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Original Article

Depressive symptoms in older patients undergoing electrical cardioversion of persistent atrial fibrillation. A possible association with clinical complexity, physical performance and inflammation

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ABSTRACT

Introduction: Atrial fibrillation (AF) is frequently diagnosed in older subjects, being often associated with frailty. In AF patients, depression is important, increasing mortality when heart failure is present, reducing adherence to therapy, and contributing to dementia development. Aim of this study was to identify the variables associated with depressive symptoms in older subjects with persistent AF.

Methods: All consecutive patients undergoing electrical cardioversion of the arrhythmia were enrolled and evaluated with the Comprehensive Geriatric Assessment (CGA). In particular, the Mini-Mental State Examination (MMSE) explored neurocognitive profile, the Geriatric Depression Scale (15-item version; GDS) depressive symptoms, and the Short Physical Performance Battery (SPPB) physical performance. Interleukine-6 (IL-6) levels were determined with ELISA kits.

Results: Overall, 258 patients were enrolled (age: 78±8 years; women: 41.1%; CHA_2DS_2-VA: 3.5±1.4). Hypertension was highly prevalent (81.8%); left ventricular ejection fraction was normal (58±12%), and heart rate adequately controlled (80±17 bpm). MMSE, GDS and SPPB were, respectively, 27.9±2.5, 3.3±2.9 and 8.7±2.7. IL-6 concentration, available in 59.3% of patients, was 4.3±3.5 pg/mL. A multivariate analysis model showed that depressive symptoms were directly associated with CHA_2DS_2-VA ($p=0.019$), and negatively with SPPB ($p<0.001$). When IL-6 was available, the correlation with SPPB persisted ($p<0.001$), the link with CHA_2DS_2-VA disappeared ($p=0.147$), and was replaced by that with cytokine levels ($p=0.011$).

Conclusions: Depressive symptoms in older AF patients are related to clinical complexity and to physical performance. IL-6, expression of chronic inflammation, has a significant association with GDS. These findings confirm that AF is a marker of cardiovascular aging and frailty.

Atrial fibrillation is the most frequently sustained arrhythmia diagnosed in older individuals. In 15 years, the prevalence of AF greatly increased in subjects ≥85 years approaching 40% [1]. The arrhythmia is complicated by heart failure, stroke, disability and dementia, and has a

Abbreviations: AF, Atrial fibrillation; CAVI, Cardio-Ankle Vascular Index; CGA, Comprehensive Geriatric Assessment; GDS, 15-item version of the Geriatric Depression Scale; ECV, Electrical cardioversion; HR, Heart rate; IL-6, Interleukine-6; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

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bidirectional association with frailty [2,3].

A major depressive disorder may be diagnosed in about 14% of US older subjects. Interestingly, a subsyndromal depressive form seems to be present in another 14% of individuals, who are particularly exposed to the development of a major form of the condition, and to mood alterations, disturbances related to anxiety, and disorders of personality [4].

More recently, a bidirectional association between depression and AF has been outlined [5]. The rate of depressive symptoms can be as high as 35% in patients with the arrhythmia, while the risk of AF is 1.5-fold higher in subjects with depressive symptoms. Interestingly, this association can be found in patients with paroxysmal, persistent and permanent forms of AF, and it seems to be at least in part mediated by autonomic nervous system dysfunction [6]. Hence, a neuro-cardiac link was hypothesized to explain this interaction and to guide the attempts to manage both conditions [7]. In a recent meta-analysis, it was shown that, overall, the prevalence of depression in subjects with AF was 24.3%, reaching 40.3% in older individuals [8]. Furthermore, the coexistence of AF and depression is now recognized as a potential risk factor of cognitive impairment, with an odd-ratio equal to 2.23 when comparing patients with depression with those without affective disorders [9].

Interestingly, interleukin-6 (IL-6), one of the most important inflammatory biomarkers, was a significant predictor of AF development in different studies [10], and, when the arrhythmia was present, the cytokine resulted associated with cardiovascular death, thromboembolic events, myocardial infarction, and major bleeding [11]. At the same time, IL-6 correlated with depression in older adults both in cross-sectional and in longitudinal analyses [12], with higher IL-6 levels associated with worse symptoms trajectories during the follow-up [13].

On this basis, aim of this study was to evaluate the variables associated with depressive symptoms in older patients with persistent AF undergoing electrical cardioversion (ECV), and to ascertain, also, a possible role of low-grade chronic inflammation.

1. Methods

1.1. Patients' evaluation

Consecutive older outpatients (age ≥65 years) with persistent AF directed to a rhythm-control strategy program of the arrhythmia were prospectively enrolled in the study, provided their consent to participate, after an ambulatory evaluation or a previous hospitalization. The protocol [14], approved by the local ethical committee, was conform to the Declaration of Helsinki. All patients were evaluated after the admission in a Day-Hospital setting to undergo ECV of the arrhythmia. There were no exclusion criteria except for a <3 months major surgery intervention, the presence of severe frailty and dementia, of an active cancer or of other diseases causing an overt activation of inflammation, and a life expectancy <12 months. Venous blood samples for routine laboratory analysis and IL-6 concentration determination were collected in a fasting condition. The CHA_2DS_2-VA score (Congestive heart failure, 1 point; Hypertension, 1 point; Age ≥75 years, 2 points; Diabetes mellitus, 1 point; prior Stroke/TIA/arterial thromboembolism, 2 points; Vascular disease, 1 point; Age 65–74 years, 1 point) was collected and analysed as a marker of thromboembolic risk and an index of clinical complexity, as we previously found [3,15]. Indeed, recently, the CHA_2DS_2-VASc score emerged as the most relevant factor to identify clinical complexity in two large European and Asian AF registries [16]. After a cardiology visit and the measure of arterial stiffness with the Cardio-Ankle Vascular Index (CAVI; VaSera VS-1500N, Fukuda Denshi, Japan) [17], all subjects were evaluated with the Comprehensive Geriatric Assessment (CGA) tools. In particular, the following instruments were used: 1) the Mini-Mental State Examination (MMSE; cognitive function; score range from 0 to 30, best performance), exploring orientation, short-term memory and recall, attention, calculation, language comprehension and executive functions [18]; 2) the 15-item version of the Geriatric Depression Scale (GDS; depressive symptoms; score range from 0 to 15, major burden), consisting of yes/no questions designed to evaluate mood, motivation, and overall psychological well-being, with a score >5 indicative of a depressed mood [19]; 3) the Short-Physical Performance Battery (SPPB; physical function; score range from 0 to 12, best physical performance), composed of three different tasks, analysing balance, walking speed, and strength and endurance [20]. The SPPB, also considered a measure of frailty in subjects with cardiovascular [21] and non-cardiovascular diseases [22], was used to evaluate the prevalence of the condition (identified by scores ≤8). Then, ECV was performed using a synchronized biphasic shock (mean energy value: 175 Joule) after the administration of propofol (1 mg/kg of body weight) to obtain a 5–10-minute length anaesthesia. Patients were then discharged home after 2 hours from the procedure [14].

1.2. IL-6 measure

Each sample of venous blood was centrifuged for 15 minutes (2500 rpm, 4°C) immediately after having been taken. Plasma was then collected and stored at -80°C until IL-6 levels were determined using ELISA kits (R&D Systems™ Human IL-6 Quantikine HS ELISA, Bio-Techne, MN, USA), as soon as samples from 40 different patients were available.

1.3. Statistical analysis

IBM SPPS Statistics (version 29.0; IBM Corporation) for macOS was used for statistical analysis.

Continuous variables are expressed as mean ± standard deviation and, in the case of a non-normal distribution, as median value with the 25^{th} and the 75^{th} percentile. Categorical variables are reported as an absolute number with the related percentage.

The correlation between continuous variables was evaluated with simple linear regression analysis, while the presence of a different distribution of continuous variables between two or more categories was assessed with Student's t test and analysis of variance, respectively. The related non-parametric tests, the Mann-Whitney and the Kruskal-Wallis test, were used in the case of a non-normal distribution. Post-hoc comparisons were performed with the Bonferroni test.

The chi-square test was used to ascertain a statistical different distribution of categorical variables between two or more groups of patients.

All variables significantly associated with the GDS score in univariate analysis were entered into a multivariate linear regression model with iterative backward deletion of the least significant factor. For each remaining variable, the hazard ratio (HR) with the related 95% confidence intervals (95%CI) are reported.

A p value <0.05 was considered associated with statistical significance.

2. Results

2.1. Patients' characteristics

Overall, 258 patients were enrolled (age: 78±8 years; women: 41.1%); of these, 64.0% were married and 24.0% lived alone. In the whole population, CGA showed preserved cognitive function and physical performance, and a normal depressive symptoms score (MMSE: 27.9±2.5, SPPB: 8.7±2.7, GDS: 3.3±2.9). However, a pathologic result at the GDS was observed in 21.3% of cases (N=55) (Tables 1 and 2). Frailty prevalence was 42.2%. Most of patients underwent ECV between 2 and 12 months from AF onset (82.5%). Hypertension was the most frequently observed cardiovascular risk factor with a prevalence of 81.8%; interventricular septum thickness was higher than 12 mm in only

Table 1
Continuous variables describing the enrolled patients, and their association with GDS score in linear regression analysis models.

	Mean ± s.d.	Correlation with GDS		P
		β ± e.s.	R	
Age (years)	78±8	0.11±0.02	0.293	<0.001
Height (cm)	169±10	-0.09±0.02	0.311	<0.001
Weight (Kg)	77±15	-0.05±0.01	0.252	<0.001
MMSE (score)	27.9 ±2.5	-0.18±0.07	0.150	0.015
SPPB (score)	8.7±2.7	-0.51±0.06	0.474	<0.001
HR (bpm)	80±17	0.03±0.01	0.157	0.011
SAP (mmHg)	133±20	/	0.009	0.899
DAP (mmHg)	80±11	/	0.048	0.455
CAVI	9.9±1.6	0.24±0.11	0.140	0.027
Ankle-Brachial Index	1.0±0.1	-4.04±1.16	0.214	<0.001
LAD (mm)	52±7	/	0.020	0.754
IVS (mm)	9.8±1.5	-0.27±0.12	0.143	0.022
LVEF (%)	58±12	/	0.082	0.193
WBC ($n \cdot 10^{-3} \cdot mm^3$)	6.6±1.8	/	0.053	0.410
Hemoglobin (g/dL)	13.4±1.5	-0.24±0.12	0.126	0.048
ESR ($mm \cdot h^{-1}$)	24±18	/	0.136	0.053
Creatinine (mg/dL)	1.1±0.4	/	0.057	0.377
Creatinine Clearance	62±24	-0.04±0.01	0.293	<0.001
Na^+ (mEq/L)	141±3	/	0.048	0.455
K^+ (mEq/L)	4.2 ±0.5	/	0.061	0.363
ALT (U/L)	26±18	/	0.077	0.280
Iron (μg/dL)	77±25	/	0.067	0.245
Ferritin (ng/mL)	125±107	/	0.130	0.051
TSH (μUI/mL)	3.1±4.9	/	0.055	0.940
Uric acid (mg/dL)	5.8±1.5	/	0.049	0.451

ALT: alanine aminotransferase; CAVI: cardio-ankle vascular index; Creatinine Clearance: creatinine clearance according to the Cockcroft-Gault equation (mL/min/1.73 m^2); DAP/SAP: diastolic/systolic arterial pressure; ESR: erythrocytes sedimentation rate; HR: heart rate; IVS: interventricular septum thickness; LAD: left atrium diameter; LVEF: left ventricular ejection fraction; MMSE: Mini-Mental State Examination; SPPB: Short Physical Performance Battery; TSH: thyroid-stimulating hormone; WBC: white blood cells

Table 2
Prevalence of the categorical variables in the enrolled population, and differences in the GDS score according to the presence/absence of each condition.

	Prevalence	GDS score for condition		P
	(n, %)	Absent	Present	
Women	106 (41.1)	2.70±2.63	4.10±3.12	<0.001
Living alone	62 (24.0)	3.06±2.69	4.02±3.49	0.052
Smokers	141 (54.6)	3.27±2.88	3.31±3.09	0.920
Wine	61 (23.6)	3.73±3.04	2.46±2.43	<0.001
Heart failure	104 (40.3)	3.16±2.95	3.46±2.88	0.410
Hypertension	211 (81.8)	2.70±2.73	3.41±2.95	0.134
Diabetes	46 (17.8)	3.29±3.02	3.24±2.40	0.919
Stroke/TIA	33 (12.8)	3.12±2.90	4.33±2.85	0.013
PAD	39 (15.1)	3.14±2.82	4.05±3.36	0.118
Myocardial infarction	15 (5.8)	3.42±3.07	2.80±2.28	0.092
CKD	52 (20.2)	3.13±2.92	3.85±2.87	0.049
COPD	37 (14.3)	3.22±2.84	3.62±3.36	0.442
Hyperuricemia	57 (22.1)	3.22±3.02	3.49±2.56	0.535
Thyroid diseases	50 (19.4)	3.39±2.98	2.82±2.62	0.216
ACE-i/ARB	169 (65.5)	3.03±2.71	3.41±3.02	0.328
Alpha-blockers	55 (21.3)	3.50±3.07	2.45±2.12	0.004
Beta-blockers	210 (81.4)	2.94±3.05	3.36±2.89	0.370
Diuretics	160 (62.0)	3.01±3.05	3.44±2.84	0.248
Statins	119 (46.1)	3.53±3.24	2.99±2.48	0.136
DOACs	199 (77.1)	3.27±2.33	3.31±3.08	0.922
Digoxin	61 (23.6)	3.19±2.96	3.57±2.78	0.368
Propafenone/Flecainide	9 (3.5)	3.31±2.94	2.44±2.24	0.384
Amiodarone	107 (41.5)	3.14±2.96	3.48±2.86	0.361
Verapamil/Diltiazem	10 (3.9)	3.26±2.89	4.00±3.53	0.435
PPI	91 (35.3)	2.83±2.68	4.10±3.15	<0.001
Benzodiazepines	38 (14.7)	3.05±2.78	4.63±3.37	0.002
SSRI/SNRI	33 (12.8)	3.19±2.96	3.91±2.59	0.185
Other psychotropic Tx	23 (8.9)	3.16±2.86	4.52±3.31	0.032

ACE-i/ARB: ACE inhibitors/angiotensin receptor blockers; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DOACs: direct oral anticoagulants; PAD: peripheral artery disease; PPI: proton pump inhibitors; Smokers: past/present smokers; SSRI/NSRI: selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor; TIA: transient ischemic attack; Wine: ≥1 glass of wine a day (e.g., ≥1 alcohol unit a day)

5 patients (1.9%). In two subjects, a history of amyloidosis was found. Thromboembolic risk, expressed as CHA_2DS_2-VA score, was moderate (CHA_2DS_2-VA: 3.5±1.4) and left ventricular ejection fraction normal. Overall, 24 patients (9.3%) had undergone before to coronary artery bypass grafting. Among the other comorbidities, the proportion of chronic kidney disease (CKD) was 20.2% with a mean creatinine clearance of 62±24 mL/min/1.73m^2 (Table 1). Abnormalities of thyroid function were observed in 19.4% of cases, even if TSH concentration in the whole population was normal. Heart rate was well controlled (HR: 80±17 bpm) such as arterial blood pressure (Tables 1 and 2).

Beta-blockers and antagonists of the renin-angiotensin system were widely prescribed. Among the other drugs, amiodarone was the anti-arrhythmic agent more frequently used. Overall, 77.1% of the enrolled patients received a DOAC, with the other cases treated with warfarin. The proportion of subjects prescribed with benzodiazepines and serotonin reuptake inhibitors (SSRI/SNRI) was 14.7 and 12.8%, respectively (Table 2).

IL-6 levels were measured in 153 (59.3%) of the enrolled patients. Mean concentration was 4.3±3.5 pg/mL (median: 3.2 pg/ml; 25^{th}-75^{th} percentile: 1.8-5.4 pg/mL).

2.2. Univariate associations of clinical, instrumental and laboratory variables with the GDS score

Univariate analysis showed that GDS score was directly associated with age and higher in women (Fig. 1). An inverse relation existed with body size (Tables 1 and 2). When studying civil status, an increase was evident going from those who were married (64.2%; GDS: 2.8±2.4), to those separated / unmarried (11.3%; GDS: 3.4±3.0), with the highest value reached in widowed subjects (24.5%; GDS: 4.5±3.7) (p<0.001).

The analysis of the CGA instruments demonstrated an inverse association between depressive symptoms and cognitive functioning, measured with the MMSE, and physical performance, evaluated with the SPPB (Table 1 and Fig. 2). Such a relation was observed also with each of the components of the SPPB, that is, with the standing balance, the walking and the chair standing tests (all p values <0.001).

A previous cerebrovascular event and CKD were associated with a higher burden of depressive symptoms (Tables 1 and 2). When the CHA_2DS_2-VA was higher also depressive symptoms were more relevant (p<0.001) (Fig. 1).

No GDS differences were observed by type of oral anticoagulant and use of SSRI/SNRI. However, patients taking proton pump inhibitors and benzodiazepines showed higher GDS scores (Table 2).

Heart rate at baseline and arterial stiffness had a direct association with depressive symptoms. No relation existed with left ventricular ejection fraction, while to a higher interventricular septum thickness corresponded lower values of GDS (Table 1).

Last, the burden of depressive symptoms was more relevant in subjects showing a higher concentration of IL-6 (p<0.001) (Fig. 3).

To strengthen these results, we compared the characteristics of patients with and without an abnormal GDS score (i.e., >5). We found that when a depressive mood was present, subjects were older (81±7 vs. 77 ±8 years), more often women (29.2 vs. 15.8%), lived more frequently alone (33.9 vs. 17.5%), and showed a higher CHA_2DS_2-VA score (4.0 ±1.2 vs. 3.4±1.4), and a worse physical performance at the SPPB (6.4 ±3.0 vs. 9.3±2.3) (all p values <0.05).

2.3. Association between clinical, instrumental and laboratory variables with GDS. Results of the multivariate models

The multivariate model evaluating the whole series of AF patients

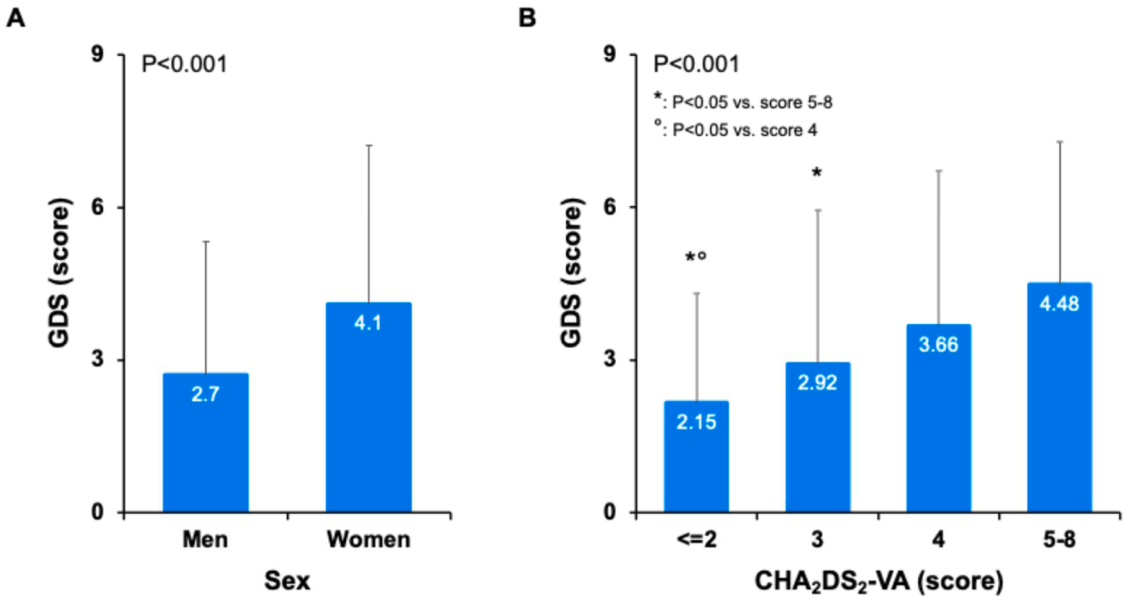

Fig. 1. Score of the 15 items GDS by sex (panel A) and CHA_2DS_2-VA (panel B). Depressive symptoms are higher in women and in patients with a worse thromboembolic risk.

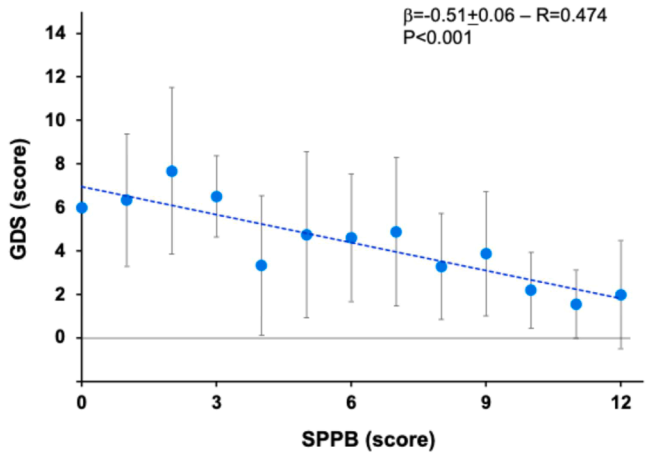

Fig. 2. The inverse correlation between the SPPB, index of physical performance, and depressive symptoms. To increase clarity, for each score of the SPPB, we represented the mean GDS value with the related standard deviation.

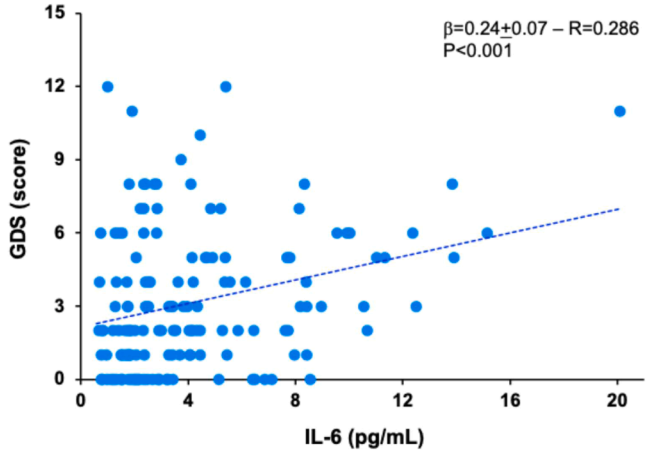

Fig. 3. The direct correlation between IL-6 concentration and the GDS score.

enrolled in the study showed the direct correlation between the GDS and the CHA_2DS_2-VA score. Depressive symptoms were inversely associated with the interventricular septum thickness, and, importantly, with the SPPB, the index of physical performance (Table 3, Model A).

When we studied the 153 patients in whom IL-6 levels were measured, we found the significant, direct, relation between the cytokine concentration and the GDS score. As previously observed, interventricular septum thickness and SPPB were inversely associated with depressive symptoms. The CHA_2DS_2-VA score lost its statistical correlation and was deleted from the model (p=0.147) (Table 3, Model B).

Table 3
Variables associated with depressive symptoms measured with the 15-item GDS.
Model A - Results of the multivariate linear regression analysis including all patients (R=0.527; p<0.001)
Model B - Results of the multivariate linear regression analysis including patients in whom IL-6 concentration was available (R=0.473; p<0.001).

Model A	β ± e.s.	P	95% CI
Constant	10.69±1.38	<0.001	7.98 – 13.41
SPPB (Δ·1 point increment)	-0.51±0.07	<0.001	- (0.66 – 0.37)
CHA_2DS_2-VA (Δ·1 point increment)	0.43±0.18	0.019	0.07 – 0.79
IVS (Δ·1 mm increment)	-0.39±0.12	0.001	- (0.63 – 0.16)
Variables excluded from the model - age (p=0.777); height (p=0.128); weight (p=0.243); MMSE (p=0.631); HR (p=0.065); CAVI (p=0.127); ABI (p=0.279); creatinine clearance (p=0.694); sex (p=0.194); civil status (p=0.742); wine (p=0.055); alpha-blockers (p=0.226); PPI (p=0.165)			

Model B	β ± e.s.	P	95% CI
Constant	9.48±1.73	<0.001	6.05 – 12.91
SPPB (Δ·1 point increment)	-0.38±0.10	<0.001	- (0.58 – 0.19)
IVS (Δ·1 mm increment)	-0.37±0.14	0.011	- (0.65 – 0.09)
IL-6 (Δ·1 pg/mL increment)	0.18±0.07	0.011	0.04 – 0.31

Variables excluded from the model - age (p=0.144); height (p=0.154); weight (p=0.362); MMSE (p=0.974); CHA_2DS_2-VA (p=0.147); HR (p=0.441); CAVI (p=0.982); ABI (p=0.418); creatinine clearance (p=0.371); sex (p=0.712); civil status (p=0.223); wine (p=0.241); alpha-blockers (p=0.562); PPI (p=0.160)
ABI: Ankle-Brachial Index; CAVI: cardio-ankle vascular index; Creatinine Clearance: creatinine clearance according to the Cockcroft-Gault equation (mL/min/1.73 m^2); GDS: Geriatric Depression Scale; HR: heart rate; IL-6: interleukin-6; IVS: interventricular septum thickness; MMSE: Mini-Mental State Examination; PPI: proton pump inhibitors; SPPB: Short Physical Performance Battery; Wine: ≥1 glass of wine a day (i.e., ≥1 alcohol unit a day)

2.4. Depressive symptoms and efficacy of electrical cardioversion

ECV was highly effective in our patients independently of the GDS score (sinus rhythm at discharge – GDS≤5: 95.6% vs. GDS>5: 96.4%; p=1.000).

3. Discussion

The results of this study demonstrate that, among older AF patients undergoing ECV, the prevalence of a significant burden of depressive symptoms is not negligible, and equal to 21.3%. At multivariate analysis, GDS score was directly associated with the CHA_2DS_2-VA and inversely related to SPPB. When analyzing also IL-6, the concentration of the cytokine showed a significant link with depressive symptoms, together with SPPB and interventricular septum thickness, while the CHA_2DS_2-VA score was deleted from the model.

It is the first time in which mood disorders in older AF patients, particularly exposed to arrhythmia complications, can be simultaneously correlated to one of the most important instruments assessing physical performance and to the CHA_2DS_2-VA score, specific measure of thromboembolic risk, and our index of clinical complexity. Further, IL-6 could help to explain this last association.

It is also known that depression and other important geriatric conditions, such as multimorbidity, a higher risk of falls, and disability, contribute to define a frail phenotype, characterized by an increased risk of major cardiovascular events [23]. Among older patients with coronary artery disease, once again depression, with malnutrition, a history of falls, sleep disorders, comorbidities, polypharmacy, disability, and living alone outlined frailty [24].

In a previous experience, in 171 patients undergoing ECV or AF ablation, the prevalence of relevant depressive symptoms was 17.2% [25]. Interestingly, when compared to subjects with paroxysmal forms of the arrhythmia, those with persistent AF showed more frequently depressive symptoms [26].

The association between the CHA_2DS_2-VA and mood can be explained by the effects of each of the components of the tool on the affective state.

In patients with heart failure, the prevalence of depression ranges between 14 and 60% [27], with the coexistence of the two conditions associated with a higher risk of mortality and hospitalizations [28].

Arterial hypertension is the most frequent risk factor for AF. In our study, it can be found in >80% of cases. When compared to hypertensive patients without the arrhythmia, hypertensive subjects with AF are characterized by worse GDS and MMSE scores, a lower left ventricular ejection fraction and a higher arterial stiffness [29]. Indeed, a correlation between depressive symptoms and arterial stiffness was found also in our experience.

Also, the coexistence of AF and diabetes was associated with a higher GDS score and a lower cognitive performance [30].

In the "PolSenior project", AF and a history of stroke were the most relevant cardiovascular conditions correlated with the presence of depression [31]. Further, the Find-$AF_{RANDOMISED}$ trial demonstrated that, post-stroke, older subjects, when compared to younger ones, more often presented significant depressive disturbances and quality of life alterations [32].

Myocardial infarction, a determinant of the "V" of the CHA_2DS_2-VA, has a bidirectional association with depression. Indeed, depressed patients have a risk higher than 28% to develop an acute coronary syndrome [33], while a major depression could be diagnosed in a proportion of cases ranging between 15 and 30% after a myocardial infarction [34].

Age also is one of the components of the CHA_2DS_2-VA. We found a direct association between age and the GDS score. The inverse correlation linking depressive symptoms with weight and height may be explained by their negative association with age itself (p values <0.001 in both cases).

In our study, SPPB has an inverse relation with depressive symptoms. A similar finding was shown in hospitalized older patients when analyzing the association between physical performance, malnutrition, cognitive status and the burden of affective alterations [35]. In the "Systematic Assessment of Geriatric Elements in Atrial Fibrillation" (SAGE-AF) study, an abnormal gate speed characterized patients at risk to develop relevant depressive symptoms [36]. Last, the SPPB and the CHA_2DS_2-VASc score contributed to define the frail phenotype in an older population with persistent AF [37].

In the present study, the thickness of the interventricular septum was inversely correlated with the GDS score. It is not easy to defend this finding. Related evidence is scant and conflicting with our results. In the 6025 patients of the ARIC ("Atherosclerosis Risk in Communities") study, the CES-D ("Center for Epidemiologic Studies Depression Scale") score was associated with prevalent and incident cases of heart failure with preserved ejection fraction [38], often linked to cardiac hypertrophy. Among Chinese centenarians, interventricular septum was directly correlated to GDS score [39]. We can only hypothesize that the negative association we found between the burden of depressive symptoms and interventricular septum thickness could be explained by the inverse correlation linking the echocardiographic measure with female gender and body weight (p=0.029 and p=0.037, respectively, after adjustment for age, arterial stiffness and left ventricular ejection fraction). Indeed, women and lean subjects showed also a worse GDS score.

When analyzing patients in whom IL-6 concentration was measured, the multivariate model showed that SPPB total score and interventricular septum thickness maintained their statistical association with depressive symptoms, while the CHA_2DS_2-VA score was deleted, being substituted by the cytokine levels. In a previous series of patients, we found a direct relation linking CHA_2DS_2-VASc and IL-6 [15]. Also, the cytokine contributes to define the frail phenotype in older AF patients [37].

Depression at older ages originates from a complex interplay of social, biological and psychological factors. A hypothesis supports that a depressive state is based on inflammation. Really, inflammatory and neuro-inflammatory markers are elevated in older depressed patients. Cellular aging and, particularly, cardiovascular and metabolic diseases could contribute to these alterations [40]. Last, inflamm-ageing proved to be a determinant of cardiovascular diseases at older ages [41].

In the present study, a pathologic burden of depressive symptoms (GDS>5) was unrelated to ECV efficacy. This result can be justified by the high success rate of the procedure, which is linked to the physical characteristics of the chest and to the intensity of electrical current going through the heart [42]. Affective disorders could exert a relevant role to determine a post-ECV arrhythmia relapse and to increase the incidence of AF-related unfavorable events during the follow-up [9,43].

This study has some limitations. First, it is observational with a prospective enrollment of patients. Accordingly, the results we obtained just illustrate statistical associations between clinical, instrumental or laboratory variables and depressive symptoms. They are only hypotheses generating and need to be confirmed by specifically designed clinical trials. However, the great number of subjects participating to the protocol, and the high number of analyzed variables should have allowed to run adequately adjusted statistical models. Indeed, the results we obtained are clinically plausible. IL-6 levels were measured in the 59.3% of the enrolled patients. Hence, it cannot be excluded that the findings we obtained could have been different if we had had a larger number of available samples. Furthermore, many geriatric conditions, such as AF itself, can influence low-grade chronic inflammation. Once again, from a biological point of view, it is plausible that the introduction of an inflammatory marker can make not significant the influence of the CHA_2DS_2-VA, given that some, if not all, of its components are almost always associated with a low-grade inflammatory status. Indeed, we found a direct relation between the CHA_2DS_2-VA score and IL-6 concentration in our population (p=0.002). However, also in this case, our experience should have to be corroborated by specific protocols. We

evaluated only patients with persistent forms of AF undergoing ECV. Accordingly, our results cannot be extended to subjects with paroxysmal or permanent forms of the arrhythmia. Our index of frailty was a SPPB score $\leq$8. The prevalence of the condition would have been certainly diverse if we had used another instrument. Indeed, a universal definition of frailty is now strongly needed in cardiovascular medicine [44]. Nevertheless, the proportion of frail subjects we found is comparable to that seen in other observational studies [45]. Unfortunately, we did not have measures giving a detailed economic and social representation of the population we enrolled. However, the approach based on universalism guaranteed by the Italian National Health Service should, at least in part, mitigate the influences derived by domains not directly related to health. Given the composition of the Italian population, all the enrolled patients are Caucasian; the results could have been different if other ethnic groups were present. Last, we did not analyze follow-up data, and we preferred to focus on the description of the variables associated with baseline depressive symptoms, given their complex and multidimensional interactions, which request, in accordance with guidelines, a true multidisciplinary approach [3].

In conclusion, a relevant burden of depressive symptoms is frequently found in older patients with persistent AF. Clinical complexity, as evaluated with the CHA_2DS_2-VA, and physical performance, measured with the SPPB, are the two domains of the CGA which may help to explain the affective state alterations in subjects with the arrhythmia. IL-6, one of the most important markers of low-grade inflammation, replaces clinical complexity in describing depressive symptoms. We think that these results can be of help in the management of older patients with AF and can contribute to better delineate the interactions linking age, mood and cardiovascular disease.

Informed consent

The protocol of the study, approved by the local ethical committee, was conform to the Declaration of Helsinki. All patients gave their informed consent to participate.

Declaration of generative AI in scientific writing

The Authors do not use generative AI in the preparation of any part of the manuscript or in the submission process.

Research data

The datasets generated during this study are not publicly available until the completion of the analyses of the CAFFE study, which was supported by the Italian Ministry of University and Research. Data will be available from the corresponding author, on reasonable request, after the publication of the reports concerning the main endpoints of the study.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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