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Right ventricular diameter predicts all-cause mortality in heart failure with preserved ejection fraction

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Abstract
Left ventricular ejection fraction (EF) is helpful to differentiate heart failure (HF) phenotype in clinical practice. The aim of the study was to identify simple echocardiographic predictors of post-discharge all-cause mortality in hospitalized HF patients. Patients with acute HF (75 ± 9.8 years), classified in preserved (≥ 50%) and reduced (< 50%) EF (HFpEF and HFrEF, respectively), were enrolled. The mean follow-up period was of 25.4 months. Patients definitively analyzed were 135. At multivariate Cox model, right ventricular diameter (RVd), inferior vena cava diameter (IVCd) and blood urea nitrogen (BUN) resulted to be significantly associated with all-cause mortality in HFpEF (HR 2.4, $p = 0.04$; HR 1.06, $p = 0.02$; HR 1.02, $p = 0.01$), whereas, left atrial volume (LAV) was significantly associated with mortality in HFrEF (HR 1.06, $p = 0.006$). Excluding LAV from the model, only COPD remained an independent predictor of all-cause mortality (HR 2.15, $p = 0.04$) in HFrEF. At Kaplan–Meier analysis, no differences of survival between HFrEF and HFpEF were found, however, significantly increased all-cause mortality for higher values of basal-RVd, BUN, and IVCd (log-rank $p = 0.0065$, 0.0063, 0.0005) in HFpEF, and for COPD and higher LAV (log-rank $p = 0.0046$, $p = 0.033$) in HFrEF. These data are indicative that in patients hospitalized with HF, EF is not a suitable predictor of long-term all-cause mortality, whereas, right ventricular volumetric remodeling and IVCd have a prognostic role in HFpEF as well as LAV in HFrEF. Our study suggests that besides EF, other echocardiographic parameters are helpful to optimize the phenotyping and prognostic stratification of HF.

Keywords Heart failure · Ejection fraction · Cardiac remodeling · Right ventricular diameter · Mortality

Introduction

Heart failure (HF) is a major public health problem today responsible for a considerable number of deaths and hospitalizations. Despite current therapeutic advances, mortality remains still high in the community with 50% of people who die within 5 years from diagnosis [1]. Thus, survival improvements require a better understanding of the reasons that may adversely impact outcome at identifying which patients are candidates to a strict clinical follow-up or new targets of treatment. Left ventricular ejection fraction (EF) has proven to be a powerful predictor of cardiovascular events and it is commonly used to differentiate HF phenotype and describe its severity [2]. However, EF may be a limited parameter because it does not describe right cardiac involvement in HF and cardiac remodeling of left sides. Indeed, the role of the right heart in the pathophysiology, clinical presentation and outcome of the HF syndrome has been recently re-evaluated [3]. The aim of this study was to investigate the predictive role of simple echocardiographic parameters on long-term all-cause mortality in patients hospitalized with acute HF.

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Methods

Patient population

Consecutive adult patients admitted to Internal Medicine Department at University Hospital "Paolo Giaccone" of Palermo between January and November 2015 with diagnosis of acute HF and a comprehensive echocardiogram were enrolled. Eligible patients were admitted with dyspnea as the main complaint (NYHA functional classes III or IV), and were diagnosed with acute HF based on symptoms and signs according to the European Society of Cardiology Guidelines (e.g. breathlessness, ankle swelling, fatigue, elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality confirmed by echocardiography performed within the first 48 h from hospitalization [4]. Exclusion criteria included acute myocardial infarction or myocardial ischemia within the past 30 days, acute myocarditis, pulmonary embolism, pneumonia or other severe pulmonary disease, sepsis, end-stage renal disease specified as a glomerular filtration rate (GFR) < 15 mL per min per 1.73 m^2, and cancer. Data about patients and current medication were obtained from the records of hospitals. All patients underwent medical history questionnaire, clinic visit and laboratory tests. The study was performed in accordance with the principles of Declaration of Helsinki and its appendices, and with local and national laws. Approval was obtained from the Hospital's Institutional Review Board and Ethics Committee (A.O.U.P. Paolo Giaccone).

Echocardiographic study

A comprehensive transthoracic echocardiography was performed using a digital ultrasound machine (Vivid 7, general electric ultrasound). Two-dimensional and color Doppler imaging were performed in standard parasternal long- and short-axis, and apical views and analyzed off-line by an experienced echo-cardiographer who was blinded to the clinical data. All reported echocardiographic measurements were averaged from three consecutive cycles. Right ventricular global systolic function was assessed as tricuspid annular plane systolic excursion (TAPSE), by two-dimensional difference of end-diastolic and end-systolic lines (expressed in cm) traced between the center of the ultrasound fan origin and the junction of the right ventricular lateral tricuspid annulus, in apical four-chamber view. Basal right ventricular end-diastolic diameter (Basal-RVd) was measured as maximal transversal dimension in the basal one-third of RV inflow at end-diastole in the RV-focused view.

Inferior vena cava (IVC) images were obtained in the sub-xiphoid view and the transverse diameter (IVCd) was measured anterior to posterior at 2 cm from the IVC right atrial junction using M-mode at maximum diameter during expiration. Continuous Color Doppler echocardiography was used to measure pulmonary artery and aortic velocities, tricuspid regurgitation velocity, and mitral regurgitation velocity. Tricuspid and mitral valve insufficiency were defined as mild, moderate and severe according to ASE Guidelines criteria [5] and we considered in the statistical analysis only moderate to severe valve insufficiency. Pulsed Doppler echocardiography for the assessment of the ventricular diastolic filling velocities was performed using the apical four-chamber view. Thus, the peak early diastolic filling velocity (E-wave) and peak late diastolic filling velocity (A-wave) were recorded. Right and left atrial volumes were calculated from the apical four-chamber view at end systole [6].

Follow-up and clinical endpoint

After discharge, patients were treated by their primary physicians. Survival status was assessed by a telephone contact with patients, family members, and patients' physicians, and also verified by hospital charts. The endpoint of the present study was defined as all-cause death occurred during 3 years of follow-up.

Statistical analysis

Data were collected with a predefined pro forma. Continuous variables were summarized as mean ± standard deviation and categorical variables as frequency and percentage. We performed the sample size calculation on the basis of estimated 50% reduction post-discharge mortality with an α value of 0.5 (95% power) and a β value of 0.05. The sample size obtained was 115, and this number was considered the minimum for the study.

To evaluate the best predictor of all-cause mortality among clinical and echocardiographic parameters on admission, univariate and multivariate Cox proportional hazards analyses were performed. Hazard ratio (HR) and 95% CI were calculated for the strength of association and adjusted for the potential confounders. Receiver-operating characteristic (ROC) curves were used to determine the optimal cut-off, the sensitivity and specificity in predicting the primary endpoint. Simple and multiple linear regression models were used to identify variables associated with independent predictors of mortality. Study's groups were also subdivided in

tertiles of the significant predictors of mortality to identify the cluster of patients at higher risk. Kaplan–Meier methods with the log-rank test were used to compare survival curves and rates. A p value < 0.05 was considered statistically significant and all analyses were performed using MedCalc software (Version 14.12, Belgium).

Results

One hundred sixty-two patients were consecutively admitted with acute HF, 4 died during in-hospital stay and 158 were discharged alive. Enrolled patients were classified in preserved ($\geq 50\%$) and reduced ($< 50\%$) EF (HFpEF and HFrEF, respectively). Post-discharge follow-up data for all-cause mortality were completed in 135 patients, which were definitely analyzed (23 subjects were lost during follow-up and were not included in the final analysis) (Fig. 1).

The mean age of entire population was 75 ± 9.8 years and 57% (77 patients) was female.

63.7% (86 patients) were in NYHA class IV and 36.3% (49 patients) in NYHA class III on admission, and 90.3% (122 patients) in NYHA class II on discharge. A total of 54.1% of the study population (73 patients) had a preserved EF.

Baseline clinical and laboratory findings of study population according to EF are shown in Table 1. During a mean follow-up period of 25.4 ± 14.2 months, 57 patients (42.2%) died; 29 pts (46.8%) with HFrEF and 28 pts (38.3%) with HFpEF. The median time to death was 12 months (median 13.2) in HFrEF and 4 months (median 9.6) in HFpEF. The cause of death was the following: acute HF (8 patients in HFpEF, 9 in HFrEF), sepsis (4 patients in HFpEF, 3 in HFrEF), major bleeding (3 patients in HFpEF, 2 in HFrEF), acute myocardial infarction (3 patients in HFpEF, 4 in HFrEF), sudden death (4 patients in HFpEF, 5 in HFrEF), pneumonia (3 patients in HFpEF, 4 in HFrEF), and other (3 patients in HFpEF, 2 in HFrEF).

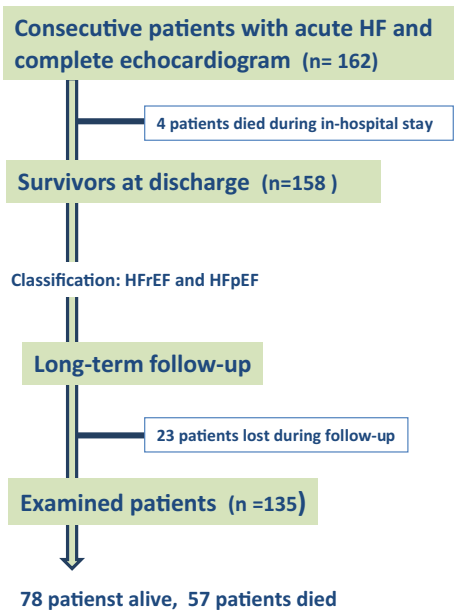

Fig. 1 Flow chart of the study population

Between HFpEF and HFrEF groups, no differences were found in age, NYHA class and other clinical variables except for chronic ischemic heart disease (42% vs 62.9%, $p = 0.024$), male sex (34% vs 54%, $p = 0.03$), differential arterial pressure (60 ± 19 mmHg vs 54 ± 14 mmHg, $p = 0.041$), left ventricular mass (191 ± 70 g vs 260 ± 94 g, $p < 0.0001$), left ventricular end-diastolic volume (92 ± 27 ml vs 163 ± 64 ml, $p < 0.0001$), EF ($58.7 \pm 6.7\%$ vs $34 \pm 8.2\%$, $p < 0.0001$) and mitral valve insufficiency (71% vs 95%, $p = 0.0007$).

According to the last ESC guidelines classification of HF [7], we also subdivided study population in reduced (EF < 40%), mid-range (EF 40–49%), and preserved EF groups ($\geq 50\%$). Patients in mid-range sub-group (22 patients) had the following main features: age was 74.7 ± 9.8 years, 13 were female, 59% were in NYHA class IV (the other in NYHA class III), EF was $43.4 \pm 2.8\%$, IVC was 24.2 ± 5.1 mm, basal RVd was 3.9 ± 0.94 cm, BUN was 37.2 ± 23.4 mg/dl, GFR 49.3 ± 27.6 ml/min, LAV was 107.8 ± 43.2 ml. However, at statistical analysis, no significant differences were found in clinical data between mid-range and the other sub-groups. Instead, patients in preserved EF sub-group were older ($p = 0.04$) and more in NYHA class IV ($p = 0.02$) than reduced EF sub-group.

Patients lost during follow-up had the following main features: age was 74.8 ± 9.3 years, 14 were female, 73.9% were in NYHA class IV (the other in NYHA class III), EF was $51.7 \pm 13.1\%$, IVC was 21.2 ± 4.1 mm, basal RVd was 3.6 ± 0.58 cm, BUN was 38.5 ± 19.5 mg/dl, GFR 50.5 ± 26.6 ml/min, LAV was 91.17 ± 30.4 ml.

Predictors of mortality in HFpEF group

The univariate Cox proportional hazard analysis (Table 2) showed Basal-RVd, blood urea nitrogen (BUN) and IVCd as factors directly associated with all-cause mortality risk during the follow-up period (HR 1.99, $p = 0.019$; HR 1.01, $p = 0.033$; HR 1.07, $p = 0.0008$; respectively), and mean arterial pressure, systolic blood pressure, serum sodium level and estimated GFR (eGFR) as factors inversely associated with this risk during follow-up (HR 0.97, $p = 0.044$; HR 0.97, $p = 0.026$; HR 0.90, $p = 0.0024$; HR 0.98, $p = 0.043$, respectively). A trend of significance was found for hypertension ($p = 0.054$).

The final Cox multivariate analysis (Table 2) showed that Basal-RVd and BUN were the independent factors related

Table 1 Clinical characteristics of HF patients with preserved (HFpEF) and reduced ejection fraction (HFrEF)

	HFpEF group $N = 73$	HFrEF group $N = 62$	p
Arterial pressure			
DBP (mmHg)	71 ± 13	75 ± 12	NS
SBP (mmHg)	132 ± 24	129 ± 20	NS
Deaths, *n* (%)	28 (38%)	29 (46%)	NS
Males, *n* (%)	25 (34%)	34 (54%)	0.03
Mean age	76 ± 8.4	73 ± 11	NS
NYHA class III, *n* (%)	21 (30%)	28 (45%)	NS
NYHA class IV, *n* (%)	52 (71%)	34 (54%)	0.06
Echocardiographic parameters			
Aortic valve stenosis, *n* (%)	6 (8%)	6 (9%)	NS
Basal RVd, (cm)	3.9 ± 0.7	3.9 ± 0.7	NS
E/e'	15.4 ± 5.3	17.7 ± 5.7	NS
IVC diameter, (mm)	24 ± 7.2	23 ± 4.7	NS
Left atrial volume, (ml)	116 ± 107	116 ± 38	NS
Left ventricular mass, (g)	191 ± 70	260 ± 94	<0.0001
LV EDV, (ml)	92 ± 27	163 ± 64	<0.0001
Mean LVEF, %	58.7 ± 6.7	34 ± 8.2	<0.0001
Mitral valve insufficiency, *n* (%)	52 (71%)	59 (95%)	0.0007
PAPs, (mmHg)	51 ± 9.9	51 ± 12	NS
Right atrial area, (cm^2)	24 ± 7.8	25 ± 7.6	NS
TAPSE, (cm)	1.7 ± 0.35	1.7 ± 0.51	NS
Tricuspid valve insufficiency, *n* (%)	64 (87%)	49 (79%)	NS
Laboratory evaluations			
BUN, (mg/dl)	37.8 ± 22	38.6 ± 25	NS
Creatinine, (mg/dl)	1.6 ± 0.9	1.52 ± 0.85	NS
Fasting glycemia, (mg/dl)	136 ± 62	133 ± 0,73	NS
GFR ml/min/1.73 m^2	45.9 ± 24	51.8 ± 28	NS
Hemoglobin, (g/dl)	11.4 ± 2	11.7 ± 2	NS
Serum potassium, (mEq/l)	4.5 ± 0.7	4.4 ± 0.7	NS
Serum sodium, (mEq/l)	137 ± 5	138 ± 4.8	NS
Medications			
ACEIs, *n* (%)	20 (27%)	23 (37%)	NS
Antiaggregants, *n* (%)	28 (38%)	27 (43%)	NS
Anticoagulants, *n* (%)	25 (34%)	21 (34%)	NS
ARBs, *n* (%)	16 (22%)	16 (25,8%)	NS
β-Blockers, *n* (%)	30 (41%)	30 (48%)	NS
Digoxin, *n* (%)	12 (16%)	12 (19%)	NS
Furosemide, *n* (%)	55 (75%)	55 (88%)	NS
Statins, *n* (%)	26 (35%)	25 (40%)	NS

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *Basal RVd* basal right ventricular diameter, *BUN* blood urea nitrogen, *Central obesity* waist circumference ≥ 102 cm in man and ≥ 88 cm in woman, *DBP* diastolic blood pressure, *DP* differential pressure, *GFR* glomerular filtration rate, *HDL-C* high-density lipoprotein-cholesterol, *IVC* inferior vena cava, *LDL-C* low-density lipoprotein-cholesterol, *LVEF* left ventricular ejection fraction, *LV EDV* left ventricular end-diastolic volume, *MAP* mean arterial pressure, *NYHA* New York Heart Association, *PAPS* pulmonary artery systolic pressure, *PV Acc T* pulmunary velocity acceleration time, *RWT* relative wall thickness, *SBP* systolic blood pressure, *TAPSE* tricuspid annular plane systolic excursion, *T-C* T total cholesterol, *NS* non-significant ($p > 0.05$)

to the risk for all-cause mortality at follow-up (HR 2.4, $p = 0.041$; HR 1.023, $p = 0.013$, respectively).

If Basal-RVd was excluded from the model, IVCd and BUN resulted as the significant predictors of all-cause mortality (HR 1.06, $p = 0.023$; HR 1.02, $p = 0.031$, respectively).

Table 2 Univariate and Multivariate Cox proportional hazard analyses to determine factors associated with all-cause mortality HFpEF

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age	0.98 (0.94–1.02)	0.3929		NS
Males	0.66 (0.29–1.49)	0.3231		NS
NYHA class	1.31 (0.56–3.09)	0.5259		NS
Echocardiographic parameters				
Aortic valve stenosis	1.36 (0.41–4.49)	0.6118		NS
Basal RVd (cm)	1.99 (1.11–3.54)	0.0197	2.4 (1.03–5.5)	0.041
E/e'	1.03 (0.95–1.12)	0.3557		NS
IVC diameter (mm)	1.07 (1.03–1.12)	0.0008	1.06 (1.00–1.11)	0.023
Left atrial volume (ml)	1.00 (0.99–1.00)	0.1963		NS
Left ventricular mass (g)	1.00 (0.99–1.00)	0.8386		NS
LV EDV (ml)	1.00 (0.98–1.01)	0.9964		NS
Mean LVEF %	1.01 (0.96–1.08)	0.5017		NS
Mitral valve insufficiency	0.82 (0.37–1.18)	0.6346		NS
PAPs (mmHg)	1.01 (0.97–1.05)	0.3767		NS
Right atrial area (cm^2)	1.03 (0.98–1.08)	0.2212		NS
TAPSE (cm)	0.50 (0.13–1.93)	0.3222		NS
Tricuspid valve insufficiency n(%)	4.82 (0.66–35)	0.1222		NS
Laboratory evaluations				
BUN (mg/dl)	1.01 (1.00–1.03)	0.0330	1.02 (1.00–1.04)	0.013
Creatinine (mg/dl)	1.21 (0.86–1.70)	0.2543		NS
GFR ml/min/1.73 m^2	0.98 (0.96–0.99)	0.0433		NS
Hemoglobin (g/dl)	0.87 (0.73–1.04)	0.2108		NS
Serum potassium (mEq/l)	0.95 (0.53–1.72)	0.2299		NS
Serum sodium (mEq/l)	0.90 (0.85–0.97)	0.0024		NS

Predictors of mortality in HFrEF group

The univariate Cox proportional hazard analysis (Table 3) showed age, chronic obstructive pulmonary disease (COPD) and left atrial volume (LAV) as factors directly associated with all-cause mortality risk during the follow-up period (HR 1.04, $p=0.043$; HR 2.15, $p=0.04$; HR 1.01, $p=0.016$; respectively).

In the final Cox multivariate model (Table 3), LAV and age remained the only significant factors related to all-cause mortality risk at follow-up (HR 1.06, $p=0.0063$; HR 1.06, $p=0.027$, respectively).

If LAV was excluded from the model, only COPD was found as independent predictor of all-cause mortality (HR 2.15, $p=0.04$).

Predictors of mortality in mid-range, reduced and preserved EF

According to the last HF guidelines classification [7], the Cox proportional hazard analysis showed the following results. In reduced EF group, only LAV was confirmed as an independent predictor of all-cause mortality also after adjustment for age (HR 1.018, $p=0.02$). In mid-range EF group, serum sodium was found the unique predictor of mortality (HR 0.88, $p=0.027$). In preserved EF group, Basal-RVd and BUN were the independent factors related to the risk for all-cause mortality at follow-up (HR 2.4, $p=0.041$; HR 1.023, $p=0.013$, respectively). If Basal-RVd was excluded from the model, IVCd and BUN resulted as the significant predictors of all-cause mortality (HR 1.06, $p=0.023$; HR 1.02, $p=0.031$, respectively).

Receiver-operating characteristic (ROC) curves

To assess the accuracy and best values of Basal-RVd, BUN, IVCd in HFpEF, and LAV, age, and COPD in HFrEF as predictors of long-term all-cause mortality, ROC curves were obtained with the following results:

- Basal-RVd: criterion > 4.2 cm; sensitivity 52.4% (29.8–74.3%); specificity 83.3% (65.3–94.4%); AUC 0.701.
- BUN: criterion > 22.89 mg/dl; sensitivity 85.7% (67.3–96.0%); specificity 46.7% (31.7–62.1%); AUC 0.668.
- IVCd: criterion > 20.87 mm; sensitivity 96.4% (81.7–99.9%); specificity 44.4% (29.6–60%); AUC 0.686.
- LAV: criterion > 103 ml; sensitivity 81.8% (59.7–94.8%); specificity 63% (42.4–80.6%); AUC 0.736.

Table 3 Univariate and Multivariate Cox proportional hazard analyses to determine factors associated with all-cause mortality in HFrEF

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age	1.04 (1.00–1.08)	0.0435		NS
Males	1.40 (0.66–2.96)	0.3231		NS
NYHA class	1.78 (0.83–3.82)	0.1395		NS
Echocardiographic parameters				
Aortic valve stenosis	2.20 (0.76–6.31)	0.1449		NS
Basal RVd (cm)	1.49 (0.80–2.75)	0.2021		NS
E/e'	0.93 (0.84–1.02)	0.1478		NS
IVC diameter (mm)	1.07 (0.99–1.15)	0.0841		NS
Left atrial volume (ml)	1.01 (1.00–1.02)	0.0161	1.05 (1.00–1.10)	0.02
Left ventricular mass (g)	0.99 (0.99–1.00)	0.8386		NS
LV EDV (ml)	1.00 (0.98–1.01)	0.4750		NS
Mean LVEF %	0.99 (0.99–1.00)	0.9594		NS
Mitral valve insufficiency	1.72 (0.23–12)	0.5914		NS
PAPs (mmHg)	1.01 (0.98–1.04)	0.4408		NS
Right atrial area (cm^2)	1.04 (0.98–1.11)	0.1457		NS
TAPSE (cm)	0.66 (0.24–1.83)	0.4362		NS
Tricuspid valve insufficiency n(%)	1.02 (0.42–2.51)	0.9510		NS
Laboratory evaluations				
BUN (mg/dl)	0.99 (0.98–1.01)	0.9077		NS
Creatinine (mg/dl)	1.11 (0.75–1.64)	0.5883		NS
GFR ml/min/1,73 m^2	0.99 (0.98–1.00)	0.5274		NS
Hemoglobin (g/dl)	0.85 (0.71–1.01)	0.0828		NS
Serum potassium (mEq/l)	1.03 (0.62-1.71)	0.8807		NS
Serum sodium (mEq/l)	0.97 (0.90-1.04)	0.4057		NS

- Age: criterion > 78 years; sensitivity 51.7% (32.5–70.6%); specificity 69.7% (51.3–84.4%); AUC 0.658.
- COPD: criterion: presence; sensitivity 55.2% (35.7–73.6%); specificity 75.8% (57.7–88.9%); AUC 0.684.

To test the predictive power of these optimal cut-off values, the areas under ROC curves were compared and no significant differences between curves in both HFrEF and HFpEF were found ($p > 0.05$).

Kaplan–Meier analysis

HFpEF and HFrEF did not show significant differences in survival during follow-up period (log-rank $p = 0.41$) (Fig. 2).

In HFpEF, Kaplan–Meier curves for optimal cut-off value determined using ROC analysis showed a significant increased all-cause mortality for patients with higher values of Basal-RVd, BUN, and IVCd (log-rank $p = 0.0065$, 0.0063 and 0.0005, respectively) (Fig. 3).

In HFrEF, a significant reduced survival was observed for patients with higher values of LAV or those affected by COPD (log-rank $p = 0.0046$ and $p = 0.033$, respectively) (Fig. 3).

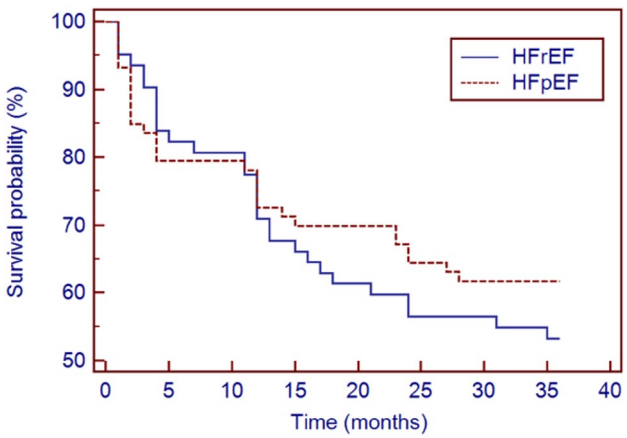

Fig. 2 Kaplan–Meier curve showing survival during follow-up according to reduced or preserved ejection fraction

A trend of significance was found for age (> 78 years), diabetes and smoking habits (Log-rank $p = 0.06$).

Considering the results at Cox proportional hazard analysis, study's population was subdivided into tertiles of Basal-RVd, BUN, IVCd in HFpEF group and LAV in HFrEF group to identify clusters at higher risk.

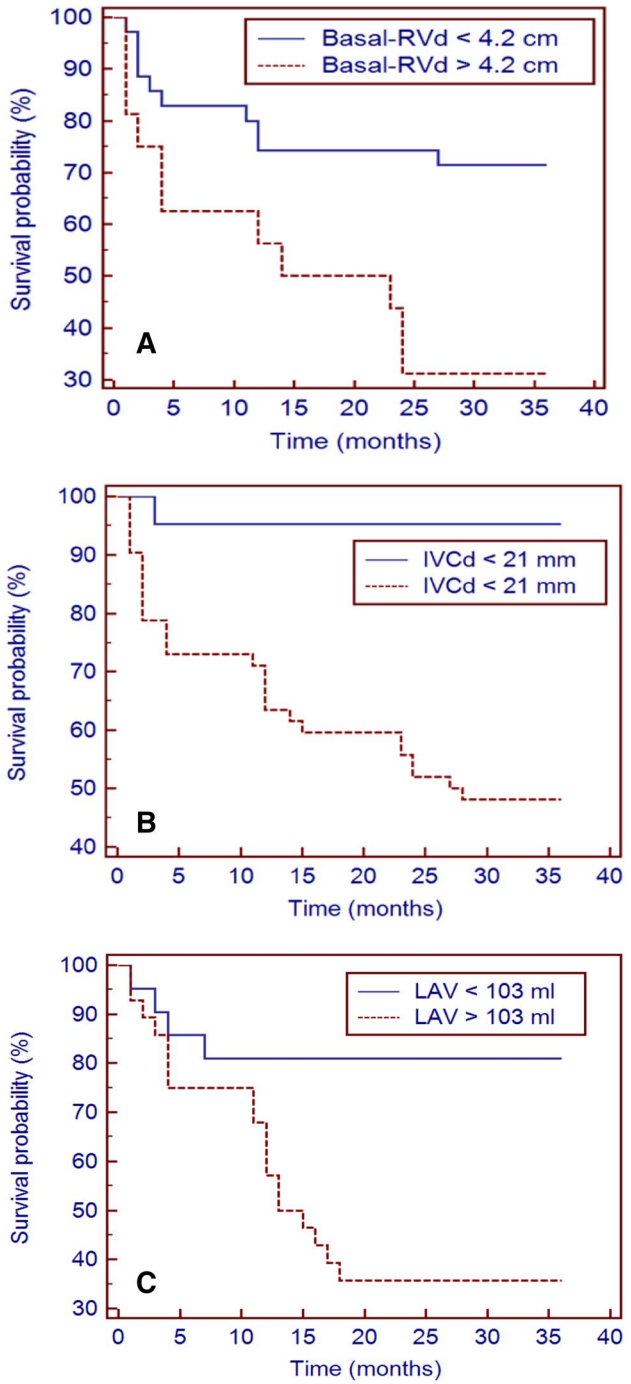

Fig. 3 Kaplan–Meier curve showing survival during follow-up according to cut-off values at ROC analysis for Basal-RVd (**a**) and IVCd (**b**) in HFpEF, and LAV (**c**) in HFrEF

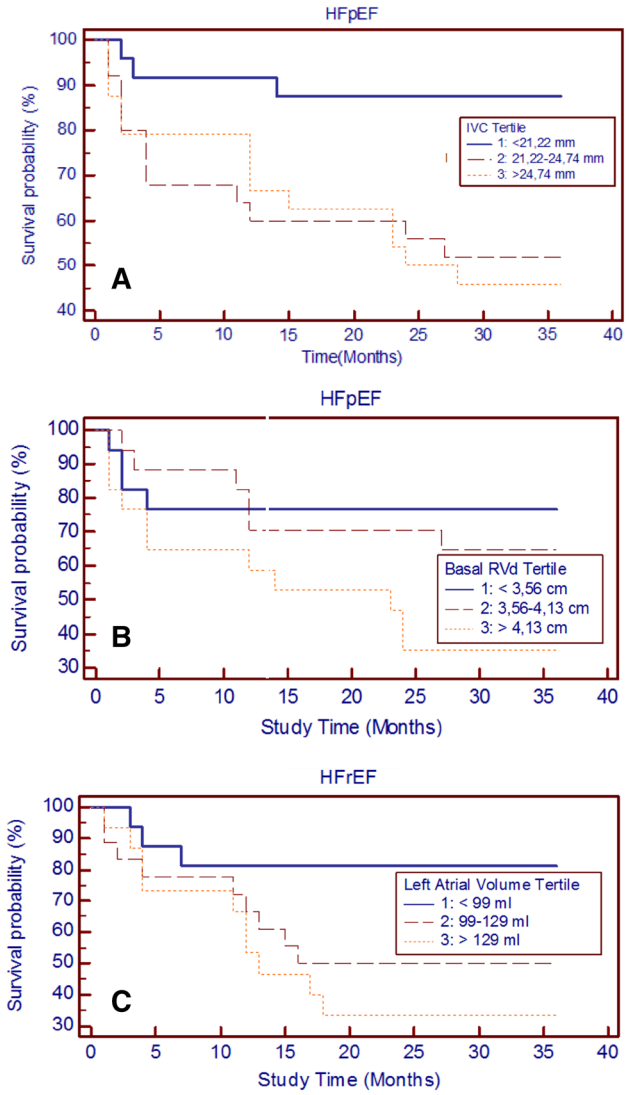

Fig. 4 Kaplan–Meier curves showing survival during follow-up according to IVCd (**a**) and Basal RVd (**b**) tertiles in HFpEF patients and LAV tertiles (**c**) in HFrEF patients

The Kaplan–Meier analysis for tertiles showed that HFpEF patients with Basal-RVd > 4.13 cm had a significantly higher all-cause mortality than patients with Basal-RVd ≤ 3.56 cm (log-rank *p* 0.028) and a trend of significance than patients with Basal-RVd is comprised between 3.56 and 4.13 cm (log-rank *p* 0.083) (Fig. 4); HFpEF patients with BUN ≥ 22.89 mg/dl had a significantly higher all-cause mortality than patients with BUN ≤ 22.89 mg/dl (log-rank $p < 0.05$); HFpEF patients with IVCd ≥ 21.22 mm had a significantly higher all-cause mortality than patients with IVCd ≤ 21.22 mm (log-rank *p* 0.012) (Fig. 4); HFrEF patients with LAV > 129 ml had a significantly higher all-cause mortality than patients with LAV < 99 ml (log-rank *p* 0.012) and a trend of significance between patients with LAV is comprised between 99 ml and 129 ml (log-rank $p = 0.06$) (Fig. 4).

Discussion

In spite of the success of current therapeutic approaches, the burden of morbidity and mortality in HF continues to increase worldwide. Indeed, outcome of patients hospitalized for HF remains suboptimal with a 1-year mortality rate of 30% and 5-year mortality rate up to 50% [8]. Therefore, it is required to identify those patients at higher risk to plane a careful clinical follow-up. Moreover, there is a critical need for a large pipeline of new targets and developing novel strategies of treatment.

The main finding of the present study is that in hospitalized patients with acute HF, no significant differences in long-term survival according to EF were found, and conversely simple parameters of cardiac remodeling (BasalRVd, IVCd and LAV) were significantly associated with all-cause mortality.

In particular, for each phenotype of HF (HFpEF or HFrEF) we observed a different behaviour on long-term survival in accordance with the type of cardiac remodelling.

HFpEF patients

In HFpEF patients, Cox multivariate analysis showed that Basal RVd, as well as BUN, was independently related to the risk for all-cause mortality during follow-up. Moreover, when Basal RVd was excluded from the model, also IVCd resulted as a significant predictor of mortality. The data revealed that the long-term outcome in these patients may be influenced by right heart and renal factors which, apparently uncorrelated, impact together on survival.

First, the result is consistent with previous works, which demonstrated adverse outcomes in patients with HF and elevated BUN, especially in the setting of acute decompensation [9, 10]. Several studies point to the prognostic role of BUN across a broad clinical spectrum of HF, including also patients with renal dysfunction, and it is not consistently seen with other measures of renal function [9–12].

The differential impact of BUN and serum creatinine (or estimated GFR) on HF outcomes implies that BUN might indeed not simply reflect the degree of renal function but rather represent a marker for heart disease severity. Thus, it is conceivable that BUN represents a surrogate marker for "renal response" to systemic hemodynamic changes related to pathophysiologic mechanisms of HF and in particular for neurohormonal activation. The observation that BUN predicts survival in patients with HF better than other renal parameters further supports this hypothesis [13]. Moreover, considering that its prognostic impact was observed only in HFpEF, we argue that congestive kidney disease related to right heart involvement may be a likely pathogenic mechanism.

Second, the burden of BasalRVd on mortality suggests that RV remodeling might be considered a further prognostic factor in HFpEF. Moreover, BasalRVd is easily obtainable and a simple and fast measure [6]. Right ventricle has been an undiscovered land for a long time; however, our results imply its important role in the natural history of HFpEF. In HF, abnormal loading conditions may alter homeostasis of right heart pulmonary circulation unit, leading to a pathologic increase first on exercise (early stage disease) and afterward on resting pulmonary pressure (advanced disease). The right ventricle can adapt to increased afterload by hypertrophy and increased contractility (LaPlace's law). However, these mechanisms are often insufficient and maladaptive changes can subsequently occur, leading to right ventricle dilation and decreased contractility up to progressive right ventricle failure, disability, and death [14].

To the best of our knowledge, there is no study investigating the prognostic value of RV diameter in HF. Instead, previous studies have been demonstrated that RV dysfunction is frequently found in HFpEF and associated with poor long-term prognosis [15].

Therefore, it may be questioned whether RV involvement in HFpEF is primarily the result of worsening HF and increased afterload in pulmonary hypertension, or is also related to shared underlying pathophysiological mechanisms between left and right heart [16–18].

Our study revealed the predictive power of volumetric adaptation of RV. Volumetric adaptation by means of dilation and reducing stroke volume occurs at the cost of increased wall tension (stress) and increased pressure. The consequences of these changes include increased oxygen consumption, together with deterioration of oxygen efficiency, changes at the myocyte level, leftward septal bowing and impairing LV and RV function [19, 20].

Until today, a systematic assessment of the right heart on transthoracic echocardiogram is often not carried out uniformly because of the enormous attention given to the left heart evaluation and the challenging assessment due to complex morphology of right ventricle and some difficulties in visualization. Future hope is to expand and refine the right chamber measurements and analyze their impact on outcome. In this view, considering that the right heart pulmonary circulation unit may be a key determinant of prognosis, a comprehensive cardiovascular ultrasound approach including advanced ultrasound techniques (standard echocardiography, strain, three-dimensional echocardiography, lung ultrasound, stress echocardiography) is an essential step in the diagnostic–prognostic clinical pathway of patients with HF and latent or overt pulmonary hypertension [14].

HFrEF patients

In patients with HFrEF, Cox multivariate analysis showed that LAV is a powerful predictor of mortality. It is recognized that left atrium (LA) is a key player in HF owing to its important role in the maintenance of cardiovascular hemodynamics and neurohumoral homeostasis [21]. Accordingly, increase in LA size might indicate the severity of diastolic dysfunction [22]. LA macroscopic remodeling develops in response to volume/pressure overload and it is fundamental to ensure the best ventricular filling despite elevated wall stiffness and high diastolic pressures, until very advanced stages of dysfunction. On the other hand, the LA preserves pulmonary capillary circulation from hemodynamic overload for a long time and, consequently, preserves the patients from symptoms 'onset' [23]. Previous studies observed LA dilation in both HFpEF and HFrEF [24]; however, LA volume is higher in HFrEF compared with HFpEF, also at identical mean LA pressure [25].

The dimensions of the LA were a significant predictor of mortality and HF hospitalization after adjusting for several factors, as reported in some large prospective studies as SOLVD (Studies of Left Ventricular Dysfunction) trials [26] and MeRGE (Meta-Analysis Research Group in Echocardiography) [27].

Our results pose attention on the prognostic meaning of cardiac remodeling in HF. The failing heart is characterized by a complex tissue remodeling, including structural (dilation, fibrosis) and functional (mechanical and electrical dysfunction) changes in the cardiac chambers, which occur in response to stressors (such as tachycardia and volume/pressure overload) and adapts myocardial geometry to new conditions of pathophysiological functioning [28, 29].

Increased cardiac stress produces a requirement for increased tensile strength and, whilst subsequent remodeling is a necessary adaptation, increasing interstitial fibrosis can increase myocardial stiffness with associated cardiac dysfunction [30]. Cardiomyocyte death also results in recruitment of myofibroblasts for cardiac repair [31]. Currently, this area of cardiac interstitial remodeling is severely under investigation with, consequently, few potential therapies. Modulating the extracellular matrix to attenuate myocardial stiffness may be particularly important in the future, especially in HFpEF, a frequent cause of HF with no proven evidence-based therapies to date.

Indeed, therapeutic approaches for HF have improved survival; however, there is an ongoing inertia in optimizing treatment and current therapy has still a limited capacity to restore muscle function fully. Therefore, to produce a more successful therapeutic strategies, it is necessary a myocardial-centric approach to better understand the cellular/molecular basis of the failing heart.

A mayor limitation of the study was that 23 subjects were lost during follow-up. These subjects were not included in the final analysis.

Conclusions

The post-discharge survival of HF patients is highly variable and still poor. In our cohort study, we found that EF is not a suitable predictor of long-term all-cause mortality in hospitalized patients with acute HF, whereas, cardiac remodeling parameters (Rvd and IVCd in HFpEF and LAV in HFrEF) identified patients with worse prognosis who need a closer clinical-therapeutic surveillance. Thus, these results focused attention on the cardiac remodeling as a prognostic factor and a potential target of treatment. In particular, the data implicate the need to carefully investigate the right heart volumetric adaptation and its potential causes in HFpEF.

We argue that clinicians have to look at these indexes in addition to EF to optimize the phenotyping and management of HF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement on human and animal rights The study was performed in accordance with the principles of Declaration of Helsinki and its appendices, and with local and national laws. Approval was obtained from the Hospital's Institutional Review Board and Ethics Committee (A.O.U.P. Paolo Giaccone).

Informed consent For this study, formal consent was not required.

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