that the omission of this marker in review articles [1], deprives the medical community of potentially useful information.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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A novel indicator for assessment of mitral regurgitation severity: Pro-adrenomedullin

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Surgery is recommended in symptomatic patients with chronic severe mitral regurgitation (MR) and in asymptomatic severe MR with left ventricular (LV) dysfunction [1]. When guideline indications for surgery are reached, early surgery is associated with better outcomes, since the development of even mild symptoms by the time of surgery is associated with deleterious changes in cardiac function after surgery [2,3]. However, difficulties in detecting early LV dysfunction, accurately assessing the severity of valve involvement, or recognizing early cardiac symptoms often make it difficult to determine the optimal timing of mitral valve surgery [4]. In many patients, the development of symptoms is clear, but in others, symptoms are difficult to assess because of inactivity and it may also be unclear whether symptoms are related to severe MR or comorbidities [5,6]. Adrenomedullin is a vasodilating and natriuretic peptide of vascular endothelial and smooth muscle cell origin [7]. It is expressed in cardiovascular tissue such as the cardiac atria and ventricles and helps to maintain blood supply to the organs [8]. This peptide could function as an atrial natriuretic peptide in the control of cardiorenal homeostasis and may influence cardiovascular function [9]. The aim of this study was to evaluate the association between plasma pro-adrenomedullin levels and MR and its prognostic value as indicator of cardiovascular prognosis in patients with moderate/severe MR.

A total of 221 consecutive patients with isolated and organic moderate MR, moderate to severe MR or severe MR were included in the study. Exclusion criteria were as follows: a history of myocardial infarction, previous cardiac surgery, associated valve disease, ischemic MR, significant liver or renal disease, the presence of moderate or severe respiratory disease, malignant or hematologic disease and the presence of local or systemic infection, patients with poor echocardiographic acoustic window. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Patients were categorized according to the New York Heart Association (NYHA) functional class. A cardiologist who was blinded to the pro-adrenomedullin results performed clinical evaluation. In all participants, transthoracic M-mode, two-dimensional, pulsed-wave, continuous-wave and color Doppler echocardiographic examinations were performed with a Vingmed Vivid 7 ultrasound system (GE Vingmed, Horten, Norway) using 2.5–3.5 MHz transducers. We assessed and graded the severity of MR using a multiparametric approach as follows: *moderate MR* (jet area/left atrial area 10%–30%, diastolic dominancy

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Table 1
Demographic and clinical characteristics of patients with mitral regurgitation and comparison between asymptomatic and symptomatic patients.

	All patients (n = 221)	Asymptomatic (n = 62)	Symptomatic (n = 159)	P value
Mean age, years	61.6 ± 12.5	52.5 ± 12.5	65.2 ± 10.7	<**0.001**
Female, n (%)/male, n (%)	129 (58.4)/ 92 (41.6)	47 (75.8)/ 15 (24.2)	82 (51.6)/ 77 (48.4)	**0.001**
Hypertension, n (%)	158 (71.5)	32(51.6)	126(79.2)	<**0.001**
Cigarette smoker, n (%)	29 (13.1)	10 (16.1)	19 (11.9)	0.506
Diabetes mellitus, n (%)	38 (17.2)	7 (11.3)	31 (19.5)	0.102
BMI (kg/m2)	29.8 ± 6.0	28.9 ± 3.6	30.2 ± 6.7	0.132
BMI ≥ 30 kg/m2, n (%)	86 (39.4)	18 (29)	68 (43.6)	0.065
NYHA class				
I	62 (28.19)	62 (100)	–	
II	87 (39.4)	–	87 (54.7)	
III	54 (24.4)	–	54 (34)	
IV	18 (8.1)	–	18 (11.3)	
Atrial fibrillation, n (%)	108 (49.5)	23 (37.1)	85 (53.5)	**0.024**
Lower-extremity edema, n (%)	91 (41.2)	6 (9.7)	85 (53.5)	<**0.001**
Medication				
Beta blockers, n (%)	115 (52.8)	26 (41.9)	89 (57.1)	0.510
ACEI/ARBs, n (%)	168 (77.1)	41 (66.1)	127 (81.4)	**0.020**
Diuretics, n (%)	102 (46.8)	15 (24.2)	87 (55.8)	<**0.001**
CCB, n (%)	16 (7.3)	6 (9.7)	10 (6.4)	0.399
Digoxin, n (%)	33 (15.1)	6 (9.7)	27 (17.3)	0.209
Baseline hemodynamics				
Systolic BP, mmHg	127.9 ± 20.7	124.6 ± 16.6	129.1 ± 21.9	0.809
Diastolic BP, mmHg	78.2 ± 19.2	77.9 ± 7.1	78.3 ± 10.0	0.169
Heart rate, beats/min	80.9 ± 19.2	72.5 ± 15.0	84.3 ± 19.7	<**0.001**

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BP, Blood pressure; BMI, body mass index; CCB, Calcium channel blockers; and NYHA, the New York Heart Association. Values are mean ± SD (range) or n (%).

in pulmonary vein flow, regurgitant volume 30–44 ml, regurgitant fraction 30%–39%), *moderate to severe MR* (jet area/left atrial area >30%–<40% pulmonary vein flow is all diastolic, regurgitant volume:

Table 2
Echocardiographic and laboratory parameters of patients with mitral regurgitation and comparison between asymptomatic and symptomatic patients.

	All patients (n = 221)	Asymptomatic (n = 62)	Symptomatic (n = 159)	P value
Echocardiographic findings				
LVEDD (mm)	51.4 ± 6.3	49.6 ± 3.9	52.1 ± 6.9	**0.008**
LVESD (mm)	36.2 ± 7.3	33.5 ± 6.1	37.2 ± 7.5	**0.001**
LA (mm)	43.8 ± 5.0	42.0 ± 5.0	44.5 ± 4.9	**0.001**
Ejection fraction (%)	54.1 ± 11.5	61.3 ± 7.6	51.4 ± 11.5	<**0.001**
PAP (mm Hg)	36.5 ± 9.5	33.8 ± 6.9	37.6 ± 10.2	**0.008**
Mitral regurgitation severity				<**0.001**
Moderate	118 (53.4)	59 (95.2)	59 (37.1)	
Moderate to severe	62 (28.05)	3 (4.8)	59 (37.1)	
Severe	41 (18.55)	–	41 (25.8)	
Laboratory findings				
Hemoglobin (g/dl)	12.7 ± 1.2	13.0 ± 0.9	12.6 ± 1.3	**0.031**
BUN (mg/dl)	18.8 ± 7.7	17.8 ± 6.5	19.3 ± 8.1	0.192
Serum creatinine (mg/dl)	0.92 ± 0.3	0.87 ± 0.3	0.94 ± 0.3	0.084
Fasting glucose (mg/dl)	113.2 ± 42.4	96.7 ± 13.6	119.8 ± 47.8	<**0.001**
FT3 (pg/ml)	2.88 ± 0.73	2.75 ± 0.72	2.94 ± 0.74	0.147
FT4 (ng/dl)	1.28 ± 0.29	1.27 ± 0.18	1.29 ± 0.33	0.654
TSH (μIU/ml)	1.55 ± 2.50	1.77 ± 1.50	1.46 ± 2.48	0.423
Total cholesterol (mg/dl)	186.6 ± 41.6	211.3 ± 45.1	175.8 ± 35.1	<**0.001**
HDL (mg/dl)	47.7 ± 12.9	50.3 ± 10.8	46.6 ± 13.5	0.065
LDL (mg/dl)	107.4 ± 33.6	127.4 ± 36.8	98.5 ± 28.0	<**0.001**
Triglyceride (mg/dl)	144.2 ± 59.2	141.3 ± 47.8	145.5 ± 63.9	0.646
Calcium (mmol/l)	9.29 ± 0.72	9.31 ± 0.46	9.2 ± 0.80	0.839
Potassium (mmol/l)	4.5 ± 0.5	4.39 ± 0.37	4.53 ± 0.48	**0.048**
Sodium (mmol/l)	140.1 ± 3.0	140.0 ± 2.1	140.1 ± 3.3	0.902
Pro-adrenomedullin (pmol/l)	7.50 ± 7.15	3.54 ± 3.51	9.04 ± 7.62	<**0.001**

FT3, free triiodothyronine; FT4, free thyroxine; PAP: Pulmonary artery pressure; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; and TSH, thyroid-stimulating hormone. Values are mean ± SD (range) or n (%).

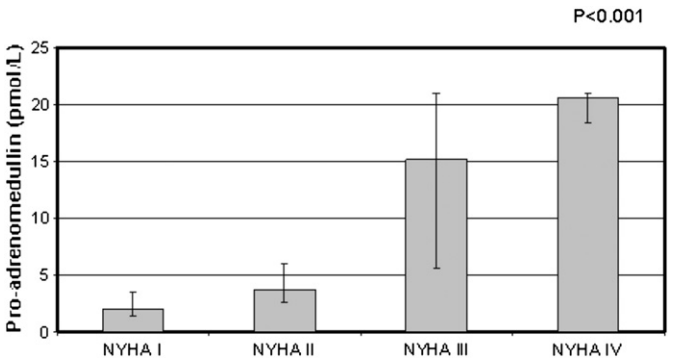

Fig. 1. Pro-adrenomedullin levels according to NYHA functional class. Top of the bar presents median and, whiskers present the 25th and 75th percentile of concentrations. P_1; NYHA I vs NYHA II, P_2; NYHA I vs NYHA III, P_3; NYHA I vs NYHA IV, P_4; NYHA II vs NYHA III, P_5; NYHA II vs NYHA IV, and P_6; NYHA III vs NYHA IV. $P_1 = 0.001$, $P_2 < 0.001$, $P_3 < 0.001$, $P_4 < 0.001$, $P_5 < 0.001$, and $P_6 = 0.045$.

45–59 ml, regurgitant fraction 40%–49%) and *severe MR* (jet area/left atrial area >40%, systolic reversal pulmonary vein flow, regurgitant volume ≥60 ml, regurgitant fraction ≥50%) [10,11].

Pro-adrenomedullin was measured with ELISA method (Micro ELISA Autoreader, Bio Tek Instruments, Inc., Burlington, VT), by using Human Pro-adrenomedullin N-20 terminal peptide ELISA kit (Cusabio Biotech Co., Wuhan, China).

Patients were followed-up by outpatient assessments and telephone contact. Patients who died or underwent surgery were censored the same day, and those who remained alive were censored at the end of follow-up.

We performed statistical analysis by means of SPSS software, version 13.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as mean ± SD or median (25th–75th percentile) categorical variables are presented as percentages and frequencies. The Student's *t*-test was used to compare the continuous variables in two groups and Kruskall Wallis was used to compare abnormal distributed continuous variables in the different groups. Bonferroni adjusted Mann Whitney *U* test was used for multiple comparisons. Chi-square test was used for categorical variables between two groups. Variables with a p value of <0.05 in univariate analyses were then entered into a multivariate Cox proportional hazards regression analysis to estimate the independent predictors of mortality during follow up. A p value of less than 0.05 was considered statistically significant.

Among the 221 patients with moderate, moderate to severe and severe MR included in the study, 62 were asymptomatic while 159 were

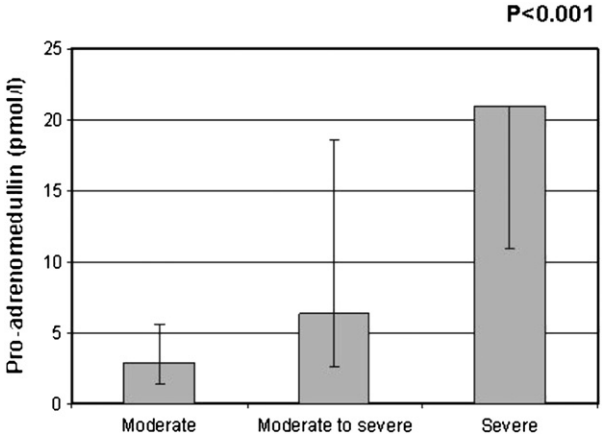

Fig. 2. Pro-adrenomedullin levels according to the degree of mitral regurgitation. Top of the bar presents median and, whiskers present the 25th and 75th percentile of concentrations. P_1; moderate vs moderate to severe, P_2; moderate vs severe, and P_3; moderate to severe vs severe. $P_1 = <0.001$, $P_2 < 0.001$, and $P_3 < 0.001$.

Table 3
Results of univariate and multivariate Cox proportional hazard analysis for all-cause mortality at 12 months for the patients with mitral regurgitation.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P value	HR	95% CI	P value
Gender	0.208	0.057–0.757	0.017	0.631	0.27–5.565	0.681
NYHA class			<0.001			<0.001
NYHA I vs II	0.795	0.152–4.271	0.823	0.448	0.060–3.378	0.665
NYHA I vs III	4.235	1.480–13.84	0.026	2.374	0.449–12.54	0.157
NYHA I vs IV	32.87	4.938–82.40	<0.001	41.56	4.524–183.5	0.026
Serum creatinine	10.865	3.052–38.684	<0.001	2.715	0.153–17.89	0.618
Pro-adrenomedullin	1.168	1.079–1.264	<0.001	1.062	0.975–1.157	0.169
Ejection fraction	0.869	0.812–0.929	<0.001	0.891	0.807–0.984	0.023

NYHA, the New York Heart Association.

symptomatic. Baseline demographic and clinical characteristics of the study population are listed in Table 1. Echocardiographic and laboratory parameters of patients with MR and comparison between asymptomatic and symptomatic patients are listed in Table 2.

Median pro-adrenomedullin levels increased significantly with NYHA class (NYHA class I = 1.94 pmol/l (1.32–5.33), NYHA class II = 3.68 pmol/l (2.56–5.97), NYHA class III = 15.19 pmol/l (5.55–21.0), NYHA class IV = 20.65 pmol/l (18.3–21.0), $P < 0.001$; Fig. 1).

Median pro-adrenomedullin levels increased significantly with higher degrees of MR (moderate = 2.86 pmol/l (1.39–5.53), moderate to severe = 6.31 pmol/l (2.56–18.58), severe = 21.0 pmol/l (10.95–21.0), $P < 0.001$; Fig. 2).

During 1-year follow-up, 21 patients (9%) died, 33 patients (14%) underwent heart valve surgery, 6 patients (2.6%) developed new-onset AF and 7 patients (3.1%) developed cerebrovascular events. Increased levels of serum creatinine, pro-adrenomedullin level, male gender, reduced LVEF, and higher NYHA functional classes were significantly associated with an increased risk of death during follow-up. In multivariate analysis, LVEF and NYHA classes were the only independent predictors of death (Table 3).

Sutton et al., investigated the brain natriuretic peptide (BNP) levels in patients with severe MR and found an increase in BNP levels in symptomatic patients compared with asymptomatic patients [12]. Our study supports their finding and further revealed that symptomatic patients with MR also have higher proadrenomedullin levels. The present study also showed a significant correlation between pro-adrenomedullin levels and degree of MR and NYHA functional class. Therefore, pro-adrenomedullin may be used to estimate the severity of MR when echocardiography is technically difficult or not available.

Advanced increased levels of pro-adrenomedullin were significantly associated with an increased risk of death in univariate analysis. Although in multivariate analysis it was not an independent predictor, studies with larger groups and longer follow ups may show a positive relationship in the multivariate analysis as well.

In conclusion, pro-adrenomedullin levels can help to identify patients with asymptomatic moderate/severe mitral regurgitation from the symptomatic ones. This may be useful in the optimal timing of mitral valve surgery in certain subset of patients.

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