2022

UNIVERSITY OF MEDICINE AND PHARMACY
„CAROL DAVILA”, BUCHAREST
DOCTORAL SCHOOL
DOMAIN MEDICINE

Clinical and evolutive particularities of patients with heart failure with preserved ejection fraction and atrial fibrillation

PHD THESIS SUMMARY

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2022

Summary

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Abbreviations

AF – atrial fibrillation

AS – aortic stenosis

CAD – coronary artery disease

CKD – chronic kidney disease

COPD – chronic obtrsuctive pulmonary disease

DM – diabetes mellitus

DT – deceleration time of E wave

ECG - electrocardiogram

HF – heart failure

HFmrEF – heart failure with mildly reduced ejection fraction

HFpEF – heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

HTN – arterial hypertension

HR – heart rate

LA – left atrium

LAV – left atrium volume

LAVi – left atrium volume index

LV – left ventricle

LVEDD – left ventricle end-diastolic diameter

LVEDV – left ventricle end-diastolic volume

LVEDVi – left ventricle end-diastolic volume index

LVESD – left ventricle ens-systolic diameter

LVESV – left ventricle end-systolic volume

LVESVi – left ventricle end-systolic volume index

MR – mitral regurgitation

SAS – sleep apnoea syndrome

SR – sinus rhythm

TR – tricuspid regurgitation

TRV – tricuspid regurgitation velocity

Thanks

In this way, I would like to express my gratitude to the people who made this work possible.

Special thanks to Ms. Univ. Lecturer. Dr. Camelia Cristina Diaconu for the special opportunity she offered me to be part of her first generation of PhD students, for the careful coordination of my work and for the professional support offered both for the realization of this work and for numerous scientific articles and presentations in multiple congresses and conferences.

Thanks Mr. Prof. Univ. Dr. Lucian Negreanu, Mrs. Prof. Univ. Dr. Laura Iliescu and Mr. Conf. Dr. Mircea Mănuc, who as members of the guidance committee offered me support for the completion of this work.

Thanks to Ms. Dr. Claudia Ionescu who offered me the opportunity to collaborate in order to recruit the patients included in this study.

Thanks to all the doctors from the Cardiology Department of the Emergency Clinical Hospital of Bucharest who offered me the support to perfect myself in standard transthoracic echocardiography and in special echocardiography techniques.

Thanks to my family and friends who believed in my ability to complete this work and understood me when I was not there for them.

I.Current state of knowledge

1. Association between heart failure with preserved ejection fraction and atrial fibrillation

Heart failure (HF) and atrial fibrillation (AF) are related, no matter the left ventricle ejection fraction (LVEF), and each one of the two pathologies predispose to the other development or worsening. The association of AF with heart failure with preserved ejection fraction (HFpEF) is more frequent than with heart failure with reduced ejection fraction (HFrEF) [1,2]. Both pathologies may lead to the other through mechanisms such as structural remodelling, neurohormonal activation and left ventricle (LV) disfunction [1-5]. AF represents one of the causes that can favor the development of HFpEF, and on the other hand, most of the patients with ICFEP will eventually develop AF [6]. AF leads to systolic and diastolic dysfunction and worsening of HF symptoms. Usually, AF precedes HFpEF, leading to the appearance of the latter by favoring LV fibrosis and by hemodynamic effect [7]. The appearance of AF in patients with chronic HFpEF usually has a worse prognosis compared to patients who initially develop AF and subsequently HF on the background of tachycardiomyopathy, because it signifies the worsening of HF and affects additionally cardiac function [8]. Patients with chronic HF and permanent AF have a worse prognosis compared to patients with chronic HF in sinus rhythm (SR) [9]. AF and HFpEF have multiple similar risk factors, such as advanced age, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, obesity, sleep apnea syndrome, myocardial ischemia, that partly explains the frequent association of the two pathologies [10,11]. Thus, in patients with HFpEF and AF, the following elements should be taken into account:

- Identification of potentially reversible causes of AF, such as hyperthyroidism, dyselectrolytemia, uncontrolled HTN

- Identification of precipitating factors, such as recent surgical interventions, exacerbation of chronic obstructive pulmonary disease (COPD), exacerbation of bronchial asthma, chest infections, acute myocardial infarction, ethanol intoxication

- Symptomatic management of HF

- Assessment of the risk of thromboembolic events, especially stroke, and the need to initiate anticoagulant treatment

- Assessment of heart rate (HR) and its control

- Rhythm control.

II.Personal contribution

2. Hypothesis of work and general objectives of the study

HF is a global health problem with significant morbidity and mortality [12-16]. AF is the most frequently sustained arrhythmia in clinical practice, and its association with HF is also common [17]. The coexistence of HF and AF leads to a significant increase in mortality [18-21]. Patients with HF and AF may have distinct clinical characteristics and evolution according to LVEF. Given the impact of HF and AF on mortality and morbidity in the general population globally, and working in a hospital with many cases of HF and AF, we start from the following general hypothesis:

- Clinical and echocardiographic evolution, prognosis and mortality risk of patients with HF and AF may have distinct characteristics depending on LVEF.

The novelty of this study consists in the analysis of the particularities regarding echocardiographic parameters and at the same time of the comorbidities that can influence the risk of death in patients with HF and AF, according to LVEF, which allowed to identify multiple predictive factors of one year mortality. Based on the identified predictors of mortality, we want to create a questionnaire that will be applied in the future to patients with HF and AF, in order to evaluate the predictive power of their mortality risk on a larger group of patients and at the same time if these predictive factors are maintained on long term.

Consequently, the following general objectives of the doctoral thesis were formulated:

- Identification of clinical and especially echocardiographic particularities of patients with HF and AF, depending on LVEF;

- Echocardiographic evolution of the group of patients with HF and AF at one year after inclusion;

- Identification of clinical factors and echocardiographic parameters that influenced one year mortality in patients with HF and AF, depending on FEVS;

- Identification of comorbidities that influenced one year mortality in patients with HF and AF, according to LVEF.

3. General methodology of research

3.1. Population included in the study

The study that is the subject of the thesis included a total of 418 patients diagnosed with chronic HF with different values of LVEF and AF (paroxysmal, persistent, permanent), hospitalized or consulted in the Bucharest Emergency Clinical Hospital during January 2018 - June 2021, selected based on the inclusion and exclusion criteria that will be mentioned below and who provided their written informed consent for the use of their medical data for medical education. This was a prospective study with a retrospective component, observational, nonrandomized, case-control.

The study followed the ethical standards of the 1975 Declaration of Helsinki, revised in 2008(5). Patients' rights were protected and data confidentiality was preserved. I also mention that I obtained the approval of the medical ethics committee of the Bucharest Emergency Clinical Hospital in order to collect medical data from the patients' files and carry out this study (approval number 4714/24.05.2019).

Given that the present study is observational, without impact on the health of the patients, it was not necessary to obtain additional consent from the medical ethics committees.

The inclusion criteria in the study were:

- Patients with the concomitant diagnosis of chronic HF and paroxysmal, persistent or permanent AF;
- Patients older than 18 years age;
- Signed informed consent without constraint in any way to participate in the study.

The exclusion criteria from the study were:

- Cases in which complete echocardiography could not be performed or its result was not available;
- Suboptimal echographic window that led to the impossibility of obtaining the echocardiographic data that are part of the study protocol;
- Other cardiac rhythms than AF at the time of inclusion in the study;
- Patients with constrictive pericarditis;
- Patients with medium or large amount of pericardial effusion;
- Patients with congenital heart disease.

Patients were divided into three subgroups: subgroup 1 included 276 patients with HFrEF and AF, subgroup 2 included 36 patients with HFmrEF and AF, and subgroup 3 included 106 patients with HFpEF and AF.

3.2. Transthoracic echocardiography – examination protocol

2D transthoracic echocardiography was performed in all patients included in the study, either at inclusion or echocardiographic data were extracted from the patients' medical records, only if they fit with the examination protocol of the current study. Echocardiography was also performed (screening echocardiography in most patients) at the one-year follow-up. Three types of machines were used: Vivid E9, Sonoscape and Phillips CX50.

Conventional measurements such as LV wall dimensions, LVEDD, LVESD, LVEDV, LVESV by two-dimensional echocardiography, LA size and function (diameter, LAV calculated by two-dimensional echocardiography using the biplane Simpson method from the four and two-chamber apical windows, the longitudinal strain of the LA – PALS, the contractile strain of LA -PACS), diameter, area and volume of the right atrium, the diameter of the right ventricle, the systolic function of the right ventricle assessed by the systolic change of the tricuspid annulus and by the systolic velocity of the tricuspid annulus by tissue Doppler. LV systolic function was assessed by calculating LVEF from the apical two- and four-chamber windows using the modified biplane Simpson method and global longitudinal strain (GLS). LV diastolic function was assessed using pulsed and tissue Doppler examination, calculating the mitral diastolic pattern and diastolic velocities at the level of the septal and lateral mitral annulus. Valvular disease was evaluated with the help of the pulsed, continuous and color Doppler examination, focusing mainly on evaluating the presence of valvular diseases, and in the case of mitral and tricuspid regurgitation, we also quantified their degrees of severity. The presence of pulmonary arterial hypertension and estimated pulmonary artery systolic pressure were assessed. The aorta and pericardium were also evaluated.

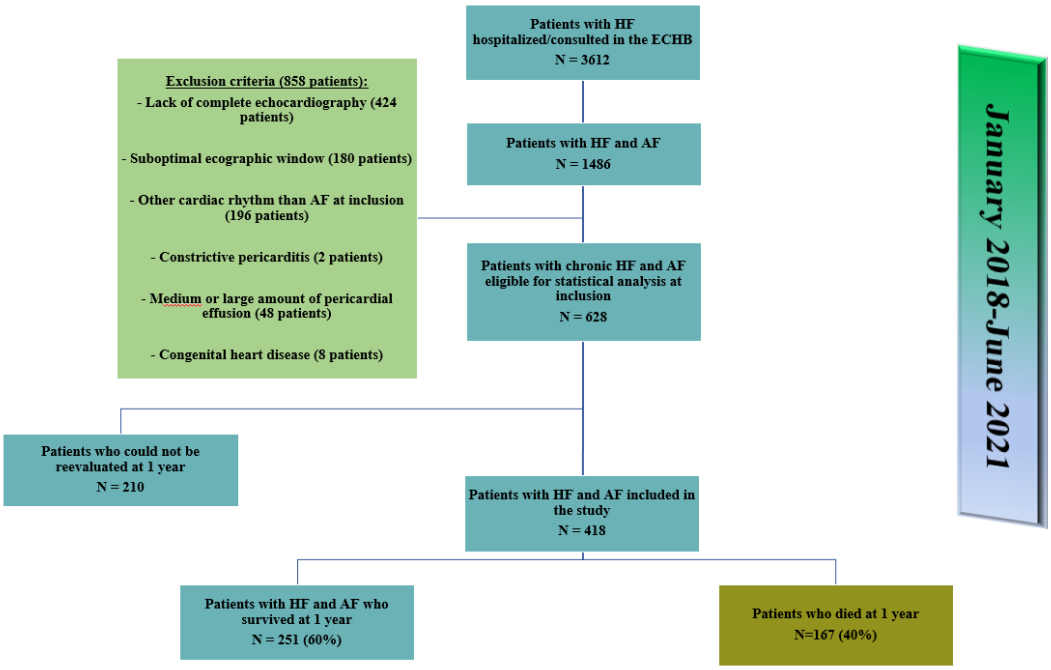

Fig. 3.1. Selection of the patients included in the study

Legend: ECHB – Emergency Clinical Hospital of Bucharest

3.3. Statistical analysis

The data obtained from the anamnesis, the objective examination, the biological tests and the imaging studies were sorted according to the previously mentioned inclusion and exclusion criteria, and the data of the patients who remained in the study were included in a digital database (Microsoft Office Excel). General, clinical, paraclinical information and patient comorbidities were mentioned in the database. To perform the statistical analysis, several software were used in parallel: Microsoft Office Excel 2016 and the R program, version 4.0.2 Copyright (C) 2020 The R Foundation for Statistical Computing, R Core Team (2020). A: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Initially, the general characteristics of the group (distribution by sex, by age category), echocardiographic parameters of the group, clinical particularities and comorbidities were described. For this type of data, tables and graphics such as "Pie-Chart" or "Bar-Graphs" were used. Descriptive analysis was presented as absolute frequencies, mean values ± standard deviation, medians with interquartile ranges. Analysis of variance (ANOVA) and chi-square ($\chi 2$) test were used to estimate statistically significant differences between the three subgroups

of patients regarding various parameters included in the database. In order to identify the factors that may influence mortality, a simple univariate binomial logistic regression was used, with a single predictor, with the dependent variable the absence or presence of death and with independent variables demographic parameters (sex, age), clinical parameters (HF symptoms based on NYHA classification), echocardiographic parameters and associated pathologies. Independent predictors of mortality were identified using multiple binomial logistic regression. The α significance level for the tests in the study was 0.05 and p values less than 0.05 were considered statistically significant.

4. Analysis of clinical and echocardiographic particularities and comorbidities in patients with heart failure and atrial fibrillation, according to LVEF

4.1. Introduction

Patients with HF and AF present specific clinical, demographic and echocardiographic particularities according to LVEF. Also, patients with HF and AF may associate different comorbidities according to LVEF. Study 1 aimed to investigate statistically significant differences between various clinical and echocardiographic parameters in patients with HF and AF according to LVEF. The etiology of HF, the types of AF, the most frequent comorbidities were also analyzed.

The specific hypothesis was formulated as follows:

- Patients with HF and AF present distinct clinical, demographic, echocardiographic particularities and comorbidities according to LVEF.

To evaluate this study hypothesis, we developed the following specific objectives:

- *Evaluation of statistically significant differences between the three subgroups of patients, with HFrEF and AF, HFmrEF and AF, HFpEF and AF, regarding demographic, clinical and echocardiographic data*

- *Identification of the most common comorbidities in the three subgroups of patients.*

4.2. Material and method

All 418 patients with HF and AF participating in the study were included in this subanalysis, and they were divided into three subgroups according to LVEF: subgroup 1

included 276 patients with HF and AF, subgroup 2 included 36 patients with ICFEUR and AF, and subgroup 3 included 106 patients with ICFEP and AF.

4.3. Results

Table 4.1. Analysis of demographic, clinical and echocardiographic factors in patients with HF and AF, according to LVEF

LVEF	**HFpEF**, N=106	**HFmrEF**, N=36	**HFrEF**, N=276	**p-value**[1]
Age,Mean (SD)	76.74 (10.26)	77.69 (9.72)	70.02(12.27)	<0.001
Sex, n / N (%)				<0.001
F	65/106(62%)	19/ 36(52%)	88 / 276 (32%)	
M	41/106(38%)	17/ 85(48%)	188/276(68%)	
LVEF,Mean (SD)	55.51(1.88)	47.84 (2.62)	26.11 (8.63)	<0.001
IVS, Mean (SD)	12.10(2.88)	11.95 (2.62)	10.68 (2.19)	<0.001
PW, Mean (SD)	11.32(2.30)	11.75 (2.57)	10.47 (1.91)	<0.001
E, Mean (SD)	1.33 (0.51)	1.25 (0.53)	1.10(0.40)	0.003
DT, Mean (SD)	212.42(42.9)	212.62(41.65)	200.43(37.17)	<0.001
LAV,Mean (SD)	107.33(52.24)	109.6(69.93)	106.1(48.11)	0.93
LAVi,Mean (SD)	55.90(26.39)	61.19(41.20)	56.72(24.11)	0.84
LVEDD,Mean(SD)	48.26 (6.87)	48.52 (7.60)	58.42 (9.31)	<0.001
LVEDV,Mean (SD)	106.25(26.31)	116.20(33.27)	164.24(59.10)	<0.001
LVEDVi,Mean (SD)	56.39(12.60)	64.13(19.11)	87.43 (29.09)	<0.001
LVESD,Mean (SD)	32.81 (4.58)	33.93 (5.30)	42.77 (9.50)	<0.001
LVESV,Mean (SD)	52.70 (8.11)	55.21 (15.25)	84.42 (43.78)	<0.001

LVEF	**HFpEF**, N=106	**HFmrEF**, N=36	**HFrEF**, N=276	**p-value**[1]
LVESVi, Mean(SD)	28.04 (3.55)	30.16 (8.12)	44.80 (21.63)	<0.001
E/e', Mean (SD)	12.74 (4.64)	12.60 (5.06)	14.63 (5.47)	<0.001

[1] Pearson's Chi-squared test; Kruskal-Wallis rank sum test; Fisher's exact test

Table 4.2. GLS differences in patients with HF and AF, according to LVEF

LVEF	**GLS - Beta (95% CI)**[1]	**p-value**
HFrEF	—	
HFmrEF	7.4 (6.0 to 8.8)	<0.001
HFpEF	7.3 (6.4 to 8.2)	<0.001

Table 4.3. LVEF influence on PALS/PACS in patients with HF and AF

LVEF	**Beta (95% CI)**[1]	**p value**
PALS		
HFrEF	—	
HFmrEF	6.2 (3.8 la 8.5)	<0.001
HFpEF	9.9 (8.4 la 11)	<0.001
PACS		
HFrEF	—	
HFmrEF	1.4 (0.47 la 2.4)	0.004
HFpEF	1.9 (1.3 la 2.6)	<0.001

Patients with HFpEF and AF had hypertensive etiology of HF most frequently ($\chi 2$ test (2, N = 417) = 65.21, p < 0.01) in contrast to those with HFmrEF or HFrEF who had most frequently tachycardiomyopathy in the context of AF with fast HR as the etiology of HF. Ischemic etiology was the second most common in patients with HFrEF and AF, with a significant statistical difference from the other two subgroups ($\chi 2$ (2, N = 418) = 15.48, p < 0.01). In patients with

HFrEF, persistent AF was the most common and in those with HFmrEF and HFrEF permanent AF was the most common. MR was the most frequent valvular disease in all three subgroups of patients, being more frequent in patients with HFrEF (94.2% of all patients with HFrEF) and in those with HFmrEF (91.7% of patients with HFmrEF) than in those with HFpEF (80.2% of all patients with HFpEF). Patients with HFpEF and AF presented more frequently comorbidities such as HTN, DM, CKD, SAS, unlike those with HFrEF who had more frequently CAD.

4.4. Discussions

Patients with HFpEF (mean age 76 years) or HFmrEF (mean age 77 years) and AF were older than those with HFrEF and AF (mean age 70 years), the difference being statistically significant ($p < 0.001$). Patients with HFmrEF had slightly older ages than those with HFpEF, but without statistical significance. Patients with HFpEF (62%) and those with HFmrEF (52%) were mostly women in contrast to those with HFrEF who were mostly men (68%).

LV hypertrophy was more important in patients with HFpEF (mean IVS diameter 12 mm, mean PW diameter 11 mm) compared to those with HFrEF (mean IVS diameter 10 mm, mean PW diameter 10 mm), with significant statistical difference. Patients with HFmrEF had intermediate values between the other two subgroups. On the other hand, patients with HFrEF had the LV more dilated than those with HFpEF, showing higher values of all the parameters used to highlight LV dilatation. Patients with HFpEF, although they had the highest GLS values in the study group, had GLS values below the normal limit of $\geq 20\%$, revealing that GLS has greater accuracy in assessing systolic function than LVEF [22,23]. They have longitudinal systolic dysfunction despite being classified as having preserved LVEF. Patients with HFrEF had more dilated LA than patients with HFpEF. LA dysfunction assessed by LA strain (PALS, PACS) was more severe in patients with HFrEF than in those with HFpEF. LA strain correlates well with invasively measured filling pressures according to the study by Kurt et al [24]. Moreover, Cameli et al. demonstrated that LA strain is the parameter with the highest sensitivity and specificity in the non-invasive assessment of LV filling pressures [25]. LA strain can help differentiate subclinical diastolic dysfunction from HFpEF and has prognostic impact in patients with HF, being used as an indicator of treatment response or as a predictor of the risk of death [26,27]. Decreased LA strain usually occurs before LA dilation and may predict earlier onset of AF [27]. Reduction of LA strain is an important predictor of the progression of paroxysmal AF

to persistent AF [27]. Also, LA strain is useful in evaluating the risk of AF recurrence after RA [27]. Diastolic dysfunction was more severe in patients with HFrEF than in those with HFpEF (HFrEF patients had higher values of E/e' ratio, TRV and lower values of DT). According to several studies, the E/e' ratio represents an accurate and easy to obtain parameter that correlates satisfactorily with LV filling pressures determined invasively by pulmonary catheterization [28-36].

5. Particularities of evolution in patients with heart failure and atrial fibrillation at one year after inclusion in the study

5.1. Introduction

Patients with HF and AF may evolve differently in the short, medium or long term depending on their individual clinical and echocardiographic characteristics. Study 2 aimed to investigate the clinical and echocardiographic evolution of surviving patients at one year. The specific hypothesis is the following:

- Patients with HF and AF have distinct evolution at one year according to various clinical and echocardiographic parameters.

To evaluate this hypothesis, we developed the following specific objectives:

- Evolution of LVEF at one year after inclusion in the study in patients with HF and AF, according to initial LVEF.

- Evolution of LVEF at one year after inclusion in the study in patients with HF and AF, according to the persistence/absence of AF.

- Identification of other clinical/echocardiographic factors that may influence the evolution one year after inclusion in the study in patients with HF and AF.

5.2. Material and method

In study 2, were included the 251 surviving patients at one year. At the one-year follow-up, they were reevaluated clinically, regarding the severity of HF symptoms, echocardiographically (screening 2D transthoracic echocardiography was performed in most patients) and by ECG. The classification into the three subgroups according to LVEF was

maintained as follows: subgroup 1 included 154 patients with ICFER, subgroup 2 included 28 patients with ICFEUR, and subgroup 3 included 69 patients with ICFEP.

5.3. Results

At the one-year follow-up, AF was present in 75% of all surviving patients (189 patients). Thus, AF was present in 73% of patients with HFrEF, in 71% of patients with HFmrEF and in 85% of patients with HFpEF. Tachyarrhythmic etiology of HF was less frequent compared to baseline in all subgroups.

Table 5.1. Random effects in patients with HF and AF regarding the evolution of LVEF at 1 year

Random effect	**Avg**	**CI 90%**
Intergroup intercept 1 yrs	-0.30	-1.30 la 0.40
Intercept LVEF Reduced 1 yrs	REFERENCE	-
LVEF MR 1 yrs	0.20	-0.50 la 1.10
LVEF Preserved 1 yrs	0.20	-0.70 la 1.20

Table 5.2. Fixed effects according to the presence/absence of AF at one year follow-up

Predictor	**Coefficient**	**CI 90%**
AF Yes	REFERENCE	-
AF No	-2.20	-4.90 la 0.40

Average LVEF is lower by 2.20% in patients without AF than in those with AF at one year follow-up.

Tavle 5.3. Random effects according to the presence/absence of AF at one year follow-up

Random effect	**Avg**	**CI90%**
Intercept Intergroup 1 yrs	-0.50	-2.90 la 1.70
Intercept AF Yes 1 yrs	REFERENCE	-
AF No 1 yrs	-0.30	-2.50 la 2.00

From Table 5.3. it is observed that the trend of decreasing LVEF from the initial moment is confirmed (the general intercept is negative). In patients without AF at one year, the intercept is also negative showing that the decrease of LVEF in these patients is greater compared to patients who had AF at one year.

Table 5.4. Echocardiographic differences in patients with HF and AF at inclusion versus one year

Parameter	**Initial** N = 251	**1 year** N = 251	**p**[1]
IVS, Mean (SD)	11.19 (2.40)	11.19 (2.40)	>0.99
PW, Mean (SD)	10.94 (2.20)	10.94 (2.20)	>0.99
E, Mean (SD)	1.19 (0.48)	1.24 (0.42)	0.037
DT, Mean (SD)	205 (40)	196 (38)	<0.001
LAV, Mean (SD)	108 (55)	113 (54)	<0.001
LAVi, Mean (SD)	58 (30)	63 (41)	0.004
LVEDD, Mean (SD)	55 (10)	57 (11)	<0.001
LVEDV, Mean (SD)	146 (58)	153 (62)	<0.001
LVEDVi, Mean (SD)	78 (29)	82 (32)	<0.001
LVESV, Mean (SD)	75 (41)	77 (42)	<0.001
LVESVi, Mean (SD)	40 (20)	41 (21)	<0.001

Parameter	Initial N = 251	1 year N = 251	p[1]
E/e', Mean (SD)	13.6 (5.2)	14.8 (4.9)	<0.001
TRV, Mean (SD)	2.21 (1.44)	2.25 (1.42)	0.51

5.4. Discussions

The one-year survival rate was 60%. Surviving patients had a lower mean age compared to those who died at 1 year regardless of LVEF. Tachycardiomyopathy in the context of AF was the most common initial etiology in patients with HFrEF and in those with HFmrEF, its prevalence decreasing considerably at one year with restoration of SR or optimal HR control in patients with permanent AF.

There was an overall decreasing trend of the LVEF at the one-year follow-up, evidenced by the negative mean of the intergroup intercept at one year, but there are patients who may have slight increases (the upper limit of CI is positive); the biggest decreases were in patients with HFrEF; we can see that in patients with HFmrEF and HFpEF the intragroup intercepts are positive, partially canceling the general decrease. The prognosis of patients with HF and their survival rate over different periods of time have been investigated in several clinical trials over time, showing that patients with HFpEF have a higher survival rate compared to those with HF in the majority of studies [14, 37].

Patients without AF at one year had greater decreases in LVEF than those who remained in AF, demonstrating that AF is not the primary cause of systolic dysfunction. According to the AFFIRM trial, rhythm control and AV control in patients with AF had similar effects on their survival [38]. A sub-analysis of the AFFIRM trial, which evaluated the survival rate according to the individualized and updated treatment (this changed from the moment of inclusion in the AFFIRM trial) of the patients, however, demonstrated that the restoration and maintenance of SR is a significant determinant of survival [38]. These data are similar to the data from the DIAMOND trial which also revealed that patients in whom SR is spontaneously or therapeutically restored have a better prognosis compared to those who remain in AF [38].

6.One-year mortality in patients with heart failure and atrial fibrillation

6.1. Introduction

HF and AF represent cardiovascular pathologies associated with significant risk of hospitalization and mortality [12-16, 39-41]. The association of the two pathologies leads to unfavorable prognosis and increased risk of morbidity and mortality [18-21]. The prognosis of patients with HF and AF has been studied in various studies over time [14,15,37,39-44].

The specific hypothesis is the following:

- **Evaluation of the predictors that led to the increased risk of mortality at one year in patients with HF and AF.**

To evaluate this hypothesis, we developed the following specific objectives:

- *Identifying the demographic and clinical factors that led to the increased risk of mortality at one year in patients with HF and AF*

- *Identification of the echocardiographic parameters that led to the increased risk of mortality at one year in patients with HF and AF*

- *Identification of the comorbidities that led to the increased risk of mortality at one year in patients with HF and AF.*

6.2. Material and methods

In Study 3, all 418 patients participating in the study were included. We used the original digital database created in Microsoft Office Excel 2016 to which we added additional mortality data during the initial hospitalization and during the one-year follow-up period.

6.3. Results

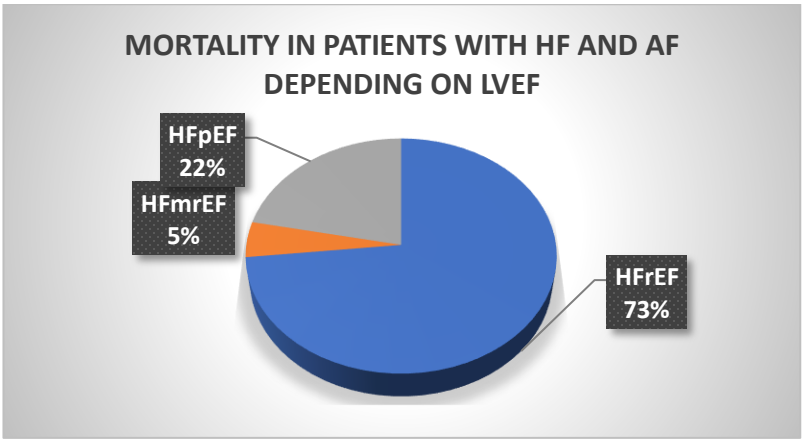

Fig. 6.1. Mortality rate in patients with HF and AF, depending on LVEF

Table 6.1. Influence of E/e' ratio on one-year mortality in patients with HF and AF

Parameter	**N**	**Deaths**	**OR (95% CI)[1]**	**p**
E/e'	418			
< 13.20		73	—	
≥ 13.20		94	1.57 (1.06 la 2.34)	0.024

In patients with E/e' ratio ≥ 13.20, mortality was almost 1.6 times higher compared to patients with E/e' ratio < 13.20, with statistically significant difference.

Table 6.2. AS impact on mortality in patients with HF and AF

Caracteristica	**N**	**Deaths**	**OR (95% CI)[1]**	**p**
AS	418			
Yes		41	—	
No		126	0.55(0.33 la 0.90)	0.017

[1] OR = Odds Ratio, CI = Interval Confidență

Patients without AS had a 50% lower risk of death than those with AS.

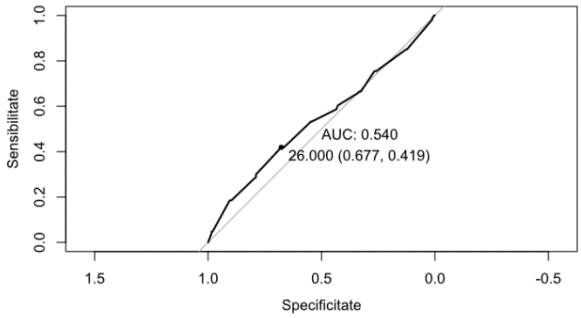

Fig. 6.2. ROC analysis for mortality versus LVEF in patients with HF and AF

The cut-off value was used to create two categories of LVEF, respectively < 26% and ≥ 26%, with statistical differences between them.

Table 6.3. LVEF influence on mortality in patients with HF and AF, according to ROC analysis

Parameter	N	Deaths	OR (95% CI)[1]	p
LVEF	418			
< 26%		70	—	
≥ 26%		97	0.66 (0.44 to 0.99)	0.045

[1] *OR = Odds Ratio, CI = Interval Confidenta*

Patients with LVEF ≥ 26% have a probability of death reduced by one third compared to patients with LVEF < 26%.

Table 6.4. GLS influence on mortality in patients with HF and AF

Predictor	N	OR (95% CI)[1]	p
GLS	418	0.96 (0.92 to 1.00)	0.034

[1] **OR = Odds Ratio, Interval Confidență**

The analysis shows a negative association, patients with low GLS values have a higher risk of death, a 1% decrease in GLS being associated with a 4% increase in the probability of death at one year. A value of GLS ≤ 7.45% is associated with a risk of death more than 2 times higher, compared to a value of GLS > 7.45%.

Table 6.5. Influence of GLS cut-off value on mortality risk in patients with HF and AF

Predictor	N	OR (95% CI)[1]	p
GLS	418		
≤ 7.45		—	
> 7.45		0.45 (0.28 to 0.73)	0.001

[1] OR = Odds Ratio, CI = Confidence Interval

6.4. Discussions

The association of HF with AF leads to an increased risk of mortality compared to patients with HF without AF [18-21]. Thus, taking into account the important mortality risk of patients with HF and AF globally and working in a center where a considerable number of patients with these two pathologies are evaluated or admitted, we chose to evaluate the factors that influence one year mortality in these patients. One year mortality in the study group was 40% of all included patients, respectively 167 patients, the majority being from the subgroup with HFrEF (73%) compared to those with HFpEF (22%) or HFmrEF (5 %). Taking into account each subgroup separately, we observe that patients with HFpEF and AF had a lower mortality risk than those with HFrEF (34% versus 44%), but higher than those with HFmrEF (34% versus 22%).

Predictors of mortality were assessed using simple and multiple binomial logistic regressions. Firstly, we applied a simple logistic regression, detecting the following predictors of mortality: age ≥ 73 years; permanent or paroxysmal AF compared with persistent AF was associated with approximately twice the likelihood of death compared to the other types of AF; LVEF < 26% compared to LVEF ≥ 26%; GLS < 7.45% compared to GLS ≥ 7.45%; the ratio

E/e' ≥ 13.2 compared to E/e' < 13.2; severe MR compared to mild/moderate MR or no MR; AS presence; TRV ≥ 2.67 m/s, compared to its lower speeds of 2.67 m/s; presence of CAD or CKD.

Subsequently, we used multiple logistic regression to detect which of the previously mentioned factors are independent predictors of mortality. The independent predictors leading to increased mortality risk were: age ≥ 73 years which led to an almost threefold increase in the probability of death compared to age < 73 years; LVEF < 26% which led to an approximately 50% increase in the risk of death; severe MR that was associated with an approximately two-fold increase in the risk of mortality; CAD that resulted in a 36% increased risk of death compared to patients without CAD. Persistent AF was associated with a 1.8-fold decreased probability of death compared to paroxysmal or permanent AF.

Conclusions and personal contribution

Patients with HF and AF present distinct characteristics according to LVEF. Both pathologies have a significant risk of mortality, and the association of the two pathologies increases this risk. During the development of the thesis, the research objectives were achieved, demonstrating the following:

- *Patients with HF and AF show distinct clinical and demographic particularities, depending on LVEF.*

Patients with HFpEF and AF included in the study were older than those with HFrEF and AF, but had a lower mean age than those with HFmrEF and AF. Patients with HFpEF and those with HFmrEF were more frequently female and those with HFrEF were more frequently male. Patients with HFpEF and AF most frequently had hypertensive etiology, and those with HFrEF and HFmrEF had most frequently tachycardiomyopathy in the context of AF as the etiology of HF. Ischemic etiology was the second most common in the subgroup of patients with HFrEF and AF. Patients with HFpEF and with HFmrEF had most frequent permanent AF in contrast to those with HFrEF who had most frequent persistent AF.

- *Patients with HF and AF have distinct echocardiographic characteristics, according to LVEF.*

Patients with HFpEF had a more hypertrophied LV, but less dilated than those with HFrEF. Patients with HFpEF and AF, although they had the highest GLS values of all patients

included in the study, had values below the normal limit, indicating that they have systolic dysfunction even though they are classified as having preserved LVEF. Patients with HFpEF and AF had less dilated LA and less severe LA dysfunction than the other two subgroups, but nevertheless presented PALS and PACS values below the normal limit. Diastolic function was evaluated using multiple echocardiographic parameters, namely E/e' ratio, TDE, TRV, LAVi. Diastolic dysfunction was more severe in patients with HFrEF compared to those with HFpEF.

-Evaluation of LVEF evolution one year after inclusion according to initial LVEF.

An overall decreasing trend in LVEF was observed in all patients regardless of baseline subgroup, as evidenced by the negative intergroup intercept mean at one year, but there were patients in whom a slight increase in LVEF was noted. The greatest decreases in LVEF were observed in patients with HFrEF. In patients with HFmrEF and HFpEF, intragroup intercepts were positive, which led to a partial diminish in the overall decrease of the LVEF. Thus, the overall decrease of LVEF in the whole study group was mainly caused by the decrease of LVEF in the subgroup of patients with HFrEF.

Secondary to the comparison between various echocardiographic parameters at baseline versus at one-year follow-up, it was observed that LV and LA were more severely dilated at one year compared to the time of inclusion in the study in all patients. Diastolic dysfunction was more severe at one year in all patients, with higher E-wave, E/e' ratio, TRV values and lower DT values , all differences between these parameters at baseline compared to one year reevaluation were statistically significant.

- Evolution of LVEF one year after inclusion in the study in patients with HF and AF, according to the persistence/absence of AF.

AF was present in 75% of all patients at the one-year reassessment, being more frequent in patients with HFpEF (85%) compared to those with HFrEF(73%) or HFmrEF (71%). The decrease of the LVEF at one year was more important in patients without AF at that time compared with patients who remained in AF at one year.

- Identification of demographic, clinical, echocardiographic factors and comorbidities that led to increased risk of mortality at one year in patients with HF and AF.

The one-year mortality rate in the study group was 40% (167 patients out of the total number of patients included in the study). Analyzing the mortality rate in each subgroup of patients separately, we observe that patients with HFpEF and AF had a lower one-year death

rate than those with HFrEF and AF (34% versus 44%), but higher than patients with HFmrEF and AF (34% versus 22%). Also, among the deceased patients, the majority were with HFrEF and AF (73%), those with HFpEF and AF represented 22% and those with HFmrEF and FA only 5%. Thus, we note that patients with HFpEF and AF have a lower risk of mortality compared to those with HFrEF and AF, but more important than those with HFmrEF and AF.

In this study, we focused on identifying clinical, demographic, echocardiographic factors and comorbidities that had impact on one-year mortality. The influence of LVEF on the mortality rate was analyzed in detail, applying multiple methods and using as potential predictors the numerical value of LVEF, the three types of HF according to which the patients were initially divided into the three subgroups. Using a ROC curve we obtained the cut-off value of LVEF of 26%, according to which patients with were divided into two subgroups, those with LVEF less than 26% having a higher risk of death compared to those with LVEF ≥ 26%.

Predictors of mortality were assessed using simple and multiple binomial logistic regressions. Firstly, we applied a simple logistic regression, detecting the following predictors of mortality: age ≥ 73 years; permanent or paroxysmal AF compared with persistent AF; LVEF < 26% compared to LVEF ≥ 26%; GLS < 7.45% compared to GLS ≥ 7.45%; ratio E/e' ≥ 13.2 compared to E/e' < 13.2; severe MR compared to mild/moderate MR or no MR; AS presence; TRV ≥ 2.67 m/s, compared tovalues lower than 2.67 m/s; presence of CAD or CKD.

The independent predictors leading to increased mortality risk were: age ≥ 73 years which led to an almost threefold increase in the probability of death compared to age < 73 years; LVEF < 26% which led to an approximately 50% increase in the risk of death; severe MR that was associated with an approximately two-fold increase in the risk of mortality; CAD that resulted in a 36% increased risk of death compared to patients without CAD. Persistent AF was associated with a 1.8-fold decreased probability of death compared to paroxysmal or permanent AF.

Limits of the study

The limits of this study are represented by: the relatively small number of patients with HFmrEF and AF included, smaller compared to the other 2 subgroups; carrying out a single revaluation every year; failure to differentiate between cardiovascular and non-cardiovascular causes of death.

Research perspectives

Mortality risk in patients with HF and AF can be assessed individually according to its cause, namely cardiovascular or non-cardiovascular. Moreover, in patients with death from a cardiovascular cause, it can be investigated whether it was due to HF or AF or another cardiovascular disease (for example, an acute coronary syndrome, pulmonary thromboembolism, etc.).

Patients can be followed over a longer period of time and it can be assessed whether predictors with an impact on one-year mortality risk hold up as predictors of long-term mortality. It can also be investigated whether there are other predictors that may influence long-term death. We want to make a questionnaire for predicting the risk of death based on the identified predictors that will be applied to patients with HF and AF in order to evaluate their predictive power in a larger group of patients and on long term. By constantly updating and improving the questionnaire, it could be standardized for routine use in the evaluation of patients with HF and AF.

Personal contribution

My personal contribution to the realization of this thesis consisted in the design of the database and its constant updating with new cases. Given the working regime in an emergency hospital, it was not always possible to acquire data in real time and I had to perform a retroactive data collection as well.

Regarding the practical part of this study, I mention that I performed a significant part of the complete echocardiographies of the patients included in the study at inclusion and the screening echocardiographies performed during the one-year follow-up of the patients.

Last but not least, this database was used to write articles containing partial results of the thesis, published in international journals. Thus, three original articles were published: an article about the one year mortality risk and its predictors published in the journal Healthcare, an article that assessed the differences in diastolic function in patients with HF and AF according to the type of HF according to LVEF published in the journal Diagnostics and an article investigating the impact of DM in patients with HFpEF published in the American Journal of Cardiovascular Diseases. Also, I made 5 oral presentations at conferences or congresses on the subject of this work.

In view of the aforementioned, I consider that I had a significant personal contribution in collecting data for the database, in performing transthoracic echocardiographies and in formulating valid conclusions supported by descriptive and especially analytical statistical analysis.

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List of published articles

1. ISI indexed journals with impact factor:
   - **Horodinschi RN**, Diaconu CC. Heart Failure and Atrial Fibrillation: Diastolic Function Differences Depending on Left Ventricle Ejection Fraction. *Diagnostics*, 12, 839, 2022. doi.org/10.3390/diagnostics12040839. ***IF 3.992*** (Chapter 6. Analysis of clinical and echocardiographic particularities and comorbidities in patients with heart failure and atrial fibrillation depending on the left ventricle ejection fraction)

   - **Horodinschi RN**, Diaconu C. Comorbidities associated with one-year mortality in patients with atrial fibrillation and heart failure. *Healthcare*, 9, 830, 2021. doi:10.3390/healthcare9070830. ***IF 3.160*** (Chapter 8. One-year mortality risk in patients with heart failure and atrial fibrillation)

2. ISI indexed journals without impact factor:
   - **Horodinschi RN**, Diaconu C. Diastolic function in patients with heart failure with preserved ejection fraction and atrial fibrillation:impact of diabetes. Am J Cardiovasc Dis, 11, 564-575, 2021. PMCID: PMC8611268. (Chapter 6. Analysis of clinical and echocardiographic particularities and comorbidities in patients with heart failure and atrial fibrillation depending on the left ventricle ejection fraction)

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