ORIGINAL RESEARCH ARTICLE

Predictive value of heart failure with reduced versus preserved ejection fraction for outcome in pulmonary embolism

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Abstract

Aims   This study aimed to investigate whether the risk of short-term mortality is different in pulmonary embolism (PE) patients who have heart failure with reduced ejection fraction (HFrEF) as compared with those with heart failure with preserved ejection fraction (HFpEF).

Methods and results   Predictive value of HFrEF or HFpEF for 7-day (intrahospital) and 30-day all-cause mortality was determined in the cohort of 1055 out of 1201 consecutive acute PE patients from the Serbian multicentre PE registry. Patients were classified into either HFrEF or HFpEF group, according to guideline-proposed criteria. A 7-day (intrahospital) and 30-day all-cause mortality was 18.5% vs. 7.3% vs. 4.5% ($P < 0.001$) and 22.2% vs. 16.3% vs. 7.9% ($P < 0.001$) for patients with the history of HFrEF, HFpEF, and without HF, respectively. Multivariable analysis adjusted to age, gender, history of chronic obstructive pulmonary disease, diabetes mellitus, arterial hypertension, presence of atrial fibrillation, and mortality risk assessment at admission has shown that only HFrEF, but not HFpEF, was an independent predictor for 7-day mortality (hazard ratio 2.22, 95% confidence interval 1.25-4,38.41, $P = 0.021$) and neither HFrEF or HFpEF was an independent predictor for 30-day mortality. Among various admission parameters associated to PE outcome, only systolic pressure in HFrEF patients ($P < 0.001$), heart rate ($P = 0.01$), and right ventricle systolic pressure ($P = 0.039$) in HFpEF patients were significantly different in patients who died compared with those who survived at 7 days.

Conclusions   Our study has shown that the presence of previous history of HFrEF, but not HFpEF, in acute PE is an independent risk factor for mortality at 7 days.

Introduction

Heart failure (HF) is a common comorbidity in patients with acute pulmonary embolism (PE).[1–3] Patients with HF are more prone to develop acute PE and have a worse short-term and long-term prognosis after PE.[4–6] Regarding the level of left ventricle (LV) ejection fraction (LVEF) and according to current European Society of Cardiology (ESC) guidelines, HF patients are classified into the three different groups, such as the one with HF with reduced ejection fraction (HFrEF) (LVEF < 40%), then those with HF with middle-range ejection fraction (HFmrEF) (LVEF 40–49%), and those with HF with preserved ejection fraction (HFpEF) (LVEF ≥ 50%).[7] In patients with HFrEF, both systolic and diastolic myocardial functions are impaired, while in patients with HFpEF, diastolic dysfunction predominates. In general, the prognosis of HFrEF and HFpEF regarding all-cause mortality is similar during the follow-up period of 5 years.[8] However, patients with HFrEF die more frequently from cardiovascular reasons, while patients with HFpEF die mostly from some other non-cardiovascular diseases.[8] Cardiovascular events after acute PE are common, and the presence of HF enhances the possibility of PE recurrence and all-cause death.[4,5] However, the pathophysiology of HFrEF and HFpEF is different and it is unknown whether these two basic types of HF have a diverse impact on PE outcome.

The purpose of this study was to investigate the incidence of early all-cause and PE-related mortality regarding the type of HF. In addition, the aim was to compare predictive values of HFrEF and HFpEF adjusted to age and PE mortality risk assessment proposed by the 2019 ESC guidelines for 30-day mortality.[9] Finally, we assessed the correlation between various prognostic parameters on admission to the hospital with 30-day all-cause and PE-related mortality regarding the type of HF.

Methodology

The source of data was the Serbian multicentre PE registry, which successively included eight hospitals (seven university hospitals and one hospital of general practice) during the period from 2014 to 2020. Acute PE was diagnosed according to the ESC algorithm.[9] Pulmonary angiography with multidetector computed tomography was performed to all patients included in the study. The majority of patients were admitted to intensive care units for the initial evaluation. Among 1201 patients included in the registry, 1055 had all relevant data for diagnosis and were suitable for classification into one of HFrEF, HFpEF, or control (without HF) group. Among excluded patients, 25 had HFmrEF and 121 patients had incomplete data to be classified into any group (*Figure 1*, flow chart of the study).

Definitions

Classification of patients into HFrEF, HFpEF, or control group was performed according to previous medical history and LVEF measurements on admission, following the ESC guidelines for HF.[7] All patients with HF had medical reports that confirmed typical signs and symptoms of HF, and the majority of them had at least one episode of hospitalization or detailed outpatient cardiology reports from the control visits in the last year with available echocardiography imaging and laboratory findings of elevated BNP or NT-proBNP values (*Figure 1*). Patients classified into the HFrEF group had medical documentation that confirmed the diagnosis of HF and LVEF < 40%. In 73 out of 81 HFrEF patients, echocardiography was performed on admission, confirming the LVEF < 40%. Echocardiography was not performed on admission in eight cases, and they were classified in the HFrEF group according to at least one available echocardiographic report performed in the last year. Patients with HFpEF had medical documentation that confirmed the previous episode of HF and LVEF ≥ 50%. Echocardiography on admission confirmed HFpEF in 100 of 123 patients, while others had a respectable echocardiography report in the last year, which confirmed diastolic dysfunction (preserved LVEF ≥ 50% and objective evidence of other cardiac functional and/or structural cardiac abnormalities underlying HF: enlarged left atrium volume index, increased LV mass and E/e′).[7] The majority of patients with HF used recommended therapy according to ESC guidelines for the management of HF.[7] Among patients with HFrEF, 80% and 73% of them used beta-blockers and angiotensin-converting enzyme inhibitors, respectively. Among patients with HFpEF, 70%, 65%, and 15% were treated with beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, respectively. Valsartan-sacubitril was not used in any patient in the study. In about 10% of patients from both groups, we had no reliable data regarding medication used before PE.

Patients with HFmrEF, where LVEF is 40–49%, were excluded from the study because of the low frequency in the registry and low event rate (25 patients and 5 all-cause deaths), which preclude statistical analysis.

Data extraction

Relevant data were derived from medical history during hospitalization by trained doctors who assisted in administrative work on the database. All patients were asked about comorbidities and had measurements of oxygen saturation, systolic arterial pressure, and heart rate. Echocardiography imaging, cTnI, and BNP or NT-proBNP blood levels were obtained on the first hospitalization day for a considerable number of patients (see footnote of *Table 1*). According to the presence of severe hypotension or right ventricle (RV) dysfunction, acute

FIGURE 1 Flow chart of the study. BNP, brain natriuretic peptide; CHF, chronic heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LVEF, left ventricle ejection fraction; PE, pulmonary embolism.
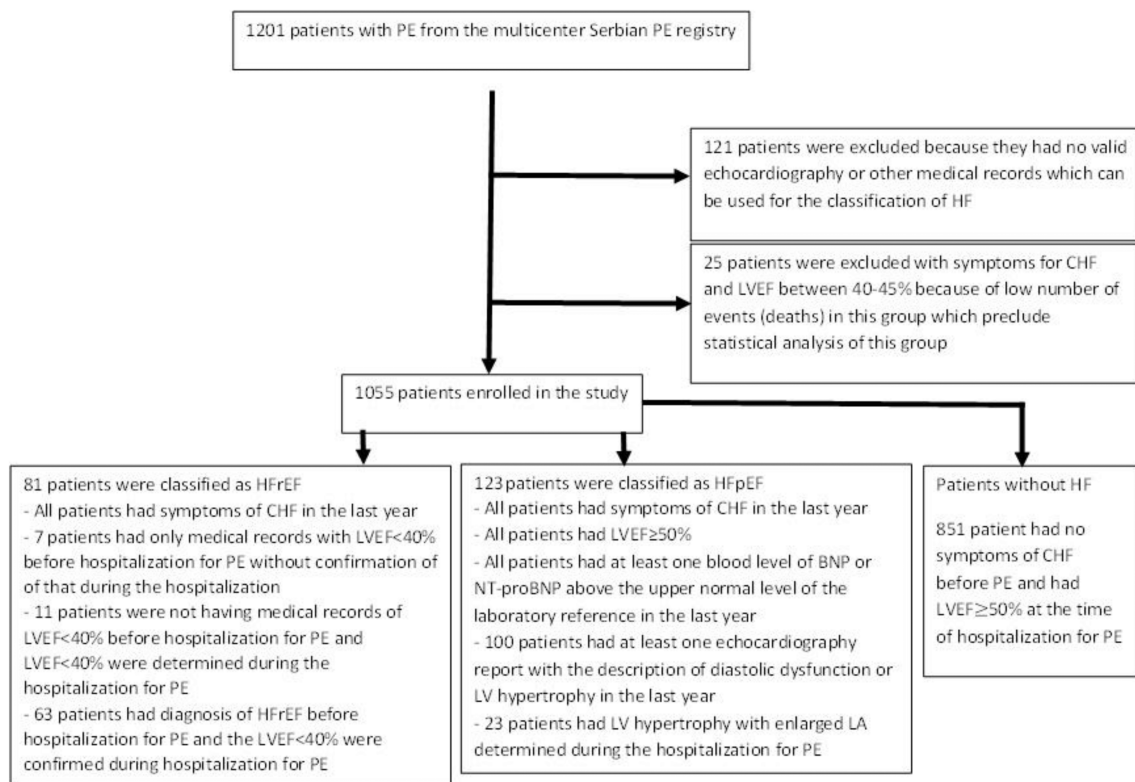
PE patients were stratified into high-risk, intermediate-risk, or low-risk patient groups, according to the 2019 ESC PE guideline.[9]

Echocardiographic measurements

Echocardiographic measurements were done using standard 2D and Doppler methods. LVEF was obtained by biplane Simpsons' method. LV diastolic function was confirmed if criteria were fulfilled as follows: LVEF $\geq$ 50% and enlarged left atrium and/or increased LV mass and/or E/e′ $\geq$ 13.[7] Data for the LV performance were obtained indirectly through the reports from the previous echocardiography examinations. Echocardiography examination at hospitalization for PE was focused on the RV performance with obligatory measurements of LVEF and additional semiquantitative descriptions of LV performance like LV hypertrophy and enlarged left atrium. Diastolic function of LV was not determined during the hospitalization for PE. Measured RV parameters included RV basal end-diastolic diameter (EDD) (four-chamber view), RV-to-LV EDD ratio (RV/LV EDD), and RV systolic pressure (RVSP), which was derived using peak tricuspid regurgitation jet velocity, with simplified Bernoulli equation and adding an estimated right atrial pressure 5–15 mmHg. Tricuspid

annular plane systolic excursion (TAPSE) was measured in four-chamber view on basal part of lateral RV wall with M mode. We also assessed the presence of paradoxical septal movements (movement of the interventricular septum away from the LV free wall during systole) and McConnell sign (hypokinesia of the mid-RV free wall with preserved contractility of the RV apex).

Right ventricular dysfunction was defined as RV EDD enlargement more than 3 cm and RV/LV EDD > 0.9. We additionally assessed the presence of pressure overload with elevated RVSP up to around 60 mmHg, decreased TAPSE (<1.6 cm), and a paradoxical septal motion or McConnell sign.

Endpoints

The primary endpoint was death at 7 days (7-day intrahospital death). This outcome is a very accurate endpoint for early intrahospital deaths in which the participation of PE was mostly pronounced. The cause of death in patients with PE and HF is multifactorial, and both PE and HF more or less contribute to this outcome and that was the reason why we choose this outcome instead of PE-related death, which is more inaccurate and speculative. The secondary endpoint of

Table 1 Baseline patients' characteristics according to the presence of HFrEF, HFpEF, and without HF

Patients' characteristics, N of total (%) according to bleeding status, or mean ± SD, or median (IQR)	History of heart failure			
	HFrEF N = 81 (7.7%)	HFpEF N = 123 (11.7%)	Without HF N = 851 (80.7%)	P^1 and P^2 values
Female gender	30 (37.0)	68 (55.3)	464 (54.5)	0.010 0.015
Age in years	67 ± 14	72 ± 10	62 ± 16	<0.001 0.036
Medical history				
COPD	5 (6.2)	29 (23.6)	82 (9.6)	<0.001 0.001
Coronary artery disease	35 (43.8)	36 (29.5)	64 (7.6)	<0.001 0.050
Prior stroke	8 (9.9)	17 (13.9)	55 (6.5)	0.010 0.514
Diabetes mellitus	33 (40.7)	31 (25.2)	143 (16.8)	<0.001 0.021
Arterial hypertension	54 (66.7)	100 (81.3)	491 (57.7)	<0.001 0.020
Renal failure				
GFR < 60 mL/min	40 (49.4)	58 (47.2)	254 (29.9)	<0.001 0.766
GFR < 30 mL/min	11 (13.9)	17 (13.8)	49 (5.8)	<0.001 1.000
Abnormal liver function	11 (13.6)	9 (7.3)	32 (3.8)	<0.001 0.155
Surgery within 6 months	7 (8.6)	24 (19.5)	134 (15.7)	0.110 0.045
Cancer in last 6 months	7 (8.6)	20 (16.3)	107 (12.7)	0.270 0.141
Clinical and laboratory findings at admission				
SaO$_2$ < 90%	30 (38.5)	47 (40.2)	202 (24.8)	<0.001 0.881
Admission SAP in mmHg	120 ± 28	120 ± 28	124 ± 24	0.120 1.000
Heart rate in bpm	106 ± 30	100 ± 25	98 ± 22	0.007 0.168
Atrial fibrillation	38 (46.9)	33 (27.0)	93 (11.0)	<0.001 0.004
RVSP[a] in mmHg	46.7 ± 13.9	57.6 ± 19.9	46.9 ± 17.5	<0.001 <0.001
RV dysfunction[a]	48 (65.8)	75 (75.0)	486 (59.6)	0.009 0.235
TAPSE	1.47 ± 0.44	1.87 ± 0.58	1.92 ± 0.46	<0.001 0.010
LVEF[a]	30.9 ± 7.8%	59.3 ± 5.5%	60.7 ± 5.4%	<0.001 <0.001
BNP[b] in pg/m	943 (378–1424)	357 (176–709)	124 (43–330)	<0.001 0.002
NT-proBNP[c]	3011 (610–9493)	5103 (1791–14 197)	1255 (287–4236)	<0.001 0.155
Troponin I[d] in μg/L	0.06 (0.02–0.26)	0.10 (0.04–0.38)	0.05 (0.01–0.30)	0.067 0.260
PE severity				
PE mortality risk[e]				
Low risk	17 (21.0)	24 (19.5)	326 (38.3)	<0.001
Intermediate risk	44 (54.3)	78 (63.4)	422 (49.6)	0.343
High risk	20 (24.7)	21 (17.1)	103 (12.1)	

BNP, brain natriuretic peptide; bpm, beats per minute; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; LVEF, left ventricle ejection fraction; PE, pulmonary embolism; RVSP, right ventricular systolic pressure; SaO$_2$, oxygen saturation; SAP, systolic arterial pressure; SBP, systolic blood pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

P^1 denotes the significance of comparisons between all three groups. P^2 denotes the significance of comparison between HFrEF and HFpEF groups.

[a] RVSP, RV dysfunction, and LVEF were determined at admission in 73, 100, and 815 patients with HFrEF, HFpEF, and without HF, respectively.

[b] BNP was measured in 26, 46, and 356 patients with HFrEF, HFpEF, and without HF, respectively.

[c] NT-proBNP was measured in 17, 53, and 197 patients with HFrEF, HFpEF, and without HF, respectively.

[d] Cardiac troponin I was measured in 48, 57, and 542 patients with HFrEF, HFpEF, and without HF, respectively.

[e] PE mortality risk was estimated for the entire duration of hospitalization according to 2019 PE ESC guidelines.[9]

the study was all-cause mortality at 30 days from the first day of hospitalization. All patients were scheduled for follow-up visits or connected by phone after 30 days from the discharge.

Statistics

Patients' characteristics are presented as frequencies for categorical variables and as mean ± standard deviation or median with the interquartile range depending on the normality of the numerical variables. Differences between three groups (i.e., HFrEF, HFpEF, and control groups) were tested with χ^2 test, one-way ANOVA test with Bonferroni corrections for P values for multiple comparisons, or with independent samples Kruskal–Wallis test depending on the normality distribution of variables. Kaplan–Meier curve analysis with a log-rank test was used for the comparison of survival rates between patients within the HFrEF, HFpEF, and the control groups. Unadjusted and adjusted for age, gender, history of arterial hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, presence of atrial fibrillation (AF), and PE mortality risk[9] as to the most important confounders, Cox regression models were tested for the prediction power of HFrEF and HFpEF regarding the timing for 7-day (intrahospital) and 30-day all-cause mortality. Several established parameters associated with increased risk for death in PE patients obtained at admission to hospital were compared between patients who survived and those who died regarding the presence of HFrEF, HFpEF,

or without HF, using non-parametric Mann–Whitney U test. P value <0.05 was considered significant for all statistical tests.

Results

Among 1201 consecutive PE patients from the Serbian multicentre PE registry, 1055 fulfilled all necessary criteria regarding the adequate echocardiographic data on LVEF and reliable history of HF; among them, 81/1055 (7.7%) patients were classified as HFrEF and 123/1055 (11.7%) as HFpEF. Flow chart of the study is presented in *Figure 1*. A 7-day intrahospital mortality was 18.5% vs. 7.3% vs. 4.5% and 30-day all-cause mortality was 22.2% vs. 16.3% vs. 7.9% (log-rank $P < 0.001$ for both comparisons) (*Figure 2A,B*) in patients with HFrEF, HFpEF, and without HF, respectively. The relevant characteristics of patients regarding the presence of HFrEF and HFpEF are presented in *Table 1*. Men predominate in HFrEF group, and the patients in HFpEF group were older than patients in the other two groups. Patients with HFrEF had more often a history of coronary artery disease, diabetes, and liver dysfunction, whereas patients with HFpEF had more frequently a history of arterial hypertension, COPD, and stroke. The frequency of the presence of AF was significantly higher in both HF groups compared with patients without HF, and the patients with HFrEF also had higher frequency of AF than patients with HFpEF. Patients with HFrEF and HFpEF had more frequently chronic renal failure as compared with patients without HF. Those with HFrEF

FIGURE 2 Kaplan–Meier curves for 7-day (intrahospital) (A) and 30-day all-cause (B) mortality according to the presence of HFrEF, HFpEF, or without HF. Log-rank $P < 0.001$ for both comparisons. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
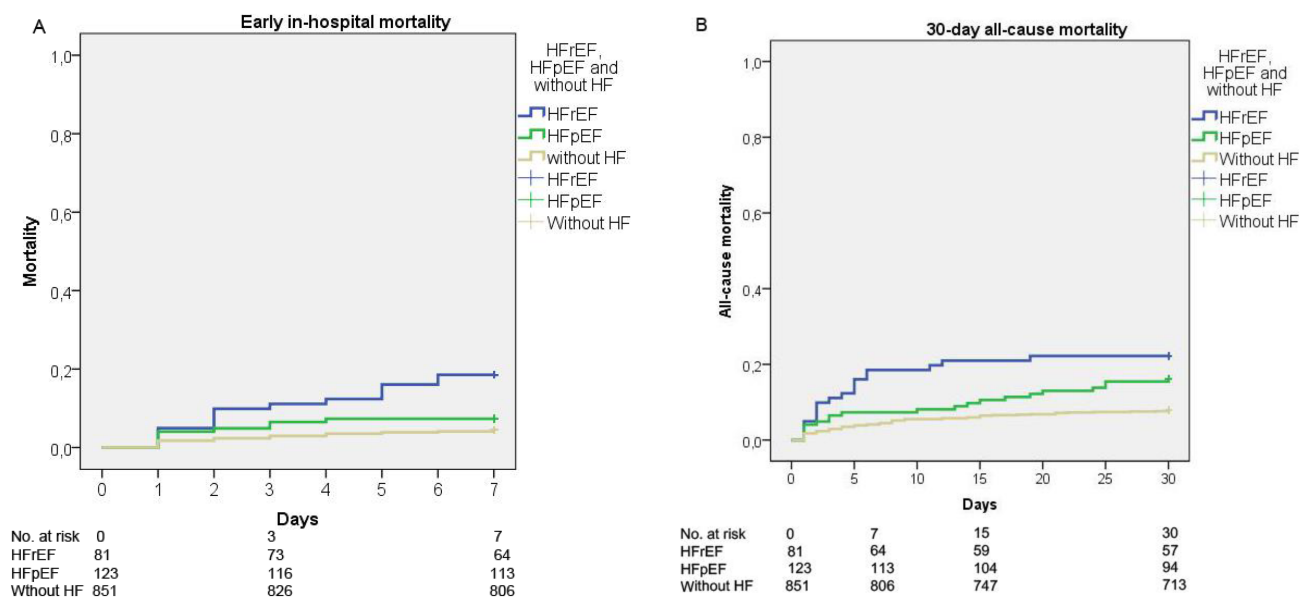
had the highest BNP values. Furthermore, patients with HFrEF and HFpEF were hypoxic on admission to the hospital, more often than patients without HF. Patients with HFpEF had the highest level of admission RVSP and cTn blood level. On the other hand, patients with HFrEF had the lowest TAPSE at admission and patients with HFpEF and without HF had very close TAPSE levels. LVEF was similar between patients with HFpEF and patients without HF. Patients with HFrEF were most frequently classified into the high-risk group, and those with HFpEF were more frequently into the intermediate-risk group.

A 7-day (intrahospital) and 30-day all-cause mortality was 18.8% vs. 7.3% vs. 4.5%.1% (log-rank *P* = 0.001) and 22.2% vs. 16.3% vs. 7.9% (log-rank *P* < 0.001) for patients with a history of HFrEF, HFpEF, and without HF, respectively (*Figure 2A, B*). Although the unadjusted hazard ratios (HRs) for 7-day (intrahospital) mortality (*Table 2*) were higher in both HF groups compared with patients without HF [HR 3.11, 95% confidence interval (CI) 1.85–5.24, *P* < 0.001 for HFrEF; HR 2.13, 95% CI 1.29–3.51, *P* = 0.003 for HFpEF], regression analysis adjusted to age, gender, positive history of COPD, diabetes mellitus, arterial hypertension, presence of AF, and mortality risk revealed HFrEF as the only significant predictor of mortality (HR 2.22, 95% CI 1.12–4.38, *P* = 0.021). For 30-day all-cause mortality, only the presence of HFrEF had the predictive value in the unadjusted regression analysis (HR 4.37, 95% CI 2.40–7.94, *P* < 0.001) and the predictive value of HFrEF has lost statistical significance after adjustment to several mentioned confounding factors (HR 1.54, 95% CI 0.86–2.75, *P* = 0.142) (*Table 2*).

Comparison of various parameters associated to increased risk for death in PE patients between patients who survived and those who died at 7 days regarding the presence of HFrEF, HFpEF, or absence of HF is presented in *Table 3*. Systolic arterial pressure at admission was significantly lower in

deceased patients in HFrEF group and not in HFpEF group. Heart rate at admission showed the opposite direction with significantly higher HR in patients who died compared with those who survived in HFpEF and no difference in admission HR between patients who died and those who survived in HFrEF group. Patients with HFpEF who died had higher RVSP at admission than those who survived. Troponin levels and embolic burden at MDCT-PA at admission were not significantly different in patients who died compared with those who survived in either HFrEF or HFpEF. In patients without HF, all parameters were significantly different between patients who died and those who survived.

Discussion

Heart failure and PE are associated in many ways.[1,2] Patients with HF have venous stasis, hypercoagulability state, and endothelial dysfunction, and all of these represent a classical Virchow triad for thrombosis. It has been documented that patients with HFrEF and HFpEF have an approximately fivefold increased risk of venous thromboembolism during 10 years.[3] Patients with HFrEF had excessive cathecholaminergic activity, enhanced renin angiotensin aldosterone axis activation, pro-inflammatory cytokine profile, and profound endothelial dysfunction.[10,11] All these mechanisms together with reduced mobility of the patients with HFrEF lead to increase coagulability and platelet activation, which can be detected through the measurements with various blood markers of activated haemostasis such as d-dimer, thrombin-antithrombin complex, prothrombin fragment F1+2, soluble P selectin, and CD40L, which correlate well to LV function.[12,13] Endothelial dysfunction is manifested by the decrease in NO production and increase in secretion of

Table 2 Hazard ratios for HFrEF, HFpEF, age, mortality risk, and right ventricular dysfunction according to 7-day all-cause (intrahospital) and 30-day all-cause mortality

	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*
7-day mortality				
HFrEF	4.37 (2.40–7.94)	<0.001	2.22 (1.12–4.38)	0.021
HFpEF	1.67 (0.81–3.45)	0.168	1.07 (0.50–2.27)	0.861
Age (years)	1.03 (1.01–1.05)	0.001	1.04 (1.02–1.06)	0.003
Mortality risk				
High risk	24.18 (8.58–68.16)	<0.001	17.98 (6.27–51.56)	<0.001
Intermediate risk	4.07 (1.41–11.74)	0.009	3.27 (1.13–9.48)	0.029
30-day all-cause mortality				
HFrEF	3.11 (1.85–5.24)	<0.001	1.54 (0.86–2.75)	0.142
HFpEF	2.13 (1.29–3.51)	0.003	1.15 (0.68–1.94)	0.606
Age (years)	1.04 (1.03–1.06)	<0.001	1.03 (1.02–1.05)	<0.001
Mortality risk				
High risk	13.45 (6.77–26.74)	<0.001	9.84 (4.87–19.87)	<0.001
Intermediate risk	3.53 (1.79–6.96)	<0.001	2.72 (1.37–5.38)	0.004

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PE, pulmonary embolism.
[a]In adjusted model, age, gender, mortality risk,[9] COPD, history of arterial hypertension, diabetes mellitus, and the presence of atrial fibrillation were used as cofounders.

Table 3 Comparisons of risk associated clinical, echocardiographic, radiographic, and biomarker parameters at admission between patients who died and those who survived at 7 days after admission regarding the presence of HFrEF, HFpEF, and without HF (medians and interquartile ranges)

Parameters at admission	Mortality at 7 days after hospitalization for PE								
	HFrEF			HFpEF			Without HF		
	No (N = 66)	Yes (N = 15)	P	No (N = 114)	Yes (N = 9)	P	No (N = 813)	Yes (N = 38)	P
HR (beat/min)	104 (80–120)	102 (88–130)	0.601	95 (80–111)	120 (100–147)	0.010	97 (80–110)	110 (93–120)	0.003
SAP (mmHg)	127 (110–140)	100 (80–110)	<0.001	120 (104–135)	130 (77–153)	0.744	125 (110–140)	95 (80–130)	<0.001
MDCT-EBSI	9 (5–14)	10 (5–15)	0.668	12 (7–15)	10 (6–12)	0.472	12 (7–18)	16 (14–18)	<0.001
RVSP (mmHg)	46 (39–55)	55 (30–65)	0.323	52 (42–70)	73 (63–78)	0.039	45 (35–57)	55 (48–65)	<0.001
Troponin I (ng/mL)	0.05 (0.02–0.28)	0.13 (0.02–0.25)	0.697	0.11 (0.04–0.38)	0.13 (0.02–0.31)	0.317	0.05 (0.01–0.30)	0.24 (0.11–1.24)	<0.001

EMSI, embolic burden score index; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MDCT, multidetector computed tomography; RVSP, right ventricular systolic pressure; SAP, systolic arterial pressure.

von Willebrand factor in circulation from the endothelial cells.[14,15] Finely, patients with HFrEF also have evidence of impaired fibrinolysis with elevated blood levels of plasminogen activator inhibitor 1—the main suppressor of fibrinolytic system.[16] Thus, patients with HFrEF are in the permanent procoagulation state, which can contribute to the development and outcome of venous thromboembolism. The presence of HF seems to be also important for PE outcomes. Patients with HFrEF have predominately LV systolic dysfunction, so they are more susceptible to haemodynamic deterioration caused by acute pulmonary artery obstruction. On the other hand, patients with HFpEF have diastolic LV dysfunction and increased LV filling pressure, which, via pulmonary veins, ultimately leads to pulmonary hypertension. The health status of these patients can easily deteriorate during acute PE. Among patients with acute PE, HF can be present in 10–20% of patients.[4,17,18] In our registry of hospitalized PE patients, the history of previous HF was present in 19.4%. HF is a well-recognized risk factor for an adverse outcome in patients with PE. HR or odds ratios for early mortality vary in the interval of 1.3–4.2 in various registries, depending on the severity of PE patients enrolled.[19–21] Moreover, the presence of HF is included in most commonly used and validated scores for the prediction of early PE outcomes, such as PE severity score (PESI) or its simplified version (sPESI), as well as the Registro Informatizado de Enfermedad TromboEmbólica-RIETE score.[17,22]

According to current literature, the presented study seems to be the first to compare separately predictive values of the presence of HFrEF versus HFpEF for the prediction of early PE outcome. Age, gender, the positive history for COPD, arterial hypertension, diabetes, presence of AF, and mortality risk variables were obtained for all patients, and we used them as the most important confounders in the regression analysis, which took into account the most important comorbidities, haemodynamic, demographic, and imaging characteristics of patients with a possible influence on PE outcome.[10] Our results have shown that the presence of HFrEF had independent prediction value for 7-day (intrahospital) mortality in both unadjusted and adjusted regression model. On the contrary, the presence of HFpEF was not associated with 7-day (intrahospital) mortality in both unadjusted and adjusted analysis. In addition, both subgroups of HF had significant predictive values for 30-day all-cause mortality in an unadjusted analysis, but these were lost in the multivariable regression model. Thus, only the presence of HFrEF was a significant, independent predictor for 7-day (intrahospital) mortality in PE patients.

Patients with HFrEF have significantly reduced capacity to compensate for decreased LV preload and hypoxaemia during PE. Reduced myocardial contractility and the use of beta-blockers impaired inotropic and chronotropic response in these patients.[23] Hypoxia may have an even more deleterious effect in HFrEF patients and can cause myocardial

ischaemia because many of these patients may have also a significant coronary artery disease with reduced coronary flow reserve.[24] Increased end-diastolic pressure to LV walls may also contribute to myocardial ischaemia. Decreased LV preload, diminished coronary flow, hypoxaemia, reduced compensatory mechanisms, and increased LV end-diastolic pressure may lead to *circulus vitiosus* of irreversible HF in HFrEF patients.[25] Because LV diastolic dysfunction is the dominant pathophysiology mechanism in HFpEF, it is of interest whether LV diastolic parameters are associated with the worse outcome in PE patients. In one relatively small study, diastolic LV dysfunction was not significantly associated with early death in haemodynamically stable PE patients.[26] We also found that the presence of HFpEF was not an independent risk factor for both 30-day all-cause and early intrahospital mortality. The explanation for this could be a better preserved inotropic and chronotropic reserve in patients with HFpEF, which is important for maintaining haemodynamic stability in acute PE.

In our study, only the presence of HFrEF was an independent predictor of early intrahospital death. The cause of death in patients with PE and severe comorbidities is always multifactorial.[27] Patients with HFrEF represented such group, and the mechanisms of death in them are very often sudden death or death because of progression of HF. Acute PE can significantly contribute to HF, and massive PE can cause sudden death especially in vulnerable HFrEF patients and pre-existing RV failure.[28] Our data have shown that the majority of deceased HFrEF patients died in the first week of admission, which suggested that PE contributed significantly for outcome. The treatment strategy for PE depends mostly to the mortality risk estimation at admission, and aggressive therapy could also cause fatal complications in HFrEF patients. These are the reasons why we choose 7-day mortality as a second primary outcome and not PE-related death, which is a more speculative and inaccurate endpoint. As the time from the hospitalization of PE patients passed, the probability that the presence of initial PE is the main cause of death decreases, and earlier epidemiology studies overestimate the role of PE as a main cause of death.[29]

The estimation of mortality risk in HFrEF patients with PE might be different compared with other patients. Our study provided some evidence regarding this. Only systolic arterial pressure at admission was significantly lower in HFrEF patients who died compared with those who survived. Heart rate, embolic thrombus burden on MDCT-PA, RVSP, and troponin values did not differ between those who died and those who survived in this group of patients. This might mean that the initial cardiac reserve is the most important factor for the adverse outcome in HFrEF patients with PE and to emphasize the treatment of HF per se. On the other hand, in patients with HFpEF, admission heart rate and increased RVSP at admission were associated with early death. The reason for the first might be that patients with HFpEF have

more preserved chronotropic reserve and they used much less beta-blockers. Higher RVSP may be explained with long-standing advanced HFpEF with exhausted compensatory mechanisms. Patients with initially higher levels of RVSP could not further increase RV performance, and acute additional RV overload as a result of PE could not be overcome. Elevated pulmonary arterial pressure is one of the features of the HFpEF, which is associated with the worse prognosis in HFpEF patients.[30] In addition, HFpEF patients have some important compensatory mechanisms, such as increased LVEF and RV hypertrophy, that may overcome the acute raise of pulmonary arterial pressure as a consequence of acute PE, and the cardiac output might be preserved despite the haemodynamic effects of acute PE.[31,32]

The number of patients who died at 7 days in HFpEF was low, and the analysis of risk factors in our study should be taken with caution especially in this subgroup of patients.

The predictive value of brain natriuretic peptides and cardiac troponins in HFrEF and HFpEF patients with acute PE might be attenuated and misleading for several reasons. The blood concentration of BNP in PE patients depends on the RV overload in the setting of normal LV function.[33] However, in the case of LV dysfunction either with reduced or preserved EF by the pre-existing disease, both BNP and NT-proBNP in blood derived mainly from LV and depend a lot on concomitant comorbidities.[34] We could not observe a difference between cTnI blood levels between patients who died and those who survived in both HF subgroups. These biomarkers are often already elevated in HF patients depending on the severity of HF and the presence of comorbidities. Cardiac troponins are also elevated in patients with acute decompensated HF.[35] Frequently associated features in HF patients with acute PE such as chronic renal failure, hypertrophic cardiomyopathy, valvular disease, and ischaemia from the underlying coronary disease might have strong impact on the cardiac troponin blood levels.[36]

Limitations

Because this is a retrospective analysis, data were collected from the medical documentation, which is frequently imperfect. However, we excluded all patients who did not have clear previous medical documentation, meaning a reliable history of HF. The inadequate number did not allow the analysis of a group of patients with HFmrEF. Nevertheless, several classic risk factors almost perfectly predicted early mortality in patients without HF. The number of early deceased patients in both HF groups was relatively small and precludes any firm conclusion about the value of some risk factors at admission for the prediction of early death.

Conclusions

Our study revealed that the history of HFrEF in patients with acute PE appears to be an independent risk factor for mortality at 7 days. Moreover, the presence of neither HFrEF nor HFpEF is not independently associated with 30-day all-cause mortality after acute PE.

Conflict of interest

None declared.

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