (20 patients)	$P \chi^2$
Duration of hospitalization >7 days	15 (30%)	8 (40%)	0.421
Atrial fibrillation	19 (38%)	7 (35%)	0.814
History of kidney disease	7 (14%)	9 (45%)	0.005
History of stroke	8 (16%)	4 (20%)	0.688
History of beta-blockers	34 (68%)	12 (60%)	0.524
History of ACEI/ARB	34 (68%)	14 (70%)	0.871
History of diuretics	26 (52%)	9 (45%)	0.597
Leg edema	8 (16%)	9 (45%)	0.011
Rhythm disorder	17 (34%)	10 (50%)	0.214
Intraventricular block	11 (22%)	7 (35%)	0.715
AST/ALT increase	11 (22%)	3 (15%)	0.485
Mitral regurgitation	40 (80%)	18 (90%)	0.316
Mitral stenosis	2 (4%)	0 (0%)	0.364
Aortic regurgitation	13 (26%)	4 (20%)	0.597
Aortic stenosis	10 (20%)	3 (15%)	0.627
Tricuspid regurgitation	32 (64%)	14 (70%)	0.633
Pleural effusion	9 (18%)	7 (35%)	0.126
Non-invasive CPAP	11 (22%)	5 (25%)	0.704
Chronic kidney disease	16 (32%)	12 (60%)	0.031
Anemia	7 (14%)	9 (45%)	0.005
COPD	5 (10%)	4 (20%)	0.223
Beta-blockers treatment	41 (82%)	13 (65%)	0.298
ACEI/ARB treatment	43 (86%)	13 (65%)	0.047
Antibiotic treatment	21 (42%)	10 (50%)	0.543
ACEI/ARB treatment at discharge	18 (36%)	5 (25%)	0.156
Diuretics at discharge	22 (44%)	10 (50%)	0.347
Diabetes mellitus	19 (38%)	14 (70%)	0.015

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; AST: Aspartate transaminase; ALT: Alanine transaminase; CPAP: Continuous positive airway pressure; COPD: Chronic obstructive pulmonary disease.

Table 2 – Patients characteristics according to outcome (continuous variables)

Parameter	Not worsening (50 patients)	Worsening (20 patients)	p Mann-Whitney
Age [years]	70.54±9.23	76±9.24	0.0283
Duration of hospitalization [days]	7.16±2.96	7.25±4.2	0.9163
BMI [kg/m ²]	26.68±4.34	28.51±5.17	0.2266
SaO ₂ at admission [%]	83.54±14.15	83.5±9.13	0.648
Systolic BP at admission [mmHg]	174.58±25.21	153.45±37	0.0478
Diastolic BP at admission [mmHg]	95.72±13.64	83.2±18.11	0.0104
Heart rate at admission [bpm]	104.24±25.68	93.55±24.01	0.0996
Systolic BP at discharge [mmHg]	126.78±16.71	123.88±14.98	0.4737

Parameter	Not worsening (50 patients)	Worsening (20 patients)	p Mann-Whitney
Diastolic BP at discharge [mmHg]	74.22±12.51	73.82±8.2	0.6411
Heart rate at discharge [bpm]	77.18±14.1	78.18±11.48	0.4344
QRS duration [ms]	103.54±27.53	96.75±17.25	0.5478
Hemoglobin [g/dL]	13.73±2.07	12.8±2.68	0.1349
Creatinine at admission [mg/dL]	0.99±0.29	1.44±0.53	0.0001
Creatinine at discharge [mg/dL]	1.03±0.32	1.38±0.5	0.0107
Change in creatinine	-0.05±0.2	0.08±0.47	0.0005
eGFR at admission [mL/min/1.73 m ²]	72.61±23.51	48.36±19.85	0.0002
eGFR at discharge [mL/min/1.73 m ²]	69.53±25.17	50.8±20.97	0.0052
Change in eGFR	4.42±21.90	-3.3±16.03	0.1775
Serum Na at admission [mmol/L]	139.76±4.15	135.8±5.30	0.0002
Serum Na at discharge [mmol/L]	138.4±4.19	137.5±4.74	0.7196
Change in serum Na	1.36±5.11	-1.94±4.6	0.0057
Serum K at admission [mmol/L]	4.31±0.76	4.6±0.84	0.3109
Serum K at discharge [mmol/L]	4.27±0.71	4.38±0.72	0.5726
Change in serum K	-0.01±0.9	0.27±0.63	0.3076
NT-proBNP at admission [pg/mL]	7144.96±5839.82	12627.95±10844.65	0.101
NT-proBNP at discharge [pg/mL]	2382.95±2992.25	8351.65±9638.97	0.0051
Change in NT-proBNP	4853.03±4589.45	4494.88±4879.71	0.6102
Serum glucose [mg/dL]	146.04±57.23	163.2±94.8	0.8505
Blood pH	7.28±0.09	7.27±0.09	0.567
TnI [ng/mL]	0.24±0.47	0.39±0.89	0.5949
LVEF [%]	39.69±11.15	39.2±12.74	0.6956
LVEDV [mL/m ²]	79.85±32.12	72.37±20.22	0.3907
E/e' <15	18.24±8.72	19±6.51	0.3605
TAPSE [mm]	18.58±4.56	18±3.57	0.6245
RVFAC [%]	43.14±6.72	39±8.91	0.0495
Sm RV TDI [cm/s]	10.76±2.66	10.45±2.04	0.6962
LA volume index [mL/m ²]	51.32±20.89	62.5±22.11	0.0488
Tricuspid systolic gradient [mmHg]	31.32±15.96	33.1±10.96	0.3385
PASP [mmHg]	40.04±18.02	43.05±12.94	0.286
RA volume index [mL/m ²]	34.22±12.97	32.2±9.62	0.7897
Furosemide in first 12 h [mg]	59.6±27.77	57.5±20.23	0.7768
Diuresis in first 12 h [mL]	1940.82±937.84	1973.53±1085.43	0.9181

BMI: Body mass index; SaO₂: Oxygen saturation; BP: Blood pressure; bpm: Beats per minute; eGFR: Estimated glomerular filtration rate; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; TnI: Troponin I; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end-diastolic volume; E/e': The ratio between early mitral inflow velocity and mitral annular early diastolic velocity; TAPSE: Tricuspid annular plane systolic excursion; RVFAC: Right ventricular fractional area change; Sm: Systolic myocardial velocity; RV: Right ventricle; TDI: Tissue Doppler imaging; LA: Left atrium; PASP: Pulmonary artery systolic pressure; RA: Right atrium. Values are expressed as mean ± standard deviation (SD).

Because some parameters [creatinine, estimated glomerular filtration rate by modification of diet in renal disease (eGFR_{MDRD}), serum Na, NT-proBNP] had multiple measurements, which were highly correlated, we kept for further analysis only the value at admission. Between

history of kidney disease and chronic kidney disease diagnosis at discharge, we preferred the former, because of its better significance level.

For all variables that showed significant differences between worsening and non-worsening patients, and for

variables that were mentioned in literature, without being significant in our study, such as serum K, LVEF, body mass index (BMI), and pleural effusion, we conducted simple binary logistic regression analysis, with the following results (Table 3).

Table 3 – Coefficients obtained performing simple binary logistic regression analysis

Parameter	B	Standard error	Wald χ^2	p value	Exp(B) = OR (95% CI)
Age [years]	0.065	0.031	4.513	0.034	1.067 (1.005–1.134)
Systolic BP at admission [mmHg]	-0.025	0.01	6.385	0.012	0.976 (0.957–0.995)
Diastolic BP at admission [mmHg]	-0.056	0.02	7.627	0.006	0.946 (0.909–0.984)
Creatinine at admission [mg/dL]	2.936	0.871	11.367	0.001	18.845 (3.419–103.876)
eGFR at admission [mL/min/1.73 m ²]	-0.051	0.015	11.161	0.001	0.951 (0.923–0.979)
Serum Na [mmol/L]	-0.196	0.076	6.645	0.01	0.822 (0.709–0.954)
Serum K [mmol/L]	0.475	0.341	1.942	0.164	1.608 (0.824–3.136)
NT-proBNP [pg/mL]	0	0	6.082	0.014	1 (1–1)
LA volume index [mL/m ²]	0.024	0.012	3.63	0.057	1.024 (0.999–1.049)
LVEF [%]	-0.004	0.023	0.028	0.868	0.996 (0.952–1.043)
RVFAC [%]	-0.065	0.036	3.319	0.068	0.937 (0.874–1.005)
BMI [kg/m ²]	0.087	0.059	2.194	0.139	1.091 (0.972–1.224)
Pleural effusion (categorical)	0.897	0.596	2.266	0.132	2.453 (0.763–7.89)
Anemia (categorical)	1.615	0.607	7.082	0.008	5.026 (1.53–16.507)
Leg edema (categorical)	1.458	0.592	6.056	0.014	4.295 (1.345–13.715)
History of kidney disease (categorical)	1.615	0.607	7.082	0.008	5.026 (1.53–16.507)
ACEI/ARB treatment (categorical)	0.435	0.596	0.533	0.466	1.545 (0.48–4.975)
Diabetes mellitus (categorical)	1.337	0.568	5.533	0.019	3.807 (1.25–11.597)

BP: Blood pressure; eGFR: Estimated glomerular filtration rate; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; LA: Left atrium; LVEF: Left ventricular ejection fraction; RVFAC: Right ventricular fractional area change; BMI: Body mass index; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; OR: Odds ratio; CI: Confidence interval.

In order to create a multiple logistic regression model, we had to take into consideration multicollinearity issues that could occur.

By computing the Spearman's correlation matrix, we found correlation coefficients greater than 0.385 (equivalent to $p=0.001$) between age and glomerular estimated filtration rate by MDRD formula (eGFR_{MDRD}) ($\rho=-0.43$), systolic BP and diastolic BP ($\rho=0.696$), creatinine and eGFR_{MDRD} ($\rho=0.707$), creatinine and serum K ($\rho=0.504$), creatinine and kidney disease ($\rho=0.596$), eGFR_{MDRD} and left atrium volume index ($\rho=-0.391$), eGFR_{MDRD} and kidney disease ($\rho=-0.388$), serum potassium and kidney disease ($\rho=0.395$). In the models we tested, we avoided using these pairs of parameters together. Also, the correlations between anemia and creatinine or eGFR_{MDRD} were strong enough to be mentioned ($\rho=0.379$, and $\rho=-0.365$), as well as systolic BP and leg edema ($\rho=-0.367$).

Because of the multiple correlations encountered, we performed a factor analysis to better understand the relationships among the variables used in our study. We analyzed the first seven common factors identified among the data, because they account for more than 50% of the variability (52.36%), while each of them explains more than 2% of it, the first four explaining each more than 5% of the variability. Analyzing the seven common factors among the variables, we decided to create a model based on creatinine, diastolic BP, age, Na, diabetes mellitus, pleural effusion, and prior treatment with angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (ACEI/ARB), considering as significant

a p -value less than 0.1. Pleural effusion and ACEI/ARB treatment proved to be non-significant. This was somehow expected, because they also proved to be non-significant when we performed simple logistic regression.

This model correctly classified 46 (92%) patients without worsening and 13 (65%) patients with worsening, providing an overall accuracy of 84.3%. The likelihood and “goodness-of-fit” tests for this model yielded the following results: Cox & Snell $R^2=0.410$, Nagelkerke $R^2=0.587$, Hosmer & Lemeshow test $p=0.314$.

Further refining the model, we decided to keep only five variables in the regression analysis, resulting in the following model coefficients. All of them had p -values less than 0.1 (Table 4).

Table 4 – Coefficients for the second logistic model

Model 2	B	S.E.	Wald	p	Exp(B) = OR
Creatinine	2.988	1.099	7.395	.007	19.844
Diastolic BP	-.057	.027	4.333	.037	.945
Serum Na	-.126	.068	3.423	.064	.882
Age	.083	.042	3.862	.049	1.087
Diabetes mellitus (categorical)	1.824	.836	4.761	.029	6.196
Constant	10.987	9.375	1.373	.241	59072.805

S.E.: Standard error; BP: Blood pressure; OR: Odds ratio.

This model correctly classified 48 (96%) patients without worsening and 13 (65%) patients with worsening, providing an overall accuracy of 87.1%.

The likelihood and “goodness-of-fit” tests for this model yielded the following results: Cox & Snell $R^2=0.398$, Nagelkerke $R^2=0.571$, Hosmer & Lemeshow test $p=0.687$. For this model, both the classification table and Hosmer

& Lemeshow “goodness-of-fit” test had better results, so we recommend using this model when assessing the outcome for the type of patients discussed in this study.

We tried replacing creatinine with $eGFR_{MDRD}$ or kidney disease (factor 1), diastolic BP with systolic BP (factor 2), or serum Na with serum K (factor 4), but the resulting models were inferior to the one already discussed.

The histological and IHC study was performed for confirming the diagnosis of acute cardiogenic PE, and also for identifying the possible particularities of every case.

In the left ventricle myocardium, there were present larger or smaller myocardial fibrosis areas, where the myocardial fibers were completely or partially replaced by collagen fibers, thus confirming the reduction of the pump function of the myocardium, which led to PE. In some myocardial fibrosis areas, the microvascularization was completely altered by fibroblast proliferation and deposits of interstitial conjunctive matrix (Figures 1 and 2).

In the lung, the histopathological changes varied widely from one patient to another, probably caused by the recurrence of subclinical PEs or by the presence of associated lung diseases. Still, in all cases, the lung alveoli were larger in size, with the lumina completely or almost completely covered by an eosinophilic liquid (Figure 3). Some alveolar septa appeared thickened, with uneven limits and congested capillaries (Figure 4). Most often, in the lung alveoli lumina, we identified few inflammatory cells (Figure 5), but, in some cases, the lung alveoli contained numerous inflammatory cells, mainly macrophages (Figure 6).

In other patients, there was observed destruction of interalveolar septa, creating large spaces filled with plasma exudate and numerous inflammatory cells (Figure 7). Also, there were more or less extended areas in the architecture of the lung parenchyma, which were completely remodeled by the presence of inflammatory process, associated with collagenous fibrosis (Figure 8).

By the use of immunohistochemistry techniques, we intended to differentiate the types of inflammatory cells present in the lung parenchyma in patients with acute PE.

The T-lymphocytes were selectively highlighted by using the anti-CD3 antibody. As observed from our images, T-lymphocytes were present in small number, with no associated inflammatory processes (Figure 9), but they were identified in a large number in the areas with abundant inflammatory infiltrates of the lung parenchyma (Figure 10). B-lymphocytes were electively highlighted by using the anti-CD20 antibody. Similarly to T-lymphocytes, B-lymphocytes also had a heterogeneous intensity and distribution in patients with acute PE. There were highlighted areas of pulmonary parenchyma with a very small number of B-lymphocytes (Figure 11) and areas where B-lymphocytes were quite abundant (Figure 12).

The macrophages were identified by the anti-CD68 antibody marking. They were the most numerous inflammatory cells present in the pulmonary parenchyma. In patients with acute PE with no inflammatory reaction, we identified macrophages only in the alveolar septa, where their presence is normal (Figure 13), but in patients with PE associated with other lung inflammatory processes the macrophages were the most numerous cells identified (Figure 14).

For highlighting the chronic character of the inflammatory infiltrates present in the pulmonary parenchyma, we searched to identify the presence of plasmocytes, by using the anti-CD79 α antibody. In patients with acute PE without any inflammatory processes, plasmocytes were absent (Figure 15); but, in patients in which acute PE was associated with lung inflammatory processes, plasmocytes were quite numerous (Figure 16).

Regarding the microvascularization of the lung parenchyma, electively highlighted by using the anti-CD34 antibody, in acute PE, we observed the presence of a higher number of capillaries in the alveolar septa, associated with arteriolar and venular congestion (Figures 17 and 18).

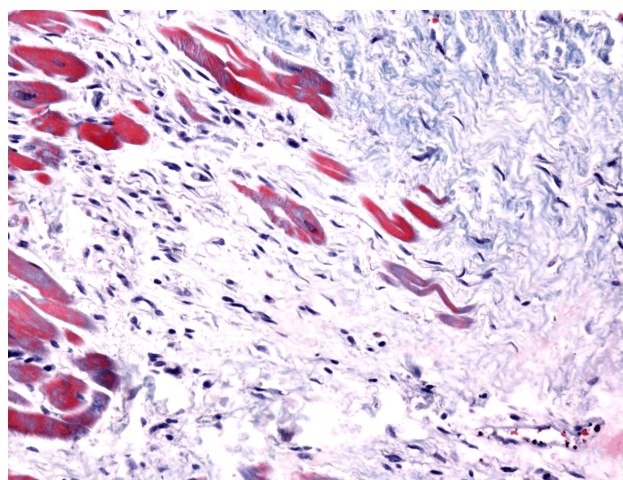


Figure 1 – Myocardium from left ventricle, highlighting an area of myocardial fibrosis, characterized by myocardiocyte disappearance, fibroblast proliferation and replacement of myocardial fibers with collagen fibers (GS trichrome staining, $\times 200$).

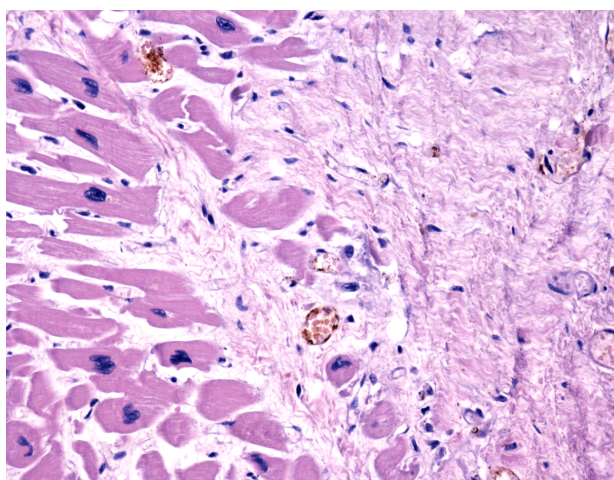


Figure 2 – Myocardium area with extended fibrosis and disappearance of capillaries (HE staining, $\times 200$).

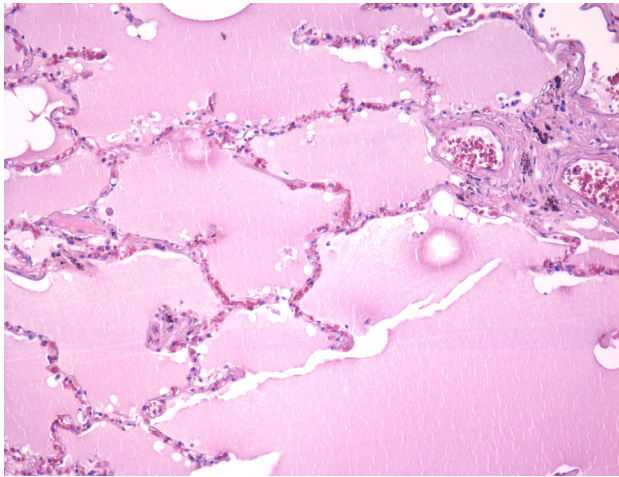


Figure 3 – Lung parenchyma with large alveoli, filled with an eosinophilic liquid (HE staining, ×100).

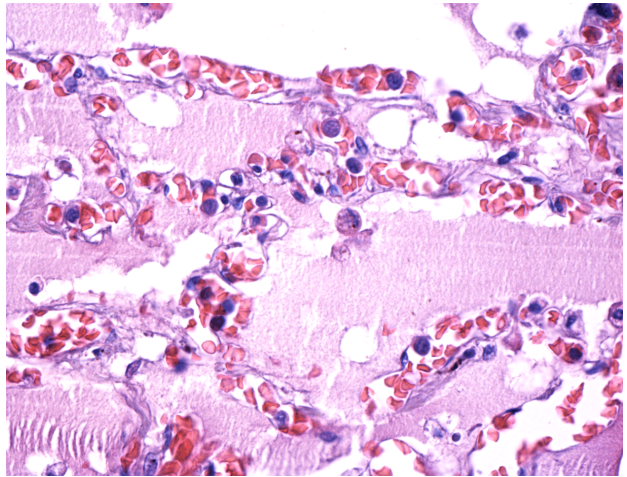


Figure 4 – Thickened alveolar septa associated with congestion of lung capillaries (HE staining, ×400).

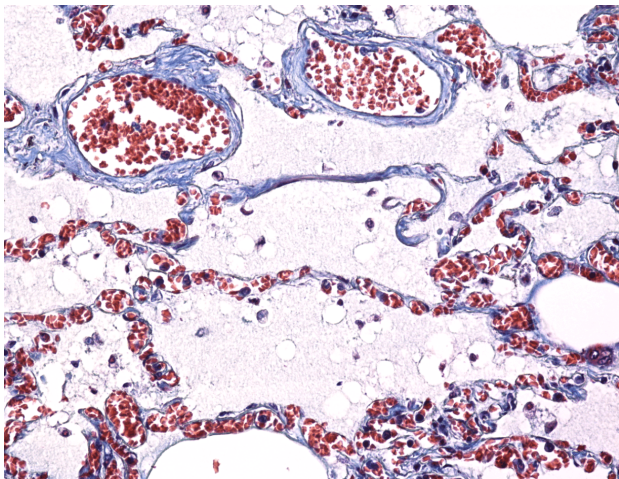


Figure 5 – Large lung alveoli, filled with plasmatic exudate and rare inflammatory cells (GS trichrome staining, ×200).

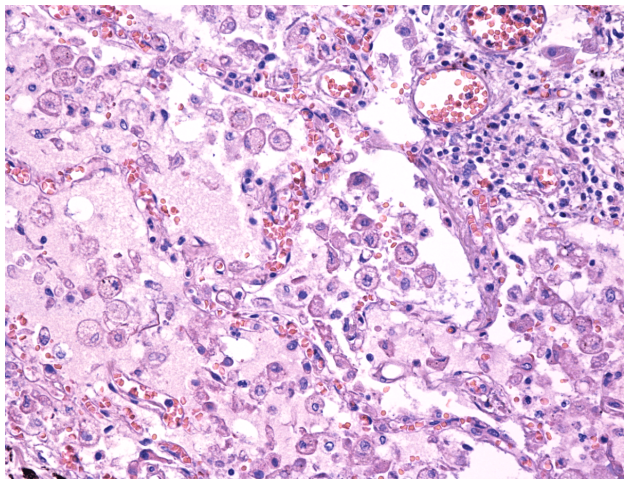


Figure 6 – Image of pulmonary edema with numerous inflammatory cells in the alveolar exudate (HE staining, ×200).

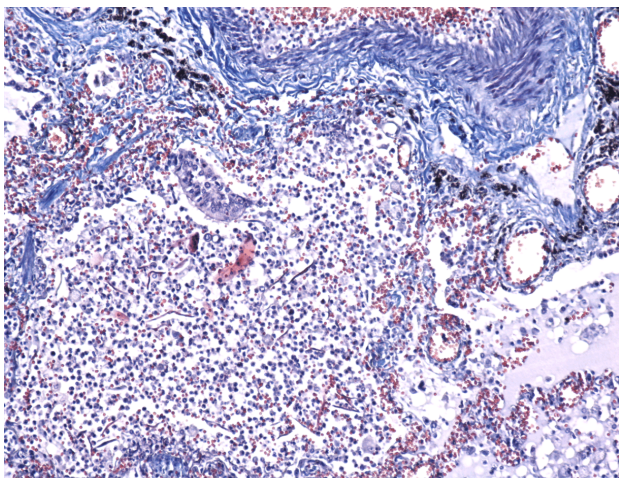


Figure 7 – Area of lung parenchyma, presenting an abundant inflammatory infiltrate associated with the destruction of interalveolar septa (GS trichrome staining, ×100).

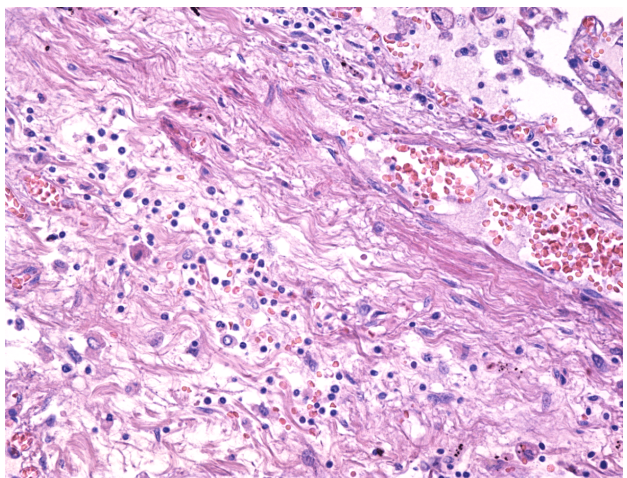


Figure 8 – Lung parenchyma completely remodeled by the presence of a chronic inflammatory process, associated with the formation of collagen fibers (HE staining, ×200).

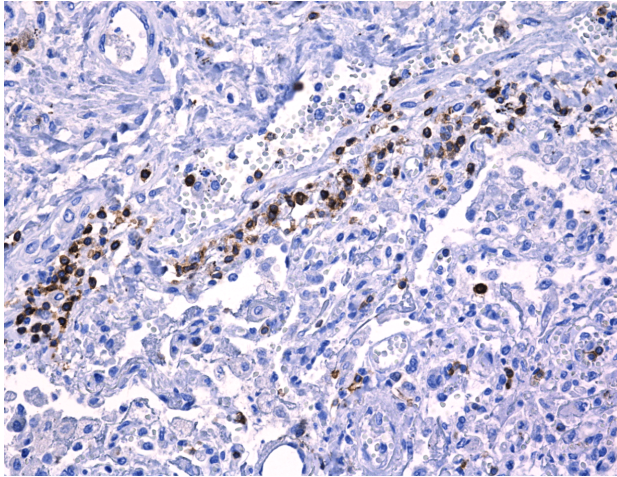


Figure 9 – T-lymphocytes present in a lower number in the lung parenchyma of the patients with acute pulmonary edema (Anti-CD3 antibody immunostaining, ×200).

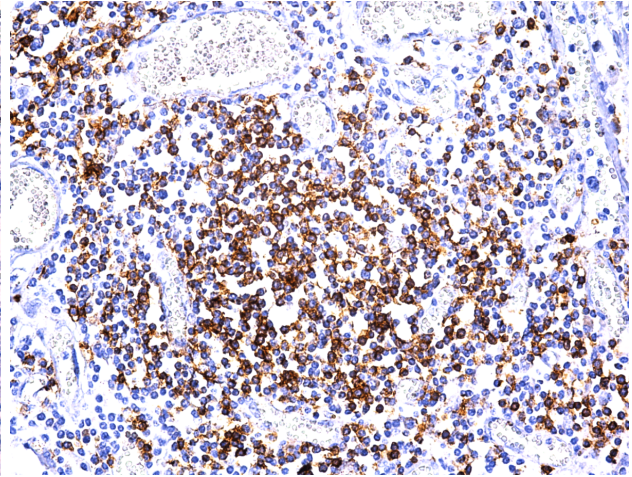


Figure 10 – Area of lung parenchyma with an abundant inflammatory infiltrate, mainly formed of T-lymphocytes (Anti-CD3 antibody immunostaining, ×200).

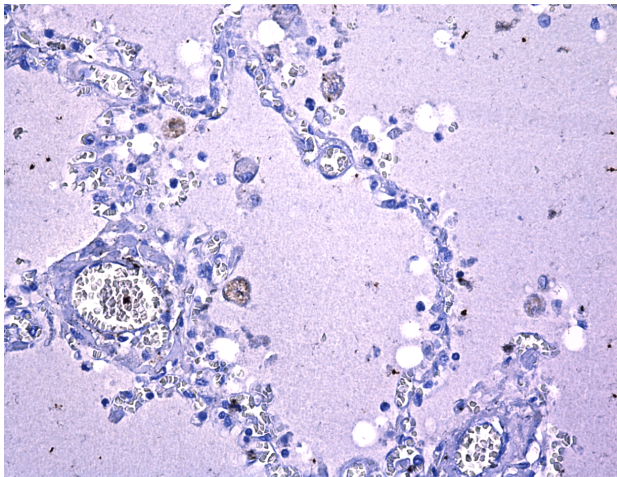


Figure 11 – Lung parenchyma with rare B-lymphocytes present perivascular or in the interalveolar septa (Anti-CD20 antibody immunostaining, ×200).

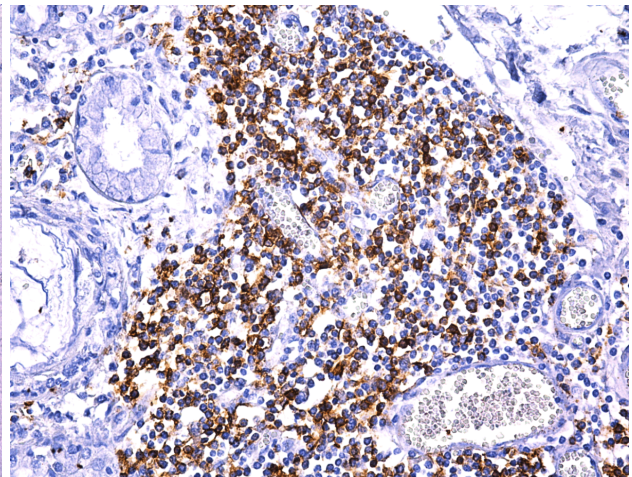


Figure 12 – Area of lung parenchyma strongly infiltrated with inflammatory cells, where B-lymphocytes are present in a large number (Anti-CD20 antibody immunostaining, ×200).

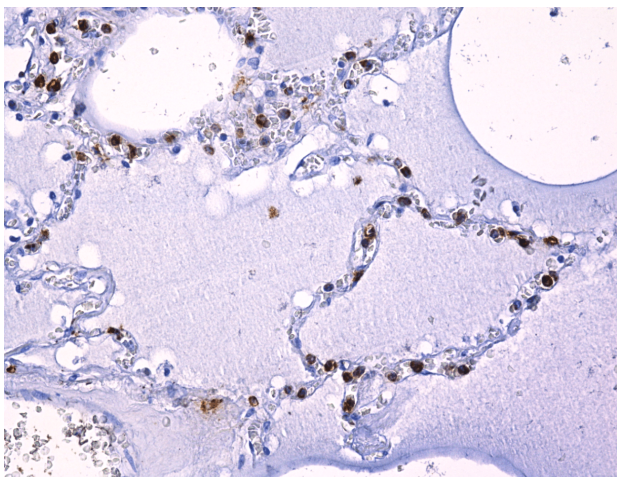


Figure 13 – Image of acute lung edema with dilated alveoli, with a plasma extravasation in the alveoli and numerous macrophages in the alveolar walls (Anti-CD68 antibody immunostaining, ×200).

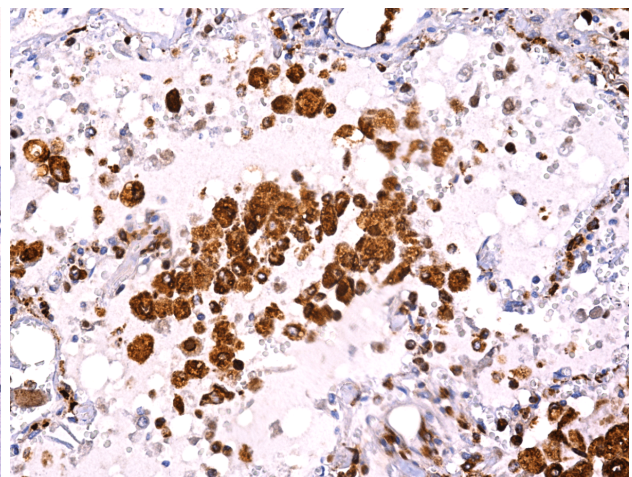


Figure 14 – Acute lung edema with numerous macrophages present in the alveolar and interalveolar septa (Anti-CD68 antibody immunostaining, ×200).

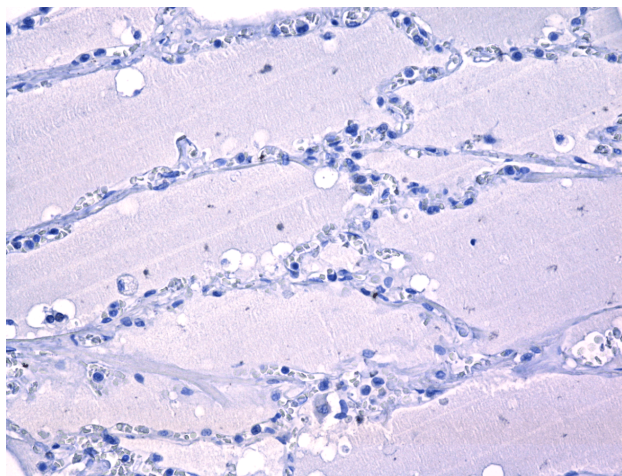


Figure 15 – Area of acute lung edema, where there may be observed the absence of plasmacytes (Anti-CD79- α antibody immunostaining, $\times 200$).

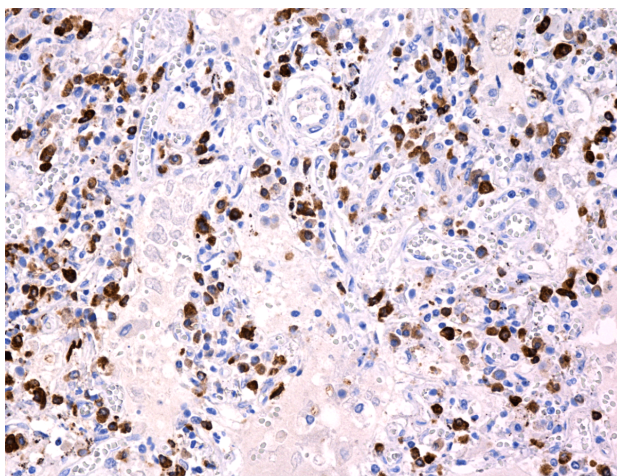


Figure 16 – Acute lung edema associated with a chronic inflammatory process, where plasmacytes are relatively numerous (Anti-CD79- α antibody immunostaining, $\times 200$).

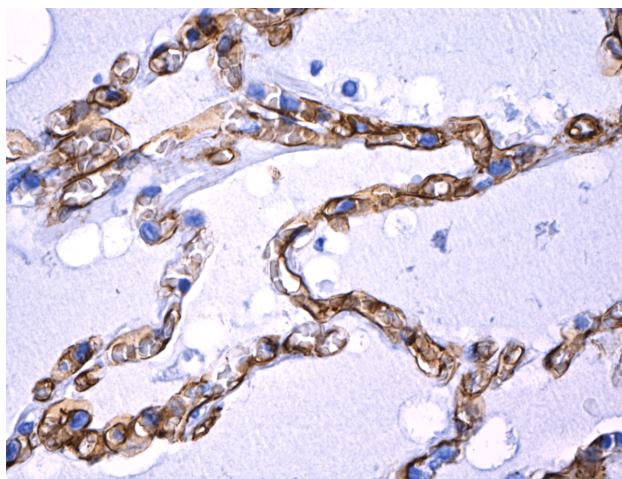


Figure 17 – Interalveolar wall with a normal network of lung capillaries (Anti-CD34 antibody immunostaining, $\times 400$).

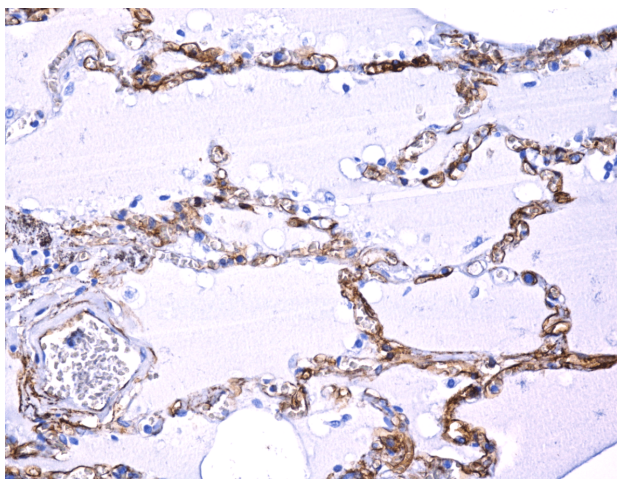


Figure 18 – Image of a pulmonary edema, where there can be observed the presence of vascular congestion (Anti-CD34 antibody immunostaining, $\times 200$).

Discussion

In a number of AHF records, in-hospital PE mortality was reported to be 5 to 9%, which is higher than our study – 4.28% [1–8]. Contrasting with the wider category of acute HF, prognosis in acute PE was addressed in only a few small studies.

In the univariate analysis of our patients, several parameters correlated significantly with a negative short-term outcome, *i.e.*, death or re-hospitalization for HF. Older people had a worse prognosis than younger ones, which is concordant with results from OPTIMIZE-AF registry, where every 10-year increase was associated with a 33% higher risk for in-hospital mortality [12]. Older patients have more comorbidities, present multiple and severe impairments of physical function, which can explain higher rehospitalization rates.

Most of the AHF studies have similar results to our study, showing a correlation between renal function (blood urea nitrogen, creatinine, eGFR, cystatin C) and the prognostic of patients. In both, OPTIMIZE-AF and ADHERE records, in-hospital mortality increased at patients with renal dysfunction [12, 13].

The prognostic value of BP in PE has been recognized starting with older papers, like that of Goldberger *et al.* [14], in which patients with an initial systolic BP ≥ 160 mmHg had a better six-month survival than patients with a systolic BP less than 160 mmHg. Also, in OPTIMIZE-HF registry, an increased systolic BP at admission, up to 160 mmHg was associated with a lower risk of in-hospital mortality [12]. In our study, the systolic and diastolic BP at admission were significantly lower in patients with short-term worsening; the differences in discharge BP were not significant. Heart rate at admission or discharge was not associated with prognosis.

Serum sodium level was a predictor of short-term worsening (139.76 ± 4.15 mmol/L in patients without worsening *versus* 135.8 ± 5.3 mmol/L in patients with worsening, $p=0.0002$). Hyponatremia is a predictor of poor prognosis in acute HF, and its improvement during hospitalization is associated with lower mortality rate [15].

High plasma level of NT-proBNP has prognostic implications in chronic and acute HF. Few studies approached its role in acute PE. Chuang *et al.* [16] showed that increased NT-proBNP within 24 hours after admission is an independent prognostic predictor of long-term

mortality and major cardiac events in acute cardiogenic PE, including patients with preserved and reduced LVEF. In our group, only NT-proBNP at discharge was significantly higher in the worsening patients (2382.95 ± 2992.25 pg/mL *versus* 8351.65 ± 9638.97 pg/mL, $p=0.0051$); also, the change in NT-proBNP during hospitalization did not differ significantly. Metra *et al.* also confirmed the role of NT-proBNP level at discharge as an independent prognostic marker, documented decline of NT-proBNP at 24 hours and especially 48 hours (when is the nadir) after the initiation of intravenous therapy [17].

Troponin level was not correlated with short-term worsening in our study. Troponin is an important biomarker in HF and in the context of an acute presentation, troponin I or T should be measured to exclude myocardial infarction, which is a frequent cause of AHF [18]. Ofra *et al.* [19], in a retrospective study of 124 patients with acute PE, demonstrated that patients with troponin T levels ≥ 0.1 ng/mL had significantly increased rates of ischemic events (sudden death, fatal, non-fatal myocardial infarction or admission for acute coronary syndrome). Troponin T levels did not predict recurrent PE. Authors concluded that routine measurement of troponin T level was beneficial in identifying low- and high-risk patients in acute PE.

Echocardiography is an important tool in establishing the diagnosis and etiology of acute HF, but it offers prognostic information also [20]. In the group we studied, the echocardiography parameters that were correlated with poor short-term prognosis were right ventricular fractional area change (FAC) ($39 \pm 8.91\%$ in patients with worsening *versus* $43.14 \pm 6.72\%$ in patients without worsening, $p=0.0495$) and left atrium volume index (LAVi) (62.5 ± 22.11 mL/m² *versus* 51.32 ± 20.89 mL/m², $p=0.0488$). Right ventricular dysfunction has been linked to negative prognosis in acute decompensated and also new onset HF [21, 22], but, to our knowledge, there are no studies in APE patients. In a study on mechanically ventilated patients with acute PE [23], tricuspid annular plane systolic excursion (TAPSE) and right ventricle tissue Doppler imaging (RV TDI) velocities were significantly correlated with E/e', LVEF and length of ventilatory support, but mortality was not analyzed.

Although serum glucose at admission was not predictive of outcome, diabetes mellitus (either present at admission or diagnosed during hospitalization) was one of the variables associated with short-term worsening as seen at multivariate analysis. This was also observed in larger records. In the *ESC-HFA Heart Failure Long-Term Registry* [24], the presence of diabetes was independently associated with an increased risk of in-hospital mortality, one-year all-cause mortality, and one-year re-hospitalizations for HF. Unlike in the present study, in this cohort of 6926 patients elevated blood glucose at admission was powerfully prognostic for in-hospital mortality.

Despite the important advances in the management of acute PE (and generally in the field of AHF), prognosis assessment remains an ongoing challenge, with a high rate of mortality and rehospitalization and a huge financial burden.

Therefore, there is a need for models to guide prognosis evaluation, to identify high-risk patients, who

should have a more attentive follow up and intensive care. Our study proposes a logistic model for identifying high-risk patients with acute PE.

Study limitations

The main limitation of the study was the relatively small number of patients. It is possible that some parameters did not reach statistical significance because of this reason. Also, it is unclear if the findings can be generalized, as all the data was collected from just two hospitals. The predictive model developed needs to be validated on another larger group of patients. And finally, there is a need for larger studies to analyze short, but also long-term prognosis of PE patients.

Conclusions

PE patients present a high risk of in-hospital and short-term adverse events. The factors that best predicted in-hospital mortality and one-month death or rehospitalization were age, diabetes, diastolic BP, creatinine, serum sodium. Patients at risk should be identified and more closely monitored both during hospitalization, but also after discharge. Morphological features of PE are myocardial fibrosis and larger than normal alveoli filled with eosinophilic fluid and inflammatory cells.

Conflict of interests

The authors report no conflict of interests.

Author contribution

Cristian Militaru and Cristina Maria Mărginean equally contributed to the study design and manuscript proofing.

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Received: January 25, 2017

Accepted: March 5, 2018