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A Lower Cognitive Function in Patients with Severe Mitral Regurgitation Compared to those with Non-severe Mitral Regurgitation

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ABSTRACT

Background: Cognitive function includes cognitive domain such as memory, attention, execution function, psychomotor speed, language (speech), and visuospatial ability. Cardiac disease leads to cognitive impairment which may worsen its prognosis and further impact on increased mortality. However, there was limited study that explained the relationship between the severity of mitral regurgitation (MR) and cognitive function.

Aim: To compare the levels of cognitive function between patients with severe MR and non-severe MR.

Method: This was an observational study with cross-sectional design using consecutive sampling method. There were 276 subjects that consist of 134 subjects with severe MR and 142 subjects with non-severe MR, aged 20-65 years hospitalized in Dr.Kariadi hospital Semarang and Diponegoro National Hospital Semarang from February 2016 to February 2018. Subjects were examined for their cognitive function using MoCA-Ina score with blinding for their diagnosis. Statistical test were performed using chi-square test, Mann-Whitney test and non-parametric Spearman correlation test. $p<0.05$ was considered as statistically significant.

Results: Cognitive function by MoCA-Ina score in patients with severe MR was lower than those with non-severe MR (20.6 ± 3.9 vs 23.6 ± 4.2, $p=0.000$, respectively). There were higher proportions of atrial fibrillation, left atrial (LA) dilatation with LA diameter >40 mm, and left ventricle (LV) dilatation with LV diameter >55 mm, in group with severe MR compared to that with non-severe MR ($p<0.05$). There were larger LA diameter (47.5 ± 8.2 vs 41.8 ± 10.1, $p=0.000$) and larger LV diameter (56.9 ± 8.1 vs 49.2 ± 10.7, $p=0.000$) in group with severe MR compared to that with non-severe MR.

Conclusion: The severity of MR might impact on impaired cognitive function. This might be through LA remodeling and atrial fibrillation. Optimal management should be given in preventing cognitive decline in severe MR.

Keywords: Mitral regurgitation, severe MR, non severe MR, cognitive function, MoCA Ina score

INTRODUCTION

Valvular heart abnormalities or diseases are one of the main causes of disabilities, decrease quality of life, and early death in cardiovascular diseases. Since 1950, the etiology of valvular heart disease has been shifted from rheumatic heart disease to degenerative diseases in developed countries.[(1)] Meanwhile in developing countries, valvular heart diseases was still mainly caused by rheumatic heart disease,[(2)] especially mitral valve disease[1-6].

Mitral regurgitation (MR) is the most common valve lession in clinical practice. Significant mitral regurgitation is found in about 2% of all population with the same prevalence between men and women[4-7].

In an epidemiological study in the United States, mitral valve regurgitation occurs in 1.7% of the population,[(6)] and according to The Euro Heart Survey, mitral valve regurgitation occurs in 24% of the population in 25 European countries.[(8)] Epidemiological data indicated that moderate or severe mitral regurgitation was the most common valve disease in the United States, and was the second most common form of valvular heart disease requiring surgery in Europe[8,9].

Mitral regurgitation (MR) may result from systolic back flow from the left ventricle (LV) to the left atrium (LA) due to a lack of adequate coaptation of the mitral valve and the presence of a pressure gradient between the two cavities[10]. Mitral regurgitation can be divided into 2 groups, namely primary (structural) MR and secondary (functional) MR. Primary MR is caused due to valve or subvalvular apparatus problems, whereas secondary MR has normal valve and subvalvular apparatus conditions but a functional abnormality of the LV which interferes with the coaptation of the valve leaflets.[(5, 10-12)] The most common causes of primary MR in developed countries are mitral valve prolapse, rheumatic heart disease, endocarditis, and cordal rupture[2,4,5,8,11,12].

Mitral regurgitation in the early stages proceeds without causing significant clinical symptoms, because heart can compensate for the increased volume of regurgitation with left atrial enlargement. At an advanced stage, MR can lead to increased LV volume load, LV dysfunction, and impaired cardiac output[13]. A heart with MR must accommodate the ejection volume and the regurgitant volume in each heartbeat. The left ventricle commonly becomes hyperdynamic in compensation[10,11,13].

In acute severe MR, the pressure of the LA and pulmonary vein increases rapidly, causing pulmonary congestion and pulmonary edema. In chronic MR, the size of the LA increases gradually to compensate so that causes the increased pulmonary venous and LA pressure in the later stages of the disease[14]. Then, progressive LV dilatation eventually leads to increased afterload, contractile dysfunction, and heart failure[10,11,13]. The relationship between chronic MR that causes recurrent

hypoxia due to recurrent pulmonary edema with the decreased cognitive function still requires further research[15].

Cognitive function is a superior cortical function and involves multiple processes in the brain, allowing a person to receive information, learn and remember specific knowledge and use it for problem solving and action plans in facing challenges in everyday life. Cognitive domain which includes memory, attention, execution function, psychomotor speed, language or speech, and visuospatial abilities[15,16]. Cognitive impairment is a broad term for disorders of higher cognitive function such as thinking, remembering, learning new things, concentrating, planning, analysing, or making decisions that affect everyday life[15,16,17].

Impaired cognitive function can range from mild to severe. A study showed a link between heart disease and early cognitive decline which often lead to vascular dementia. This association became known as "cardiogenic dementia", which is linked to cognitive impairment and dementia triggered by a malfunctioning heart[15-20].

Cognitive disorders may not only lead to dementia but also become an individual hindrance in managing his/her health when dealing with complex chronic diseases.[21] Cognitive decline in cardiac patients can interfere with disease management.[15] Brain hypoperfusion due to low cardiac output or hypotension has been shown to correlate to cognitive deficits in attention and memory[22,23], microthrombus and microembolism[24] in the heart and inflammation[25] also correlated with impaired cognitive function[26].

One of several methods to determine an impairment in cognitive function is the Indonesian version of the Montreal Cognitive Assessment (MoCA) method or commonly referred to as MoCA-Ina. Montreal Cognitive Assessment (MoCA) was developed to detect mild cognitive impairment (MCI) in which it had sensitivity of 90% and specificity of 87% to detect MCI. A study showed that the MoCA method was more sensitive than the Mini-Mental State Examination (MMSE) method in detecting MCI. The MoCA method has a cutoff point of <26 for MCI out of a total score of 30[27-30].

Most studies on the relationship between cardiac function and cognitive function has focused on cognitive performance in patients with heart failure, low ejection fraction, hypotension, and shock.[15-18, 20, 22, 23, 26] There was limited study that explained the correlation between severity of mitral regurgitation with the incidence of impaired cognitive function. Hence, we performed this study to determine the relationship between the degree of severity of mitral regurgitation and cognitive function value that was based on the MoCA-Ina method. We compared the levels of cognitive function between patients with severe MR and non-severe MR.

METHODS

This was an observasional study with cross-sectional design conducted in in-patient ward of dr. Kariadi Central Hospital Semarang and Diponegoro National Hospital Semarang from February 2016 to February 2018. Study subjects were patients with mitral regurgitation aged of 20–65 years old that were hospitalized in dr. Kariadi Central Hospital Semarang and Diponegoro National Hospital Semarang, were included with consecutive sampling. Patients with history of stroke or transient ischemic attack (TIA), central nerve system infection, head trauma, intracranial tumor, and inability to independently respond to the study questionnaires due to language (speech) or visual obstacle were excluded[27].

All subjects (n=276) were divided into two groups, i.e. group with non-severe mitral regurgitation (n=142) and group with severe mitral regurgitasi (n=134). Data were obtained from direct assessment and interview with patients and medical records data. Direct cognitive function assessment was using MoCA-Ina which able to screen mild cognitive impairment (MCI) that consist of 4 cognitive domains, i.e. execution function, attention, memory, language, and visuospatial. It was consist of 30 points within one page and was given within 10 minutes.

Excecutive function was assessed by rotating assignment that was assessed with the Trail Making B task (1 point), phonemic fluency task (1 point), and verbal abstraction (1 point). Visuospatial ability was assessed with the task of drawing a clock (3 points) and drawing a 3-dimensional cube (1 point). Attention, concentration, and working memory were evaluated using continuous attention tasks, namely target detection by tapping (1 point), serial subtraction tasks (3 points), and forward and backward numbers (1 point each). Language or speech was assessed by mentioning 3 unknown animal names, namely lion, camel, rhino (3 points), repetition of 2 complex sentences (2 points), and fluency (1 point). Abstraction was assessed by comparing the similarity of an object (2 points). Memory (short-term memory recall and delayed recall) was assessed by repeating the words mentioned by the examiner (0 points) and recalling the words after 5 minutes (5 points). Orientation was assessed by stating time and place (6 points).

Mitral regurgitation severity was diagnosed by echocardiography by two blinded cardiologists. We divided MR into two groups only, i.e. severe MR and non-severe MR (mild and moderate MR). The severity of MR was assessed comprehensively with qualitative, semi-quantitative, and quantitative methods, i.e. regurgitation volume (RVol), regurgitation fraction, and effective regurgitant orifice area (EROA). Other methods were quantitative doppler and proximal isovelocity surface area (PISA) which was based on proximal flow convergence analysis[31,32,33].

Qualitative analysis of MR were including colour flow MR jet and continuous wave doppler of MR jet (CW signal of MR jet). By colour flow MR jet, mild MR was if there was small-central-colour flow MR jet, moderate MR was if there was intermediate colour flow MR jet, and severe MR was if there was very huge central jet or eccentric jet, rotated or reached the posterior wall of the left atrium. By continuous wave doppler of MR jet signal (CW signal of MR jet), mild MR was if there was weak or parabolic MR jet, moderate MR was if there was dense or parabolic MR jet, severe MR was if there was dense and triangular MR jet[32,33].

Semi-quantitave methods were including vena contracta (vc), pulmonary vein flow (PV flow), and mitral

inflow. By vena contracta, mild MR was if there was vc <3 mm, moderate MR was if there was vc 3-6 mm, severe MR was if there was vc ≥7 mm[34]. By pulmonary vein flow (PV flow), mild MR was if there was dominant systolic PV flow, moderate MR was if there was systolic blunting, severe MR was if there was systolic flow reversal. By mitral inflow, mild MR was if there was dominant A wave, moderate MR was if there was variable, severe MR was if there was dominant E wave[32,33].

Quantitative methods were EROA. Mild MR was if EROA <20 mm^2, moderate MR was if EROA = 20–29, 30–39 mm^2, and severe MR was if EROA ≥40 mm^2. Mild MR was diagnosed if regurgitation volume <30 mL, moderate MR was diagnosed if regurgitation volume 30–44; 45–59, and severe MR was diagnosed if regurgitation volume ≥60 mL. Mild MR was diagnosed if regurgitation fraction <30%, moderate MR was diagnosed if regurgitation fraction between 30% and 50%, and severe MR was diagnosed if regurgitant fraction was >50%[32,33].

The Kolmogorov-Smirnov test was conducted to determine the distribution or normality of data. Chi-square test was used to compare baseline characteristics in patients with non-severe MR and in those with severe MR. Mann-Whitney test was used to compare the cognitive function values between both groups. Spearman Correlation test was used to find out the correlation between several variables with the cognitive function. Differences were considered statistically significant if the *p* value <0.05. Ethical clearance for this study has been received from Ethics Committee of Medical and Health Research, Faculty of Medicine Diponegoro University.

RESULTS

Baseline characteristic of subjects is presented in table 1. There was a younger age in group with severe MR (40.5±9.17 years old) compared to non-severe MR (43.2±11.31 years old) (*p*=0.015). Meanwhile, there were no differences between group with severe MR and non-severe MR in gender, basic education, anthopometric status, and rough hemodynamic findings, such as systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). There were also no differences in history of hypertension and smoking status between group with severe MR and non-severe MR (table 1).

There was a higher proportion of atrial fibrillation in group with severe MR 104(37.7%) compared to that with non-severe MR 20(7.2%) (*p*=0.000). There was a higher history of coronary artery disease (CAD) in group with non-severe MR 28(10.1%) compared to that with severe MR 4(1.4%) (*p*=0.000) (table 1).

The structural characteristic is presented in table 2. There was more proportion of structural MR in group with severe MR 121(43.8%) compared to that with non-severe MR 84(30.4%) (*p*=0.000). There was a bigger proportion of left atrial (LA) dilatation with LA diameter >40 mm in group with severe MR 130(47.1%) compared to group with non-severe MR 94(34.1%) (*p*=0.000). Consistently, there was a larger mean LA diameter in group with severe MR compared to that with non-severe MR (47.5±8.2 vs 41.8±10.1, *p*=0.000, respectively) (table 2).

There was a bigger proportion of left ventricle (LV) dilatation with LV diameter >55mm in group with severe MR 105(38.0%) compared to group with non-severe MR 28(10.1%) (*p*=0.000). Consistently, there was a larger mean LV diameter in group with severe MR compared to that with non-severe MR (56.9±8.1 vs 49.2±10.7, *p*=0.000, respectively). There were also significant differences in right ventricular diameter (RVIDd), interventricular septum wall thickness (IVSd), and left ventricular ejection fraction (LVEF) between group with severe and that with non-severe MR (*p*<0.05) (table 2). Meanwhile, there were no differences in the level of ureum, creatinine, uric acid, and random blood glucose between both groups (table 3).

Analysis between MoCA-Ina score with several variabels is presented in table 5. The cognitive function that was represented with MoCA-Ina score was associated with the severity of MR, the existence of atrial fibrillation (AF), LA dilatation, and RV dilatation (*p*<0.05). There was a negative weak correlation between LA diameter and MoCA-Ina score (r = -0.204, *p*=0.001) (Table 5).

There was a significant difference in cognitive function that was represented by MoCA-Ina score between group with severe and that with non-severe MR (20.6 ± 3.9 vs 23.6 ± 4.2, *p*=0.000, respectively). Group with non-severe MR showed a better cognitive function than severe MR (table 4, figure 1).

Table 1 Baseline Characteristic of Subjects between Group with Severe and that with Non-Severe Mitral Regurgitation (MR) (n=276)

Characteristic	Diagnosis		*p*	Total
	Severe MR (n= 134)	Non-severe MR (n= 142)		
Age (years)	40.5 ± 9.17; 37 (21 – 65)	43.2 ± 11.31; 43 (20 – 65)	0.015 [c] *	41.9±10.4; 39(20– 65)
Gender (n, %)				
Female	64 (23.2%)	72 (26.1%)	0.625 [a]	136 (49.3%)
Male	70 (25.4%)	70 (25.4%)		140 (50.7%)
Basic Education (n, %)				
≤ 12 years	108 (39.1%)	90 (32.6%)	0.314 [a]	198 (71.7%)
>12 years	26 (9.4%)	52 (18.8%)		78 (28.3%)
Bodyweight (kg)	59.4 ± 6.71; 59 (38 – 80)	61.7 ± 9.46; 59 (34 – 90)	0.118 [c]	60.6 ± 8.30; 59 (34 – 90)
Height (cm)	163.0 ± 3.47; 165 (150 – 176)	162.3 ± 4.42; 164 (147 – 175)	0.238 [c]	162.6 ± 3.99; 165 (147 – 176)
BMI (kg/m^2)	22.3 ± 2.19; 21.6 (14.8 – 28.3)	23.3 ± 3.33; 22.5 (13.7 – 35.1)	0.184 [c]	22.8 ± 2.87; 21.6 (13.7 – 35.1)
Overweight (n, %)				
Yes	10 (3.6%)	38 (13.8%)	0.058 [a]	48 (17.4%)
No	124 (44.9%)	104 (37.7%)		228 (82.6%)
Smoking (n, %)				
Yes	32 (11.6%)	12 (4.3%)	0.056 [a]	44 (15.9%)
No	102 (37.0%)	130 (47.1%)		232 (84.1%)
Hypertension (n, %)				
Yes	32 (11.6%)	44 (15.9%)	0.187 [a]	76 (27.5%)

No	102 (37.0%)	98 (35.5%)		200 (72.5%)
Dyslipidemia (n, %)				
Yes	25 (9.1%)	48 (17.4%)	0.004 [a] *	73 (26.4%)
No	109 (39.5%)	94 (34.1%)		203 (73.6%)
Diabetes Mellitus (n, %)				
Yes	4 (1.4%)	26 (9.4%)	0.000 [a] *	30 (10.9%)
No	130 (47.1%)	116 (42.0%)		246 (89.1%)
Atrial Fibrillation (n, %)				
Yes	104 (37.7%)	20 (7.2%)	0.000 [a] *	124 (44.9%)
No	30 (10.9%)	122 (44.2%)		152 (55.1%)
History of CAD				
Yes	4 (1.4%)	28 (10.1%)	0.000 [a] *	32 (11.6%)
No	130 (47.1%)	114 (41.3%)		244 (88.4%)
SBP (mmHg)	119.0 ± 21.5; 110 (83 – 200)	120.2 ± 22.2; 117.5 (83 – 200)	0.613 [c]	119.6 ± 21.8; 112 (83 – 200)
DBP (mmHg)	74.8 ± 12.1; 70 (48 – 110)	76.2 ± 12.5; 80 (48 – 110)	0.130 [c]	75.5 ± 12.4; 75 (58 – 110)
MAP (mmHg)	89.5 ± 14.3; 87 (63 – 140)	90.9 ± 14.9; 90 (63 – 140)	0.232 [c]	90.2 ± 14.6; 90 (63 – 140)

Data is presented as mean ± standard deviation (SD), median (min – max)
*p<0.05 is considered as statistically significant
[a] Chi-square test
[b] Independent *t*-test
[c] Mann-Whitney test

Table 2: Structural Characteristic between Group with Severe and that with Non-Severe Mitral Regurgitation (MR) (N=276)

Characteristic	Diagnosis		*p*	Total
	Severe MR (n= 134)	Non-severe MR (n= 142)		
Type of MR				
Structural	121 (43.8%)	84 (30.4%)	0.000 [a] *	205 (74.3%)
Functional	13 (4.7%)	58 (21.0%)		71 (25.7%)
Tricuspid valve disease				
Yes	58 (21.0%)	64 (23.2%)	0.765 [a]	122 (44.2%)
No	76 (27.5%)	78 (28.3%)		154 (55.8%)
Aortic valve disease				
Yes	30 (10.9%)	38 (13.8%)	0.399 [a]	68 (24.6%)
No	104 (37.7%)	104 (37.7%)		208 (75.4%)
Pulmonary valve disease				
Yes	40 (14.5%)	38 (13.8%)	0.569 [a]	78 (28.3%)
No	94 (34.1%)	104 (37.7%)		198 (71.7%)
Pulmonal Hypertension (PH)				
Severe PH	4 (1.4%)	10 (3.6%)	0.088 [a]	14 (5.1%)
ModeratePH	24 (8.7%)	14 (5.1%)		38 (13.8%)
Mild PH	4 (1.4%)	2 (0.7%)		6 (2.2%)
No PH	102 (37.0%)	116 (42.0%)		218 (79.0%)
Left Atrial diameter (LAd)				
> 40 mm	130 (47.1%)	94 (34.1%)	0.000 [a] *	224 (81.2%)
≤ 40 mm	4 (1.4%)	48 (17.4%)		52 (18.8%)
LAd (mm)	47.5 ± 8.2; 44 (34 – 88)	41.8 ± 10.1; 38 (23 – 83)	0.000 [c] *	44.5 ± 9.6; 43 (23 – 88)
Left Ventricle end-diastolic diameter (LVEDD)				
> 55 mm	105 (38.0%)	28 (10.1%)	0.000 [a] *	133 (48.2%)
≤ 55 mm	29 (10.5%)	114 (41.3%)		143 (51.8%)
LVEDD (mm)	56.9 ± 8.1; 57 (35.9 – 74.0)	49.2 ± 10.7; 48 (35 – 82)	0.000 [c] *	52.9 ± 10.2; 55 (35 – 82)
Right ventricular diameter (RVID)				
> 35 mm	134 (48.6%)	10 (3.6%)	0.000 [a] *	144 (52.2%)
≤ 35 mm	0 (0%)	132 (47.8%)		132 (47.8%)
Right ventricular diameter (RVID)	35.5 ± 1.9; 35 (35 – 39)	33.3 ± 1.0; 34 (31 – 35)	0.000 [c] *	34.4 ± 1.4; 35 (31 – 39)
Interventricular septum wall thickness (IVSd)				
> 10 mm	111 (40.2%)	0 (0%)	0.002 [a] *	111 (40.2%)
≤ 10 mm	23 (8.3%)	142 (51.4%)		165 (59.8%)
Interventricular septum wall thickness (IVSd)	11.0 ± 1.7; 11 (9 – 13)	9.5 ± 1.6; 10 (8 – 10)	0.000 [c] *	10.2 ± 1.0; 10 (8 – 13)
Left ventricular hypertrophy (LVH)				
Concentric	21 (7.6%)	50 (18.1%)	0.000 [a] *	71 (25.7%)
Eccentric	95 (34.4%)	9 (3.3%)		104 (37.7%)
No LVH	18 (6.5%)	83 (30.1%)		101 (36.6%)
Left ventricular ejection fraction (LVEF)				
<50%	24 (8.7%)	42 (15.2%)	0.023 [a] *	66 (23.9%)
≥50 %	110 (39.9%)	100 (36.2%)		210 (76.1%)
LVEF (%)	62.3 ± 9.4; 65 (35 – 88)	58.1 ± 12.3; 63 (33 – 78)	0.027 [c] *	60.2 ± 11.2; 63 (33 – 88)

Data is presented as mean ± standard deviation (SD), median (min – max)
*p<0.05 is considered as statistically significant
[a] Chi-square test [b] Independent *t*-test [c] Mann-Whitney test

Table 3: Laboratoric Findings between Group with Severe and that with Non-Severe Mitral Regurgitation (MR) (n=276)

Variables	Diagnosis		*p*	Total
	Severe MR (n= 134)	Non-severe MR (n= 142)		
Ureum	39.5 ± 29.3; 36 (15 – 175)	37.4 ± 15.0; 34 (13 – 99)	0.160 [c]	38.1 ± 25.5; 35 (13 – 175)
Creatinin	1.0 ± 0.3; 0.9 (0.5 – 2.3)	1.1 ± 0.8; 1.0 (0.3 – 6.3)	0.134 [c]	1.1 ± 0.6; 0.9 (0.3 –6.3)
Uric acid	6.9 ± 1.8; 6.9 (4.0 – 15.5)	5.9 ± 1.6; 5.5 (4.1 – 12.9)	0.087 [c]	6.4 ± 1.8; 5.5 (4.0 –15.5)
Random blood glucose (mg/dl)	154 ± 17.9; 159 (121 – 210)	152 ± 26.6; 157 (121 – 223)	0.309 [c]	153 ± 22.8; 159 (121 – 223)

Data is presented as mean ± standard deviation (SD), median (min – max)
*p<0.05 is considered as statistically significant
[a] Chi-square test [b] Independent *t*-test [c] Mann-Whitney test

Table 4: MoCA-Ina Score between Group with Severe and that with Non-Severe Mitral Regurgitation (MR) (n=276)

	Diagnosis		*p*	Total
	Severe MR (n= 134)	Non-severe MR (n= 142)		
MoCA-Ina score	20.6 ± 3.9; 21 (12 – 30)	23.6 ± 4.2; 25 (15 – 30)	0.000 [c] *	22.1 ± 4.3; 22 (4 – 30)

Data is presented as mean ± standard deviation (SD), median (min – max)
*p<0.05 is considered as statistically significant
[a] Chi-square test [b] Independent *t*-test [c] Mann-Whitney test

Figure 1: The MoCA-Ina Score between Group with Severe and that with Non-Severe Mitral Regurgitation (MR).

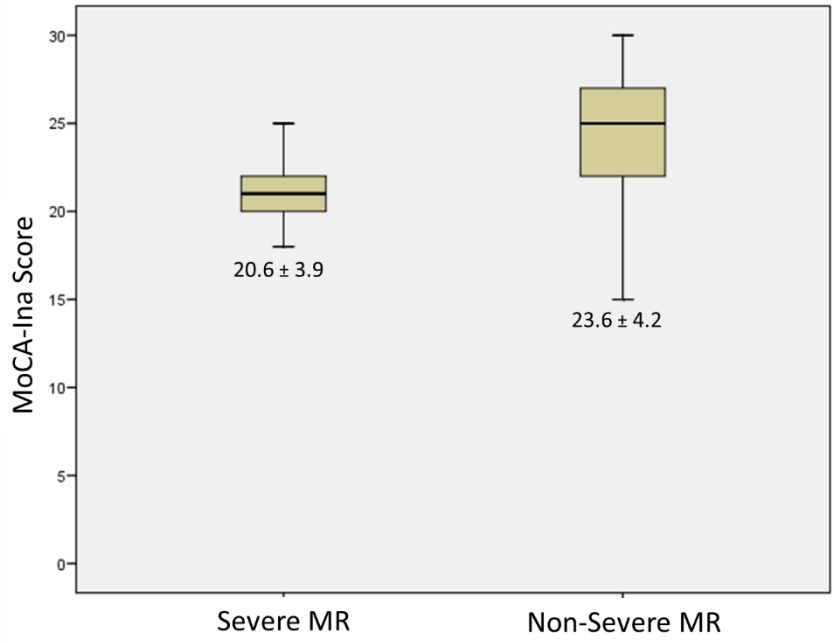

Table 5: Analysis between MoCA-Ina score with several variabels

Variables	MoCA-Ina Score	*p*
	Mean±SD; Median (Min-Max)	
Severity of MR		
Severe MR	20.6 ± 3.9; 21 (12 – 30)	0.000 [c] *
Non-severe MR	23.6 ± 4.2; 25 (15 – 30)	
Age (years)		0.211 [d]
Dyslipidemia		
Yes	22.1 ± 3.7; 23 (12 – 27)	0.241 [c]
No	22.1 ± 4.5; 22 (14 – 30)	
Diabetes mellitus		
Yes	21.2 ± 4.7; 22 (12 – 26)	0.131 [c]
No	22.4 ± 4.2; 22 (14 – 30)	
History of CAD		
Yes	21.9 ± 4.5; 23.5 (12 – 27)	0.904 [c]
No	22.2 ± 4.3; 22 (14 – 30)	
Atrial fibrillation		
Yes	20.6 ± 3.7; 21 (14 – 25)	0.000 [c] *
No	23.4 ± 4.4; 24 (12 – 30)	
Type of MR		
Structural	22.5 ± 4.0; 22 (14 – 30)	0.273 [c]
Functional	21.1 ± 5.1; 22 (12 – 28)	
LA dilatation		

LAd >40 mm	21.1 ± 4.4; 21 (14 – 30)	0.044 [c] *
LAd ≤40 mm	23.3 ± 4.1; 23 (12 – 29)	
LA diameter (mm)	r = -0.204	0.001 [d] *
LV dilatation		
LVEDD > 55 mm	21.6 ± 3.5; 21 (12 – 30)	0.091 [c]
LVEDD ≤ 55 mm	22.6 ± 4.9; 24 (14 – 30)	
Left Ventricle end-diastolic diameter (LVEDD) (mm)	r = -0.050	0.411 [d]
Right ventricular diameter (RVID)		
> 35 mm	20.7 ± 3.9; 21 (14 – 30)	0.000 [c] *
≤ 35 mm	23.8 ± 4.2; 25 (12 – 30)	
RVID (mm)	r = -0.375	0.000 [d] *
Interventricular septum wall thickness (IVSd)		
> 10 mm	21.6 ± 3.7; 21 (14 – 30)	0.084 [c]
≤ 10 mm	22.2 ± 4.4; 22 (12 – 30)	
IVSd (mm)	r = -0.314	0.137 [d]
LVH		
Concentric	22.3 ± 5.1; 22 (14 – 29)	0.094 [c]
Eccentric	21.1 ± 3.1; 21 (12 – 30)	
No LVH	23.7 ± 4.6; 24 (14 – 30)	
LVEF		
<50%	21.2 ± 5.7; 23 (14 – 30)	0.563 [c]
≥50 %	22.4 ± 3.8; 22 (12 – 30)	
LVEF	r = 0.023	0.703 [d]

[c] Mann-Whitney test [d] Bivariate analysis with Spearman Correlation *p<0.05 is considered as statistically significant

DISCUSSION

There are **s**everal factors that affect on cognitive function, such as gender, age, cardiovascular risk factors named hypertension, dyslipidemia, diabetes mellitus, stroke or transient ischemic attact (TIA), central nervous system (CNS) infection, and head trauma.[18, 23, 27] In our study, we have eliminated the confounding factors such as stroke or TIA, CNS infection, and head trauma by exclusion of patients with those histories.

Our study showed that there was a significant difference in cognitive function that was represented by MoCA-Ina score between group with severe and that with non-severe MR. Group with severe MR showed a lower cognitive function than non-severe MR. This meant that we should not ignore the possibility of cognitive decline in patients with severe MR. Sangha et al stated that the ignorance of cognitive dysfunction might cause lack of independence in patients, which in turn resulted in increased mortality[26].

Our study also showed that there were higher proportion of LA dilatation and atrial fibrillation in group with severe MR compared to that with non-severe MR. Consistently, our study also showed larger LA diameter in group with severe MR compared to that with non-severe MR.[35] This larger LA diameter might represent structural and electrical remodelling in LA due to severe MR in which further caused atrial fibrillation[14,36].

Our study further showed that subjects with atrial fibrillation showed a lower cognitive function compared to that without atrial fibrillation (20.6±3.7 vs 23.4±4.4, respectively)[36]. We also found that subjects with LA dilatation represented with LA diameter >40 mm showed a lower cognitive function compared to that without LA dilatation (21.1±4.4 vs 23.3±4.1, respectively). This finding was similar to previous study by Alosco et al which showed that LA was independently associated with cognitive function[35].

The sensitivity of LA size underlies the severity of cardiovascular disease because it reflects abnormal diastolic filling and is closely related to LV diastolic pressure. The enlargement of LA also results in secretion of atrial natriuretic peptide (ANP) which plays a role in the regulation of various physiological processes such as natriuresis, diuresis, and lowers arterial blood pressure due to its vasodilator activity. ANP is also involved in the regulation of various physiological processes associated with cognitive decline[35].

Left ventricular ejection fraction (LVEF) is commonly used to assess cardiac function in patients with cardiovascular disease. Congestive heart failure may cause cardiac microemboli or stroke[24,37] and chronic repetitive cerebral ischemic or hypoperfusion that related to cognitive dysfunction[22,37,38]. Study by Almeida OP et al showed that 35% to 50% of patients with heart failure showed cognitive dysfunction[39].

Our study failed to get significant association between (LVEF) with cognitive function represented by MoCA-Ina score. Our finding was in line to previous studies which showed that the correlation between LVEF and cognitive function were vary between studies.[18, 19] Our finding was different to study by Zuccala et al which showed that LVEF had an independent effect on cognitive function in which a very low LVEF namely ≤30% showed significantly lower cognitive function[19,40,41].

An alternative mechanism that causes impaired cognitive function scores in subjects with MR may be due to impaired hemodynamic function. In severe MR, there is a volume overload in the LV. This volume overload can increase left ventricular end-diastolic pressure (LVEDP) and impaired LV diastolic filling leading to pulmonary congestion and shortness of breath. If severe and prolonged, it can cause LV fatigue and lead to decreased LV contractility function (LVEF). Decreased LVEF in patients with MR is often accompanied by clinical manifistation of decreased functional class and functional capacity[10,12,13]. EF is sensitive to the changes in hemodynamic load conditions in the LV. Meanwhile, the decrease in systemic blood flow triggers vascular, cytokine, and humoral responses[25].

Mitral dysfunction is one of the common disorders causing pulmonary edema. Study by Schnyder et al

showed that subjects with severe MR were dominating as a disorder causing pulmonary edema episode.[42] Patients with MR have experienced at least once or more pulmonary edema by chest radiogram. We assumed that chest radiogram could not perform every time, thus there were probabilities of pulmonary edema episode out of routine examination that were not reported.[12]

Shortness of breath, dyspnoea, or pulmonary edema can cause repeated hypoxia and cerebral ischemia.[12, 38, 42] Impaired cerebral perfusion or cerebral hypoxia can contribute to clinical or subclinical brain injury by precipitating or exacerbating cerebrovascular disease through changes in microvascular structure and permeability, expression of vascular cell receptors, changes in small vessel permeability, and vascular remodeling.[37-39]

Several previous studies also showed that the chronic duration of cerebral blood flow reduction or cerebral hypoxia also determines the extent of cognitive decline. Prolonged cerebral ischemia can cause degenerative brain disorders, including subcortical lesions or progression of white matter changes[34,44].

Hypoxemia during awake and sleep can cause biochemical and hemodynamic disturbances of the central nervous system (CNS). Arterial hypoxia in humans with reduction of O_2 arterial tension to 35 mmHg followed by increased glucose use and increased lactate production. Lactic acid accumulates in the brain during hypoxia[45,46]. Cerebral hypoxemia impairs concentration, memory, and processing abilities[38,39].

The phases in chronic severe MR can be divided into three based on clinical and hemodynamic profiles. The first is the initial compensatory phase in which there is eccentric hypertrophy of the LV due to volume overload so that the contents of the pumped valve are larger.[12, 13] The LA is also enlarged so that it is able to adapt to large volume regurgitation without a significant increase in LA pressure (LAP) and thus LVEDP remains low[13,14]. Left ventricular contraction function and pulmonary artery pressure (PAP) are normal and the patient is still asymptomatic in this phase[10,12]. However, in the late decompensated phase, symptoms of heart failure are associated with a progressive decrease in LV contraction function, an increase in maladaptive LV dimensions resulting in increased wall tension during systole,[13] increase LV diastolic filling, and worsening pulmonary hypertension. It seemed that EF could be a relevant clinical index of LV systolic function in MR and could be a basic for decision making[12,13].

Increased LAP may increase the secretion of ANP regardless of changes in LA diameter. The increase in LVEDP is also proportional to the increase in ANP secretion.[47] Level of the precursor of ANP hormone, midregional proatrial natriuretic peptide (MR-proANP), was significantly increased in patients with Alzheimer's disease when compared to healthy people. A study showed that plasma MR-proANP level was able to predict the conversion from mild cognitive impairment predementia to an Alzheimer's disease.[47-49]

Pump failure due to LV fatigue due to volume overload can increase the inflammatory response and secretion of inflammatory cytokines such as TNF-α, IL-1β, and also some chemokines such as MCP-1, IL-8, and MIP 1α. Humoral signaling of cytokines such as TNF-α, IL-1β, and IL-6, circulate in the blood and give signaling to the CNS via an in-patent blood brain barrier (BBB), or deliver signaling in the BBB via receptors expressed on the endothelium. Signaling to the brain via these routes evokes a microglia response. Systemic inflammatory mediator signaling overloads cerebral inflammatory mediators. This is likely to lead to a neurodegeneration process which ultimately has an impact on cognitive.[25, 50]

A study by Karatasakis et al showed that even patients with non-significant MR were at high risk for thrombus formation in LA and embolization at a later stage.[51] While Tse et al found that the severity of MR showed a correlation with platelet activation shown by plasma platelet factor 4 (PF4) dan Beta-thromboglobulin (BTG). PF4 and BTG are specific platelet proteins stored in alpha granules and released in plasma during platelet activation. These findings were consistent with clinical observations that patients with severe MR had a higher incidence of thromboembolism[52].

Other possible mechanism associated with cognitive function is thromboembolic due to hypercoagulable state in which often happens in atrial fibrillation[36], stasis state in cardiac chambers, abnormalities in hemostasis and thrombosis, low EF, or congestive heart failure. Hypercoagulable state may be an important factor in the pathogenesis of embolic related-cerebral ischemic or infarction, in which this cerebral ischemic or infarction could manifest clinically or subclinically[15,16,17,20.37].

Our study revealed that subjects with severe MR showed LA dilatation and atrial fibrillation. Subjects with MR often result in structural and electrical LA remodeling[14]. However, cardiac embolism may also happen in subjects with MR or heart failure with sinus rhythm, but may be with undocumented paroxysmal atrial fibrillation[36,53]. Subjects with MR who experienced paroxysmal atrial fibrillation also showed stasis, clinical or subclinical thromboembolic stroke, or microembolization[24] which all caused to cognitive decline[36,51]. These are through heart chambers dilatation[35], decreased myocardial contractility, thrombomodulin downregulation, and potential for blood stasis correlated to thromboembolic formation[24,52,53].

This study had some limitations in which this was a cross-sectional study that could not show “cause-effect relationship” between research variables. It is needed to perform further studies with cohort design with larger sample amount to get “cause-effect relationship” between patients with MR to the cognitive function and analysed for each cognitive domain. We need to confirm the levels of inflammatory and coagulable markers in patients with MR to the cognitive decline.

CONCLUSION

There was a significant association between the severity of MR and cognitive function. Patients with severe MR showed worse cognitive impairment compared to those with non-severe MR. Optimal managements should be needed to prevent declined cognitive function in MR.

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