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Nötrofil-lenfosit oranı mitral kapak çökmesi olan hastalarda akut göğüs ağrısı ile ilişkilidir

The neutrophil-to-lymphocyte ratio is associated with acute chest pain in patients with mitral valve prolapse

Nizamettin Selçuk Yelgeç, Mehmet Baran Karataş, Yiğit Çanga, Özge Güzelburç, Dilaver Öz, Ahmet Zengin, Ayşe Emre
Dr Siyami Ersek Göğüs Ve Kalp Damar Cerrahisi Hastanesi, Kardiyoloji Kliniği, İstanbul, Türkiye

ÖZ

GİRİŞ ve AMAÇ: : *Mitral kapak çökmesi (MVP) tanılı hastaların yarısında akut göğüs ağrısı mevcuttur. MVP tanılı hastalardaki bu ağrının tam sebebi bilinmemektedir. Diğer taraftan Nötrofil/Lenfosit oranı (NLO), birçok kardiyovasküler hastalıkta prognoz ve sonuçlar ile ilişkili olduğu bulunmuştur. Bu çalışmada, NLR ile MVP tanılı hastalardaki göğüs ağrısı arasındaki ilişki araştırılmıştır.*

YÖNTEM ve GEREÇLER: *Bu retrospektif çalışmada 2016 ve 2019 yılları arasında enstitümüz kardiyoloji polikliniklerine başvuran MVP tanılı hastaların tıbbi kayıtları incelenmiştir. Göğüs ağrısı ile başvuran MVP tanılı hastaların bazal karakteristikleri, biyokimyasal parametreleri ve NLR değerleri, göğüs ağrısı olmayan MVP tanılı hastalar (kontrol grup) ile mukayese edilmiştir. MVP tanılı hastalardaki göğüs ağrısının bağımsız belirteçleri lojistik regresyon yöntemi ile araştırılmıştır*

BULGULAR: *Göğüs ağrısı olan MVP tanılı hastalarının vücut kitle endeksleri, Sistolik kan basınçları göğüs ağrısı olmayan MVP hastalarına göre anlamlı olarak daha düşük; kalp hızı, panik atak oranı, kadın cinsiyet, NLO, beyaz küre anlamlı olarak daha yüksek olarak saptandı. Regresyon analizinde, düşük vücut kitle endeksi (OR = 0.76, P<0.01), kadın cinsiyet (OR = 2.86, P<0.01) ve NLO (OR = 2.91, P<0.01) MVP tanılı hastalarda göğüs ağrısının bağımsız belirteçleri olarak tespit edilmiştir.*

TARTIŞMA ve SONUÇ: *Çalışma grubumumuzda, NLO' nın MVP tanılı hastalarda göğüs ağrısının bağımsız bir belirteci olduğu saptanmıştır. NLO, MVP hastalarında görülen hiper-adrenerjik durum ile ilşkili olabilir. NLO klinik pratikte hemen ulaşılabilen ve ucuz bir yöntem olduğundan; MVP tanılı hastalarının göğüs ağrısının değerlendirilmesinde ve hangi hastalarının beta blokerden fayda görebileceğinin tespit edilmesinde, klinik kullanım alanı bulabilir.*

Anahtar Kelimeler: : *Mitral Kapak Prolapsusu, Kan hücresi sayımı, Göğüs ağrısı*

ABSTRACT

INTRODUCTION: *Nearly half of the patients with mitral valve prolapse (MVP) complain of chest pain. The precise cause of chest pain MVP is unknown. On the other side, the neutrophil /lymphocyte ratio (NLR) has been reported to be a useful marker of prognosis and outcomes for many cardiovascular diseases. In this study, we aimed to investigate the relationship between NLR and chest pain in patients with MVP.*

METHODS: *In this retrospective study, we screened medical records of all consecutive patients with MVP applied to outpatient clinics between the years 2016 and 2019 at our institution. Basal characteristics, biochemical parameters, and NLR were compared between the patients with MVP and chest pain and the patients with MVP and without chest pain (control group). Independent predictors of chest pain in MVP patients were determined by logistic regression analysis.*

RESULTS: *The patients with MVP and chest pain had significantly lower body mass index and systolic blood pressure compared to the control group. Heart rate, the number of patients with panic disorder, the number of females, NLR, and white blood cell count (WBC) were significantly higher in patients with MVP and chest pain. In the regression analysis, lower body mass index (OR= 0.76, P<0.01), being female (OR= 2.86, P<0.01), and NLR (OR= 2.91, P<0.01) remained independent predictors of pain in patients with MVP*

DISCUSSION AND CONCLUSION: *NLR was an independent predictor of the presence of chest pain in our study population. NLR might be associated with the hyperadrenergic state in patients with MVP. Since it is a readily available and cheap method, it can be of clinical value in the evaluation of chest pain in patients with MVP and to determine which patients might benefit from the beta-blockade.*

Keywords: *Mitral Valve Prolapse, Blood Cell Count, Chest Pain*

İletişim / Correspondence:

Dr. Nizamettin Selçuk Yelgeç
Dr. Siyami Ersek Göğüs Ve Kalp Damar Cerrahisi Hastanesi, Kardiyoloji Kliniği,İstanbul, Türkiye
E-mail: yelgec@gmail.com
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INTRODUCTION

Mitral valve prolapses (MVP) is a common disorder worldwide. The prevalence of MVP has been reported to be 2.4% by the Framingham Heart Study and is identified in 7% of autopsies (1,2). Many patients with MVP may experience chest pain that is atypical for angina. Notably, atypical or non-anginal chest pain is the most common symptom reported in patients with MVP. The mechanism by which this pain occurs is unknown. The pain is generally mild but may be frighting, recurrent and debilitating to the patient and extremely frustrating for physicians.

The neutrophil-to-lymphocyte ratio (NLR) has recently gained popularity as a reliable prognostic biomarker and an auxiliary tool in various medical fields. Currently, there are almost 6.000 publications about NLR in PubMed. Clinicians use this marker widely to assess physiological stress and prognosis in many situations. In cardiology, NLR emerges to be a useful marker for prognostic evaluation of many cardiac disorders. NLR was correlated with arterial stiffness, progression of atherosclerosis, high coronary calcium scores, and increased frequency of first-detected atrial fibrillation. Clinical evidence has shown that NLR is also an independent predictor of mortality in acute coronary syndromes, cardiac arrhythmias, stable coronary artery disease, coronary artery bypass surgery, aortic dissections, in primary percutaneous coronary interventions and heart failure (3–10).

NLR value may rise due to lymphopenia, which is a marker of poor general health and physiological stress. Many patients with MVP have stressful conditions (like panic disorder and hyperadrenergic status) that may affect NLR. Therefore, this research aims to study the association between chest pain in patients with MVP and their baseline NLR.

METHODS

Clinical history of patients with MVP visiting the outpatient clinics at our institution during the period between 2016 and 2019 was screened retrospectively from the hospital database. Patients who had atypical chest pain with an additional normal noninvasive diagnostic testing with the final diagnosis of nonspecific chest pain were included in our study. For patients with chest pain but less than 40 years of age, we only included the patients who had low-risk exercise treadmill scores after treadmill exercise testing and finished at least three steps of exercise test in the study. For patients over 40 years of age with chest pain suggestive of angina, we only included patients who had normal perfusion with stress imaging examination. The patients who had been diagnosed as a panic disorder by a psychiatrist and using related medications were categorized as having panic disorder. We excluded the patients with coronary artery disease and other life-threatening cardiac and non-cardiac problems such as malignancy and decompensated heart failure, patients with troponin elevation and/or positive noninvasive diagnostic testing. We also excluded the patient with secondary MVP, significant valvular heart disease, previous cardiac surgery, renal or hepatic failure, acute or chronic infectious disease, autoimmune diseases, rheumatological diseases, anemia, active hematologic disorder, and acute or chronic pulmonary disease from the study. Data about clinical and demographic variables, laboratory parameters, and echocardiographic findings were collected from the clinical and echocardiographic database.

Fasting venous blood samples were obtained from the antecubital vein puncture into EDTA-treated or plain tubes according to hospital protocol. The full blood count analysis was performed by Beckman Coulter Automated CBC Analyzer (Beckman Coulter, Inc., Fullerton, CA, United States) within 30 minutes after blood sampling. Complete blood counts with automated differential count, including total white blood cells (WBC), neutrophils, and lymphocytes, red cell distribution width (RDW), platelet count, and mean platelet volume (MPV) were obtained. NLR was calculated using the absolute count as the ratio of the absolute neutrophil count and absolute lymphocyte count, obtained from the same automated blood samples.

Standard 2-dimensional and Doppler echocardiographic measurements were performed in all patients by echocardiographers with considerable expertise by using the General Electric Vivid 7 (GE Health Medical, Horten, Norway) ultrasound

machine with 2.5 to 4-MHz transducers. The guidelines published by the American Society of Echocardiography were followed for all measure¬ments(11). MVP was diagnosed if echocardiography demonstrated a systolic posterior excursion of any portion of mitral leaflets more than 2 mm relative to the mitral valve annüler plane in parasternal or apical three-chamber views. Using the M-mode echocardiography, the left ventricular end-diastolic diameter (LVEDD) and left atrial diameter (LAD) were determined in the parasternal long-axis view. Left ventricular ejection fraction was measured quantitatively by using the modified Simpson rule. Mitral regurgitation was determined and graded according to previously established methods.

The study protocol was approved by the local research and ethics committee. The study was compliant with the ethical principles described by the Declaration of Helsinki.

Statistical analysis

SPSS 20.0 Statistical Package Program for windows (SPSS 20.0 for Windows, SPSS, Inc., IL, USA) was used for statistical analysis of the data collected in this study. Continuous variables are presented as mean±SD, and categorical variables presented as frequency and percentages for descriptive statistic purposes. Kolmogorov-Smirnov test was used to evaluate the normality of distribution of continuous variables. For normally distributed variables, differences between the patients with MVP and chest pain and without chest pain were evaluated by using student t-test. Categorical variables were compared by the chi-square or Fisher's Exact test depending on necessity. Models for univariate as well as multivariate logistic regression analysis were developed to analyze how covariates influence the chest pain in individuals having MVP. Forward stepwise multivariate regression models using parameters with p <0.10 were created. P values were two-sided, and values <0.05 were considered statistically significant. Finally, Receiver operating curves (ROC) were generated to find out the best cut-off level for NLR values to predict chest pain.

RESULTS

A total of 352 consecutive patients with MVP were enrolled in the study. The mean age of the patients was 39±9.2 years, and 253(72 %) were female. Patients with MVP were divided into two groups; the first group consists of the patients with MVP who had chest pain (n:228). The second group (control group) consists of the patients with MVP and no chest pain (n:124). The baseline characteristics of groups are presented in Tables 1 and 2.

Table 1. Demographic and Clinical characteristics of the study population according to the presence of chest pain in patients with MVP

Parameters	MVP with Chest pain n=228	MVP without Chest pain n=124	P-value
Age, years	38.2±11.2	40.6±13.0	0.07
Female gender , n (%)	181 (79)	72 (58)	**0.01**
Body mass index (kg/m2)	23.8±2.68	24.6±2.9	**0.01**
Systolic blood pressure (mm Hg)	105±13	110±12	**0.01**
Hypertension, n (%)	8 (4)	6 (5)	0.35
Diabetes mellitus, n (%)	11 (16)	6 (14)	0.59
Smokers, n (%)	69 (21.6)	40 (13.7)	0.39
Heart rate (beats/min)	70±12	62±9	**0.01**
Palpitations, n (%)	172 (75)	98 (79)	0.34
Dizziness, n (%)	20 (9)	6 (5)	0.12
Panic disorder, n (%)	31(13.6)	7 (6)	**0.02**
CCB, n (%)	14 (6.0)	6 (5)	0.64
Beta-blocker, n (%)	36 (16)	14 (11)	0.26
Mitral regurgitation			
No, n (%)	68 (28)	27(20)	0.06
Mild, n (%)	127 (52)	60 (47)	0.51
Moderate, n (%)	26 (12)	21 (25)	0.88
Severe, n (%)	7(3)	5(4)	0.42
LVEF, %	65.1±5.1	64.3±4.4	0.14
LAD, cm	35.2±4.1	35.9±3.9	0.12

Data are given as mean±SD OR %.
CCD-calcium channel blocker; LVEF - left ventricular ejection fraction; LAD - left atrial diameter.
Bolded values indicate statistical significance (p < 0.05)

The patients with chest pain and MVP had significantly lower body mass index, and systolic blood pressure compared to the control group (23.8±2.68 vs. 24.6±2.9, p=0.01; 105±13 vs. 110±12, p=0.01 respectively).

Table 2. Comparison of laboratory parameters in the study population

Parameters	MVP with Chest pain n=228	MVP without Chest pain n=124	P
Glucose, mg/dL	94 ±15.5	97±14.6	0.30
Hemoglobin, g/dL	12.3 ±2.34	11.9 ±1.97	0.21
Platelets, 10^3/mm^3	252 ±44.6	242±39.2	0.07
Mean platelet volume, fL	8.6 ±1.58	9 ±1.51	0.35
White blood cell, 10^3/mm^3	7.86 ±1.71	7.43±1.36	**0.02**
Neutrophil count (10^3/µL)	5.60±1.11	5.41±0.91	0.09
Lymphocyte count (10^3/µL)	1.45±0.21	1.90±0.28	**0.01**
NLR	3.04±0.45	2.32±0.38	**0.01**
RDW	14.2 [2.6]	13.3 [3.4]	**0.04**
Creatinine, mg/dL	0.94 [0.30]	0.96 [0.20]	0.12
Total cholesterol, mg/dL	192.4±26.4	198.0±34.6	0.07
HDL-cholesterol, mg/dL	44.1±9.4	45.4±9.7	0.22
LDL-cholesterol, mg/dL	127.2±31.1	131±28.1	0.25
Triglyceride, mg/dL	158.3±30.2	154.6±33.2	0.29

Data are given as mean±SD or medians with IQR in square brackets.
NLR - neutrophil-to- lymphocyte ratio; RDW-red cell distribution width ; HDL - high-density lipoprotein;
LDL - low-density lipoprotein.
Bolded values indicate statistical significance (p < 0.05)

Heart rate, panic disorder, and female gender were significantly higher in patients with chest pain and MVP (70±12 vs. 62±9, p=0.01; 31(13.6%) vs. 7(6%), p=0.01; 181 (79%) vs. 72 (58%) , p=0.01 respectively). No significant differences were found with regard to hypertension, diabetes mellitus, and degree of mitral regurgitation, ejection fraction, and left atrial dimensions between groups. The patients with chest pain had significantly elevated NLR, WBC and RDW values compared to the control group (3.04±0.45 vs. 2.32±0.38, p=0.01; 7.86 ±1.71 vs.7.43±1.36, p=0.02; 14.2 [2.6] vs 13.3 [3.4], p=0.04 respectively). However, absolute lymphocyte count was significantly lower in patients with MVP and chest pain (1.45±0.21 vs. 1.90±0.28, p=0.01).

In the univariate logistic regression analysis, lower body mass index, being female, NLR, RDW and having panic disorder were possible independent predictors of pain in patients with MVP. In the multiple logistic regression analysis, lower body mass index (OR= 0.76, 95% CI: 0.67-0.85, P=0.01) ,being female (OR= 2.86, 95% CI: 1.54-5.31, P=0.01) , and NLR (OR= 2.91, 95% CI: 1.23-4.74, P=0.01) remained independent predictors of pain in patients with MVP (Table 3).

Table 3. Multiple logistic regression analysis of patients with MVP and chest pain

Variable	*P	Odds ratio (95% CI)
Body mass index	**0.01**	0.76 (0.67-0.85)
Female gender	**0.01**	2.86 (1.54-5.31)
Panic disorder	0.42	1.55 (0.52-4.56)
Neutrophil-to-Lymphocyte ratio	**0.01**	2.91 (1.23-4.74)
RDW	0.22	1.07 (0.95-1.21)

RDW-red cell distribution width
Bolded values show statistical significance (p < 0.05)
** Multiple logistic regression analysis*

In the ROC curve analysis, an NLR level cutoff point of more than 2.85 predicted the presence of chest pain with a sensitivity of 59 % and specificity of 90.3% (Area under the curve = 0.814, p < 0.001) (Fig. 1).

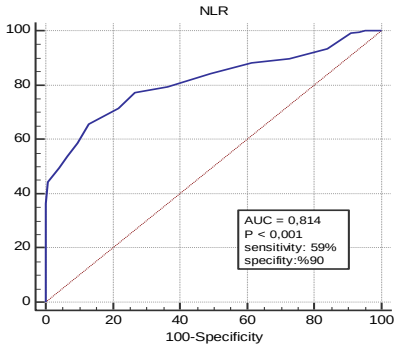

Figure 1. ROC curve analysis for neutrophil-to-lymphocyte ratio as a predictor of chest pain in patients with MVP

DISCUSSION

This research was conducted to check out if NLR could serve as a chest pain predictor in patients with MVP. We found that NLR, the prevalence of panic disorder, the frequency of female gender, RDW, and WBC were significantly higher, but systolic blood pressure was lower in patients with MVP and chest pain when compared with the control group. In addition to this, the results of this study demonstrated that NLR, lower body mass index, and being female were independent predictors of chest pain in patients with MVP.

In developed countries of the world, including the United States, MVP has turned into the most common form of valvular heart disorder. Its incidence in females is slightly higher as compared to males(12). The majority of MVP patients experience mitral regurgitation (MR) (70 percent in one cross-sectional population-based study), but most patients with MVP (around 75 percent in the same study) have a mild, trace, or no MR (1). Similarly, in our study, 74% percent of patients had mild or no MR. There was no difference between the patients with chest pain and the control group concerning the severity of mitral regurgitation.

It has been proposed by Devereux et al., that lower blood pressure and lower body weight in patients with MVP can offer a selective advantage for reproduction, which could be responsible for the increased prevalence of inherited MVP. These patients might suffer less from hypertensive complications of pregnancy and the risk of eclampsia (13). In the report of the Framingham Heart Study, asthenic body habitus was more common in MVP than matched controls (12). Similarly, in our study, we also found that low body mass index was an independent predictor of chest pain. Low blood pressure and low intravascular volume might result in a smaller LV cavity, which may predispose mitral valve and corda tendineae to prolapse into the left atrium. Papillary muscle ischemia caused by traction exerted by the prolapsing mitral leaflets might cause chest pain (14).

Many patients with MVP reports numerous nonspecific complaints such as non-anginal chest pain, palpitations, shortness of breath on exertion, effort intolerance, dizziness or syncope, palpitations, fatigue, and anxiety-related symptoms like panic attacks. Patients with MVP frequently have signs such as asthenic build, skeletal abnormalities, low blood pressure, and electrocardiographic evidence of repolarization abnormalities. The term mitral valve prolapse syndrome used to indicate the auscultatory or echocardiographic evidence of mitral valve prolapse plus any combination of these symptoms and signs (15). However, subsequent controlled studies such as Framingham Heart Study found little or no evidence that these symptoms and signs, with the exception of asthenic body habitus and a higher degree of mitral regurgitation, are more common among patients with MVP. Approximately 40% to 50% of patients with mitral valve prolapse complain of chest pain (16,17). Atypical or non-anginal chest pain is the most common symptom attributed to MVP. In our study, 65 percent of patients suffered from chest pain.

The current literature is unable to describe the exact reason for chest pain in individuals with MVP. It has been proposed that papillary muscle ischemia due to traction brought about by prolapsing mitral leaflets and extreme stretching of chordae tendineae are responsible for chest pain. Some other suggested mechanisms that might cause chest pain in patients with MVP include compression of the circumflex coronary artery's atrioventricular groove branch, esophageal dysmotility, metabolic abnormalities, and extreme contraction of the poster-dorsal or mid-left ventricle, coronary artery spasm and congenital absence of atrioventricular groove branch of the circumflex coronary artery (14,18).

NLR can be increased by any physiologic stress. Lymphopenia and leukocytosis can be caused by high concentrations of cortisol and/or endogenous catecholamines like epinephrine. Hence, without any sign of infection or inflammation, endogenous cortisol and catecholamines may affect NLR(19). It has been reported by Pasternac et al., that concentrations of norepinephrine and total plasma catecholamine are increased in patients with MVP in comparison to healthy individuals, the same group has also shown that patients with MVP syndrome have hyper-increased adrenergic tone (14). Thus, the association of NLR with chest pain in patients with

MVP in our study might be due to the hyperadrenergic status of MVP patients. NLR can help to diagnose occult physiologic stress among patients with similar presentations. On the other hand, high NLR might warn us about the presence of inflammatory conditions that might cause chest pain in patients with MVP, such as pleurisy, myositis, esophageal diseases. RDW levels have been claimed to reflect the degree of neurohormonal activity, particularly in patients with heart failure (20). However, in this study, we were unable to determine an independent correlation between RDW levels and chest pain in patients with MVP.

CONCLUSION

Before interpreting these results, some restrictions need to be emphasized. This study is a small-scale, retrospective study. We do not know and could not measure cortisol and endogenous catecholamines levels of patients at the time of chest pain. However, in conclusion, this study shows that NLR is associated with chest pain in patients with MVP. High adrenergic tone observed in some patients with MVP might be responsible for the increase in NLR. Since the patients with a high adrenergic tone may benefit from beta-blockade, high NLR levels might be useful to determine which patients will benefit from beta-blockers. Our findings call for further prospective and multicenter studies with a larger sample size to clarify the underlying mechanisms for chest pain in patients with MVP and to confirm our results.

REFERENCES

1. Freed LA, Benjamin EJ, Levy D, Larson MG, Evans JC, Fuller DL, et al. Mitral valve prolapse in the general population: The benign nature of echocardiographic features in the Framingham Heart Study. J Am Coll Cardiol. 2002;
2. Luxereau P, Dorent R, De Gevigney G, Bruneaval P, Chomette G, Delahaye G. Aetiology of surgically treated mitral regurgitation. Eur Heart J. 2012;
3. Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta. 2008 Sep;395(1–2):27–31.
4. Park B-J, Shim J-Y, Lee H-R, Lee J-H, Jung D-H, Kim H-B, et al. Relationship of neutrophil-lymphocyte ratio with arterial stiffness and coronary calcium score. Clin Chim Acta. 2011 May 12;412(11–12):925–9.
5. Zazula AD, Précoma-Neto D, Gomes AM, Kruklis H, Barbieri GF, Forte RY, et al. An assessment of neutrophils/lymphocytes ratio in patients suspected of acute coronary syndrome. Arq Bras Cardiol. 2008 Jan;90(1):31–6.
6. Duffy BK, Gurm HS, Rajagopal V, Gupta R, Ellis SG, Bhatt DL. Usefulness of an Elevated Neutrophil to Lymphocyte Ratio in Predicting Long-Term Mortality After Percutaneous Coronary Intervention. Am J Cardiol. 2006 Apr 1;97(7):993–6.
7. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, et al. Usefulness of Neutrophil/Lymphocyte Ratio As Predictor of New-Onset Atrial Fibrillation After Coronary Artery Bypass Grafting. Am J Cardiol. 2010 Jan 15;105(2):186–91.
8. Rudiger A, Burckhardt OA, Harpes P, Müller SA, Follath F. The relative lymphocyte count on hospital admission is a risk factor for long-term mortality in patients with acute heart failure. Am J Emerg Med. 2006 Jul;24(4):451–4.
9. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J. 2007 Nov;154(5):995–1002.
10. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013 Jan 10;11(1):55–9.
11. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;
12. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, et al. Prevalence and Clinical Outcome of Mitral-Valve Prolapse. N Engl J Med. 2002;

13. Devereux RB, Lutas EM, Ted Brown W, Kramer-Fox R, Laragh JH. ASSOCIATION OF MITRAL-VALVE PROLAPSE WITH LOW BODY-WEIGHT AND LOW BLOOD PRESSURE. Lancet. 1982;

14. Fontana ME, Sparks EA, Boudoulas H, Wooley CF. Mitral valve prolapse and the mitral valve prolapse syndrome. Curr Probl Cardiol. 1991 May;16(5):309–75.

15. Alpert MA, Mukerji V, Sabeti M, Russell JL, Beitman BD. Mitral valve prolapse, panic disorder, and chest pain. Medical Clinics of North America. 1991.

16. Devereux RB, Kramer-Fox R, Kligfield P. Mitral Valve Prolapse: Causes, Clinical Manifestations, and Management. Ann Intern Med. 1989 Aug 15;111(4):305.

17. de Leon AC. Mitral valve prolapse. Postgrad Med. 1980 Jan 7;67(1):66–77.

18. Boudoulas H, Kolibash AJ, Baker P, King BD, Wooley CF. Mitral valve prolapse and the mitral valve prolapse syndrome: A diagnostic classification and pathogenesis of symptoms. Am Heart J. 1989 Oct;118(4):796–818.

19. Benschop RJ, Rodriguez-Feuerhahn M, Schedlowski M. Catecholamine-Induced Leukocytosis: Early Observations, Current Research, and Future Directions. Brain Behav Immun. 1996 Jun;10(2):77–91.

20. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail. 2010;16(3):230–8.