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JOURNAL OF Cardiovascular Medicine and Cardiology OPEN ACCESS JOURNAL

ISSN: 2455-2976 DOI: https://dx.doi.org/10.17352/jcmc

Research Article

# Mitral Valve Syndrome in older patients with and without depression: A cross-sectional study

**Grazia D'Onofrio[1]*, Mariangela Pia Dagostino[2], Filomena Addante[2], Filomena Ciccone[1], Maria Grazia Longo[2], Michele Pacilli[3], Daniele Sancarlo[2], Michele Lauriola[2], Leandro Cascavilla[2] and Antonio Greco[2]**

[1]Clinical Psychology Service, Department of Health, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

[2]Complex Unit of Geriatrics, Department of Medical Sciences, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

[3]Complex Unit of Cardiology, Department of Cardiovascular, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

**Received:** 13 May, 2021
**Accepted:** 24 May, 2021
**Published:** 26 May, 2021

***Corresponding author:** Grazia D'Onofrio, Clinical Psychology Service, Department of Health, Fondazione IRCCS Casa Sollievo della Sofferenza, Viale Cappuccini 1, 71013 San Giovanni Rotondo, Foggia, Italy, Tel: +39 0882-410271; Fax: +39 0882-410271; Email: g.donofrio@operapadrepio.it

**Keywords:** Depression; Mitral valve prolapse; Mitral regurgitation; Doppler echocardiography; Comprehensive geriatric assessment

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## Abstract

Study aim was to determine whether Late Life Depression (LLD) is associated with Mitral Valve Syndrome (MVS) presence, and to assess direct proportionality between MVS and LLD severity.

A total of 504 consecutive patients (M=260, F=244; Mean Age 79.74±7.83, range=60-98) were included and divided in 2 groups: 1) 360 patients with LLD and MVS (Group 1), and 2) 144 patients without LLD and with MVS (Group 2). All patients were assessed by Doppler echocardiography, complete standardized Comprehensive Geriatric Assessment (CGA) [including basal/instrumental Activities of Daily Living (ADL/IADL), Short Portable Mental Status Questionnaire (SPMSQ), Cumulative Illness Rating Scale Comorbidity Index (CIRS-CI), Mini Nutritional Assessment (MNA), Exton-Smith Scale (ESS), medication use and social aspects], Mini Mental State Examination (MMSE), Clock Drawing Test (CDT), and Frontal Assessment Battery (FAB).

Group 1 were more females (p<0.0001), showed higher cognitive damage (MMSE: p=0.001) and a major impairment in several CGA domains: ADL (p<0.0001), IADL (p<0.0001), SPMSQ (p=0.003), CIRS-CI (p=0.003), MNA (p<0.0001), ESS (p<0.0001), and medication number (p=0.002). Group 2 were more no smokers (p=0.030). Group 1 were more without hypertension (p=0.036), dyslipidemia (p=0.025), and diabetes (p=0.048). Patient groups did not differ in other parameters. Significant association between MVS severity and LLD severity showed (OR = 2.140, CI 95% = 1.261-3.630, p = 0.005). LLD patients had higher interventricular septum values (p=0.030), progressively increased with LLD severity (p=0.039).

Subjects with LLD and MVS were more implicated in cognitive, functional, clinical and nutritional aspects. LLD severity seems to be associated to MVS severity.

## Abbreviations

LLD: Late Life Depression; MVS: Mitral Valve Syndrome; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; DSM 5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; CGA: Comprehensive Geriatric Assessment; HDRS-21: Hamilton Rating Scale for Depression with 21 items; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; SPMSQ: Short Portable Mental Status Questionnaire; CIRS-CI: Cumulative Illness Rating Scale



**Citation:** D'Onofrio G, Dagostino MP, Addante F, Ciccone F, Longo MG, et al. (2021) Mitral Valve Syndrome in older patients with and without depression: A cross-sectional study. J Cardiovasc Med Cardiol 8(2): 048-054. DOI: https://dx.doi.org/10.17352/2455-2976.000169

Comorbidity Index; MNA: Mini Nutritional Assessment; ESS: Exton-Smith Scale; MMSE: Mini Mental State Examination; CDT: Clock Drawing Test; FAB: Frontal Assessment Battery; ASE/ESE: American Society of Echocardiography/European Association of Echocardiography; ANOVA: Analysis of Variance; OR: Odds Ratios; CI: Confidence Interval.

## Background

Worldwide, depression is a common issue among older adults[1], but it is not a normal component of aging [2]. Depressive syndromes that begin in old age are tagged as Late-life depression (LLD) [3], that has a pooled prevalence of 7% and accounts for 5.7% of years occurred with disability in over 60-year people [4]. The serious consequences of persistent depressive symptoms in older persons include functional disability[5], increasing of health care utilization [6], relapse and recurrence [7], cognitive decline owing in part to the impact of long periods of untreated depression on hippocampal volume [8], and increased mortality [9].

The association between LLD and mitral valve syndrome (MVS) has been little studied. Previous literature regards the rapport between MVS and psycho-emotional status that is focused on anxiety and consisted of contentious evidence [2] that was insufficient for establishing or excluding the relationship [1].

MVS is common in most older patients, with consequent mitral regurgitation and other serious issues, including ruptured chordae, stroke, and death [10,11].

In a recent study, it was shown that MVS is not a determinant of the patient's psycho-emotional status (anxiety, posttraumatic stress symptoms and depression) or quality of life. It is explained, in fact, that the psycho-emotional state and the quality of life are caused by the patient's perception about the MVS severity, instead of the presence of mitral valve prolapse [12]. Nevertheless, research on the subject presents controversial evidence and lacks diagnosis reliability [13-15].

This cross-sectional study explored the presence/absence of LLD in MVS patients compared with patients without MVS, using meticulous quantitative measures and current diagnostic criteria of mitral valve prolapse and mitral regurgitation. The aim of the study was to investigate whether LLD is associated with presence of MVS, and to assess the direct proportionality between MVS and LLD severity.

## Methods

### Subjects

This cross-sectional study was conducted on the basis of the guidelines for Good Clinical Practice, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and was approved by the local ethics committee. Written informed consent for research was obtained from each patient or from.

Patients and healthy controls consecutively were evaluated from May 2015 to February 2020 in two different evaluation units: 1) Ageing Evaluation Unit, and 2) Echocardiography Evaluation Unit of Complex Structure of Geriatrics, performed by three experienced physicians (M. P. D., F. A., and A. G.) of the IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy.

Patients were eligible for study inclusion if they had reached the age ≥ 60 years, the ability to provide an informed consent or availability of a relatives or a legal guardian in the case of patients with severe cognitive impairment, the LLD diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM 5) criteria [16], a complete comprehensive geriatric assessment (CGA), a clinical and cognitive-affective assessment, and a complete Doppler echocardiography and mitral valve prolapse and mitral regurgitation comprehensively assessed as recommended [17].

Controls were eligible if they were without any history of mental disorders according to the DSM 5 criteria.

Exclusion criteria were: functional mitral regurgitation due to ischemic disease or cardiomyopathy; mild mitral stenosis (gradient ≥5 mm Hg); other clinically significant valve disease; severe comorbid conditions (for example, cancer, overt renal failure); ejection fraction <50%; imminent suicide intent, ongoing compulsory treatment, a history of head trauma causing more than 2 minutes of unconsciousness, mental disorders according to sections F00–F29 of International Classification of Diseases, Tenth Revision (e.g., organic mental disorders, disorders due to psychoactive substance use, and schizophrenia), epilepsy, or body mass index > 35 kg/m2.

### Ageing evaluation unit: LLD diagnosis, affective, clinical and cognitive evaluation

The diagnostic criteria for major depression in the DSM-5, require the presence of either sadness or anhedonia with a total of five or more symptoms over a 2-week period [16].

Depressive symptoms were evaluated using the Hamilton Rating Scale for Depression with 21 items (HDRS-21)[18]. The scoring is based on the first 17. It generally takes 15-20 minutes to complete the interview and score the results. Severity depression grades were valued as shown below: no depression (HDRS-21 score = 0-7), mild depression (HDRS-21 score = 8-13), moderate depression (HDRS-21 score = 14-18), severe depression (HDRS-21 score = 19-22), very severe depression (HDRS-21 score ≥ 23) [19].

Clinical history was achieved through a semi-structured interview. Clinical assessment was completed by Comprehensive Geriatric Assessment (CGA) [19]. The CGA was carried out using assessment instruments widely employed in geriatric practice and comprehend eight domains: 1) Activities of Daily Living (ADL)[20] and 2) Instrumental Activities of Daily Living (IADL) scales [21] to evaluate the functional status, 3) Short Portable Mental Status Questionnaire (SPMSQ) [22] to screen the ccognitive status, 4) Cumulative Illness Rating Scale Comorbidity Index (CIRS-CI)[23] to examine the comorbidity, 5) Mini Nutritional Assessment (MNA) [24] to explore nutritional status, 6) Exton-Smith Scale (ESS) to evaluate



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the risk of developing pressure sores [25], 7) medication use is defined according to the Anatomical Therapeutics Chemical Classification code system, and the number of drugs used by patients is recorded, and finally 8) social aspects that include household composition, home service, and institutionalization.

In all patients, cognitive status was assessed with the Mini Mental State Examination (MMSE)[26], Clock Drawing Test (CDT) [27], and Frontal Assessment Battery (FAB) [28].

### Echocardiography evaluation unit: Risk factor assessment, laboratory test and ultrasound scan

Through a semi-structured interview medical history and milestones from the patient's life were performed as below shown: 1) life time tobacco use, 2) psychoactive substance use and abuse, 3) vascular disease history (myocardial infarction, stroke, and/or cardiac arrhythmia), 4) weight and height, and 5) blood pressure.

According to the Guideline for the diagnosis and management of hypertension in adults, hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or current antihypertensive treatment [19,29].

Hyperlipidemia was defined according to the Guidelines for management of dyslipidemia and prevention of cardiovascular disease [19,30].

Diabetes mellitus was defined according to the Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm [19,31].

Body mass index was defined as weight (in kilograms) divided by height (in meters) squared.

The diagnosis of MVS in the selected cases was performed through clinical examination and Doppler echocardiography by B-Mode Ultrasound scan and Color Doppler ultrasound scan of the mitral valve prolapse and mitral regurgitation using APLIO 500 (Toshiba, Tokyo, Japan) [32]. Mitral valve prolapse diagnosis was established according the current criteria [33-36] defining the prolapse presence when one or both leaflets are displaced ≥ 2 mm in systole above a line connecting the annular extremities in the parasternal or apical long-axis view.

The approach is measurement of the narrowest segment of the jet, or vena contracta, on color flow imaging. Mitral regurgitant severity has been measured more precisely by calculation of the regurgitant volume, regurgitant fraction, and effective regurgitant orifice area using Doppler approaches [37] . As noted in the 2017 update to the 2014 American Heart Association/American College of Cardiology guidelines for management of patients with valvular heart disease and the 2017 ASE/ESE recommendations for quantitation of valvular regurgitation, the following findings are consistent with severe mitral regurgitant [38-41]:

- Vena contracta width ≥0.7 cm
- Effective regurgitant orifice area ≥0.40 $cm^2$
- Regurgitant volume ≥60 mL
- Regurgitant fraction ≥50 percent
- Regurgitant jet area >40 percent of left atrial area, or a holosystolic eccentric jet.

The diagnosis of severe mitral regurgitant is most secure when more than one of these findings is present.

### Statistical analyses

For dichotomous variables, hypotheses regarding differences between the groups were tested using the Fisher's exact test. This analysis was made using the 2-Way Contingency Table Analysis available at the Interactive Statistical Calculation Pages (The R Project for Statistical Computing; available at URL http://www.r-project.org/). For continuous variables, normal distribution was verified by the Shapiro-Wilk normality test and the one-sample Kolgomorov-Smirnov test. For normally-distributed variables, hypotheses regarding differences among the groups were compared by means of the Welch two sample t-test or by means of the analysis of variance (ANOVA) under general linear model. For non-normally-distributed variables, hypotheses regarding differences among the groups were compared by means of the Wilcoxon rank sum test with continuity correction or by means of the Kruskal-Wallis rank sum test. Risks will be reported as odds ratios (OR) along with their 95% confidence interval (CI). All the statistical analyses were made with the R Ver. 2.8.1 statistical software package (The R Project for Statistical Computing; available at URL http://www.r-project.org/). Tests in which the p value was smaller than the type I error rate $\alpha = 0.05$ were declared significant.

## Results

During the enrolment period, 1531 elderly patients were screened for the inclusion in the study.

Of these, 128 patients were excluded because they were younger than 60 years, 13 patients had an incomplete examination, 424 patients had a history of vascular diseases (179 patients had a history of stroke, and 245 patients had myocardial infarction and/or a significant cardiac arrhythmia), and 462 patients had a body mass index > 35 $kg/m^2$. Thus, the final population included 504 patients, 260 men (51.6%) and 244 women (48.4%) with a mean age of 79.75 years ± 7.83 (range=60-98 years).

Therefore, the patients were divided in 2 groups: 1) 360 patients with LLD and MVS (Group 1), and 2) 144 patients without LLD and with MVS (Group 2).

According to the aforesaid group distribution, the demographic, affective, cognitive and clinical characteristics of patients are summarized in Table 1. The groups of patients did not differ in following parameters: age (p = 0.431), CDT (p = 0.056), FAB (p = 0.196), and Social Support Network (p = 0.774).



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**Table 1:** Demographic, affective, cognitive and clinical characteristics of patients with/without Late Life Depression (LLD) and with Mitral Valve Syndrome (MVS).

| | Group 1 n=360 | Group 2 n=144 | P-value |
|---|---|---|---|
| Sex - *Males/Females* | 162/198 | 98/46 | <0.0001 |
| *Males* - % | 45.00 | 68.10 | |
| Age* | | | |
| Mean ± SD | 79.57 ± 8.00 | 80.18 ± 7.40 | 0.431 |
| Range | 60 – 98 | 60 – 98 | |
| HRSD-21 (score)* | | | |
| Mean ± SD | 16.89 ± 6.63 | 3.31 ± 2.36 | <0.0001 |
| Range | 8 – 46 | 0 – 7 | |
| MMSE (score)* | | | |
| Mean ± SD | 20.94 ± 5.08 | 22.58 ± 5.40 | 0.001 |
| Range | 6 – 30 | 5 – 30 | |
| CDT (score)* | | | |
| Mean ± SD | 3.73 ± 1.90 | 3.29± 1.98 | 0.056 |
| Range | 1 – 6 | 1 – 6 | |
| FAB (score)* | | | |
| Mean ± SD | 10.26 ± 5.11 | 11.10 ± 5.89 | 0.196 |
| Range | 0 – 18 | 0 – 18 | |
| ADL (score)* | | | |
| Mean ± SD | 4.47 ± 1.68 | 5.39 ± 1.20 | <0.0001 |
| Range | 0 – 6 | 2 – 6 | |
| IADL (score)* | | | |
| Mean ± SD | 3.53 ± 3.07 | 5.57 ± 2.94 | <0.0001 |
| Range | 0 – 8 | 0 – 8 | |
| SPMSQ (score)* | | | |
| Mean ± SD | 3.65 ± 1.59 | 3.17 ± 1.73 | 0.003 |
| Range | 0 – 9 | 0 – 9 | |
| CIRS-CI (score)* | | | |
| Mean ± SD | 2.53 ± 1.55 | 2.04 ± 1.23 | 0.003 |
| Range | 0 – 9 | 0 – 5 | |
| MNA (score)* | | | |
| Mean ± SD | 22.56 ± 4.30 | 26.54 ± 2.18 | <0.0001 |
| Range | 8 – 28 | 18 – 29 | |
| ESS (score)* | | | |
| Mean ± SD | 17.24 ± 2.38 | 18.71 ± 1.60 | <0.0001 |
| Range | 10 – 20 | 14 – 20 | |
| N of medications (score)* | | | |
| Mean ± SD | 3.59 ± 1.53 | 3.11 ± 1.63 | 0.002 |
| Range | 0 – 7 | 0 – 7 | |
| Social support network | | | |
| Living with family N (%) | 64 (65.30) | 61 (61.00) | 0.774 |
| Institutionalized N (%) | 8 (8.20) | 7 (7.00) | |
| Living alone N (%) | 26 (26.50) | 32 (32.00) | |

*Values are presented as mean ± standard deviation.

HRSD-21: Hamilton Rating Scale for Depression with 21 items; MMSE: Mini Mental State Examination; CDT: Clock Drawing Test; FAB: Frontal Assessment Battery; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; SPMSQ: Short Portable Mental Status Questionnaire; CIRS-CI: Cumulative Illness Rating Scale-Comorbidity Index; MNA: Mini Nutritional Assessment; EES: Exton-Smith Scale.

Group 1 patients were significantly more woman (Group 1 = 55.00% *vs.* Group 2 = 31.90%, p < 0.0001), and had obviously a higher depression level (Group 1 = 16.89 ± 6.63 *vs.* Group 2 = 3.31 ± 2.36, p < 0.0001) when compared with patients of the Group 2.

Group 1 patients showed a higher cognitive damage (MMSE: Group 1 = 20.94 ± 5.08 *vs.* Group 2 = 22.58 ± 5.40, p = 0.001) and a major impairment in several CGA domains than Group 2 patients: 1) ADL (Group 1 = 4.47 ± 1.68 *vs.* Group 2 = 5.39 ± 1.20, p < 0.0001), 2) IADL (Group 1 = 3.53 ± 3.07 *vs.* Group 2 = 5.57 ± 2.94, p < 0.0001), 3) SPMSQ (Group 1 = 3.65 ± 1.59 *vs.* Group 2 = 3.17 ± 1.73, p = 0.003), 4) CIRS-CI (Group 1 = 2.53 ± 1.55 *vs.* Group 2 = 2.04 ± 1.23, p = 0.003), 5) MNA (Group 1 = 22.56 ± 4.30 *vs.* Group 2 = 26.54 ± 2.18, p < 0.0001), 6) ESS (Group 1 = 17.24 ± 2.38 *vs.* Group 2 = 18.71 ± 1.60, p < 0.0001), and 7) Number of medications (Group 1 = 3.59 ± 1.53 *vs.* Group 2 = 3.11 ± 1.63, p = 0.002).

Vascular risk assessment is summarized in Table 2. The groups of patients did not differ in BMI mean score (p = 0.055). Group 2 patients were more no smokers (Group 1 = 58.90% *vs.* Group 2 = 72.20%, p = 0.030) than other group. Group 1 patients were more without hypertension (Group 1 = 87.80% *vs.* Group 2 = 80.60%, p = 0.036), dyslipidemia (Group 1 = 78.90% *vs.* Group 2 = 69.40%, p = 0.025), and diabetes (Group 1 = 77.20% *vs.* Group 2 = 62.50%, p = 0.048), than Group 2 patients.

Figure 1 shows a visual analogic picture of the patients with and without LLD by depression severity and MVS severity. The severity of LLD seems increasing progressively with MVS severity, showing that the patients with Severe LLD were

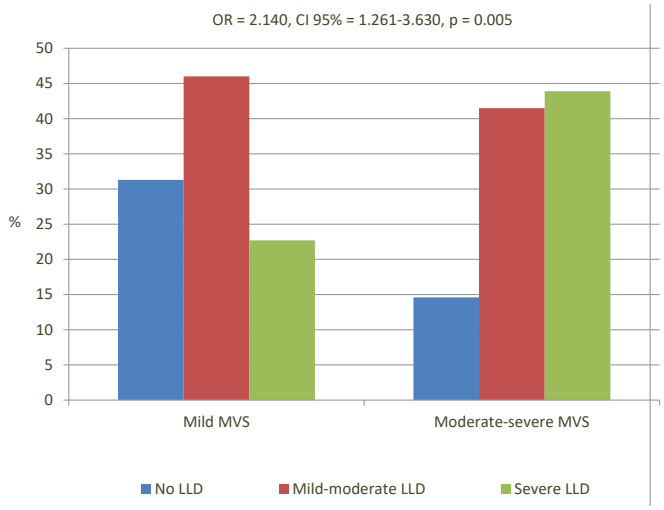


**Figure 1:** Distribution of patients with and without Late-life depression (LLD/noLLD) according to the Mitral Valve Syndrome (MVS) severity.

**Table 2:** Vascular risk assessment of older patients with/without Late Life Depression (LLD) and with/without Mitral Valve Syndrome (MVS).

| | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Tobacco use | | | 0.030 |
| Smoker – N (%) | 39 (21.7) | 5 (6.9) | |
| Ex-smoker - N (%) | 35 (19.4) | 15 (20.8) | |
| No smoker – N (%) | 106 (58.9) | 52 (72.2) | |
| Hypertension | | | 0.036 |
| Yes – N (%) | 22 (12.2) | 14 (19.4) | |
| No – N (%) | 158 (87.8) | 58 (80.6) | |
| Dyslipidemia | | | 0.025 |
| Yes – N (%) | 38 (21.1) | 22 (30.6) | |
| No – N (%) | 142 (78.9) | 50 (69.4) | |
| Diabetes | | | 0.048 |
| Yes – N (%) | 41 (22.8) | 27 (37.5) | |
| No – N (%) | 139 (77.2) | 45 (62.5) | |
| BMI | | | 0.055 |
| Mean ± SD | 27.36 ± 4.47 | 25.96 ± 3.40 | |
| Range | 16 – 41 | 20 - 34 | |

BMI: Body Mass Index



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significantly more frequent in Moderate-severe MVS (OR = 2.140, CI 95% = 1.261-3.630, p = 0.005).

Moreover, the interventricular septum measurement (Table 3) has shown a major value in LLD patients when compared with no LLD patients (p < 0.01), and in Severe LLD patients than Mild-moderate LLD patients (p<0.01).

**Table 3:** Interventricular septum in patients with and without Late Life Depression (LLD)
n.504 pts.

| | LLD | No LLD | p-value | |
|---|---|---|---|---|
| Interventricular septum (mm)* | 11.5± 1.6 | 10.9 ± 1.50 | <0.01 | |
| | Mild LLD | Moderate LLD | Severe LLD | p-value |
| Interventricular septum (mm)* | 11.2 ± 1.4 | 11.3 ± 1.4 | 12.1±2.1 | p<0.01 |
| *Values are presented as mean ± standard deviation. | | | | |

## Discussion

In the present study, using a relatively large sample of patients with and without LLD, it was found that subjects with MVS were more likely to be depressed. Moreover, the severity of LLD seems increasing progressively in patients with MVS severity, showing that the patients with Severe LLD were significantly more frequent in Moderate-severe MVS with a significantly relationship observed. Furthermore, the interventricular septum measurement has shown a major score in LLD patients when compared with noLLD patients, and in Severe LLD patients than Mild-moderate LLD patients.

Despite there are very few studies relating to the psychological aspects related to the MVS, according to our results, clinical evidences suggest that LLD may operate with several [41,42] pathophysiological mechanism in promoting and accelerating cardiovascular events and vice versa . Depression has been associated with an unhealthy lifestyle and physiological alterations increasing the risk of cardiovascular disease (such as reduced heart rate variability, catecholamine elevated baseline levels, inflammatory markers, endothelial and platelet dysfunction) [43].

A systematic review and meta-analysis reported that people with depression have 30–87% higher risk of experiencing an ischemic heart disease event, with depression accounting for 3% of the disability-adjusted life years associated with ischemic heart disease [44] . A similar pattern of associations has been described between depression and stroke: depression increases the risk of incident fatal or non-fatal strokes by 29–63% [45]. Stroke and ischemic heart disease remain the leading causes of death in middle-low to high income countries [46] so that the successful management of risk factors associated with cardiovascular diseases is expected to lead to a decrease in both disability and mortality worldwide [40]. In any cases, it could also be said that depression is associated with specific physiological changes that increase the risk of cardiovascular events that can be reversed with treatment, although what these unique physiological anomalies might be remains unclear. The vascular depression hypothesis postulates that cerebrovascular disease may influence the onset of depressive syndromes [47]. The Cardiovascular Health Study showed that the persistence of depressive symptoms was associated with small basal ganglia lesions and large cerebral cortical white matter lesion [48]. Elevated systolic blood pressure is strongly associated with these cortical lesions and is associated to a poor response to antidepressant therapy [49]. In the present study IVS thickness, a biomarker of hypertension, was significantly higher in patient with LLD suggesting a possible role as a cofactor in the LLD onset. Moreover, hypertension is frequently associated with Mitral Prolapse [50], suggesting a cluster between these two pathological conditions that may have and add on effect on the onset of depression.

Returning to our study, the role of sex seems to impact the development of LLD and MVS: certainly, patients with LLD and MVS were mainly more females. Unfortunately, we have not found studies that support this result.

Moreover, in this study, it was emerged that LLD impacts the functional (as shown through ADL and IADL scores), cognitive (as shown through MMSE and SPMSQ), and clinical (as shown through CIRS-CI, MNA and EES scores, and number of medications) aspects in older patients. Coexisting cognitive impairment is common in persons with LLD and can involve multiple cognitive domains, including executive function, attention, and memory [51]. Cognitive deficits may thus be signs of accelerated brain aging that confers a predisposition to and perpetuates depression [45].

Some limitations of the study must be recognized. Study population comprised only Caucasian race people. Moreover, the patients were recruited in a single centre. Consequently, it could be probable that the showed outcomes may not be applicable in other populations.

### Declaration

*Ethics approval and consent to participate:* The study has been granted ethical approval by the Casa Sollievo della Sofferenza's ethics committee for human experimentation. The study was an observational study, in which the assignment of an intervention to the participants, its effect assessment and health-related biomedical or behavioral outcomes are not considered.

All of the participants were given information about the purpose of the study and details of the research procedures before the interview. Written informed consent was obtained from each of the participants before the interview started. The participants were allowed to withdraw from the study at any point. All of the data were kept confidential and anonymous.

### Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due containing personal data of patients, but are available in codified form from the corresponding author on reasonable request.

### Authors' contributions

GD, MPD and FA conceived of the study. MPD, FA and



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AG created the search protocol. GD and MPD examined the literature. MPD, FA and AG had performed the Duplex ultrasound scans in Echocardiography Evaluation Unit. GD, FC, ML, LC and FP had recruited the patients in Ageing Evaluation Unit. GD contributed to manuscript preparation. MPD, FA, DS, MGL, MP, and AG contributed to review the paper. The authors confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. The authors further confirm that the order of authors listed in the manuscript has been approved by all.

## Acknowledgments

This work was fully supported by "Ministero della Salute", I.R.C.C.S. Research Program, Ricerca Corrente "Malattie complesse e terapie innovative" and by the "5 x 1000" voluntary contribution.

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Citation: D'Onofrio G, Dagostino MP, Addante F, Ciccone F, Longo MG, et al. (2021) Mitral Valve Syndrome in older patients with and without depression: A cross-sectional study. J Cardiovasc Med Cardiol 8(2): 048-054. DOI: https://dx.doi.org/10.17352/2455-2976.000169

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**Citation:** D'Onofrio G, Dagostino MP, Addante F, Ciccone F, Longo MG, et al. (2021) Mitral Valve Syndrome in older patients with and without depression: A cross-sectional study. J Cardiovasc Med Cardiol 8(2): 048-054. DOI: https://dx.doi.org/10.17352/2455-2976.000169