ORIGINAL ARTICLE

CHA$_2$DS$_2$-VASc score stratifies mortality risk in heart failure patients aged 75 years and older with and without atrial fibrillation

Andrea Sonaglioni[1] · Chiara Lonati[2] · Elisabetta Rigamonti[1] · Mauro Viganò[3] · Gian Luigi Nicolosi[4] · Marco Proietti[5,6,7] · Michele Lombardo[1] · Sergio Harari[2,5]

Abstract

Background During the last decade, the CHA$_2$DS$_2$-VASc score has been associated with adverse clinical outcomes in several cardiovascular (CV) and non-cardiovascular diseases beyond atrial fibrillation (AF). Whether the CHA$_2$DS$_2$-VASc score stratifies mortality risk in elderly patients with AF and without AF is not well established.

Methods All consecutive patients aged ≥ 75 yrs hospitalized due to heart failure (HF), between January 2020 and November 2020, were retrospectively enrolled. All patients underwent physical examination, blood tests, electrocardiography and conventional transthoracic echocardiography. Primary endpoint was all-cause mortality, while secondary endpoint was the composite of all-cause mortality + rehospitalizations for all causes over mid-term follow-up.

Results The study included 261 HF patients (86.3 ± 6.4 years, 60.5% females). 85 AF and 176 non-AF patients were separately analyzed. Compared to non-AF patients, those with AF had significantly higher CHA$_2$DS$_2$-VASc score (5.6 ± 1.4 vs 5.1 ± 1.4, $p = 0.007$) and lower ejection fraction (47.4 ± 16.5 vs 56.7 ± 15.1%, $p < 0.001$). Mean follow-up was 1.7 ± 0.5 yrs. During follow-up, 96 patients died (58.3% due to CV causes) and 79 were rehospitalized (58.2% due to CV causes). CHA$_2$DS$_2$-VASc score was independently associated with all-cause mortality in whole study population (HR 1.61, 95% CI 1.36–1.92) and in both AF (HR 1.41, 95% CI 1.09–1.82) and non-AF patients (HR 1.84, 95% CI 1.40–2.40). CHA$_2$DS$_2$-VASc score also predicted the secondary endpoint in the same study groups. CHA$_2$DS$_2$-VASc score ≥ 5 was the best cut-off value for predicting both outcomes.

Conclusion At mid-term follow-up, a CHA$_2$DS$_2$-VASc score ≥ 5 predicts increased risk of all-cause mortality and re-hospitalizations for all causes in elderly HF patients, regardless of AF.

Keywords Elderly · CHA$_2$DS$_2$-VASc score · Atrial fibrillation · Heart failure · Mortality

✉ Andrea Sonaglioni
sonaglioniandrea@gmail.com

1 Division of Cardiology, Ospedale San Giuseppe MultiMedica IRCCS, Via San Vittore 12, 20123 Milan, Italy

2 Division of Internal Medicine, Ospedale San Giuseppe MultiMedica IRCCS, Milan, Italy

3 Division of Hepatology, Ospedale San Giuseppe MultiMedica IRCCS, Milan, Italy

4 Division of Cardiology, Policlinico San Giorgio, Pordenone, Italy

5 Department of Clinical Sciences and Community Health, Università Di Milano, Milan, Italy

6 Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy

7 Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the elderly, affecting approximately 10% of individuals aged 80 yrs or older [1–3].

Current guidelines [4, 5] recommend using the CHA$_2$DS$_2$-VASc (Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥ 75 years, Diabetes, Stroke/TIA, Vascular disease, Age 65–74 years, and Sex category) score, developed in 2010 by Lip GY et al. [6], for estimating thromboembolic risk and deciding on anticoagulation therapy in AF patients.

In the last few years, the CHA$_2$DS$_2$-VASc score has been employed for mortality risk stratification [7–10] and for investigating clinical outcomes not only in AF but also in non-AF patients. Notably, this score has been strongly

associated with major adverse cardiac outcomes in several cardiovascular diseases beyond AF, such as acute coronary syndrome, heart failure (HF), hypertension, cerebrovascular disease, peripheral arterial disease, and even non-cardiovascular disease, such as chronic obstructive pulmonary disease (COPD) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [11–25].

However, all the above-mentioned studies included only a small number of elderly patients aged ≥ 75 years.

Whether the CHA_2DS_2-VASc score stratifies mortality risk in elderly patients aged ≥ 75 years with AF and without AF is not well established and literature data are scanty [26].

Accordingly, the present study was primarily designed to investigate whether the CHA_2DS_2-VASc score can predict the primary outcome of "all-cause mortality" over a medium-term follow-up in a consecutive population of elderly patients aged ≥ 75 years discharged from Division of Internal Medicine with a diagnosis of HF, and categorized in AF and non-AF patients. The prognostic value of other clinical scores for anti-coagulation and comorbidity assessment, such as the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly > 65 years, Drugs/alcohol concomitantly) score and the Charlson comorbidity index (CCI), was also examined in the same study population.

Methods

Study population

The present study retrospectively analyzed a consecutive series of patients aged 75 years and older receiving a first diagnosis of HF, hospitalized in the Internal Medicine Division of San Giuseppe MultiMedica hospital (Milan), a tertiary university institution, between January 1, 2020 and November 20, 2020.

Criteria of exclusion were the following: non-HF patients, age < 75 yrs, hemodynamic instability requiring spoke-to-hub transfer, patients who did not perform a conventional two-dimensional transthoracic echocardiography (2D-TTE) during the hospital stay and finally poor echocardiographic windows.

Heart failure was defined as a clinical syndrome consisting of symptoms (e.g., breathlessness, ankle swelling, and fatigue) and signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in elevated intra-cardiac pressures and/or inadequate cardiac output at rest and/or during exercise [27].

HF patients were divided in AF and non-AF patients. Diagnosis of AF was based on 12-lead electrocardiography (ECG) at the hospital admission, 24 h ECG Holter or cardiac telemetry monitoring performed during hospitalization, or the patient's medical history of AF [28].

Concerning HF etiology, following clinical subtypes of HF were determined: (1) HF due to acute/chronic coronary artery disease (CAD); (2) HF due to acute/chronic valvular heart disease (VHD); (3) HF due to hypertensive cardiomyopathy; (4) HF due to acute/chronic pulmonary hypertension [27].

Based on left ventricular ejection fraction (LVEF) assessment by 2D-TTE, following echocardiographic subtypes of HF were defined: (1) heart failure with reduced ejection fraction (HFrEF) when LVEF was ≤ 40%; (2) heart failure with mildly reduced ejection fraction (HFmrEF), when LVEF was between 41 and 49%; (3) heart failure with preserved ejection fraction (HFpEF), when LVEF was ≥ 50% [27].

Main etiology of HF, and both clinical and echocardiographic categories of HF were assessed according to the above-mentioned standardized criteria by two expert clinicians (C.L. and A.S.) within the first 24 h of admission to the Internal Medicine Division.

The following information was collected from the patients' hospital medical charts: age; gender; prevalence of relevant cardiovascular risk factors (hypertension, smoking, type 2 diabetes and dyslipidemia); main comorbidities, such as anemia defined as hemoglobin < 12 g/dl for females or 13 g/dl for males, chronic kidney disease defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/m² [29], obesity defined by a body mass index (BMI) ≥ 30 kg/m² [30], obstructive sleep apnea syndrome, COPD, hypothyroidism, history of CAD (previous acute coronary syndrome, previous percutaneous and/or surgical coronary revascularization), previous stroke and/or transient ischemic attack, peripheral arteriopathy, cognitive impairment assessed by interviewing patients or their relatives and by consulting the past medical history of each patient; blood tests comprehensive of complete blood count, serum creatinine and eGFR, serum levels of glucose, iron, sodium, potassium, calcium, total bilirubine, uric acid, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein colesterol, thyroid-stimulating hormone, triglycerides, C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity (HS) troponine; blood pressure measurements; ECG data (cardiac rhythm and pattern of intraventricular conduction); chest X-ray results; finally, the current medical treatment.

All procedures were in accordance with the ethical standards of our Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the local Ethics Committee (Committee's reference number CE 23.2021).

Clinical scores for anticoagulation and comorbidity assessment

For each HF patient, following scores were retrospectively calculated: (1) the CHA_2DS_2-VASc [Congestive heart failure or left ventricular dysfunction (1 point), Hypertension (1 point), Age $\geq$ 75 years (2 points), Diabetes (1 point), Stroke/TIA (2 points), Vascular disease (1 point), Age 65–74 years (1 point), and Sex category (female; 1 point)] score [6]; (2) the HAS-BLED [Hypertension (1 point), Abnormal renal/liver function (1 or 2 points), Stroke (1 point), Bleeding history or predisposition (1 point), Labile international normalized ratio (1 point), Elderly (> 65 years) (1 point), Drugs/alcohol concomitantly (1 or 2 points)] score [31]; 3) the Charlson comorbidity index, which assigned 1 point for each of the following comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes; 2 points for each of hemiplegia, moderate or severe kidney disease, diabetes with end-organ damage, tumor, leukemia, lymphoma; 3 points for moderate or severe liver disease; and 6 points for tumor metastasis or AIDS [32].

Standard echodoppler examination

All echoDoppler examinations were performed by the same cardiologist (A.S.) using Philips Sparq ultrasound machine (Philips, Andover, Massachusetts, USA) with a 2.5 MHz transducer, according to the Recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [33, 34]. Following variables were recorded: aortic root and ascending aorta dimensions; relative wall thickness; left ventricular end-diastolic dimensions; LVEF estimated with the biplane modified Simpson's method [33]; transmitral E/A ratio and average E/e' ratio, the latter as index of left ventricular filling pressures (LVFP) [34]; left atrial end-systolic dimensions; right ventricular inflow tract; tricuspid annular plane systolic excursion as index of right ventricular systolic function; systolic pulmonary artery pressure (SPAP) calculated by the modified Bernoulli equation [35]. Finally, degree of valvulopathy was evaluated according to the AHA/ACC recommendations for the management of patients with VHD [36].

Endpoint definition

The primary endpoint of the study was to identify the independent predictors of "all-cause mortality" in the whole population of HF patients and in the two groups of AF and non-AF patients separately, over a medium-term follow-up.

The secondary endpoint was to evaluate the independent predictors of the composite of "all-cause mortality + re-hospitalizations for all causes" in the same study groups.

Causes of death and rehospitalizations for each HF patient were determined by accessing medical records available in the hospital archive and/or from telephone interviews.

Statistical analysis

For the whole study population and for each group of elderly patients, continuous data were summarized as mean ± standard deviation, while categorical data were presented as number (percentage).

Each continuous variable was checked through the Shapiro–Wilk test and all data were determined to be normally distributed.

Continuous variables were compared using a two-sample independent t test, whereas categorical parameters were compared using the Chi-squared test or the Fisher's exact test.

Univariate Cox regression analysis was performed to evaluate the effect of the following variables: (1) age and female sex (as demographics); (2) CHA_2DS_2-VASc score, HAS-BLED score and CCI (as clinical predictive scores, expressed as continuous parameters); (3) serum hemoglobin, serum sodium, eGFR, serum CRP, serum NT-proBNP and serum HS Troponine (as biochemical markers); (4) heart rate and atrial fibrillation (as ECG parameters); (5) LVEF, average E/e' ratio and SPAP (as echoDoppler variables); (6) antiplatelet therapy, anticoagulant therapy, statin therapy (as concerns discharge medical treatment), on the occurrence of both primary and secondary endpoints during follow-up period, in the whole study population and in the two groups of AF and non-AF patients separately. For each variable investigated, correspondent hazard ratios with 95% confidence intervals were calculated. Only the variables with statistically significant association on univariate analysis were thereafter included in the multivariate Cox regression model.

The receiver operating characteristics (ROC) curve analysis was performed to establish the sensitivity and the specificity of the CHA_2DS_2-VASc score for predicting the above-mentioned endpoints. Area under curve (AUC) was estimated. The optimal cutoff of CHA_2DS_2-VASc score was calculated using the maximum value of the Youden Index (determined as sensitivity + [1-specificity]).

Kaplan–Meier survival curves were designed to measure differences between CHA_2DS_2-VASc score categories in the rates of "all-cause mortality" and "all-cause mortality + rehospitalizations for all causes" respectively, over a mid-term follow-up, for the whole study population and for the two groups of AF and non-AF patients separately.

Statistical analysis was performed with SPSS version 26 (SPSS Inc., Chicago, Illinois, USA), with two-tailed p values below 0.05 deemed statistically significant.

Results

Baseline characteristics

A total of 261 HF patients (mean age 86.3 ± 6.4 years, 60.5% females) were retrospectively included in the study. 85 AF (32.6% of total) and 176 non-AF patients (67.4% of total) were separately analyzed.

Main demographics and clinical parameters recorded in the whole study population and in the two groups of HF patients at hospital admission are summarized in Table 1.

Overall, 85.8% of HF patients were ≥ 80 years old, with no significant difference in the average age between AF and non-AF patients. Approximately two-thirds of HF patients had history of hypertension, dyslipidemia and chronic kidney disease, whereas one-third of them had type 2 diabetes, history of CAD and peripheral arteriopathy. Compared to non-AF patients, those with AF were found with higher prevalence of dyslipidemia, previous stroke and cognitive impairment. On the other hand, hypertension and chronic kidney disease were significantly more prevalent among non-AF patients. Analysis of comorbidities revealed a high comorbidity burden for the whole study population as assessed by the CCI, without statistically significant difference between the two groups of HF patients. Concerning clinical prediction scores for anticoagulation, CHA_2DS_2-VASc score was significantly higher in AF than non-AF patients, whereas HAS-BLED score was similar in the two groups of HF patients. In addition, blood tests revealed that eGFR was significantly lower in non-AF than AF patients, whereas serum levels of NT-proBNP and HS troponine were significantly higher in AF than non-AF patients. Finally, clinical and radiographics signs of congestive heart failure were detected in almost two-thirds of patients, especially in AF patients.

All conventional echoDoppler paramaters obtained in the whole study population and in the two groups of HF patients are listed in Table 2.

Overall, elderly HF patients were found with normal biventricular dimensions, moderate left atrial enlargement, preserved left ventricular systolic function (LVEF $54.0 \pm 16.1\%$), moderate increase in LVFP (average E/e' ratio 17.4 ± 6.8) and SPAP (42.0 ± 16.4 mmHg). Compared to non-AF patients, those with AF were diagnosed with significantly increased cardiac chambers cavity sizes, significantly lower LVEF (47.4 ± 16.5 vs $56.7 \pm 15.1\%$, $p < 0.001$), significantly higher LVFP (average E/e' ratio 20.4 ± 6.4 vs 15.9 ± 6.6, $p < 0.001$) and significantly higher SPAP (49.9 ± 17.3 vs 38.2 ± 14.5 mmHg, $p < 0.001$). Moreover, severe mitral regurgitation and severe tricuspid regurgitation were significantly more frequent in AF than non-AF patients.

A detailed analysis of hospitalization parameters and HF characteristics recorded in our study population and in the two groups of elderly HF patients is reported in Table 3.

The majority of HF patients were hospitalized due to congestive heart failure (63.6% of total), with preserved ejection fraction (62.8% of total) and advanced NYHA functional class IV symptoms (74% of total). AF patients were more commonly diagnosed with clinical, radiological and echocardiographic signs of pulmonary congestion, reduced ejection fraction and HF secondary to acute and/or chronic ischemic heart disease and/or hemodynamically significant valvular heart disease. On the other hand, non-AF patients were commonly diagnosed with HFpEF due to hypertensive cardiomyopathy. In addition, infections, severe anemia and severe chronic kidney disease were more frequently detected in non-AF patients.

Concerning the discharge therapy, the majority of elderly HF patients were prescribed with beta blockers (59.8% of total) and loop diuretics (68.6% of total). In comparison to non-AF patients, those with AF were more commonly prescribed with anticoagulants, beta blockers, digoxin, loop diuretics and aldosterone antagonists. On the other hand, antiplatelets and calcium-channel blockers were more frequently prescribed in non-AF patients.

Finally, the length of hospital stay for the whole study population was 11.1 ± 5.7 days, without statistically significant difference between the two groups of HF patients (11.3 ± 5.9 vs 11.1 ± 5.6 days, $p = 0.79$).

Survival analysis

Mean follow-up time was 1.7 ± 0.5 years. During the follow-up period, 36.8% of patients died and 30.3% were rehospitalized. All-cause mortality was significantly more prevalent among AF patients, whereas the prevalence of rehospitalizations for all causes was not statistically different between the two groups of HF patients. Both endpoints occurred significantly earlier in AF patients than non-AF patients. Compared to non-AF patients, those with AF had a significantly higher incidence of cardiovascular deaths, in-hospital deaths and rehospitalizations due to cardiovascular causes (Table 4).

Multivariate Cox regression analysis performed for identifying the independent predictors of "all-cause mortality" in the whole study population and in the two groups of AF and non-AF patients separately, is reported in Table 5. CHA_2DS_2-VASc score was independently associated with the primary outcome in the whole study population (HR 1.61, 95% CI 1.36–1.92, $p < 0.001$) and in both AF (HR 1.41, 95% CI 1.09–1.82, $p = 0.009$) and non-AF patients (HR 1.84, 95% CI 1.40–2.40, $p < 0.001$). A CHA_2DS_2-VASc score ≥ 5 showed the greatest sensitivity and specificity for predicting the primary endpoint in

Table 1 Baseline clinical characteristics of the whole study population and of the two groups of AF and non-AF patients recorded at hospital admission

Baseline clinical parameters	All patients ($n=261$)	AF patients ($n=85$)	Non-AF patients ($n=176$)	P value
Demographics				
Age (years)	86.3 ± 6.4	86.9 ± 6.6	86.1 ± 6.4	0.35
Female sex (n, %)	158 (60.5)	50 (58.8)	108 (61.4)	0.78
Cardiovascular risk factors and comorbidities				
Hypertension (n, %)	171 (65.5)	43 (50.6)	128 (72.7)	<0.001
Smoking (n, %)	48 (18.4)	13 (15.3)	35 (19.9)	0.39
Type 2 diabetes mellitus (n, %)	77 (29.5)	27 (31.8)	50 (28.4)	0.66
Dyslipidemia (n, %)	157 (60.1)	64 (75.3)	93 (52.8)	<0.001
Anemia (Hb < 12 F or 13 g/dl M) (n, %)	94 (36.0)	32 (37.6)	62 (35.4)	0.78
CKD (eGFR < 60 ml/min/m^2) (n, %)	171 (65.5)	45 (43.5)	126 (71.6)	0.003
Obesity (n, %)	28 (10.7)	10 (11.8)	18 (10.2)	0.67
OSAS (n, %)	18 (6.9)	8 (9.4)	10 (5.7)	0.30
COPD (n, %)	57 (21.8)	20 (23.5)	37 (21.0)	0.63
Hypothyroidism (n, %)	44 (16.8)	16 (18.8)	28 (15.9)	0.59
History of CAD (n, %)	76 (29.1)	30 (35.3)	46 (26.1)	0.15
Previous stroke (n, %)	55 (21.1)	26 (30.6)	29 (16.5)	0.01
Peripheral arteriopathy (n, %)	74 (28.3)	20 (23.5)	54 (30.7)	0.24
Cognitive impairment (n, %)	113 (43.3)	45 (52.9)	68 (38.6)	0.03
Charlson Comorbidity Index	8.43 ± 2.21	8.55 ± 2.16	8.37 ± 2.24	0.53
Clinical prediction scores for anticoagulation				
CHA$_2$DS$_2$-VASc risk score	5.2 ± 1.5	5.6 ± 1.4	5.1 ± 1.4	0.007
HAS-BLED score	4.2 ± 1.5	4.1 ± 1.4	4.2 ± 1.5	0.60
Physical examination				
Dyspnea (n, %)	151 (57.8)	58 (68.2)	93 (52.8)	0.02
Leg swelling (n, %)	71 (27.2)	40 (47.0)	31 (17.6)	<0.001
Body temperature $\geq 37.5°$ (n, %)	90 (34.5)	30 (35.3)	60 (34.1)	0.88
Blood pressure values				
SBP (mmHg)	130.2 ± 26.7	124.2 ± 22.9	134.2 ± 28.2	0.005
DBP (mmHg)	69.6 ± 14.4	66.6 ± 12.2	71.6 ± 15.3	0.008
Biochemical parameters				
Hb (g/dl)	10.8 ± 2.4	10.9 ± 2.1	10.7 ± 2.5	0.52
eGFR (ml/min/m^2)	26.5 ± 25.1	32.5 ± 23.3	25.1 ± 25.9	0.02
CRP (mg/dl)	7.52 ± 8.18	6.87 ± 6.70	7.83 ± 8.82	0.37
NT-proBNP (pg/ml)	4761.3 ± 7690.2	6077.2 ± 6054.0	3275.0 ± 8272.5	0.006
HS troponine (ng/ml)	295.3 ± 733.4	454.0 ± 1018.9	217.2 ± 526.0	0.01
Chest X-ray				
Normal pattern (n, %)	59 (22.6)	7 (8.2)	52 (29.6)	<0.001
Congestion (n, %)	152 (58.2)	61 (71.8)	91 (51.7)	0.002
Pneumonia (n, %)	57 (21.8)	24 (28.2)	33 (18.7)	0.11
ECG parameters				
HR (bpm)	78.7 ± 17.2	83.8 ± 20.2	76.2 ± 14.9	<0.001
LBBB (n, %)	34 (13.0)	22 (25.8)	12 (6.8)	<0.001

AF atrial fibrillation, *CAD* coronary artery disease, CHA$_2$DS$_2$-VASc, Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥ 75 years, Diabetes, Stroke/TIA, Vascular disease, Age 65–74 years, and Sex category; *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly; *Hb* hemoglobin, *HR* heart rate, *HS* high-sensitivity, *LBBB* left bundle branch block, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *OSAS* obstructive sleep apnea syndrome, *SBP* systolic blood pressure

Table 2 Conventional echoDoppler parameters measured in the whole study population and in the two groups of AF and non-AF patients

Echodoppler parameters	All patients ($n=261$)	AF patients ($n=85$)	Non-AF patients ($n=176$)	P value
IVS (mm)	13.5 ± 2.6	13.2 ± 2.8	13.6 ± 2.4	0.23
PW (mm)	10.3 ± 1.2	10.2 ± 1.4	10.8 ± 1.5	0.002
LVEDD (mm)	46.4 ± 8.4	48.5 ± 9.7	45.5 ± 7.6	0.007
RWT	0.46 ± 0.09	0.44 ± 0.11	0.48 ± 0.09	0.002
LVEDV (ml)	76.8 ± 34.3	86.0 ± 41.1	72.7 ± 29.8	0.003
LVEF (%)	54.0 ± 16.1	47.4 ± 16.5	56.7 ± 15.1	< 0.001
E/A ratio	/	/	1.03 ± 0.49	/
Average E/e' ratio	17.4 ± 6.8	20.4 ± 6.4	15.9 ± 6.6	< 0.001
LA A-P diameter (mm)	47.0 ± 9.0	53.2 ± 8.6	44.0 ± 7.5	< 0.001
LA longitudinal diameter (mm)	58.0 ± 11.0	65.3 ± 9.6	54.5 ± 9.9	< 0.001
LAV (ml)	89.1 ± 33.1	111.6 ± 31.8	78.1 ± 27.8	< 0.001
RVIT (mm)	31.4 ± 6.7	34.6 ± 7.1	29.9 ± 6.0	< 0.001
TAPSE (mm)	20.4 ± 4.5	18.3 ± 4.9	21.4 ± 3.9	< 0.001
Severe MR (n, %)	26 (9.9)	20 (23.5)	6 (3.4)	< 0.001
Severe AR (n, %)	13 (5.0)	3 (3.5)	10 (5.7)	0.55
Severe AS (n, %)	25 (9.6)	5 (5.8)	20 (11.4)	0.18
Severe TR (n, %)	27 (10.3)	22 (25.9)	5 (2.8)	< 0.001
IVC (mm)	21.0 ± 7.2	24.4 ± 6.3	19.4 ± 7.0	< 0.001
SPAP (mmHg)	42.0 ± 16.4	49.9 ± 17.3	38.2 ± 14.5	< 0.001
Aortic root (mm)	34.2 ± 4.1	34.6 ± 4.4	34.0 ± 4.0	0.27
Ascending aorta (mm)	35.8 ± 4.6	36.3 ± 5.3	35.5 ± 4.3	0.19

AF atrial fibrillation, *A-P* antero-posterior, *AR* aortic regurgitation, *AS* aortic stenosis, *IVC* inferior vena cava, *LA* left atrial, *LAV* left atrial volume, *LVEDD* left ventricular end-diastolic diameter, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation, *PW* posterior wall, *RVIT* right ventricular inflow tract, *RWT* relative wall thickness, *SPAP* systolic pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation

the whole study population (98% sensitivity, 73% specificity, AUC = 0.77) and in both AF (100% sensitivity, 66% specificity, AUC = 0.74) and non-AF (96% sensitivity, 77% specificity, AUC = 0.79) patients.

Prognostic ROC curves and Kaplan–meier survival curves drawn for comparing the rates of "all-cause mortality" in the whole study population (Panel A), in AF (Panel B) and non-AF patients (Panel C), categorized according to CHA$_2$DS$_2$-VASc score < 5 and ≥ 5 respectively, are illustrated in Fig. 1.

Table 6 shows the multivariate Cox regression analysis performed for detecting the variables independently associated with the composite of "all-cause mortality + rehospitalizations for all causes" in the whole study population and in the two groups of AF and non-AF patients separately. Atrial fibrillation (HR 1.55, 95% CI 1.11–2.16, $p = 0.009$) and CHA$_2$DS$_2$-VASc score (HR 1.78, 95% CI 1.56–2.03, $p < 0.001$) were independently associated with the secondary endpoint in the entire study population. Moreover, the CHA$_2$DS$_2$-VASc risk score was the only independent predictor of the composite outcome in both AF (HR 1.58, 95% CI 1.30–1.92, $p < 0.001$) and non-AF patients (HR 1.90, 95% CI 1.56–2.32, $p < 0.001$). A CHA$_2$DS$_2$-VASc score ≥ 5

showed the greatest sensitivity and specificity for predicting the secondary endpoint in the whole study population (98% sensitivity, 87% specificity, AUC = 0.96) and in both AF (98% sensitivity, 100% specificity, AUC = 0.99) and non-AF (98% sensitivity, 83% specificity, AUC = 0.94) patients.

Figure 2 depicts the prognostic ROC curves and Kaplan–meier curves drawn for comparing the rates of "all-cause mortality + reospitalizations for all causes" in the whole study population (Panel A), in AF (Panel B) and in non-AF patients (Panel C), categorized according to CHA$_2$DS$_2$-VASc score < 5 and ≥ 5 respectively.

Discussion

The present study carried out on a consecutive population of elderly patients aged ≥ 75 yrs hospitalized due to heart failure demonstrated that: (1) the CHA$_2$DS$_2$-VASc score was independently associated with adverse clinical outcome in the whole study population and in both AF and non-AF patients; (2) the CHA$_2$DS$_2$-VASc score showed an incremental prognostic value over the individual components of the score, over other clinical scores

Table 3 Hospitalization data and HF characteristics detected in the whole study population and in the two groups of AF and non-AF patients

Hospitalization parameters and HF characteristics	All patients (n = 261)	AF patients (n = 85)	Non-AF patients (n = 176)	P value
Reasons for hospitalizations				
Congestive heart failure (n, %)	166 (63.6)	72 (84.7)	94 (53.4)	< 0.001
Pneumonia/bronchitis/respiratory failure/PE (n, %)	57 (21.8)	24 (28.2)	33 (18.8)	0.11
Infections (urinary tract, intestine, endocarditis) (n, %)	33 (12.6)	5 (5.9)	28 (15.9)	0.02
Gastro-intestinal disorders (n, %)	27 (10.3)	6 (7.1)	21 (11.9)	0.28
Severe anemia (Hb < 8 g/dl) (n, %)	40 (15.3)	7 (8.2)	33 (18.7)	0.03
Severe CKD (eGFR < 15 ml/min/m^2) (n, %)	44 (16.8)	8 (9.4)	36 (20.4)	0.02
Cancers (n, %)	29 (11.1)	6 (7.1)	23 (13.1)	0.21
Hyponatriemia (n, %)	34 (13.0)	21 (24.7)	39 (22.2)	0.64
Hypernatriemia (n, %)	38 (14.5)	13 (15.3)	25 (14.2)	0.85
Neurological disorders (n, %)	11 (4.2)	4 (4.7)	7 (4.0)	0.75
etiology of HF				
Acute/chronic CAD (n, %)	72 (27.6)	33 (38.8)	39 (22.1)	0.007
Acute/chronic VHD (n, %)	69 (26.4)	40 (47.0)	29 (16.5)	< 0.001
Hypertensive cardiomyopathy (n, %)	91 (34.9)	6 (7.1)	85 (48.3)	< 0.001
Acute/chronic pulmonary hypertension (n, %)	29 (11.1)	6 (7.1)	23 (13.1)	0.21
Echocardiographic subtypes of HF				
HFpEF (n, %)	164 (62.8)	33 (38.8)	131 (74.4)	< 0.001
HFmrEF (n, %)	37 (14.2)	21 (24.7)	16 (9.1)	0.001
HFrEF (n, %)	60 (23.0)	31 (36.5)	29 (16.5)	< 0.001
NYHA functional class				
Class IV (n, %)	193 (74.0)	57 (67.1)	136 (77.3)	0.10
Discharge therapy				
Antiplatelets (n, %)	71 (27.2)	13 (15.3)	58 (32.9)	0.003
Anticoagulants (n, %)	89 (34.1)	63 (74.1)	26 (14.8)	< 0.001
ACEIs/ARBs (n, %)	93 (35.6)	34 (40.0)	59 (33.5)	0.33
CCB (n, %)	64 (24.5)	14 (16.5)	49 (27.8)	0.04
BB (n, %)	156 (59.8)	67 (78.8)	97 (55.1)	< 0.001
Digoxin (n, %)	33 (12.6)	30 (35.3)	3 (1.7)	< 0.001
Loop diuretics (n, %)	179 (68.6)	68 (80.0)	111 (63.1)	0.007
Aldosterone antagonists (n, %)	87 (33.3)	41 (48.2)	58 (32.9)	0.02
Statins (n, %)	98 (37.5)	35 (41.2)	63 (35.8)	0.41
Oral hypoglicemyc agents (n, %)	32 (12.3)	10 (11.8)	18 (10.2)	0.68
Insulin (n, %)	46 (17.6)	11 (12.9)	28 (15.9)	0.58
Length of hospital stay (days)	11.1 ± 5.7	11.3 ± 5.9	11.1 ± 5.6	0.79

ACEIs angiotensin-converting enzyme inhibitors, *AF* atrial fibrillation, *ARBs* angiotensin II receptor blockers, *BB* beta blockers, *CAD* coronary artery disease, *CCB* calcium-channel blockers, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *NYHA* New York Heart Association, *PE* pulmonary embolism, *VHD* valvular heart disease

for anticoagulation and comorbidity assessment and over biochemical predictors, such as eGFR and NT-proBNP; (3) all-cause mortality and re-hospitalizations for all causes, detected in approximately one-third of the study population, were significantly more prevalent among AF than non-AF patients; (4) AF patients had a significantly increased prevalence of cardiovascular deaths and cardiovascular rehospitalizations; the latter were mostly recorded within 6 months after hospital discharge in the great majority of AF patients.

Our findings revealed that a CHA$_2$DS$_2$-VASc score ≥ 5 at the ward admission allowed to distinguish, among elderly HF patients, those with increased probability of all-cause mortality, over a medium-term follow-up, regardless of AF. Interestingly, also non-AF patients with a CHA$_2$DS$_2$-VASc score ≥ 5 had an almost twofold higher

Table 4 Outcomes detected in the whole study population and in the two groups of AF and non-AF patients during follow-up period

	All patients ($n = 261$)	AF patients ($n = 85$)	Non-AF patients ($n = 176$)	P value
Deaths (n, %)	96 (36.8)	39 (45.9)	57 (32.4)	0.04
Cardiovascular deaths (n, %)	56 (21.4)	30 (35.3)	26 (14.8)	< 0.001
Non-cardiovascular deaths (n, %)	40 (15.3)	9 (10.6)	31 (17.6)	0.20
In-hospital deaths (n, %)	19 (7.3)	11 (12.9)	8 (4.5)	0.02
Time from hospital admission to death (months)	4.3 ± 5.3	2.4 ± 2.2	5.5 ± 6.4	< 0.001
Rehospitalizations (n, %)	79 (30.3)	24 (28.2)	55 (31.2)	0.66
Cardiovascular causes of rehospitalizations (n, %)	46 (17.6)	33 (38.8)	13 (7.4)	< 0.001
Congestive heart failure (n, %)	24 (9.2)	20 (23.5)	4 (2.3)	< 0.001
Acute ischemic stroke (n, %)	12 (4.6)	10 (11.8)	2 (1.1)	< 0.001
Acute coronary sindrome (n, %)	7 (2.7)	2 (2.3)	5 (2.8)	0.58
Deep venous thrombosis (n, %)	3 (1.1)	1 (1.2)	2 (1.1)	0.69
Non-cardiovascular causes of rehospitalizations (n, %)	33 (12.6)	2 (2.3)	31 (17.6)	< 0.001
Pneumonia (n, %)	7 (2.7)	1 (1.2)	6 (3.4)	0.27
Severe anemia (Hb < 8 g/dl)	7 (2.7)	1 (1.2)	6 (3.4)	0.27
Dehydration (n, %)	6 (2.3)	0 (0.0)	6 (3.4)	0.09
Gastro-intestinal disorders (n, %)	5 (1.9)	0 (0.0)	5 (2.8)	0.13
Severe CKD (eGFR < 15 ml/min/m^2) (n, %)	5 (1.9)	0 (0.0)	5 (2.8)	0.13
Infections (n, %)	3 (1.1)	0 (0.0)	3 (1.7)	0.30
Time from hospital admission to rehospitalizations (months)	6.4 ± 5.8	4.5 ± 3.9	7.7 ± 6.6	< 0.001

AF atrial fibrillation, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin

Table 5 Multivariate Cox regression analysis for identifying the variables independently associated with all-cause mortality over medium-term follow-up in the whole study population and in the two groups of AF and non-AF patients separately

	Multivariate COX regression analysis								
	All patients ($n = 261$)			AF patients ($n = 85$)			Non-AF patients ($n = 176$)		
Variables	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age (yrs)	1.02	0.99–1.06	0.20	/	/	/	1.02	0.98–1.06	0.39
Female sex	/	/	/	/	/	/	0.80	0.38–1.68	0.55
CHA$_2$DS$_2$-VASc score	1.61	1.36–1.92	< 0.001	1.41	1.09–1.82	0.009	1.84	1.40–2.40	< 0.001
HAS-BLED score	0.94	0.80–1.10	0.46	/	/	/	1.09	0.90–1.32	0.39
CHARLSON comorbidity index	1.07	0.96–1.20	0.20	1.05	0.88–1.24	0.61	1.06	0.91–1.24	0.43
NT-proBNP (pg/ml)	1.02	0.99–1.04	0.17	/	/	/	/	/	/
Serum HS Troponine (ng/ml)	/	/	/	/	/	/	1.44	1.01–2.06	0.04
Atrial fibrillation	1.22	0.79–1.90	0.37	N/A	N/A	N/A	N/A	N/A	N/A
Average E/e' ratio	1.01	0.98–1.04	0.43	1.03	0.98–1.08	0.26	1.00	0.96–1.04	0.91
Statins	0.59	0.36–0.97	0.04	/	/	/	0.49	0.26–0.93	0.03

AF atrial fibrillation, *HS* high-sensitivity, *N/A* not applicable, *SPAP* systolic pulmonary artery pressure

risk of mortality and rehospitalizations for all causes than those with a CHA$_2$DS$_2$-VASc score < 5, probably due to the increased prevalence of hypertension and chronic renal failure detected in the great majority of these individuals. On the other hand, both AF and non-AF elderly HF patients with CHA$_2$DS$_2$-VASc score < 5 had a significantly increased probability of event-free survival over the follow-up period.

The absence of statin therapy and increased serum levels of HS troponine were other independent prognostic indicators of increased risk of adverse clinical events in elderly HF patients.

Concerning the HF characteristics of our study groups, in comparison to non-AF patients, those with AF were more commonly diagnosed with HFrEF due to CAD and/or VHD and significantly higher prevalence of clinical, radiological

and echocardiographic signs of pulmonary congestion. Conversely, HF patients without AF were more frequently found with HFpEF secondary to long history of arterial hypertension, without significant clinical, echocardiographic and/or radiographic congestive signs. Finally, no statistically significant differences were observed between AF and non-AF patients concerning the hemorrhagic risk (assessed by the HAS-BLED score) and the overall comorbidity burden (assessed by the Charlson comorbidity index).

The CHA$_2$DS$_2$-VASc score was originally developed for stroke risk stratification of nonvalvular AF patients to decide on anticoagulation therapy, especially for detecting patients at low risk who require no antithrombotic therapy [37–39].

Although current guidelines [4, 5] continue to recommend using the CHA$_2$DS$_2$-VASc score for evaluating embolic risk in AF patients, during the last decade, the CHA$_2$DS$_2$-VASc score has been assessed in many patients without AF. Notably, several studies [11–25] have investigated the predictive value of CHA$_2$DS$_2$-VASc score for clinical outcomes beyond stroke, such as death, heart failure hospitalizations and cardiac hospitalizations, in various cardiovascular and non-cardiovascular diseases. In particular, CHA$_2$DS$_2$-VASc score has been strongly associated with major adverse cardiac outcomes in non-AF community populations [11] and in following categories of non-AF patients: patients discharged after an acute coronary syndrome and/or acute myocardial infarction [12–14]; patients who underwent cardiac surgery [15]; HF patients [16–18]; patients with arterial hypertension [19]; patients with peripheral artery disease [20]; ambulatory patients [21, 22]; finally patients with COPD [23, 24] and SARS-CoV-2 [25].

However, all the above-mentioned studies primarily enrolled middle-aged to elderly patients, and literature data derived from hospitalized patients aged 75 years or older with and without AF are scanty.

To the best of our knowledge, only one study performed by Xing Y et al. [26] evaluated the prognostic role of CHA$_2$DS$_2$-VASc score in the elderly patients aged ≥ 75 yrs with and without AF. The authors demonstrated that the CHA$_2$DS$_2$-VASc score was able to identify patients at high risk for stroke among AF and non-AF elderly patients; however, they did not find a significant association between the CHA$_2$DS$_2$-VASc score and all-cause mortality. Differently from the findings of Xing Y et al., our results revealed that the CHA$_2$DS$_2$-VASc score was a strong predictor of all-cause mortality in elderly HF patients aged 75 years and older, regardless of AF. Different study populations may explain the different results. Firstly, our study population had a high prevalence of relevant cardiovascular risk factors (such as advanced age, hypertension, dyslipidemia), chronic renal failure and congestive heart failure and a moderate prevalence of type 2 diabetes, chronic CAD, and peripheral

vascular disease. In addition, in our study, approximately two-third of the patients (58.3% of total) had a cardiovascular death, whereas in the study of Xing Y et al. most of the patients died from pneumonia and cancer, while a smaller percentage (approximately one-third of patients) died from myocardial infarction, stroke, or another cardiovascular disease. The increased prevalence of traditional cardiovascular risk factors (such as hypertension and type 2 diabetes mellitus), congestive heart failure and comorbidities (such as infections and cancers), together with chronic inflammation, perpetuating a prothrombotic state, might have contributed to the occurrence of major adverse clinical outcomes in our cohort of elderly HF patients and in both AF and non-AF patients [40–43].

Consistent with previous population studies [44–46], our findings confirmed the increased risk of mortality in AF patients. Cardiac remodeling, activation of neurohormonal compensatory mechanisms, loss of atrial contraction and impairment of left ventricular systolic function have been proposed as possible reasons for explaining how AF and HF can cause and exacerbate each other, as postulated by the sentence: "AF begets HF, and HF begets AF" [47].

Our results revealed that the CHA$_2$DS$_2$-VASc score had an incremental prognostic value over the HAS-BLED score and the Charlson comorbidity index both in AF and non-AF elderly HF patients. Moreover, the CHA$_2$DS$_2$-VASc score showed a high negative predictive value for future major adverse clinical events over follow-up period, similarly to that observed by previous authors [10].

In light of our findings, the CHA$_2$DS$_2$-VASc score assessment should be employed for the routine clinical evaluation not only of AF patients but also of patients without AF, for a better prognostic risk stratification of elderly HF patients.

Given that the CHA$_2$DS$_2$-VASc score is simple and only based on clinical history and no laboratory or imaging parameters, it has the great advantage that it can be quickly calculated at the patient's bedside. Moreover, the elderly HF patients with CHA$_2$DS$_2$-VASc score ≥ 5, given the highest cardiovascular risk profile, would need a more intensive treatment of comorbities, a closer clinical follow-up and/or uptitration of cardioprotective drugs, regardless of AF. Despite evidence demonstrating statins are beneficial in the elderly, literature data suggest that baseline risk and treatment are inversely related, and statins are usually underprescribed in patients aged 75 yrs and older [48]. In addition, there is a general tendency to underprescribe beta blockers in elderly AF patients with COPD [49].

Main limitations of the present study were its retrospective nature, the small sample size and heterogenous cardiac phenotypes of the elderly HF patients included. However, the great number of major adverse clinical outcomes we detected over a mid-term follow-up allowed us to perform an accurate survival analysis both in AF and non-AF patients. Furthermore, given that the elderly HF patients we enrolled were admitted to
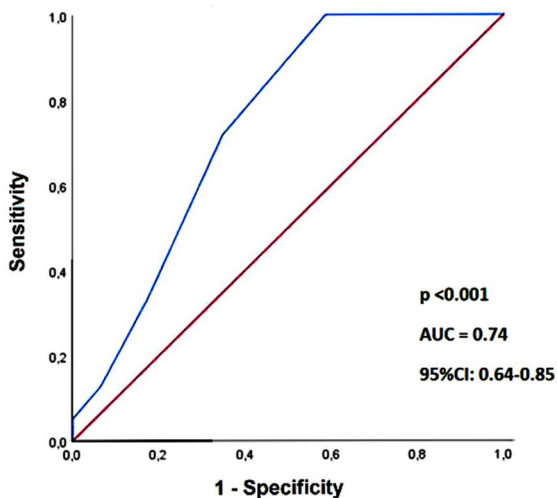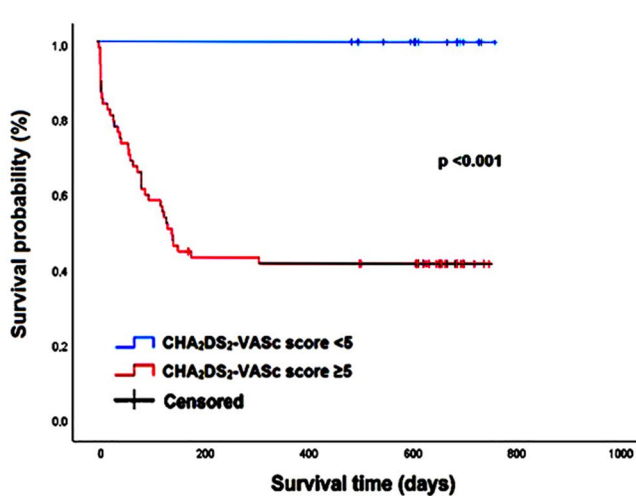
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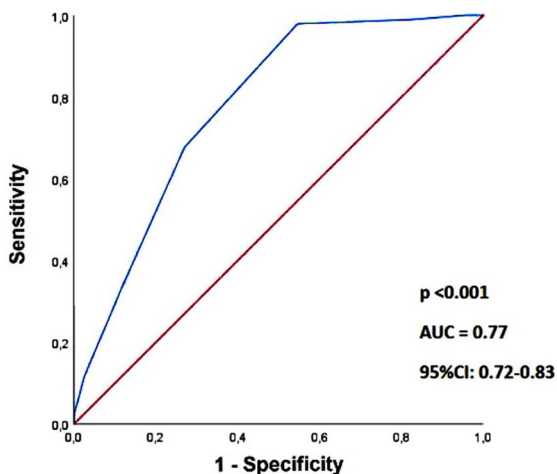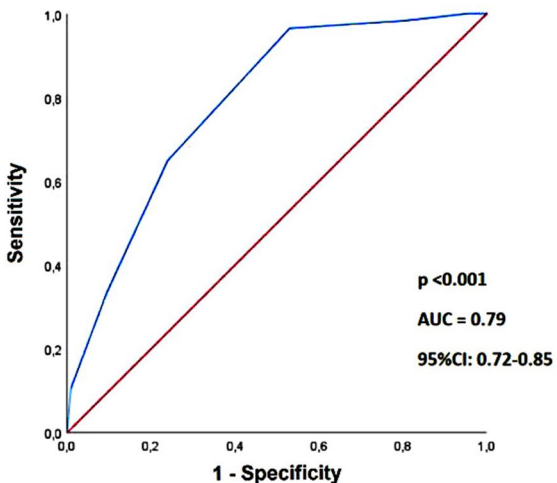
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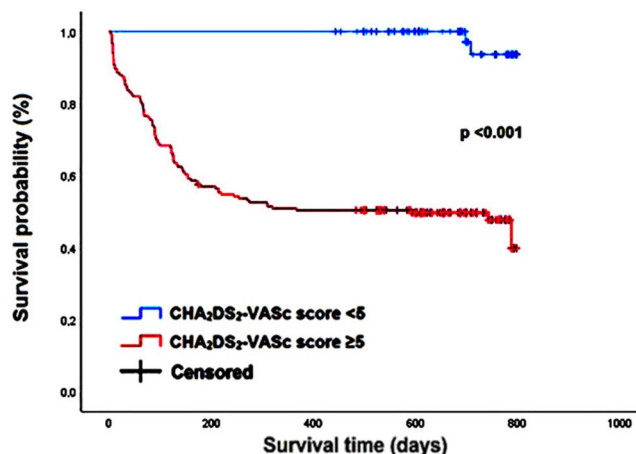
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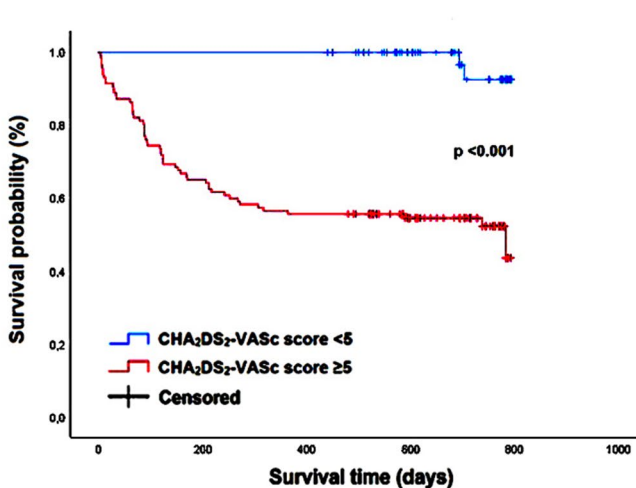
SURVIVAL PROBABILITY IN NON-AF PATIENTS

◄**Fig. 1** Prognostic ROC curves and Kaplan–Meier survival curves drawn to compare the rates of the endpoint "all-cause mortality" in all HF patients enrolled (Panel A) and in the two groups of HF patients with AF (Panel B) and without AF (Panel C), categorized according to CHA_2DS_2-VASc score < 5 and ≥ 5, respectively. AUC, area under the curve. HF, heart failure. ROC, receiver operating characteristics

a Division of Internal Medicine, and not to a Division of Geriatric Medicine, comprehensive geriatric assessment, which is the cornerstone for a reliable estimate of prognosis in older patients, was not performed; moreover, even if we did not use the Multidimensional Prognostic Index (MPI) as prognostic indicator in our study population, a detailed description of the patients' cognitive status and comorbidities was provided as accurately as possible. In addition, due to the retrospective nature of the study, it was not possible to further categorize AF patients according to the type of AF (paroxysmal, persistent, and permanent). Probably outcomes would have differed among these groups. Finally, similarly to our previous studies performed in very old hospitalized patients [50, 51], the body surface area could not be precisely assessed in all the elderly patients enrolled, due to the poor global conditions of the majority of them, bedridden and frequently uncooperative with medical assistance and/or treatment. For this reason, BMI was calculated through visual assessment of the patient's weight in the great majority of cases.

Conclusion

CHA_2DS_2-VASc score is independently associated with all-cause mortality and re-hospitalizations for all causes over a medium-term follow-up in HF patients aged 75 years and older, regardless of AF.

A CHA_2DS_2-VASc score ≥ 5 allows to identify, among elderly HF patients, those with increased risk of mortality and for whom additional preventive measures might be beneficial to improve outcomes.

CHA_2DS_2-VASc score assessment should be implemented in the clinical practive for prognostic risk stratification of elderly HF patients with and without AF.

Declarations

Table 6 Multivariate Cox regression analysis for identifying the variables independently associated with the composite of all-cause mortality and re-hospitalizations for all causes over medium-term follow-up in the whole study population and in the two groups of AF and non-AF patients separately

Variables	Multivariate COX regression analysis								
	All patients ($n=261$)			AF patients ($n=85$)			Non-AF patients ($n=176$)		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)	1.02	0.99–1.05	0.13	/	/	/	1.02	0.99–1.05	0.16
Female sex	1.08	0.75–1.56	0.66	/	/	/	1.05	0.61–1.79	0.86
CHA_2DS_2-VASc score	1.78	1.56–2.03	<0.001	1.58	1.30–1.92	<0.001	1.90	1.56–2.32	<0.001
HAS-BLED score	0.95	0.85–1.06	0.36	0.99	0.81–1.21	0.94	/	/	/
CHARLSON comorbidity index	1.06	0.98–1.16	0.15	1.03	0.89–1.19	0.66	1.08	0.97–1.21	0.14
Serum sodium (mEq/l)	/	/	/	0.97	0.94–1.00	0.12	/	/	/
Serum HS Troponine (ng/ml)	/	/	/	/	/	/	1.18	0.83–1.68	0.34
Atrial fibrillation	1.55	1.11–2.16	0.009	N/A	N/A	N/A	N/A	N/A	N/A
Average E/e' ratio	1.02	0.99–1.05	0.13	1.04	1.00–1.08	0.08	1.00	0.96–1.04	0.89
SPAP (mmHg)	1.00	0.98–1.02	0.72	/	/	/	1.00	0.98–1.02	0.90

AF atrial fibrillation, *HS* high-sensitivity, *N/A* not applicable, *SPAP* systolic pulmonary artery pressure
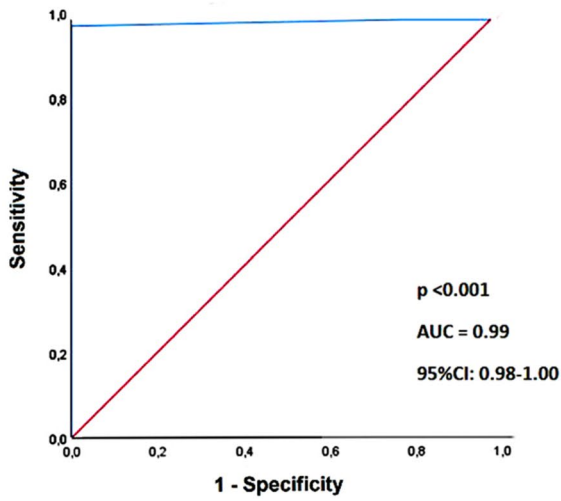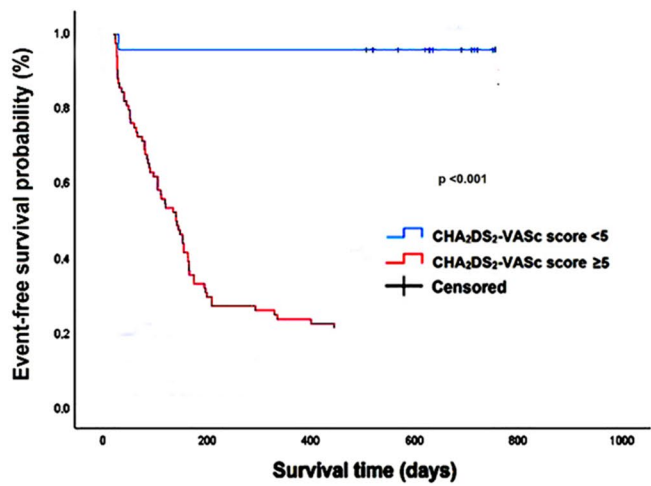
ROC CURVE IN ALL PATIENTS

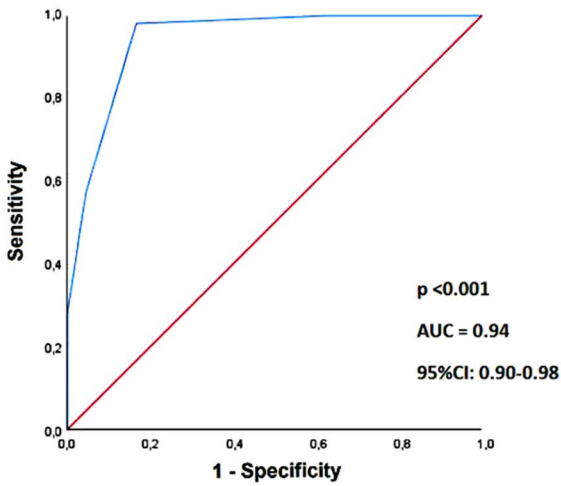## EVENT-FREE SURVIVAL PROBABILITY IN ALL PATIENTS

ROC CURVE IN AF PATIENTS

EVENT-FREE SURVIVAL PROBABILITY IN AF PATIENTS

ROC CURVE IN NON-AF PATIENTS

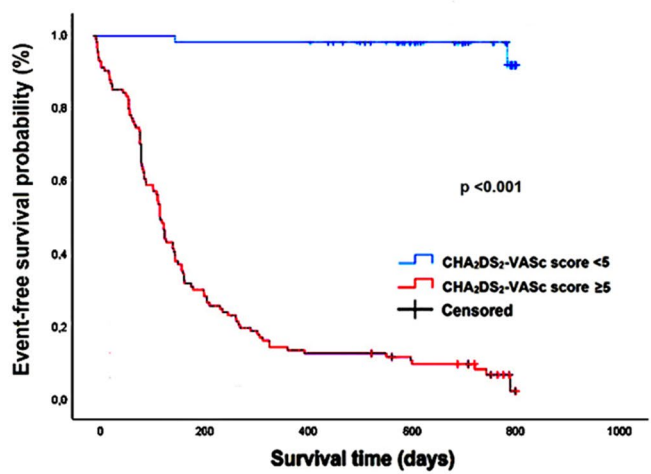## EVENT-FREE SURVIVAL PROBABILITY IN NON-AF PATIENTS

◄**Fig. 2** Prognostic ROC curves and Kaplan–Meier curves drawn to compare the rates of the endpoint "all-cause mortality + rehospitalizations for all causes" in all HF patients enrolled (Panel A) and in the two groups of HF patients with AF (Panel B) and without AF (Panel C), categorized according to CHA_2DS_2-VASc score < 5 and ≥ 5, respectively. AUC, area under the curve. HF, heart failure. ROC, receiver operating characteristics

Consent for publication The need for informed consent was not required due to the retrospective nature of this study.

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