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“CAROL DAVILA”, BUCHAREST

DOCTORAL SCHOOL

MEDICINE

ATRIAL FIBRILLATION AND RIGHT VENTRICLE

SUMMARY OF THE DOCTORAL THESIS

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Publications

Vîjan AE, Daha IC, Delcea C, Dan GA. Determinants of Prolonged Length of Hospital Stay of Patients with Atrial Fibrillation. J Clin Med. 2021 Aug 20;10(16):3715. https://doi: 10.3390/jcm10163715. PMID: 34442009; PMCID: PMC8396858. (Chapter 5)

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Vijan, Ancuta, Daha, Ioana Cristina, Delcea, Caterina and Dan, Gheorghe-Andrei. "The complex interplay between right ventricular dysfunction and atrial fibrillation – a narrative review" Romanian Journal of Internal Medicine, vol.61, no.2, 3923, pp.77-83. https://doi.org/10.2478/rjim-2023-0004 (Chapter 1)

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Delcea Caterina, Buzea Cătălin Adrian, **Vîjan Ancuţa Elena,** Bădilă Elisabeta and Dan Gheorghe-Andrei. "The platelet to lymphocyte ratio in heart failure: a comprehensive review" Romanian Journal of Internal Medicine, vol.0, no.0, 2023, pp.-. https://doi.org/10.2478/rjim-2023-0006

Caterina Delcea, Catalin Adrian Buzea, **Ancuta Vijan**, Anamaria Draghici, Laura Elena Stoichitoiu & Gheorghe-Andrei Dan (2021) Comparative role of hematological indices for the assessment of in-hospital outcome of heart failure patients, Scandinavian Cardiovascular Journal, 55:4, 227-236, DOI: 10.1080/14017431.2021.1900595

Draghici A, Buzea CA, Delcea C, **Vijan A**, Dan GA. Predictors associated with increased troponin in acute decompensated and chronic heart failure patients. Rev Romana Med Lab. 2021;29(2):153-64. doi:10.2478/rrlm-2021-001

Abreviations

AF – atrial fibrillation

AUC – Area unde the curve

CI – Confidence interval

COPD – Chronic obstructive pulmonary disease

eGFR – Estimated glomerular filtration rate

HF – Heart failure

HFmrEF - Heart failure with midly reduced ejection fraction

HFpEF - Heart failure with preserved ejection fraction

HFrEF – Heart failure with reduced ejection fraction

HR – Hazard ratio

HR – Heart rate

LA – Left atrium

LOS – length of hospital stay

LV – Left ventricle

LVEF – Left ventricle ejection fraction

MPI – Myocardial performance index

OR – Odds Ratio

r – Corelation coeficient

RA – Right Atrium

ROC – Receiver operated curve

RR –Risk Ratio

RV – Right ventricle

RV -FAC – Right ventricle fractional area change

S'RV – Peak systolic velocity of the tricuspid annulus

sPAP – Systolic pulmonary artery pressure

TAPSE - Tricuspid Annular Plane Systolic Excursion

TIA – Transient ischemic accident

Contents

Introduction

Atrial Fibrillation (AF) is a serious public health problem due to its increasing incidence and prevalence in the elderly population, associated complications, and the increased burden it places on the healthcare system. The relationship between AF and right ventricle dysfunction (RV) is bidirectional. Since both pathologies share common risk factors, AF can lead to RV dysfunction, while RV dysfunction can also initiate and complicate AF. It is important to note that these two pathologies can occur independently of each other, and not all cases of AF or RV dysfunction are connected. Furthermore, although there may be a relationship between the two, it is not always clear which one occurred first.

Recent studies have evaluated the importance of the right ventricle in multiple cardiac and non-cardiac pathologies and its implications for short- or long-term patient prognosis. However, to date, the impact of RV function on patients with AF has not been studied. The complex relationship between AF and the right ventricle is a current research topic with significant implications for severity quantification, quality of life, and prognosis estimation.

Based on the premise of the need for a detailed description of the relationship between AF and RV function, the purpose of this study was to identify the parameters associated with RV dysfunction in patients with AF and to evaluate their impact on short-term prognostic, arrhythmic burden, and quality of life.

Given the increased prevalence of AF in clinical practice and its impact on hospitalization and the burden on the healthcare system, another objective of the study was to determine the parameters that contribute to prolonged hospitalization in patients with AF and the prognostic value of functional atrial tricuspid regurgitation - a frequent complication - on mortality.

The novelty of this study lies in the comprehensive approach to patients with AF, through the identification of RV dysfunction parameters and their correlations, with the aim of improving prognosis and quality of life.

Defining the profile of patients with AF and RV dysfunction allows not only a better understanding of the disease progression but also early identification of complex cases, risk stratification, and improvement of alternative management strategies.

I. General part

1. Curent state of knowledge

Atrial Fibrillation (AF) is the most common sustained arrhythmia in current medical practice, with a rising prevalence globally and a significant impact on morbidity and mortality. [1] At the same time, right ventricle (RV) dysfunction is a well-known marker of negative prognosis in cardiac pathology. [2] [3] [4] However, the complex relationship between AF and RV function has not yet been fully studied.

Previous studies have shown an association between RV dysfunction and AF in patients with heart failure (HF). The prevalence of AF in patients with RV dysfunction ranges from 65% to 73%, whereas in those without, it ranges from 31% to 53%. [5] [6] [7] The higher prevalence of AF in this group of patients occurs independently of pulmonary pressure. [8]

A study involving 904 patients with acute decompensated HF (ADHF) showed that RV dysfunction was associated with a higher incidence of AF. Among the total number of patients who developed AF, more than two-thirds of them had RV dysfunction (a 6x higher incidence for AF). Moreover, RV dysfunction was the most important predictor of the desired outcome (hospitalization and mortality). The risk of mortality was higher in those with RV dysfunction, regardless of the presence of left ventricular dysfunction. [9]

In AF patients, the diastolic function of the left ventricle is often impaired, which can lead to RV dysfunction. [10] Although RV function in patients with AF is not well-defined, the importance of heart rhythm on RV is well-known. [11] A study conducted on a small cohort of patients showed that in those with permanent AF, RV function represented by the fractional area change (FAC) depends on the preceding RR interval and the average heart rate. [11] In another analysis of patients with paroxysmal and persistent AF, the tele-systolic diameter was significantly larger in sinus rhythm. Additionally, NT-proBNP values were significantly higher in patients with AF and correlated with RV dysfunction. [12]

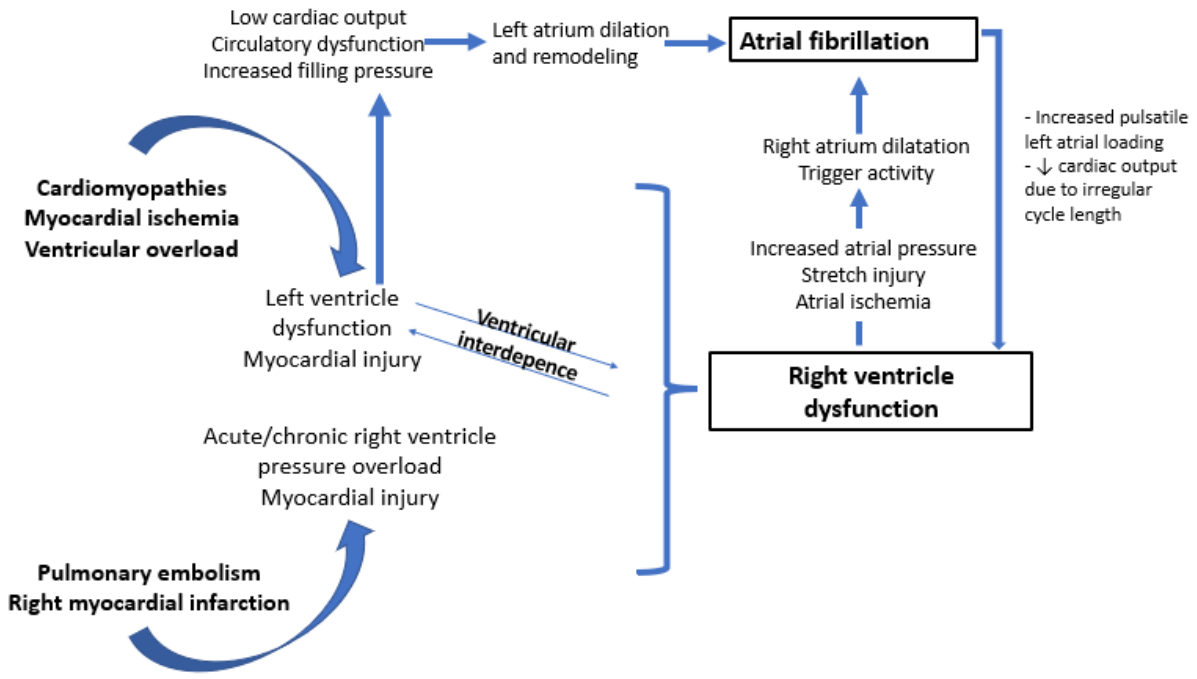


Figure No 1.1. Pathophysiological mechanisms involved in right ventricle dysfunction and atrial fibrillation

II. Personal Contributions

2. General Methodology of the Research

2.1. Study Population

The present study was conducted at a tertiary Cardiology center. The study protocol was approved by the hospital's Ethics Committee and is in accordance with the Helsinki Declaration.

2.2. Biological and Echocardiographic Parameters

Venous blood samples were collected on the day of admission. The complete blood count was analyzed using the Abbott Celldyn 3700, while biochemical and immunology samples were processed with the Hitachi Modular analyzer. The biological profile included complete blood count with leukocyte formula, NT-proBNP, creatinine, glucose, TGO, TGP, Na, K, INR. NT-proBNP values were determined using the Roche Diagnostics Elecsys® assay.

Transthoracic and transesophageal echocardiography were performed using General Electrics Vivid S6 and Philips Epiq 7 (KPI Healthcare).

2.3. Statistical Analysis

IBM SPSS Statistics 23, Epi Info 7, and MedCalc Statistical Software version 19.0.7 were used for statistical analysis. A p-value < 0.05 was considered statistically significant. Non-parametric data were expressed as the median, and normally distributed data were expressed as the mean with standard deviation. Categorical data were expressed as absolute numbers and percentages. T-test, ANOVA, and Mann-Whitney-Wilcoxon test were used to compare independent continuous variables. Chi-square test was used for categorical variables. The area under the curve (AUC) was calculated to determine correlations between numerical and categorical variables. The Youden index was used to obtain the cutoff values of variables associated with the outcome. Independent correlation between the obtained variables and the outcome was tested using multiple regression. All parameters identified in the univariate analysis were included in the regression.

3. Study I - Complex interplay between right ventricle function and atrial fibrillation

3.1. Introduction

3.1.1. Hypothesis

RV dysfunction predicts all-cause mortality in the short term, symptoms, quality of life, arrhythmic burden of atrial fibrillation, and the risk of post-electrical cardioversion recurrence in patients with AF.

Research Objectives

- Identification of determinants of RV dysfunction in patients with AF;

- Identification of echocardiographic parameters of RV dysfunction correlated with short-term mortality;

- Identification of echocardiographic parameters of RV dysfunction correlated with quality of life evaluated through the AFEQT questionnaire;

- Identification of echocardiographic parameters of RV dysfunction correlated with AF burden;

-Identification of echocardiographic parameters of RV dysfunction correlated with post-electrical cardioversion AF recurrence.

3.2. Materials and Methods

3.2.1. Study Population

The present study is an observational, prospective study conducted at the Cardiology Department from January 2021 to July 2022.

Inclusion Criteria:

- Patients with AF

Exclusion Criteria:

- Age < 18 years and readmissions of the same patient

Informed consent for study participation and the use of medical data was signed by each patient at their respective admission.

3.2.2. Definitions

Patients with AF were classified into four groups: paroxysmal AF, persistent AF, long-standing persistent AF, and permanent AF according to the current ESC guidelines. [1] The CHA2DS2-VASc score was calculated for all patients.

RV dysfunction was determined using transthoracic echocardiography by measuring parameters as: TAPSE <17mm, s'RV <10cm/s, FAC-RV <35%, MPI >0.55, RV longitudinal strain <-20%, with cutoff values in accordance with the EACVI-ASE guidelines. [13]

Patient symptoms were evaluated according to the EHRA class. [1]

Arrhythmic burden was determined by the number of episodes, and patients were classified into two groups: high arrhythmic burden and low arrhythmic burden.

Patients with long-standing persistent AF and those with permanent AF were categorized into the high arrhythmic burden group. Patients with more than 5 episodes per month were classified as having a high arrhythmic burden.

Electrical cardioversion was the method of choice for all patients in whom the restoration of sinus rhythm was attempted. Early recurrence was considered for all patients who re-entered AF within one month after the cardioversion. Facilitated cardioversion involved the use of antiarrhythmic drugs, Amiodarone 600mg/day orally for three weeks before cardioversion. [14]

Quality of life was determined using the validated AFEQT questionnaire. The AFEQT questionnaire consists of 20 questions and covers four domains: symptoms, daily activities, treatment-related concerns, and treatment satisfaction. The questionnaire has been shown to have good internal consistency. [15] The cutoff value used in the study was determined using the median obtained for each of the four domains.

3.2.3. Echocardiographic Parameters

Transthoracic and transesophageal echocardiography were performed using Philips Epiq 7 (KPI Healthcare). TAPSE was measured using M-mode in the apical four-chamber window by placing the cursor at the level of the tricuspid lateral annulus, evaluating the longitudinal excursion from telediastole to mesosystole. S'RV was measured using tissue Doppler with pulsed wave, at the level of the free wall of the right ventricle. MPI was determined based on the tissue Doppler velocities from the right ventricle: (isovolumic relaxation time - isovolumic contraction time)/right ventricular ejection time. FAC was obtained by manually tracing the right ventricular endocardium both at the end of diastole and end-systole in the apical four-chamber window, with a focus on the right ventricle, excluding trabeculation. Right ventricular longitudinal strain was measured globally, including the interventricular septum.

3.3. Results

3.3.1. General Data

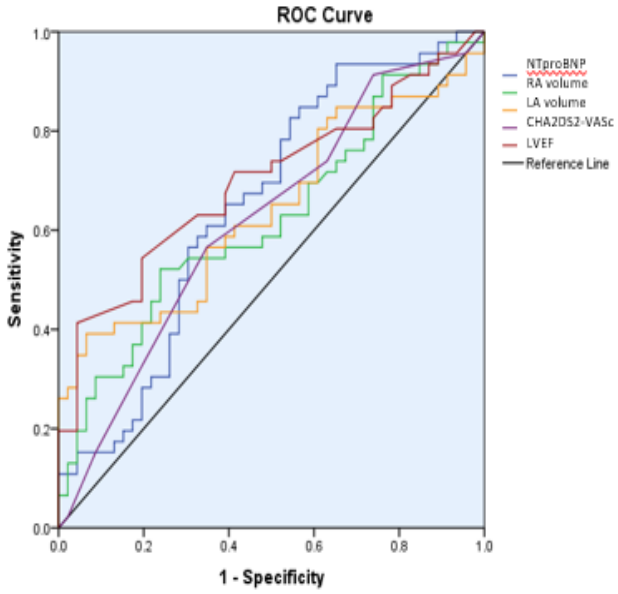
A total of 125 patients with AF were evaluated, with a mean age of 70.8±10.5 years.

3.3.2. Characteristics of Patients with RV Dysfunction

RV dysfunction was present in over 50% of the study participants. Patients with RV dysfunction were significantly older (p 0.03) and had a higher prevalence of HF, chronic kidney disease, and dementia.

3.3.3. Determinants of RV Dysfunction

In univariate analysis, among dichotomous variables, HF and permanent AF were predictors of RV dysfunction. Additionally, RV dysfunction was directly correlated with NT-proBNP levels, CHA2DS2-VASc score, heart rate at admission, left atrial and right atrial volumes, and indirectly correlated with LVEF.



Parameters	OR	95%CI	p
IC	7.7	3.03-19.7	<0.001
Permanent AF	4.82	1.8-12.9	0.009
	AUC	**95%CI**	**P**
CHA2DS2-VASc	0.633	0.536-0.731	0.011
NTproBNP	0.707	0.601-0.812	0.001
RA volume	0.634	0.531-0.736	0.015
LA volume	0.639	0.537-0.742	0.012
LVEF	0.701	0.618-801	<0.001

Figure No 3.1. Determinants of RV dysfunction – univariate analysis

Among the parameters identified in the univariate analysis, in multiple regression, the independent predictors of RV dysfunction were: HF, LVEF, permanent AF and NT-proBNP.

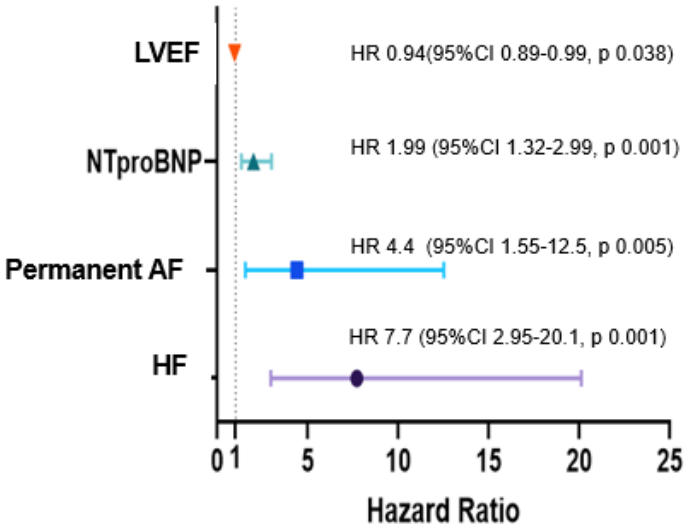
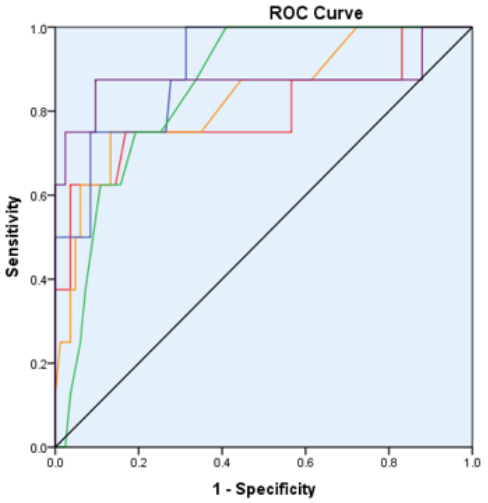


Figure No. 3.2. Determinants of RV dysfunction – multivariate analysis

3.3.4. Determinants of mortality

The all-cause mortality was 7.32% in the entire group, over a mean follow-up period of 15.4±5.8 months.

Among the parameters of RV dysfunction, in univariate analysis, we identified TAPSE, S'RV and the TAPSE/sPAP ratio as factors associated with all-cause mortality. The other parameters correlated with mortality were: HF, dementia, NT-proBNP, LVEF, and BSA.



Parameters	OR (95% CI	p
HF	1.11 (1.03-1.20)	0.03
S'RV	1.16 (1.05-1.30)	0.003
TAPSE	1.27 (1.1-1.51)	0.0001
Dementia	13.7 (2.5-75.8)	0.001
	ASC (95% CI)	**P**
NTproBNP	0.910 (0.840-0.961)	<0.001
Age	0.860 (0.77-0.94)	0.001
LA volume	0.848 (0.767-0.909)	0.014
*BSA	0.710 (0.612-0.788)	0.05
*LVEF	0.840 (0.763-0.900)	0.001
*TAPSE/sPAP	0.824 (0.740-0.890)	0.006

Figure No. 3.3. Determinants of mortality – univariate analysis

In multiple Cox regression, the independent predictors of all-cause mortality were the TAPSE/sPAP ratio with a cutoff determined by the Youden index <0.3, NT-proBNP, and LVEF.

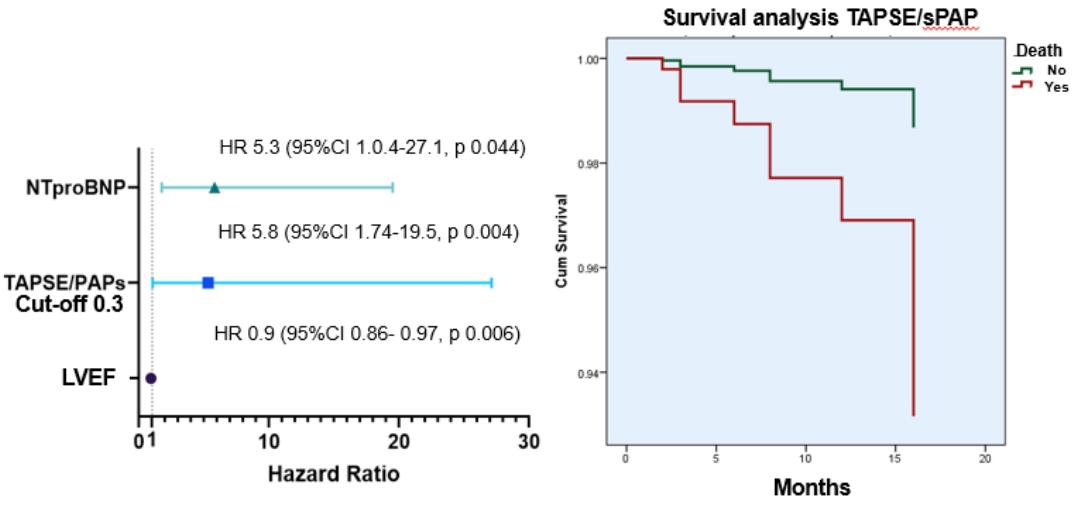
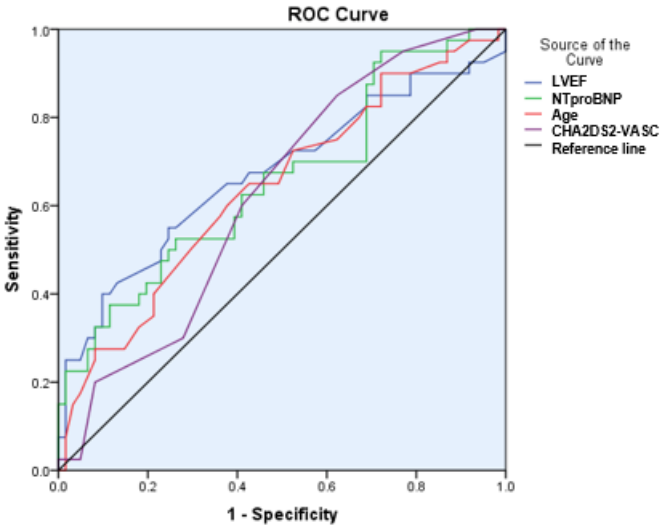


Figure No.3.4. Determinants of mortality – multivariate analysis and Kaplan Meier curve

3.3.5. Determinants of Quality of Life

The median of the AFEQT global questionnaire was 43.7 [IQR 35.1, 52.1].

In univariate analysis, both TAPSE and S'RV parameters of RV dysfunction were associated with a reduced quality of life. Other identified parameters were age, NTproBNP, LVEF, increased arrhythmic burden, and the CHA2DS2-VASC score.



Parameters	OR (95%CI)	p
Arrhythmic burden	3.6 (1.6-7.8)	0.0007
S'RV	4.9 (2.3-10.8)	0.0004
TAPSE	6.3 (2.7-14.9)	0.0005
	AUC (95% CI)	**p**
NTproBNP	0.657 (0.547-0.768)	0.008
CHA2DS2-VASC	0.663 (0.569-0.757)	0.002
Age	0.671 (0.575-0.766)	0.001
*LVEF	0.738 (0.634-0.741)	0.002

Figure No. 3.5. Determinants of poor quality of life – univariate analysis

In the multivariate analysis, the independent predictors of quality of life were RV dysfunction represented by S'RV and TAPSE, the CHA2DS2-VASC score, and age.

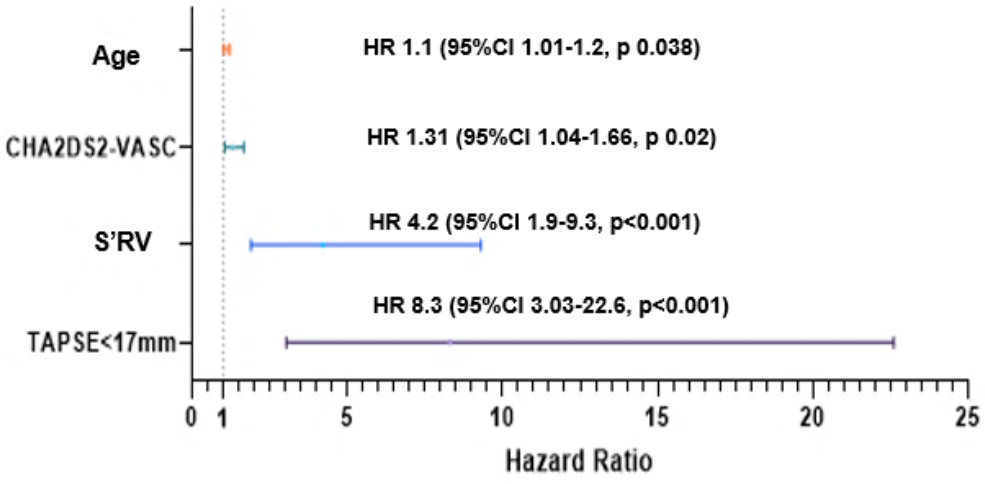
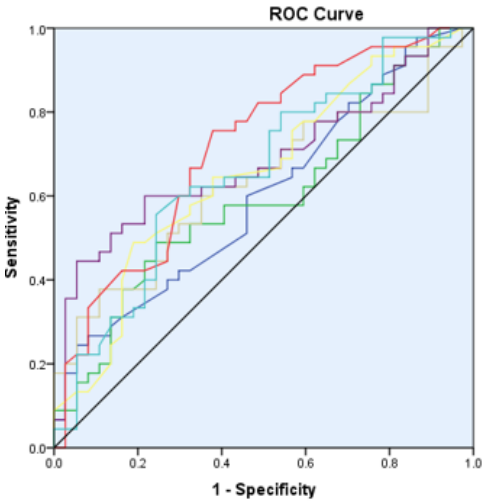


Figure No. 3.6. Determinants of poor quality of life – multivariate analysis

3.3.6. Determinants of Arrhythmic Burden

More than half of the patients had an increased arrhythmic burden (53.6%). In univariate analysis, RV dysfunction parameters represented by TAPSE and S'RV were associated with the increased arrhythmic burden. Other identified parameters were the presence of HF, LVEF, enlarged RA and LA volumes, dilated mitral and tricuspid rings, and increased NTproBNP levels.



Parameters	OR (CI 95%)	p
S'RV	2.9 (1.41-6.25)	0.001
HF	3.4 (1.49-7.94)	0.001
TAPSE	3.9 (1.65-9.24)	0.0006
RV longitudinal strain	4.5 (1.13-18.1)	0.01
	AUC (CI 95%)	**p**
NTproBNP	0.714 (0.604-0.824)	<0.001
RA Volume	0.685 (0.587-0.783)	0.001
LA Volume	0.672 (0.576-0.758)	0.001
Mitral annulus	0.634 (0.530-0.737)	0.016
Tricuspidian annulus	0.663 (0.562-0.764)	0.003
*LVEF	0.618 (0.520-0.714)	0.023
*TAPSE/sPAP	0.665 (0.568-0.752)	0.001

Figure No. 3.7. Determinants of the arrhythmic burden – univariate analysis

In the multivariate analysis, the independent predictors associated with the arrhythmic burden were TAPSE<17cm/s, HF, and RV longitudinal strain <-20%.

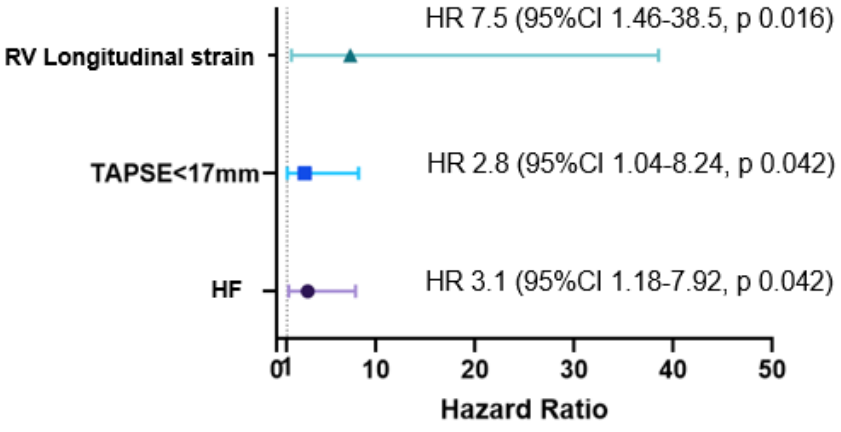


Figure No. 3.8. Determinants of the arrhythmic burden – multivariate analysis

3.3.7. Recurrence after Electrical Cardioversion

A subset of patients included in the study underwent electrical cardioversion (28.8%, n 36). In 84.2% (n 32) of these patients, sinus rhythm was achieved. Early recurrence (within 1 month) occurred in 43.2% of the patients.

None of the parameters of RV function were associated with early recurrence. In multiple regression, the independent predictors of early recurrence were the LA ejection fraction, LA stiffness index, diastolic dysfunction, and increased filling pressures of the left ventricle.

Tabel Nr. 3.1. Determinants of early recurrence – multivariate analysis

	HR	95% CI	p
LV Diastolic dysfunction	2.2	1.4-37.5	0.029
E/e’	1.4	1.1-1.8	0.011
LA stiffness index	0.92	0.87-0.97	0.003
LA ejection fraction	0.80	0.70-0.90	0.001

LA – left atrium, LV – left ventricle

3.4. Discussions

The role of RV dysfunction as a predictor of poor prognosis has been demonstrated in multiple cardiovascular pathologies. However, data on its importance in patients with AF are scarce. The current analysis is one of the few that evaluates the complex relationship between RV function and AF.

3.4.1. Determinants of RV Dysfunction

In an analysis involving 520 patients with heart failure HF, the TAPSE values were lower in patients with AF compared to those in sinus rhythm.[16] Another study on a group of 98 patients with hypertrophic cardiomyopathy showed that those who developed AF or remained in AF had significantly impaired RV function (evaluated by TAPSE) compared to those in sinus rhythm.[17]

Our study identified several parameters associated with RV dysfunction, including the presence of HF, LVEF, permanent AF, and increased NTproBNP levels. In patients with HFpEF the prevalence of RV dysfunction varied based on the presence of AF (20% in patients without AF

compared to 43% in those with a history of AF and 63% in those with current AF). Multiple studies have shown that AF leads to a decrease in RV longitudinal function, which could be a substrate for AF-induced RV dysfunction.[18],[16],[19]

Our analysis demonstrated that RV dysfunction is more frequently encountered in patients with persistent long-term AF or permanent AF. Permanent AF was found to be an independent predictor of RV dysfunction. Similarly, in a study conducted on HF patients, non-sinus rhythm, defined as AF or pacemaker rhythm, was an independent predictor of RV dysfunction.[20]

Regarding the left ventricular function and its interrelation with RV, the current analysis showed that LVEF is an independent predictor of RV dysfunction. In a study on a cohort of patients with hypertrophic cardiomyopathy, LVEF was significantly associated with RV ejection fraction, and the only independent predictor of RV dysfunction was LVEF. Similarly, LVEF has been demonstrated as a predictor of RV dysfunction in patients with pulmonary hypertension, independent of pulmonary artery systolic pressure.[22]

3.4.2. Determinants of Mortality

Previous studies have shown that RV dysfunction is a frequently observed element and has a negative prognostic impact on patients with HF.[18],[23] Our analysis revealed a significantly higher frequency of RV dysfunction in patients with HF. Regarding all-cause mortality, among the parameters of RV dysfunction, the TAPSE/sPAP ratio with a cut-off <0.3, along with LVEF and NTproBNP, remained as independent predictors.

The TAPSE/sPAP ratio has been demonstrated as a mortality predictor in various studies. A study on patients with pulmonary embolism showed that TAPSE/sPAP predicts both 7-day and 30-day all-cause mortality, while TAPSE and sPAP alone did not. The analysis concluded that the ratio is superior in predicting adverse outcomes, thus improving risk stratification and identifying high-risk patients.[24] Another study that included HF patients showed that mortality from all causes and rehospitalizations were more frequent in patients with a TAPSE/sPAP ratio ≤ 0.35. TAPSE/sPAP emerged as a predictor of the primary combined endpoint, with better statistical power than TAPSE or sPAP alone.[25] The predictive value of the TAPSE/sPAP ratio for mortality was also investigated in a cohort of patients with systemic sclerosis, where TAPSE/sPAP <0.32 was an independent predictor of all-cause mortality.[26]

In an analysis of patients with acute decompensated HF, RV dysfunction represented by TAPSE <17mm was the most important predictor of poor prognosis (hospitalization and mortality).[9] Similarly, a prospective study on 457 patients with AF and HF showed that a low value of s'RV was correlated with a worse prognosis.[19] In our analysis, although TAPSE and s'RV were associated with short-term mortality, they did not remain as independent predictors in the multivariate analysis.

The prognostic role of NTproBNP on mortality has been extensively studied. The BIOS study, conducted on a large cohort of HF patients, identified NTproBNP as a predictor of all-cause mortality and cardiovascular mortality.[27] A study by Bibings et al. demonstrated that increased NT-proBNP values predict cardiovascular morbidity and mortality in patients with stable coronary artery disease, independent of systolic and diastolic function.[28] Similarly, Paniagua et al. showed the prognostic role of NTproBNP on mortality in a cohort of patients with end-stage renal disease on dialysis.[29] Similarly, Tu et al. demonstrated the utility of NT-proBNP as an independent predictor in patients with ischemic stroke.[30] In a study on HF patients, including those with NYHA class II-IV, increased NTproBNP with a cut-off > 1958 pg/ml was identified as the most potent independent predictor of mortality at 6 months. Patients with elevated NTproBNP values were often associated with AF.[31] Also, in a cohort of patients with symptomatic AF, increased NTproBNP levels successfully predicted all-cause mortality at 6 months.[32] Similarly, in a sub-analysis of the ARISTOTLE study, cardiac biomarkers had the highest predictive power for mortality in patients with AF. In this cohort, NTproBNP was identified as an independent predictor of heart failure-related mortality.[33]

LVEF is a strong predictor of mortality in cardiac pathology. In a study on 1,418 patients with HFpEF, 32.2% had worsened LVEF, which was associated with twice the mortality rate.[34] One of the predictors of worsened LVEF was AF. An analysis of 403,977 cardiac ultrasounds on 203,135 patients showed a U-shaped relationship between LVEF and mortality, with the risk beginning at an LVEF of 60-65%. Deviations of LVEF outside this interval were associated with poorer survival, regardless of age, sex, and the presence of HF.[35] A study on 1,063 patients with AF showed that the presence of HF increased the mortality risk by twice as much in this group. The association of the two pathologies significantly increased mortality, especially in patients with LVEF below 25%.[36]

3.4.3. Determinants of Quality of Life

The AFEQT questionnaire is a validated instrument for assessing the quality of life in patients with AF, being a feasible way to evaluate the prognosis in patient follow-up and clinical studies.[37] Patients with AF generally have a lower quality of life compared to those in sinus rhythm.[38] Previous studies have shown that patients with paroxysmal or persistent AF have a poorer quality of life than those with permanent AF.[39] RV dysfunction has been associated with a lower quality of life in multiple pathologies. In a cohort of patients with systemic lupus erythematosus and pulmonary hypertension, low TAPSE values (<17mm) were associated with a lower quality of life.[40] Similarly, RV dysfunction, expressed by reduced free-wall RV strain values, was correlated with a lower quality of life in a group of patients who had undergone repair of tetralogy of Fallot.[41] In our study, RV functional parameters were significantly correlated with a reduced quality of life. Among the markers of RV dysfunction, S'RV and TAPSE were identified as independent determinants of a lower quality of life.

A study on patients with ischemic heart disease showed that age is a predictor of a lower quality of life.[42] Similarly, our analysis identified age as an independent parameter associated with a reduced quality of life.

The direct association between the CHA2DS2-VASc score and quality of life has not been studied. In our analysis, the CHA2DS2-VASc score was an independent predictor of a lower quality of life.

3.4.3. Determinants of Arrhythmic Burden

A study on a group of 904 patients with ADHF showed that RV dysfunction was associated with a higher incidence of AF. Among the total number of patients who developed AF, more than two-thirds had RV dysfunction (an incidence of 6 times higher for AF).[9] In our study, RV dysfunction, represented by TAPSE and RV longitudinal strain, was an independent predictor of increased arrhythmic burden. A prospective analysis of patients with non-permanent AF identified a history of stroke and BNP as independent markers of increased arrhythmic burden.[43] In our study, NT-proBNP was a predictor in univariate analysis but its predictive power did not persist in multiple regression. Lack of physical activity, obesity, and hypertension are factors associated with an increased arrhythmic burden.[44] Contrary to these data, in our study, none of these factors were associated with arrhythmic burden. A possible confounding

factor is that in our study, arrhythmic burden was determined from patients' symptoms and less from device interrogation and smartwatch monitoring.

3.4.4. Determinants of Recurrence

Data on the role of RV dysfunction as a predictor of AF recurrence are limited. A study on 420 patients with AF who underwent radiofrequency ablation showed that longitudinal RV dysfunction was a strong predictor of AF recurrence.[45] Similarly, Yano et al. showed that RV-pulmonary artery coupling was independently associated with late AF recurrence.[46] In our study, none of the RV dysfunction parameters were correlated with early post-cardioversion recurrence. Similar results were reported by Govidan et al. in a small cohort of 30 patients with paroxysmal AF.[47] The small sample size and short follow-up period may be confounding factors for the discordant results.

Our study identified as independent predictors of early recurrence the index of LA expansion, LA ejection fraction, increased filling pressures in the LV, and diastolic dysfunction. Consistent with our findings, Govidan et al. identified the LA expansion index as a predictor of early recurrence, while Walex et al. identified LA ejection fraction as a predictor.[48] Regarding diastolic dysfunction, several studies have supported our results, with diastolic dysfunction being an independent determinant of recurrence.[49][50] In addition to diastolic dysfunction, recent analyses have demonstrated the predictive power of increased LV filling pressures, a result confirmed by our analysis.[51]

The relationship between AF and LA indexed volume is well-known, with LA volume playing a demonstrated role in perpetuating AF. The predictive role of LA volume in AF recurrence was demonstrated by Marchese et al., where each 1 ml/m2 increase was independently associated with a 21% increase in recurrence risk after successful electrical cardioversion.[52] Similar results were confirmed by Govidan et al.[53] In our analysis, LA volume was a predictor in univariate analysis but was outperformed by more potent determinants in multiple regression, a finding reinforced by Fornenego et al.[50]

3.5. Conclusions

In conclusion, RV dysfunction and AF have a complex and bidirectional relationship. RV dysfunction may contribute to the development and recurrence of AF, while AF can cause RV

dysfunction, aggravating the patient's prognosis. Our study demonstrates that RV dysfunction is associated with mortality, arrhythmic burden and reduced quality of life. Early recurrence after conversion was not correlated with RV dysfunction in the analysis.

4. Study II - Prognostic Value of Atrial Functional Tricuspid Regurgitation in Patients with Atrial Fibrillation

4.1. Introduction

4.1.1. Hypothesis

Severe atrial functional tricuspid regurgitation (AF-TR) has a negative prognostic value regarding mortality in patients with AF.

4.1.2. Objectives

Primary Objectives:

- Prognostic impact of severe AF-TR in patients with AF;

Secondary Objectives:

- Factors associated with severe AF-TR in patients with AF;

- Factors associated with mortality in patients with AF.

4.2. Materials and Methods

4.2.1. Study Population

The present study is an observational, retrospective one, evaluating patients with AF consecutively hospitalized in the Cardiology Department from January 2018 to February 2020.

Inclusion criteria:

- Patients with AF

Exclusion criteria:

- Age under 18 years, organic TR, significant pulmonary hypertension (systolic pulmonary artery pressure (sPAP) > 50mmHg), left ventricular ejection fraction (LVEF)< 50%, other significant valvular pathology, implantable devices with leads in the right ventricle, pericardial diseases.

4.2.2. Definitions

AF-TR was defined as TR without significant pulmonary hypertension (sPAP < 50 mmHg) and no obvious cause of TR (LVEF < 50%, organic tricuspid valve disease, other significant valvular

disease, pacemaker/defibrillator lead inserted in the RV, or pericardial diseases), and no previous valve surgery. [54]

Patients with AF were classified into two groups: severe TR and non-severe TR. The non-severe TR category included patients without TR, with mild or moderate TR. The severity of TR was defined according to the 2021 ESC guidelines. [55]

sPAP was calculated as the sum of estimated RA pressure and the gradient determined by the TR jet. The RA pressure was considered 5 mmHg if the inferior vena cava (IVC) diameter was less than 21 mm, 10 mmHg if IVC was greater than 21 mm and collapsed with respiration, and 15 mmHg if IVC was greater than 21 mm and did not collapse with respiration. [56]

4.3. Results

4.3.1. General Characteristics

We evaluated a cohort of 246 patients with AF. The prevalence of AF-TR was 86.2%, of which 8.1% had severe AF-TR. The all-cause mortality for the entire group was 8.5%, and 25.0% for patients with severe AF-TR over a median follow-up period of 34 (28-39) months.

4.3.2. Determinants of Severe AF-TR

In the univariate analysis, severe AF-TR was directly correlated with ADHF, permanent AF, age, LA, RA, RV diameters, PAPs, NTproBNP, eGFR, and CHA2DS2-VASC score.

Determinants	OR (95%CI)	p
Acute decompensated HF	3.10 (1.2 - 7.8)	0.01
Permanent AF	6.40 (1.5 - 28.3)	0.005
	AUC (95%CI)	**p**
Age	0.70 (0.58 - 0.81)	0.003
LA	0.67 (0.50 - 0.80)	0.015
RA	0.81 (0.71 - 0.91)	<0.001
RV	0.80 (0.70 - 0.90)	<0.001
sPAP	0.82 (0.75 - 0.90)	<0.001
NTproBNP	0.76 (0.67 - 0.85)	0.045
CHA2DS2VASC	0.63 (0.52 - 0.74)	0.05
eGFR	0.68 (0.57 - 0.80)	0.007

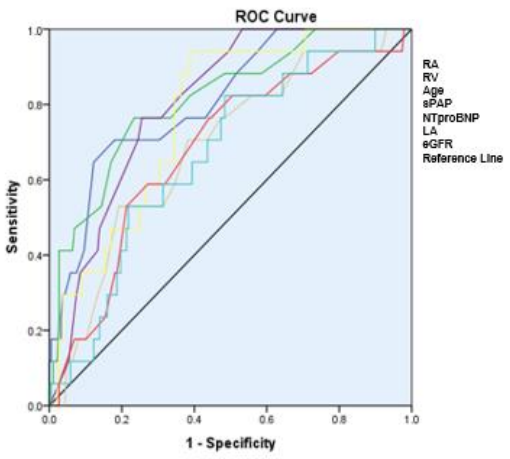


Figure No. 4.1. Determinants of the severe AF-TR – univariate analysis

Among clinical and laboratory parameters associated with severe AF-TR in univariate analysis, RA, PAPS, and NT-proBNP were independent predictors of severe valvular dysfunction in multivariate analysis.

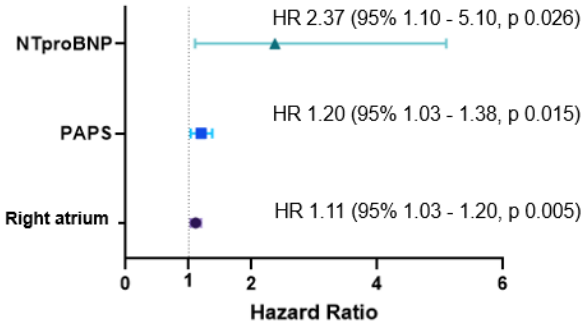


Figure No. 4.2. Determinants of the severe AF-TR – multivariate analysis

4.3.3. Severe AF-TR and Mortality

In univariate analysis, severe AF-TR was a predictor of all-cause mortality in patients with AF (OR 4.37, p 0.005). Other variables associated with all-cause mortality included ADHF, NYHA class III/IV, stroke/TIA, dementia, and infections. In ROC analysis, age, elevated NT-proBNP levels, basal diameter of the RV, and creatinine were direct predictors of all-cause mortality, while the LVEF was inversely correlated with it.

Determinants	OR (95%CI)	p
Severe TR	4.37 (1.41 - 13.57)	0.005
Acute decompensated HF	4.32 (1.72 - 10.83)	<0.001
NYHA class III/IV	5.74 (2.21 - 14.93)	<0.001
Stroke	2.81 (1.11 - 7.85)	0.04
Dementia	6.08 (1.40 - 26.34)	0.006
Infections	5.27 (2.02 - 14.21)	<0.001
	ASC (95% CI)	**p**
Age	0.770 (0.66 – 0.87)	<0.001
NTproBNP	0.802 (0.71 – 0.88)	<0.001
RV basal diameter	0.639 (0.50 – 0.77)	0.05
Creatinine	0.657 (0.53 – 0.78)	0.017
LVEF	0.704 (0.59 -0.81)	0.002

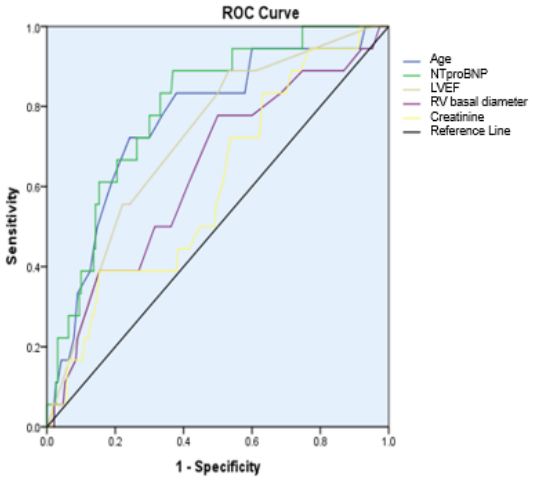


Figure No. 4.3. Determinants of mortality in AF patients – univariate analysis

In multivariable Cox survival analysis, severe AF-TR, dyspnea on mild exertion or at rest, infections, age, and LVEF were independent predictors of all-cause mortality in AF patients.

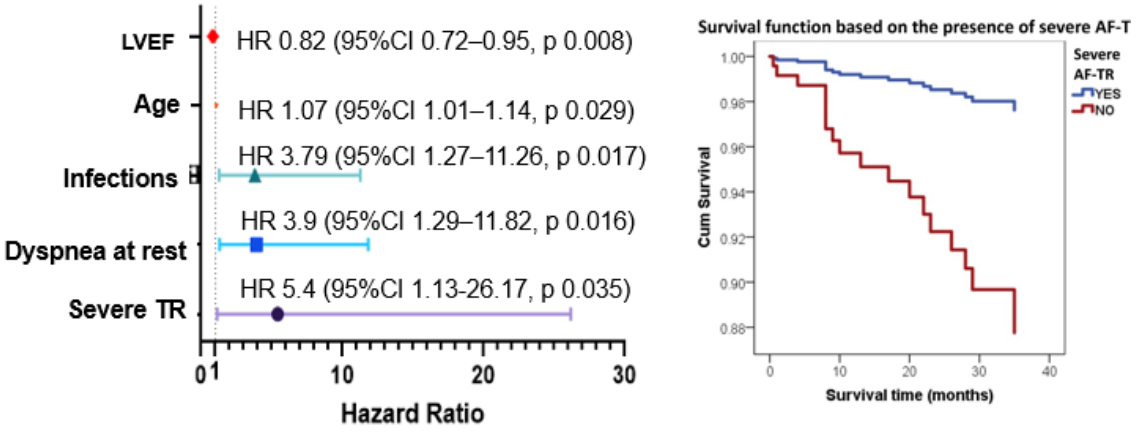


Figure No. 4.4. Determinants of mortality in AF patients – multivariate analysis and Kaplan Meir curve

4.4. Discussions

Our study is among the few analyses that evaluate the independent prognostic impact of AF-TR in patients with AF. Until recently, TR was underestimated and neglected, being considered almost exclusively as a consequence of left heart conditions or pulmonary diseases, without intrinsic prognostic value. Currently, there is a positive trend towards recognizing TR in patients with AF and its prognostic value. [57], [58], [59], [60]

In our analysis, severe TR had a prevalence of 8.1%. Two previous studies showed a significantly higher prevalence of severe TR, at 21.7% and 15%, respectively [61], [57], which can be explained by including patients with both moderate and severe RT in these studies. Previous studies have shown that TR is frequently encountered in patients with non-paroxysmal AF, mainly due to bi-atrial enlargement and tricuspid annular dilation [62]. In our analysis, patients with severe TR were older, similar to the results of previous studies [58], [63].

4.4.1. Atrial Functional Tricuspid Regurgitation

In 2020, from the retrospective analysis of a large cohort of 1552 patients, Mutlak et al. concluded that the progression of TR in AF is determined by age, AF type, and high left heart filling pressures, characterized by increased sPAP and dilation of the LA [64]. Our results confirm that patients with severe TR in AF are older, more likely to have permanent AF, a higher number of comorbidities expressed by the CHA2DS2-VASc score, as well as larger LA and

sPAP dimensions. Additionally, sPAP and NT-proBNP values were independent predictors of severe TR in the multivariate analysis, along with RA diameter. The correlation between RA dimensions and TR in AF was also reinforced by Utsunomiya et al. [65] and Dietz et al. [58]. Guta et al. concluded that the role of RA dilation exceeds that of the RV in inducing TR [66]. Our data strengthen the association of severe TR with RA diameter. In the univariate analysis, patients with severe TR had larger dimensions of both RA and the RV, but only RA diameter was an independent predictor for severe valvular regurgitation in the multivariate analysis.

4.4.2. Severe TR in AF and Patient Mortality

The survival of patients with AF has improved in recent decades, mainly due to advancements in preventing thromboembolic events. However, patients with AF still have increased mortality compared to those in sinus rhythm [67]. Recent data have linked significant TR to a worse prognosis in patients with AF. Dietz et al. correlated moderate-to-severe TR with all-cause mortality and hospitalization for HF and stroke during a median follow-up of 62 months [58]. Prapan et al. also demonstrated that moderate-to-severe TR can predict the occurrence of HF or all-cause mortality during a two-year follow-up [57]. In another cohort of AF patients with at least moderate TR, followed for a median period of 52 months, the severity of TR was associated with all-cause mortality [59]. A post-hoc analysis of the MISOAC-AF study, which followed valvular heart disease in AF patients, also confirmed the association of TR with mortality [60].

The particularity of our research compared to the mentioned studies above is the independent correlation of severe TR with midterm all-cause mortality, after adjusting for survival predictors identified in our cohort. Both Dietz et al. [58] and Prapan et al. [57] evaluated composite endpoints as adverse events, not only mortality. Fortuni et al. [59] focused only on a subset of severe TR, namely torrential TR, as a mortality factor, while Samaras et al. [60] assessed severe TR of all etiologies, not specifically functional TR in AF.

Our study correlated the prevalence of severe TR in AF with persistent and permanent AF and, subsequently, the enlargement of the RA due to atrial remodeling. The independent impact of TR on mortality in these patients could be, therefore, indirect evidence for early rhythm control and the superiority of rhythm control strategy.

In 2020, evidence emerged showing that in patients with persistent AF, a successful rhythm strategy can improve RA geometry and, consequently, the severity of AF-TR. A series of cases of two patients with AF who reverted to sinus rhythm reported by Muraru et al. [62] and a retrospective cohort study of patients with persistent AF undergoing catheter ablation, published by Itakura et al., demonstrated that the rhythm strategy can induce reverse remodeling of the RA with subsequent correction of TR severity [68].

Similar findings have been reported regarding functional mitral regurgitation in patients with AF [69]. These results confirm that the benefit of rhythm strategy in patients with AF can exceed symptomatic improvement and extend to morbi-mortality enhancement. In vitro data support the premise that AF-TR is highly dependent on the tricuspid annular geometry, developing after only 40% dilation, compared to functional mitral regurgitation, which requires a 75% increase in mitral annular diameter [12,33].

4.5. Conclusions

Functional TR is frequently present in patients with AF. Severe AF-TR is an independent predictor of mortality in AF, unlike mild-to-moderate functional TR, which did not have a significant impact. Severe AF-TR was determined by increased RA diameter and sPAP and correlated with high NTproBNP levels. Severe AF-TR had an increased prevalence in patients with non-paroxysmal AF, thereby raising the hypothesis that the rhythm strategy could prevent permanent atrial remodeling and thus the progression of TR severity.

5. Study III Determinants of prolonged hospital stay in patients with atrial fibrillation

5.1. Introduction

5.1.1. Hypothesis

The duration of hospitalization is a well-known parameter for evaluating the severity of the disease, resources used, and associated costs. It can be improved by identifying factors that prolong the hospitalization duration.

Objectives

- Identifying determinants associated with prolonged hospitalization in patients with AF

5.2. Materials and Methods

5.2.1. Study Population

This study is a retrospective, observational, which included all consecutive patients with AF, aged over 18 years, hospitalized in the Cardiology Department from January 2018 to February 2020. Re-hospitalizations of the same patient were excluded.

5.2.2. Definitions

Patients with AF were classified into three groups: paroxysmal AF, persistent AF, and permanent AF. The term "long-standing persistent AF" was rarely used in our cohort and was not included in the classification. Patients with HF were classified according to the current ESC guidelines, based on the LVEF, as follows: HF with preserved EF(HFpEF), HF with mildly reduced EF(HFmrEF), HF with reduced EF(HFrEF).

The Charlson Comorbidity Index was used to evaluate the number of comorbidities and frailty associated with advanced age. Electrical cardioversion was the chosen method for all patients who had restoration of sinus rhythm.

Prolonged hospitalization duration was defined as more than 7 days (upper limit of the third tertile). The CHA2DS2-VASc score was calculated for all patients following the ESC guidelines. eGFR (estimated glomerular filtration rate) was obtained using the CKD-EPI formula.

5.3. Results

5.3.1. General Characteristics of the Study Cohort

Our study included 949 patients with AF, of which 52.9% were females. The average age was 72.5 ± 10.4 years. The average hospitalization duration was 4 days. 28.7% had prolonged hospitalization.

5.3.2. Hospitalization Duration

In the univariate analysis, prolonged hospitalization was associated with the presence of HF and markers of HF severity (resting dyspnea, acute decompensated HF, NT-proBNP, and reduced EF) and ischemic heart disease (acute coronary syndrome, previous myocardial infarction, chest pain at admission). Among right heart-associated parameters, the RA and RV diameters and PAPs were correlated with prolonged hospitalization. Patients who had AF at admission also had prolonged hospitalization. Non-cardiac pathologies correlated with extended hospitalization included infections, dementia, history of stroke or TIA, and reduced renal function. (Table Nr. 5.1.)

Table Nr. 5.1. Determinants of prolonged LOS – univariate analysis

	RR (95%CI)	p value
Age	1.10 (1.01 – 1.20)	0.02
AF on admission	1.11 (1.01 – 1.21)	0.04
Palpitations on admission	0.84 (0.75 – 0.94)	0.02
HF	1.19 (1.09 – 1.30)	< 0.001
ADHF	1.44 (1.31 – 1.60)	< 0.001
Dyspnea at rest	2.82 (1.41 – 5.65)	< 0.001
HFrEF	1.38 (1.20– 1.59)	< 0.001
IHD	1.16 (1.05 – 1.28)	< 0.001
Prior MI	1.25 (1.04 – 1.49)	0.003
ACS	1.65 (1.05 – 2.60)	0.002
Chest pain on admission	1.33 (0.97 – 1.81)	0.04
Hypertensive emergency	0.81 (0.73 – 0.90)	0.005
Diabetes mellitus	1.12 (1.01 – 1.24)	0.01
TIA/stroke	1.18 (1.02 – 1.37)	0.008
CKD<60ml/min/1.73m2	1.10 (1.01 – 1.20)	0.03
Anemia	1.19 (1.07 – 1.32)	< 0.001
Dementia	1.44 (1.02 – 2.03)	0.006
Infection	1.48 (1.26 – 1.73)	< 0.001

ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; CI, confidence interval; CKD – chronic kidney disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; MI, myocardial infarction; RR, risk ratio; TIA, transient ischemic attack;

	AUC (95% CI)	Cut-off value	p value
Heart rate	0.56 (0.53 – 0.59)	> 104bpm	0.005

NT-proBNP	0.69 (0.66 – 0.73)	> 1986 pg/ml	< 0.001
EF	0.63 (0.60 – 0.67)	< 44%	< 0.001
CHA2DS2-VASC	0.58 (0.55 – 0.61)	> 4	<0.001
HAS-BLED	0.58 (0.54 – 0.61)	> 3	<0.001

Abbreviations: AUC, area under the curve; CI, confidence interval; EF- ejection fraction

In multivariate regression analysis, after adjusting for age and sex, we identified five independent predictors of prolonged hospitalization. ACS was the strongest predictor of prolonged hospitalization, followed by coexisting infections, NT-proBNP, ADHF, HFrEF, and an elevated HAS-BLED score. (Table Nr. 5.2.)

Table Nr. 5.2. Determinants of prolonged LOS – multivariable analysis

	HR	95% CI	p value
ACS	4.60	1.66 – 12.69	0.003
Infections	2.61	1.44 – 3.23	< 0.001
NT-proBNP > 1986 ng/ml	1.96	1.37 – 2.82	< 0.001
ADHF	1.76	1.23 – 2.51	0.002
HFrEF	1.69	1.15 – 2.47	0.007
HAS-BLED score	1.42	1.14 – 1.78	< 0.001

ACS, acute coronary syndromes; ADHF, acute decompensated heart failure; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio;

5.3.3 RV dysfunction and length of hospitalization

The subgroup of patients who underwent evaluation of RV function through TAPSE consisted of 313 patients, of which 33.2% (104 patients) experienced prolonged LOS. In the univariate analysis, we identified RV dysfunction as a predictor of prolonged hospitalization, along with other determinants assessed in the analysis of the entire group. (Table No. 5.2.)

Table Nr. 5.3. Determinants of prolonged hospital stay – univariate analisys

	RR (95%CI)	p
TAPSE <17mm	11.15 (4.68 – 26.8)	< 0.01
ADHF	2.09 (1.29 - 3.39)	< 0.001
Dyspneea at rest	2.98 (1.72 – 4.96)	0.001
HFrEF	2.21 (1.29– 3.79)	0.002
Myocardial infarction hystory	2.69 (1.32 – 5.49)	0.005
ACS	6.33 (1.25 – 31.9)	0.01
Stroke/TIA	2.81 (1.49 – 5.32)	0.001
Dementia	4.85 (1.45 – 16.16)	0.006
Infections	2.13 (1.20 – 3.78)	0.005

	AUC (95% CI)	p
NT-proBNP	0.69 (0.62 – 0.74)	< 0.001
LVEF	0.63 (0.57– 0.70)	< 0.001
CHA2DS2-VASC	0.59 (0.53 – 0.65)	0.005
HAS-BLED	0.58 (0.51 – 0.64)	0.016

ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AUC, area under the curve; CI, confidence interval,HF, heart failure; LVEF- left ventricle ejection fraction HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; MI, myocardial infarction; RR, risk ratio; TIA, transient ischemic attack;

After adjusting for sex and age, the independent predictors that remained were RV dysfunction, elevated NT-proBNP levels, ADHF, infections, and the HASBLED score. (Table No. 5.4.)

Table Nr. 5.4. Determinants of prolonged LOS- multivariable analysis

	HR	95% CI	p value
TAPSE	7.32	2.94 – 18.2	0.007
Infections[a]	2.13	1.17 – 3.86	< 0.001
NT-proBNP	1.37	1.08 – 1.73	< 0.001
ADHF	3.71	1.98 – 6.96	0.002
HAS-BLED [b]	1.46	1.04 – 2.04	0.025

5.4. Discussions

This is one of the few studies evaluating extended hospitalization in patients with AF. Our research identified several determinants of prolonged LOS in a relatively large cohort of AF patients. The average length of hospitalization in our group was 4 days, comparable to previously reported results. An analysis of AF patients hospitalized in the USA over an 11-year period found an average hospital stay of 3 days [70].

5.4.1. Risk scores in atrial fibrillation

Patel et al. documented the correlation between the CHADS2 score and the duration of hospitalization in AF patients [71]. Lahewala et al. found that LOS in AF increased directly proportional to the CHADS2 and CHA2DS2-VASc scores [72]. Our results not only confirm the association between hospitalization duration and the CHA2DS2-VASc score but also establish the independent predictive value of the HAS-BLED score for extended hospitalization in AF

patients. In our analysis, 5.45% of patients had a high bleeding score, mainly composed of non-modifiable and partially modifiable risk factors (age, history of stroke, chronic kidney disease, uncontrolled hypertension).

Age was weakly correlated with prolonged LOS. Although advanced age was associated with extended hospitalization in univariate analysis, it did not reach significant predictive value in multiple regression. As a marker of frailty, the Charlson comorbidity index was not associated with prolonged LOS in our study. In a study conducted on 302 AF patients, prolonged hospitalization was associated with frailty and advanced age, but the cohort was generally much older compared to our study sample (84.7 ± 7.1 vs. 72.0 ± 10.3 years) [73].

5.4.2. Severity of atrial fibrillation burden

Regarding the association between hospitalization duration and the type of AF, there was no independent association in our study. Similar results were obtained by Steinberg et al. [74]. In an analysis by Steinberg et al., increased heart rate was significantly correlated with hospitalization in AF patients with or without concomitant heart failure [74]. However, in our study, the heart rate at admission was weakly correlated with prolonged hospitalization, regardless of the type of AF, being overshadowed by other stronger predictors in the multivariate analysis.

The type of anticoagulant was not associated with extended LOS, contrary to previous studies associating NOACs with shorter hospital stays compared to warfarin [75], [76], [77]. We believe this might be due to the increasing prescription of NOACs in our cohort compared to previous reports [78], [79]. Additionally, as part of the ABC pathway [78], the use of rate or rhythm control therapy or urgent cardioversion did not influence hospitalization duration, while elective electrical cardioversion was associated with shorter LOS.

5.4.3. Cardiac substrate

HF is an independent predictor of prolonged hospitalization in hospitalized cardiovascular patients [80]. In a long-term registry of over 900,000 patients, Ziff et al. showed that AF patients with HF had a higher risk of prolonged hospitalization compared to those with HF alone or AF alone [81]. Similar results were reported from the ORBIT-AF registry, where significant HF at admission (NYHA class II or higher) had a major impact on hospitalization [74]. The bidirectional relationship between AF and HF was an important determinant of prolonged

hospitalization in our study, with HF affecting over 80% of patients. The highest independent risk of extended hospitalization was associated with acute decompensated HF, as well as severity markers of HF, namely, high NT-proBNP levels and reduced ejection fraction.

Elevated NT-proBNP values, as a surrogate for intracardiac volumes and filling pressures, with clinical utility not only in early diagnosis but also in risk stratification in HF [82], represented an independent predictor of prolonged hospitalization in our study. Previous data have also reported elevated NT-proBNP levels as predictors of extended hospitalization in a cohort including over 70,000 HF patients [83].

Patients with AF and acute coronary syndrome had the highest risk of prolonged hospitalization, after adjusting for all other identified risk factors in the multivariate analysis. This reciprocal relationship was also highlighted in a recent analysis of the AMIS Plus registry [84]. Among more than 35,000 patients with acute coronary syndrome, prolonged hospitalization was observed in those with preexisting or new-onset AF compared to those in sinus rhythm [84]. Moreover, preexisting AF was an independent predictor of in-hospital mortality in this study [84], [85].

An analysis from the ROCKET-AF registry showed that infections were a significant cause (47%) of hospitalization in AF [86]. Results from the EORP-Heart Failure-Polish Registry on a cohort of 1126 HF patients also confirmed the influence of infections on prolonged hospitalization [87]. Similarly, our research identified concomitant infections as independent predictors of extended hospitalization.

5.4.4. RV dysfunction and prolonged hospitalization

In our substudy, we demonstrated the role of RV dysfunction (RRV) as an independent predictor in AF patients. Similar results were reported in the analysis by Paskariatne et al. on a cohort of 259 patients with ADHF. RRV was associated with AF, prolonged hospitalization, and frequent rehospitalizations.[88]

5.5. Conclusions

In our study, the main determinants of prolonged hospitalization in AF patients included the burden of cardiovascular pathology, comorbidities, and infections, rather than specific clinical or therapeutic characteristics of AF. Independent predictors of prolonged hospitalization were acute

coronary syndromes, acute decompensated HF, reduced ejection fraction, elevated NT-proBNP levels, infections, and the HAS-BLED score. Patients with extended hospitalization had more comorbidities and severe cardiac pathology. Interventions that could optimize hospitalization duration include strategies for preventing ischemic heart disease, optimizing outpatient HF care, periodic evaluation and correction of modifiable parameters of the HAS-BLED score, early detection and prevention of infections.

6. Study Limitations

The main limitations of the prospective study are the small number of patients and the short follow-up period. Additionally, another limitation is that the assessment of arrhythmic burden was based on the number of symptomatic episodes and less on interrogation of implantable devices or Holter/loop recorder monitoring, so asymptomatic episodes could not be identified.

The main limitation of the retrospective study is the retrospective nature of data analysis, which was collected from patients' discharge documents, making it impossible to evaluate certain variables.

Both types of studies included patients from a single tertiary center, but were representative of the studied pathology.

7. Final consideration

The current thesis focused on the comprehensive approach to patients with atrial fibrillation (AF), considering the evaluation of the impact of RV dysfunction, functional atrial tricuspid regurgitation, and prolonged hospitalization.

RV dysfunction is an independent predictor of mortality, quality of life, and arrhythmic burden in a cohort of AF patients.

Severe functional atrial tricuspid regurgitation has been associated with all-cause mortality, regardless of RV function.

Regarding prolonged hospitalization, the main determinants were the complexity of the case, the burden of associated comorbidities, and to a lesser extent, specific features of AF. Furthermore,

in subgroup analysis, we demonstrated that RV dysfunction is an independent predictor of prolonged hospital stay.

Defining the profile of patients with AF and RV dysfunction allows not only a better understanding of the disease progression, early identification of complex cases, and risk stratification but also the improvement of alternative management strategies.

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