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Modes of death in patients with heart failure and preserved ejection fraction

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Abstract

Background—Recent studies suggest that reduced right ventricular function is an important predictor of outcome in patients with heart failure and preserved ejection fraction (HFpEF). Because affected patients suffer from a broad spectrum of non-cardiac co-morbidities, it remains unclear, whether they actually die from right heart failure (RHF) or as a consequence of other conditions.

Methods—Consecutive patients with a confirmed diagnosis of HFpEF were enrolled in this prospective registry. Local and external medical records, as well as telephone interviews with relatives were used to ascertain modes of death. RHF was accepted as a mode of death, if the following criteria were met: 1. right ventricular dysfunction assessed by transthoracic echocardiography, and 2. clinical signs of right heart decompensation at the time of death.

Results—Out of 230 patients with complete follow-up, 16.5% (n = 38) died after a mean of 30 ± 17 months. 60.5% deaths were classified as cardiovascular and 34.2% as non-cardiovascular. In 5.3% patients, the reason for death remained unknown. Of the cardiovascular cases (n = 23), 91.4% of deaths were attributed to RHF, 4.3% died from stroke and 4.3% from sudden cardiac death. Of the non-cardiovascular deaths (n = 13), 46.2% of deaths were attributed to major infections and 38.4% deaths were related to cancer. Other reasons for death included ileus (7.7%) and major bleeding (7.7%).

Conclusion—In our well-characterised HFpEF cohort, more than half of all deaths could directly be attributed to RHF. The right ventricle seems to be a meaningful therapeutic target in a subset of patients.

Keywords

Right heart failure; Heart failure with preserved ejection fraction; Modes of death

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Conflict of interest
The authors report no relationships that could be construed as a conflict of interest.

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1 Background

Nearly one half of all patients who present with a clinical syndrome of heart failure are found to have a preserved left ventricular ejection fraction (HFpEF). Despite unremarkable findings regarding left ventricular systolic function, affected patients face a dismal prognosis with high mortality rates [1]. Recent evidence from our group [2,3] and others [4, 5] suggests that it is primarily the function of the right ventricle that determines the clinical course of affected patients. In fact, impaired right ventricular function as visualized by transthoracic echocardiography or cardiac magnetic resonance imaging has been related to recurrent hospitalizations and death in various HFpEF cohorts [2–5].

These observations are in some disagreement with the broadly accepted notion that most HFpEF patients die from non-cardiac comorbid conditions [6]. In those who pass away from cardiac reasons, sudden cardiac death has been suggested as the primary cause of death [7].

The aim of the present study was to shed light on the actual modes of death in patients with HFpEF. To that end we studied a unique HFpEF cohort, in whom significant coronary artery disease, a frequent companion in this condition, has been ruled out at enrolment.

2 Materials and methods

2.1 Study population

This prospective, observational cohort study was performed at the Division of Cardiology of the Medical University of Vienna, a tertiary referral center for HFpEF. The study protocol adheres to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Vienna (EK #796/2010). Written informed consent was collected in all patients before study enrolment.

Eligible patients were prospectively followed in intervals of six months (or shorter) in our outpatient clinic. Telephone calls replaced visits in cases of immobility. The primary study endpoint was death from any cause.

2.2 Clinical definitions

HFpEF was diagnosed according to the current consensus statement of the European Society of Cardiology [8] and the guidelines of the American College of Cardiology Foundation/ American Heart Association [9]. The following criteria had to be fulfilled: 1. Signs or symptoms of heart failure, 2. left ventricular ejection fraction ≥50%, 3. N-terminal brain natriuretic peptide (NT-proBNP) > 220 pg/mL, 4. Evidence of left ventricular diastolic dysfunction by transthoracic echocardiography. Right heart catheterization was performed and HFpEF confirmed, if pulmonary artery wedge pressure exceeded 12 mm Hg.

Exclusion criteria were significant valvular or congenital heart disease, significant coronary artery disease requiring percutaneous coronary intervention or aorto-coronary bypass surgery, and severe congenital abnormalities of the lungs, thorax or diaphragm as previously described [10]. Additionally, patients with cardiac amyloidosis were excluded. Screening for cardiac amyloidosis was done according to current recommendations [11,12] and included

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cardiac magnetic resonance imaging, transthoracic echocardiography, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy and if necessary, endomyocardial biopsy.

2.3 Ascertainment of death

Local and external medical records, as well as telephone interviews with relatives were used to ascertain the mode of death. A detailed report was created for every death that was reviewed by two independent physicians (D.B, S.A).

A diagnosis of terminal right heart failure (RHF) was established, if the following criteria were met: 1. right ventricular dysfunction (RVD) assessed by echocardiography, 2. clinical signs of right heart decompensation at the time of death including dyspnoea, ascites, liver enzyme elevation, peripheral oedema, fluid accumulation and jugular distension. Terminal bradycardia related to HF led to a ‘heart failure death’ judgement.

Sudden cardiac death was defined as either a documented arrhythmogenic death in the absence of pre-existing circulatory failure or the out-of-hospital occurrence of an unexpected presumed pulseless condition together with the absence of an obvious non-cardiac explanation.

2.4 Imaging modalities

All patients underwent conventional transthoracic echocardiography (Vivid 5 and 7, General Electric Inc.) according to the guidelines of the American Society of Echocardiography [13]. Two independent observers blinded to clinical data assessed right ventricular function. An additional board-certified senior physician was consulted in case of disagreement.

Tricuspid annular plane systolic excursion (TAPSE) and two dimensional right ventricular fractional area change (RV-FAC) were measured according to recommended guidelines [14]. A TAPSE below 16 mm and/or a RV-FAC below 35% defined RVD [14].

End-diastolic and end-systolic volumes were used to calculate the ejection fraction using the Simpson's biplane method on the apical four- and two-chamber views [13].

Furthermore, all patients without contraindications underwent a cardiac magnetic resonance imaging study on a 1.5-Tesla scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany). Studies consisted of functional and late gadolinium enhancement imaging, according to standard protocols [15].

2.5 Cardiac catheterization

For hemodynamic confirmation of HFpEF, a 7F Swan-Ganz catheter (Baxter, Healthcare Corp, Munich, Germany) was inserted via a femoral approach. CathCorLX (Siemens AG, Erlangen, Germany) was used to measure pressures, which were recorded as average of eight measurements over eight recorded heart cycles. Cardiac output was assessed by thermodilution and by Fick's method. Pulmonary pulse pressure was calculated as the difference between systolic pulmonary artery pressure and diastolic pulmonary artery pressure and pulmonary arterial compliance as the ratio of stroke volume to pulmonary pulse

pressure. The diastolic pressure gradient was calculated as the difference between diastolic pulmonary artery pressure and pulmonary artery wedge pressure. The transpulmonary pressure gradient was calculated by subtracting pulmonary artery wedge pressure from mean pulmonary artery pressure.

2.6 Statistical analysis

All statistics were performed using STATA 11 (StataCorp LP, USA). Variables were compared using chi-squared test or fisher's exact test for categorical variables and the wilcoxon rank sum test for continuous variables. To identify variables associated with cardiac death, a univariate cox regression analysis was performed for each variable listed in Tables 1 and 2. Significant parameters ($p < 0.05$, listed in Table 3) were included in a multiple cox regression model with a stepwise forward – backward model selection starting from a null model based on the Schwarz–Bayes information criterion. Results were considered significant at a level of $p < 0.05$.

3 Results

3.1 Baseline characteristics

Between December 2010 and November 2015, a total of 292 patients were referred for suspicion of HFpEF. Of those, 62 did not enter the registry because of alternative diagnoses: 26 patients had cardiac amyloidosis and 8 patients hypertrophic cardiomyopathy. Another 28 patients did not meet the inclusion criteria, i.e. presence of significant coronary artery disease ($n = 18$) or NT-proBNP below the inclusion cut-off value ($n = 10$).

230 eligible patients (160 women and 70 men, mean age 71.4 ± 8 years) were enrolled. 96.1% had arterial hypertension, 38.0% diabetes mellitus, and 41.6% chronic obstructive pulmonary disease. Atrial fibrillation was found in 59.7% of registered patients, 10.9% were pacemaker carriers, none of the participants had an implantable cardioverter defibrillator. 35.7% of all patients had a history of cardiac hospitalisation.

3.2 Modes of death

Out of 230 patients with complete follow-up, 38 (16.5%) died after a mean of 30 ± 17 months. 60.5% ($n = 23$) of deaths were classified as cardiovascular and 34.2% ($n = 13$) as non-cardiovascular. In 2 (5.3%) patients, the reason for death remained unknown. Of the cardiovascular cases, 21 (91.4%) deaths were attributed to RHF, 1 patient (4.3%) died from stroke and 1 patient (4.3%) from sudden cardiac death. Of the non-cardiovascular deaths 13 deaths (46.2%) were attributed to major infections, such as necrotizing pancreatitis or bilateral pneumonia. 5 (38.4%) deaths were related to cancer. Other reasons for death included 1 (7.7%) ileus and 1 (7.7%) major bleeding (Fig. 1).

Patients who died had a higher baseline NYHA functional class ($p < 0.001$), shorter 6-min walk distances ($p < 0.001$), lower glomerular filtration rates ($p = 0.001$) and higher NT-proBNP serum levels ($p < 0.001$) as compared to survivors (Table 1).

RVD was present in 28.3% ($n = 65$) of all patients, in 20.8% ($n = 40$) of survivors and 65.8% ($n = 25$) of non-survivors. RVD was found in 4 patients (23.5%) who died from causes other than RHF (infection, $n = 2$; malignancy, $n = 1$; and unknown cause of death, $n = 1$).

With respect to hemodynamic parameters, non-survivors had higher mean pulmonary artery pressures ($p = 0.010$), pulmonary artery wedge pressures ($p = 0.033$), transpulmonary gradients ($p = 0.011$), pulmonary vascular resistances ($p = 0.024$) and a lower pulmonary arterial compliance ($p = 0.003$, Table 1).

3.3 Death from right heart failure

Those who died from RHF were predominantly male ($p = 0.018$), had a worse glomerular filtration rate ($p = 0.025$) and higher NT-proBNP serum levels ($p = 0.003$) compared to patients who died from another reason. Furthermore, diffusion capacity of the lung for carbon monoxide (DLCO), vital capacity and forced expiratory volume in 1 s (FEV1) were significantly lower ($p = 0.004$, $p = 0.021$ and $p = 0.030$, respectively) in those who died from RHF in comparison to the latter group. Additionally, right atrial pressure was higher in patients who died from RHF ($p = 0.021$, Table 2).

In the univariate analysis, NYHA functional class ($p = 0.001$), 6-min walk distance ($p = 0.001$), glomerular filtration rate ($p < 0.001$), NT-proBNP ($p < 0.001$), haemoglobin concentration ($p = 0.001$), DLCO ($p < 0.002$), FEV1 ($p = 0.015$), systolic pulmonary artery pressure ($p < 0.035$), the transpulmonary gradient ($p = 0.016$) and right atrial pressure ($p < 0.001$) were associated with death from RHF (Table 3).

In the multivariate analysis, only NT-proBNP ($p = 0.001$) and DLCO ($p = 0.021$) remained independently associated with death from RHF (Table 3).

4 Discussion

We demonstrate here that RHF was a leading mode of death (55.3%) in patients with HFpEF. Further fatal conditions were major infections (15.8%), such as pneumonia, and cancer (13.2%). By contrast to previous reports, the role of sudden cardiac death was negligible in our cohort (2.6%) [7].

A series of recent publications have drawn the attention to right ventricular function and its central prognostic role in HFpEF [2–5]. Mohammed et al. noted that RVD, determined by semi-quantitative echocardiographic assessment and by the TAPSE was related with increased all-cause and cardiovascular mortality as well as higher hospitalisation rates [5]. Similarly, Melenovsky et al. reported that a RV-FAC below 35% was associated with higher mortality and was the strongest single predictor of death [4]. Work from our group confirmed these findings and complemented right ventricular assessment with cardiac magnetic imaging studies and invasive haemodynamic assessments. Again, RVD represented a strong risk factor with regard to morbidity and mortality [2,3].

Although these findings may imply that a clinical picture of RHF precedes and leads into death, the actual circumstances and modes of death have not been reported in the aforementioned studies. Furthermore, the assumption that RVD is inevitably followed by

RHF and death is in conflict with recent large-scale clinical trials [16–18], where sudden cardiac death has been identified as the most frequent fatal event in HFpEF. Other authors have pointed to the pivotal role of non-cardiac co-morbid conditions as major life-limiting factors [6,19].

Indeed, pre-terminal signs and symptoms of RHF, including dyspnea, ascites, liver enzyme elevation, peripheral oedema, fluid accumulation and jugular distension, have been observed in 55.3% of deceased patients in the present study. Because all individuals in this group had also severely impaired right ventricular function, 'right heart failure' was the adjudicated mode of death. RVD was also found in 20.8% of living patients and in 23.5% of patients who have died from other modes, including 2 patients who died from infections and 1 patient who died from malignancy. The fact that more than one third of patients in the present study died from non-cardiac conditions which occurred concomitantly with the main diagnosis is in congruence with previous reports [20–22]. However, sudden cardiac death was negligible in our cohort and other smaller studies [22,23], which is in strong contrast to data from large-scale clinical trials, such as CHARM-Preserved, I-PRESERVE and TOPCAT [16–18].

Potential explanations for these discrepancies are: 1. Significant coronary artery disease, which is known to increase the risk for sudden death, was ruled out by means of coronary angiography in the present study but not by others; 2. sudden cardiac death is common in patients with cardiac amyloidosis [12,24], a diagnosis, which may be missed and misdiagnosed as HFpEF [25]. Cardiac amyloidosis has been actively screened for in the present study and all cases have been excluded from the registry. 3. On an average, left ventricular ejection fraction was lower in other studies as compared to ours. 4. Previous studies did not clearly distinguish between mode of death and cause of death [23]. Here, the actual mode of death -defined as the underlying condition that precipitates the final event- was in the focus of interest. This seems reasonable, given the fact that ultimately everybody dies from cardiac arrhythmia (asystole or ventricular fibrillation), irrespective of the underlying disease [26].

In the present study, male gender, renal failure and worse pulmonary function parameters distinguished patients who died from RHF from the remainder of the fatal cases. In the multivariate model, lower DLCO and higher NT-proBNP levels were independently associated with death from RHF. This is in line with recent work by Hoeper et al. [27]. who found male gender and a DLCO below 45% to be associated with mortality in HFpEF.

4.1 Limitations

Although our study cohort was comprehensively examined and patients were carefully followed, we cannot entirely exclude the possibility of an incorrect assignment with respect to the mode of death.

In our population, the annual mortality rate was 7%. A wide range of mortality rates has been reported by other groups, ranging from 5% to 25% [7]. It is therefore possible that our cohort was in less advanced disease stages as compared to previous cohorts. The reported

proportions with regard to modes of death may vary depending on the disease severity of respective study participants [27].

5 Conclusion

The current study challenges previous reports on mode-specific mortality and extends existing knowledge. The main finding that more than half of all deaths can be attributed to RHF shifts the right ventricle into the focus of attention. New treatment strategies that target the right ventricle and the pulmonary vasculature may be a promising way to improve outcome in HFpEF, particularly in patients with high NT-proBNP and a low DLCO.

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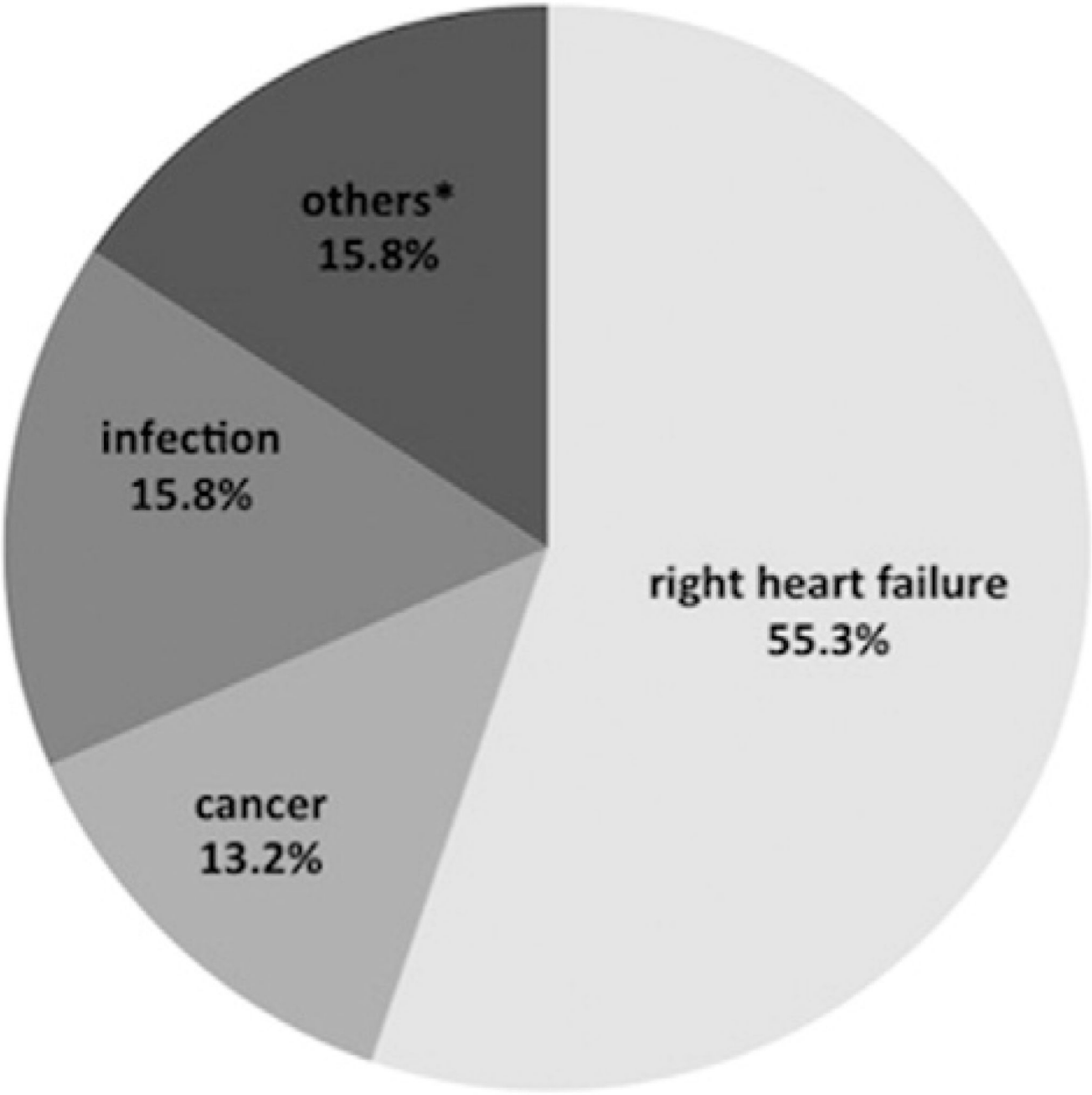

Fig. 1.

Modes of death in heart failure with preserved ejection fraction. A total of 38 total deaths had occurred within an observation period of 30 ± 17 months. *Other modes of death include one stoke, one sudden cardiac death, one major bleeding, one ileus and 2 deaths for unknown reason.

Table 1
Baseline characteristics of survivors versus non-survivors.

Variable	Survivors (*n* = 192)	Non-survivors (*n* = 38)	All patients (*n* = 230)	*P*-value
Baseline characteristics				
Age, years	71.1 ± 8.5	72.8 ± 8.2	71.4 ± 8.5	0.243
Male sex, n [%]	58 [30.2]	12 [31.6]	70.0 [30.4]	0.868
Body mass index, kg/m^2	30.5 ± 6.5	31.0 ± 8.0	30.6 ± 6.7	0.665
Diabetes mellitus, n [%]	68 [35.6]	19 [50.0]	87.0 [38.0]	0.096
Significant coronary artery disease, n [%]	43 [22.6]	9 [23.7]	52.0 [22.8]	0.888
Arterial hypertension, n [%]	181 [95.3]	38 [100]	219.0 [96.1]	0.171
COPD, n [%]	80 [41.5]	16 [41.5]	96 [41.6]	0.963
History of atrial fibrillation, n [%]	110 [57.9]	26 [68.4]	136.0 [59.7]	0.277
Heart rate, beats/min	72.2 ± 14.5	72.6 ± 12.4	72.4 ± 13.4	0.704
NYHA functional class				<0.001
II, n [%]	70.0 [37.8]	2.0 [5.3]	36.0 [21.6]	
III, n [%]	103.0 [55.7]	29.0 [76.3]	66.0 [66.0]	
IV, n [%]	12.0 [6.5]	7.0 [18.4]	9.5 [12.5]	
6-min walk distance, meters	331 ± 117	241 ± 112	316 ± 121	<0.001
GFR, mL/min/1.73 m^2	61.4 ± 20.2	49.6 ± 16.4	59.4 ± 20.1	0.001
NT-pro BNP, pg/mL	1552 ± 1976	3522 ± 4706	1875 ± 2709	<0.001
Conventional echocardiography				
Right ventricular fractional area change, %	40.9 ± 11.1	31.0 ± 3.6	39.8 ± 11.0	0.002
TAPSE, mm	19.6 ± 5.2	13.4 ± 2.1	19.3 ± 5.4	<0.001
Lung function test				*P*-value
PaO_2, mm Hg	72.3 ± 12.5	68.2 ± 12.6	71.6 ± 12.6	0.097
$PaCO_2$, mm Hg	38.0 ± 5.9	38.3 ± 6.3	38.1 ± 5.9	0.802
DLCO, % predicted	62.4 ± 17.8	55.6 ± 17.1	61.2 ± 17.8	0.111
Vital capacity, % predicted	85.1 ± 27.0	80.7 ± 4.2	84.4 ± 26.5	0.386
FEV1, % predicted	74.3 ± 26.9	69.1 ± 23.9	73.4 ± 26.5	0.309
Invasive hemodynamic parameters				*P*-value
PAP mean, mm Hg	33.7 ± 9.9	38.9 ± 10.2	34.6 ± 10.1	0.010
PAP systolic, mm Hg	52.4 ± 17.5	60.7 ± 16.0	53.9 ± 17.5	0.003
PAP diastolic, mm Hg	21.8 ± 6.9	25.8 ± 9.3	22.5 ± 7.5	0.055
PAWP, mm Hg	19.8 ± 5.2	22.1 ± 5.6	20.2 ± 5.3	0.033
Diastolic pressure gradient, mm Hg	1.8 ± 4.3	3.7 ± 6.6	2.2 ± 4.9	0.134
Transpulmonary gradient, mm Hg	13.8 ± 7.0	16.8 ± 5.4	14.4 ± 7.1	0.019
Right atrial pressure, mm Hg	12.4 ± 5.4	14.8 ± 6.9	12.8 ± 5.8	0.109
Pulse pressure, mm Hg	30.5 ± 13.2	35.0 ± 10.6	31.3 ± 12.9	0.011
LV-end diastolic pressure, mm Hg	20.2 ± 6.3	22.6 ± 6.8	20.5 ± 6.4	0.125

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Variable	Survivors (*n* = 192)	Non-survivors (*n* = 38)	All patients (*n* = 230)	*P*-value
Pulmonary vascular resistance, dynes · s · cm^{-5}	221 ± 122	281 ± 156	232.1 ± 130.4	0.024
Pulmonary arterial compliance, mL/mm Hg	2.8 ± 1.4	2.2 ± 0.8	2.7 ± 1.4	0.003
Cardiac output, L/min	2.7 ± 0.6	2.7 ± 0.8	2.7 ± 0.7	0.538

Data are presented as mean ± standard deviations or n [%]; NYHA: New York Heart Association, GFR: glomerular filtration rate, NT-pro BNP: N-terminal brain natriuretic peptide, TAPSE: tricuspid annular plane systolic excursion, PaO_2: partial arterial pressure of oxygen, $PaCO^2$: partial arterial pressure of carbon dioxide, DLCO: capacity of the lung for carbon monoxide, FEV1: forced vital capacity in 1 s; PAP: pulmonary artery pressure, PAWP: pulmonary arterial wedge pressure; LV: left ventricle.

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Table 2
Baseline characteristics of patients according to mode of death.

Variable	Right heart failure (*n* = 21)	Other mode (*n* = 17)	*P*-value
Clinical characteristics			
Age, years	73.6 ± 6.8	71.9 ± 9.8	0.638
Male sex, n [%]	10 [47.6]	2 [11.8]	0.018
Body mass index, kg/m^2	30.4 ± 7.7	31.8 ± 8.5	0.736
Diabetes mellitus, n [%]	9 [42.9]	10 [58.8]	0.958
Significant coronary artery disease, n [%]	5 [23.8]	4 [23.5]	0.984
Arterial hypertension, n [%]	21 [100]	17 [100]	
COPD, n [%]	8 [38.1]	4 [23.5]	0.337
History of atrial fibrillation, n [%]	16 [76.2]	10 [58.8]	0.252
Heart rate, beats/min	73.0 ± 13.6	72.1 ± 11.1	0.828
NYHA functional class			0.635
II, n [%]	1 [4.8]	1 [5.9]	
III, n [%]	15 [71.4]	14 [82.4]	
IV, n [%]	5 [23.8]	2 [11.8]	
6-min walk distance, meters	222.5 ± 124.8	261.1 ± 97.2	0.331
GFR, mL/min/1.73 m^2	44.3 ± 14.7	56.1 ± 16.3	0.025
NT-pro BNP, pg/mL	4596 ± 5887	2113 ± 1790	0.030
Conventional echocardiography			*P*-value
Right ventricular fractional area change, %	31.0 ± 3.6	38.2 ± 7.8	<0.001
TAPSE, mm	13.4 ± 2.1	19.1 ± 2.8	<0.001
Lung function tests			*P*-value
PaO_2, mm Hg	65.0 ± 11.7	71.5 ± 13.0	0.105
$PaCO_2$, mm Hg	39.2 ± 6.5	37.4 ± 6.2	0.461
DLCO, % predicted	42.6 ± 12.3	62.8 ± 15.7	0.004
Vital capacity, % predicted	70.9 ± 18.6	90.4 ± 25.9	0.021
FEV1, % predicted	77.2 ± 24.6	61.0 ± 21.0	0.030
Invasive hemodynamic parameters			*P*-value
PAP mean, mm Hg	39.2 ± 11.0	38.4 ± 9.5	0.890
PAP systolic, mm Hg	60.6 ± 15.1	60.9 ± 17.6	0.899
PAP diastolic, mm Hg	26.5 ± 10.3	24.8 ± 8.0	0.762
PAWP, mm Hg	22.5 ± 5.7	22.1 ± 6.2	0.713
Diastolic pressure gradient, mm Hg	4.5 ± 7.7	2.7 ± 4.9	0.523
Transpulmonary gradient, mm Hg	17.3 ± 7.1	16.3 ± 7.1	0.975
Right atrial pressure, mm Hg	17.1 ± 7.0	11.8 ± 5.7	0.021
Pulse pressure, mm Hg	34.1 ± 8.7	36.1 ± 12.8	0.588

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Variable	Right heart failure (*n* = 21)	Other mode (*n* = 17)	*P*-value
LV-end diastolic pressure, mm Hg	21.2 ± 6.4	24.4 ± 7.2	0.269
Pulmonary vascular resistance, dynes · s · cm^{-5}	284 ± 188	277 ± 109	0.484
Pulmonary arterial compliance, mL/mm Hg	2.3 ± 1.0	2.0 ± 0.6	0.321
Cardiac output, L/min	5.4 ± 1.3	4.9 ± 1.3	0.265

Data are presented asmean ± standard deviations or n [%]; NYHA: New York Heart Association, GFR: glomerular filtration rate, NT-pro BNP: N-terminal brain natriuretic peptide, TAPSE: tricuspid annular plane systolic excursion, PaO_2: partial arterial pressure of oxygen, $PaCO_2$: Partial arterial pressure of carbon dioxide, DLCO: diffusion capacity of the lung for carbon monoxide, FEV1: forced vital capacity in 1 s; PAP: pulmonary artery pressure, PAWP: pulmonary arterial wedge pressure; LV: left ventricle.

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Table 3

Predictors of death from right heart failure. Univariable and multivariable Cox regression analysis.

Variable	Event (*n* = 21)	No event (*n* = 209)	Hazard ratio	95% CI	P-value
Simple regression					
NYHA functional class	3.2 ± 0.5	2.7 ± 0.59	3.55	1.70–7.43	0.001
6 –minute walk distance, meters	223 ± 125	325 ± 117	0.99	0.99–1.00	0.001
GFR, mL/min/1.73 m^2	44.3 ± 14.7	61.0 ± 19.9	0.96	0.94–0.98	< 0.001
NT-pro BNP, pg/mL	4596 ± 5887	1596 ± 1964	1.00	1.00–1.00	< 0.001
Haemoglobin, g/dL	11.2 ± 2.09	12.3 ± 1.8	0.63	0.48–0.82	0.001
DLCO, % predicted	43.8 ± 12.56	62.4 ± 17.5	0.93	0.88–0.97	0.002
Forced vital capacity, % predicted	61.0 ± 20.99	74.6 ± 26.7	0.97	0.95–0.99	0.015
PAP systolic, mmHg	60.6 ± 15.09	53.1 ± 17.6	1.02	1.00–1.05	0.035
Transpulmonary gradient, mmHg	17.3 ± 7.10	13.5 ± 6.5	1.07	1.01–1.12	0.016
Right atrial pressure, mmHg	17.1 ± 7.04	12.3 ± 5.4	1.13	1.06–1.21	< 0.001
Multiple regression					
NT-pro BNP, 100 pg/mL			**1.06**	**1.03–1.10**	**0.001**
DLCO, % predicted			**0.94**	**0.89–1.00**	**0.021**

Values are presented as mean ± standard deviations. CI: Confidence interval; NYHA: New York Heart Association, GFR: glomerular filtration rate, NT-pro BNP: N-terminal brain natriuretic peptide, DLCO: Diffusion capacity of the lung for carbon monoxide, PAP: pulmonary artery pressure