http://www.cjmb.org

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 4, No. 4, October 2017, 167–172
eISSN 2148-9696

Heart Valves Prolapse in Population Referred to Heart Clinic in Ilam, West of Iran

Milad Azami[1], Mohammad Hossein Yekta Kooshali[2], Ramak Qavam[3], Mohammad Reza Hafezi Ahmadi[4], Samiramis Qavam[5*]

Abstract

Objective: Valvular heart diseases have gained importance in the field of cardiovascular medicine in recent years. The prevalence of heart valves prolapse has been reported in various studies. The present study was conducted to determine the prevalence of heart valve prolapsein patients referred to Ilam, Western Province of Iran, an outpatient heart clinic in 2013-2014.

Materials and Methods: In this cross-sectional study, samples were randomly chosen from patients referred to Ilam outpatient heart clinic. Data were gathered using questionnaire, physical examination, echocardiography, and electrocardiography. Data were analyzed by using the SPSS-17 software.

Results: The study was conducted using 600 participants with mean age of 44.16 ±15.34. 233 men with body mass index (BMI) of 25.23 ± 3.94 and 367 women with BMI of 27.32 ± 5.14 participated in this study. The prevalence of mitral valve prolapse (MVP) in Ilam was 4.5% and women's share was more. MVP was mostly observed in patients aged 20 to 30 (12.5%). There was a significant relationship between this disorder and patent foramen ovale (PFO) ($P=0.001$), redundant interatrial septum ($P=0.001$), weight ($P=0.001$), height ($P=0.001$), BMI ($P=0.001$), family history of MVP ($P=0.009$), and the prevalence of tricuspid valve prolapse (TVP) and aortic valve prolapse (AVP) was 16%, often observed in 50 to 60-year-old women.

Conclusion: Prevalence of heart valves prolapse in this study was similar to the studies in other countries and is more common in women. Due to a preventing program, early diagnosis and screening are recommended.

Keywords: Prevalence, Heart valve prolapse, MVP, TVP, AVP

Introduction

Valvular heart diseases have gained importance in the field of cardiovascular medicine in the last 60 years due to changes in its presentation and management. The etiology of valvular diseases in developed countries have changed from rheumatic to degenerative since 1950 (1). On the other hand, valvular diseases in developing countries are still mainly caused by rheumatic heart disease (RHD) (2-4). Progressive changes in geographical causes and differences have been specified for valvular diseases which reveal the importance of assessing the burden of disease, not only for descriptive purposes but also regarding consequences of these changes for patient care. Managing patients with valvular diseases have seen significant changes with the development of minimally invasive interventions such as percutaneous mitral commissurotomy or transcatheter aortic valve implantation (TAVI) over the past few decades (5, 6).

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is one of the most common non-ischemic causes of severe heart failure, which requires surgical intervention in developing countries (1). Increased risk of arrhythmias, sudden death, and infective endocarditis has been observed in these cases. Primary MVP is a result of progressive myxomatous degeneration and is observed in heritable disorders of connective tissue such as Marfan syndrome, Ehlers-Danlos syndrome and sporadic forms associated with the regulatory or regenerative gene of connective tissue (2). Secondary MVP is caused by a variety of conditions such as rheumatoid heart disease, ischemic heart disease or aortic regurgitation (2-4,6). This disease may be accompanied by other cardiovascular system anomalies such as tricuspid valve prolapses (TVPs) and aortic dissection (7) as well as the involvement of various organs such as brain, limbs, kidney and spleen due to high chance

Received 8 November 2016, **Accepted** 18 April 2017, **Available online** 10 June 2017

[1]Student Research Committee, Ilam University of Medical Sciences, Ilam, Iran. [2]Student Research Committee, School of Nursing, Midwifery and Paramedicine, Guilan University of Medical Sciences, Rasht, Iran. [3]Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran. [4]Department of Pathology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran. [5]Department of Cardiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran.
*Corresponding Author: Samiramis Qavam, Email: samira.qavam@yahoo.com

of thromboembolism (8,9). Clinical symptoms of this syndrome include heart palpitations, lightheadedness, syncope, fatigue, anxiety and ever sudden death (10). The prevalence of this disorder ranged from less than 1% to more than 35% in different studies (11-16). In terms of gender, women are 2 times more prone to this disease and most patients are thin (7). In the community-based Framingham Heart Study (FHS), MVP is describing as a benign disease with a low prevalence of adverse clinical effects (17).

Tricuspid Valve Prolapse

TVP is a rare echocardiographic finding, usually accompanied by MVP. Compared to patients with isolated MVP, patients with TVP are relatively older with a higher frequency of neurological symptoms, fatigue, weakness, supraventricular arrhythmias (particularly atrial fibrillation) and skeletal malformations. TVP may be a strong marker of connective tissue disorders and its identification may stimulate the most echocardiographic search for evidence of prolapse and failure of other heart valves (18-20).

Aortic Valve Prolapse

Aortic valve prolapses (AVP) is not an unusual mechanism of aortic regurgitation; often associated with an aortic valve at the two corners. Moreover, AVP is well identified with symptoms of ventricular septal defect, MVP, infective endocarditis, blunt chest trauma and Marfan syndrome (21). AVP is usually diagnosed in echocardiography of patients with floppy valve syndrome. Clinical symptoms are similar to patients with MVP. The main etiologic cause of AVP is myxomatous degeneration of valvular tissue which can affect one or more cardiac valves (21-23).

Pulmonary Valve Prolapse

Pulmonary valve prolapse (PVP) is described as related to multiple floppy valve syndrome and congenital heart diseases associated with pulmonary hypertension. This finding in adults is not specified with pulmonary hypertension like congestive heart failure, chronic obstructive pulmonary disease and high blood pressure (24).

Since there are no statistics on this field in Iran, the present study was conducted to determine the prevalence of heart valve prolapse in patients referred to Ilam heart clinic in 2014.

Patients and Methods

Study Design

This is a cross-sectional and observational study.

Study Protocol

The clinical and demographic information was gathered using questionnaire, physical examination, and echocardiography. The inclusion criteria included all patients referred to Ilam Outpatient Heart Clinic (Figure 1) and refusing to participate in this research and poor echocardiography were the exclusion criteria.

Patients

The study population included all patients referred to Ilam Outpatient Heart Clinic who randomly entered the study if they consented. The sample size was calculated according to the study of Markiewicz et al (12) with the prevalence of 21% for 126 participants using the following formula = $1/d^2(z^2\ P(1\text{-}P))$. The significance and the method of doing the task were first explained to each participant and after obtaining informed consent, a questionnaire containing demographic information and history of disease was handed to the participants.

Echocardiography

Patients were referred to a cardiologist and were echoed using VIVID4 echocardiography device (made in the USA).

Mitral prolapse was defined as ≥2 mm cusp movement above the level of mitral annulus in long axis view (20). AVP was detected in the echocardiographic long axis view when right or non-coronary aortic valve cusps demonstrated retrograde bowing towards the left ventricle beyond a line joining those focuses for connection of the annulus aortic valve leaflets (21).

The standard for TVP might have been the tricuspid leaflets in systole prolapsed superior to the annulus of tricuspid atrioventricular. The finding for prolapse for each leaflet eventually might have been aggravated by 2-D echocardiography: those 3 initial leaflets were recognized eventually by the rotational method, also each leaflet prolapse has been judged to be present when the portion of a leaflet billowed superiorly and posteriorly to the tricuspid annular plane throughout ventricular systole (25).

Electrocardiography

Electrocardiography (ECG) was performed by a cardiologist using Nihon Kohden device (Nihon Kohden Corp., Japan).

Statistical Analysis

Data analyzed by using chi-square, Pearson and sample *t* test in their individual condition after parametric and non-parametric examined by Kolmogorov–Smirnov test. SPSS 16 was used to analyze data.

Results

The study was conducted using 600 participants with a mean age of 44.16 ± 15.34. A total of 233 men with body mass index (BMI) of 25.23 ± 3.94 and 367 women with BMI of 27.32±5.14 participated in this study. Systolic and diastolic blood pressure of women was slightly higher than men; 139.90 ± 29.58 and 85.92 ± 14.87, respectively. Men (18.5%) smoke more than women and at the same time, men (33.5%) exercise more than women. Other demographics, electrographic and clinical characteristics are presented in Table 1.

Figure 1. Physical Map of Ilam (http://www.maphill.com/iran/ilam/maps/physical-map).

Mitral Valve Prolapse

The prevalence of MVP in Ilam was 4.5% and women's share was more. MVP was mostly observed in patients aged 20 to 30 (12.5%). There was a significant relationship between this disorder and patent foramen ovale (PFO) ($P=0.001$), redundant interatrial septum ($P=0.001$), weight ($P=0.001$), height ($P=0.001$), BMI ($P=0.001$), family history of MVP ($P=0.009$) and no significant relationship was found in regard with other indices (Tables 2 and 3).

Tricuspid Valve Prolapse

The prevalence of TVP was 0.16% in Ilam population, often observed in 50 to 60-year-old women. There was a significant relationship between TVP and BMI ($P=0.001$) (Tables 2 and 3).

Table 1. Demographics, Electrographic and Clinical Characteristics

Variable		Male (n=233)	Female (n=367)
Age	Mean	44.32	44.06
	SD	16.51	14.57
BMI	Mean	25.23	27.32
	SD	3.94	5.14
SBP	Mean	139.84	139.90
	SD	22.99	29.58
DBP	Mean	86.72	85.92
	SD	14.70	14.87
Smoking		43 (18.5)	6 (1.6)
Exercise		78 (33.5)	60 (16.3)
T-Wave	Invert	15 (6.4)	19 (5.2)
	Flat	5 (2.1)	8 (2.2)
	Normal	213 (91.4)	340 (92.6)
ST-Segment	Depression	25 (10.7)	42 (11.4)
	Elevation	15 (6.4)	6 (1.6)
	Normal	193 (82.8)	319 (86.9)
Patent foramen ovale		28 (12)	32 (8.7)
Family history of heart valves prolapse		48 (20.6)	111 (30.2)
Hypertension		36 (15.5)	98 (26.7)
Diabetes		11(4.7)	24(6.5)

Aortic Valve Prolapses

The prevalence of AVP was 0.16% in Ilam population, often observed in 50 to 60-year-old women. There was a significant relationship between this disease and height ($P=0.001$) and BMI ($P=0.001$) (Tables 2 and 3).

The overall prevalence of heart valves prolapse was 4.8%. 6.26% of women and 2.6% of men had at least one type of valve prolapse (Table 2).

Discussion

Since the decrease in RHDs is accompanied by an increase in degenerative valve diseases, valvular heart diseases are still common in industrial countries (26,27). The overall prevalence of heart valves prolapse was calculated to be 4.8% in this study, which is a relatively high percentage.

The prevalence of MVP in Ilam was 4.5%, mostly observed in women and patients aged 20 to 30. The prevalence of this disorder ranged from less than 1% to more than 35% in different studies (11-16). However, it is important to note that this diversity in different studies may be due to non-uniformity of diagnostic criteria (28). The prevalence of MVP was reported to be 2.4% in the study of Framingham, but Hepner et al reported the real estimate of mitral prolapse to be much less according to echocardiography (13). The study of Orourk et al indicated that 15 million Americans suffer from Barlow syndrome, often diagnosed in the second or third decade of their lives, which is not in accord with the results of the present study (29). According to the study of Surawicz and Knilans, women are 2 times more prone to this disease and most patients are thin which is in accord with the results of the present study ($P=0.001$) (10).

Prevalence of TVP and AVP in Ilam is 0.16%, often observed in 50 to 60-year-old women. According to results of Schlamowitz et al, TVP occurs at the same time with MVP and occurs with similar frequency in young and old patients (30). As the present study suggests, in the systematic review study, it was stated that low BMI is directly associated with the incidence of MVP (31).

In the present study, both normal and flat T waves in

Table 1. Frequencies of Prevalence of Valvular Disorders

Prevalence	Gender, No. (%)		Age (y), No. (%)						Total
	Male (n = 233)	Female (n = 367)	<20	20-30	30-40	40-50	50-60	>60	
MVP	6(2.6)	21(5.7)	3(8.8)	10(12.5)	9(6.7)	2(1.4)	3(2.3)	0	27(4.5)
TVP	0(0)	1(0.3)	0	0	0	0	1(0.8)	0	1(0.16)
AVP	0(0)	1(0.3)	0	0	0	0	1(0.8)	0	1(0.16)
The overall prevalence of valvular disorders	6(2.6)	23(6.26)	-	-	-	-	-	-	29(4.8)

Table 2. Correlations of Prevalence of Valvular Disorders

Prevalence	Correlations																		
	Sex	Age	Smok.	Ex.	Rhyt.	T-Wave	ST Seg.	HB	EF	PFO	Red. IAS	H	W	BMI	Fam.	Dis.	Inf.	Job	HTN	DM
MVP	0.07	0.40	0.51	0.13	0.66	0.08	0.67	0.08	0.73	0.00	0.00	0.00	0.00	0.00	0.01	0.75	0.45	0.36	0.02	0.17
TVP	0.42	1	0.97	0.58	0.93	0.96	0.98	0.99	0.10	0.74	0.73	0.57	0.71	0.00	0.55	0.99	0.89	0.98	0.06	0.80
AVP	0.42	1	0.97	0.58	0.93	0.96	0.98	0.99	0.10	0.74	0.73	0.00	0.98	0.00	0.01	0.99	0.89	0.98	0.59	0.80

Abbreviations: MVP, mitral valve prolapse; TVP, tricuspid valve prolapse; AVP, aortic valve prolapse; smok, smoking; Ex, exercise; Rhyt, rhythm; Seg, segment; HB, heart block; PFO, patent foramen ovale; H, height; W, weight; Inf, infection; DM, diabetes mellitus; HTN, hypertension; Dis, disease; Fam, family; Red. IAS, redundant inter atrialseptum; BMI, body mass index; EF, ejection fraction.

women were higher than men and the inverted T-wave in men was higher than women. ST-segment elevation in men was more than women while depression and normality of this item were more frequent in women. Furthermore, the study of Hosseinian et al (32) demonstrated that in order to differentiate prolapsed with ischemic heart disease (IHD), patients, particularly men are required to bring their ECG strip. ECG changes in patients with MVP have been stated in most of the studies and most of them included changes in ST and T waves, being in accord with the present study (10,32,33). In other studies, most common ECG changes in patients with MVP were early repolarization in the descending section of QRS and/or ST-segment elevation (34).

According to the results of the present study, 23% of participants have physical activity, however, another study revealed 9% of physical activity in Iranian society (32). In the present study, there was no significant relationship between prolapses and physical activity.

In this study, mean BMI was 25.23 ± 3.94 in men and 27.32 ± 5.14 in women, indicating an overweight society. In a study regarding 39 European countries, Silventoinen et al reported the mean prevalence of obesity to be 30%-70% (35). Prevalence of obesity in Saudi women has increased 10% to 40% (36), which can somewhat be generalized to Iranian society. Moreover, mean BMI in the present study indicates higher BMI in women. Increased obesity in Iranian society may be due to lack of adequate physical activity, increased obesity consumption and the imbalance between energy gain and fat consumption (37). Results of this study indicate a relationship between BMI and MVP ($P = 0.001$), TVP ($P = 0.001$) and AVP ($P = 0.001$).

Hypertension is another risk factor which is directly related to women's age and conforms to patterns of developed and developing countries (38). Kelishadi et al (37) showed that diastolic and systolic blood pressure increase is related to age increase in cities and villages, particularly after women's menopause. In the present study, 22.33% had hypertension, which is higher than Sweden and lower than Eastern Mediterranean and Germany (39). On the other hand, their systolic blood pressure was reported to be 139.90 ± 29.58 and their diastolic blood pressure was 85.92 ± 14.87 and regarding systolic blood pressure, women's mean blood pressure was higher.

Smoking is another risk factor and considering Iranian's refusal to admit women's smoking, the percentage is higher in men (8.16%). There are significant differences in the epidemiology of valvular diseases between developing countries and developed countries (40). Nevertheless, no significant relationship was observed between prolapse and smoking, which may be due to the small population of smokers.

For future studies, investigating other valvular disorders such as valvular failure and stenosis is recommended.

Limitations

Sampling the patients referred to the outpatient clinic is one of the limitations of this study.

Conclusion

Prevalence of heart valves prolapse in this study was similar to studies in other countries and is more common in women and older people. Therefore, it is possible to reduce the prevalence of this disease by early diagnosis and treatment, considering the effective factors and playing a preventive role.

Conflict of Interests

None.

Ethical Issues

The study protocol was approved by Ethics Committee of Ilam University of Medical Sciences.

Financial Support
Ilam University of Medical Sciences supported the study.

Acknowledgements
Herby, we would like to thank Ilam University of Medical Sciences for their financial support.

References

1. Rose AG. Etiology of valvular heart disease. Curr Opin Cardiol. 1996;11(2):98-113.
2. Jonkaitiene R, Benetis R, Ablonskyte-Dūdoniene R, Jurkevicius R. Mitral valve prolapse: diagnosis, treatment and natural course. Medicina (Kaunas). 2005;41(4):325-334.
3. Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. Lancet. 2005;366(9480):155-68. doi: 10.1016/S0140-6736(05)66874-2.
4. World Health Organization. Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation, Geneva: WHO; 2004.
5. Bohun CM, Potts JE, Casey BM, Sandor GG. A population-based study of cardiac malformations and outcomes associated with dextrocardia. Am J Cardiol. 2007;100(2):305-9. doi: 10.1016/j.amjcard.2007.02.095.
6. Hayek E, Gring CN, Griffin BP. Mitral valve prolapse. Lancet. 2005;365(9458):507-18. doi: 10.1016/s0140-6736(05)17869-6.
7. Bitar ZI, Ahmed S, Amin AE, Jamal K, Ridha M. Prevalence of mitral valve prolapse in primary spontaneous pneumothorax. Prim Care Respir J. 2006;15(6):342-345. doi: 10.1016/j.pcrj.2006.08.011.
8. Güvenç TS, Çanga Y, Karabağ Y, Özen K, Balcı B. Prevalence of mitral valve prolapse in residents living at moderately high altitude. Wilderness Environ Med. 2012;23(4):300-306.
9. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. New York: McGraw-Hill; 2008.
10. Surawicz B, Knihan T. Chou's electrocardiography in clinical practice: adult and pediatric: 5th ed. Philadelphia: Sunders; 2001:543-545.
11. Cheng TO, Barlow JB. Mitral leaflet billowing and prolapse: its prevalence around the world. Angiology. 1989;40(2):77-87.
12. Markiewicz W, Stoner J, London E, Hunt SA, Popp RL. Mitral valve prolapse in one hundred presumably healthy young females. Circulation. 1976;53(3):464-73.
13. Hepner AD, Ahmadi-Kashani M, Movahed MR. The prevalence of mitral valve prolapse in patients undergoing echocardiography for clinical reason. Int J Cardiol. 2007;123(1):55-57. doi: 10.1016/j.ijcard.2006.11.130.
14. Moro E, Mantovan R, Marcon C, et al. [An aneurysm of the interatrial septum associated with Ebstein's anomaly: a case report]. G Ital Cardiol. 1992;22(7):859-862. [Italian].
15. Shinohara T, Kimura T, Yoshizu H, Ohsuzu F. Three-year follow-up of an atrial septal aneurysm. Ann Thorac Surg. 2001;71(5):1672-1673.
16. Livneh A, Langevitz P, Vered Z. [Atrial septal aneurysm and paroxysmal atrial fibrillation]. Harefuah. 1994;126(8):441-2. [Hebrew].
17. 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. 1999;341(1):1-7. doi: 10.1056/NEJM199907013410101.
18. Raichlen J, Brest A. Tricuspid valve prolapse. Cardiovasc Clin. 1986;17(2):97-109.
19. Weinreich DJ, Burke JF, Bharati S, Lev M. Isolated prolapse of the tricuspid valve. J Am Coll Cardiol. 1985;6(2):475-481.
20. Levine RA, Stathogiannis E, Newell JB, Harrigan P, Weyman AE. Reconsideration of echocardiographic standards for mitral valve prolapse: lack of association between leaflet displacement isolated to the apical four chamber view and independent echocardiographic evidence of abnormality. J Am Coll Cardiol. 1988;11(5):1010-1019.
21. Shapiro LM, Thwaites B, Westgate C, Donaldson R. Prevalence and clinical significance of aortic valve prolapse. Br Heart J. 1985;54(2):179-183.
22. Morganroth J, Jones RH, Chen CC, Naito M. Two dimensional echocardiography in mitral, aortic and tricuspid valve prolapse. The clinical problem, cardiac nuclear imaging considerations and a proposed standard for diagnosis. Am J Cardiol. 1980;46(7):1164-1177.
23. Bergmann H Jr, Leisch F, Schützenberger W, Maschek W, Herbinger W. [Aortic valve prolapse]. Wiener medizinische Wochenschrift (1946). 1983;133(12):303-305.
24. Ogawa S, Hayashi J, Sasaki H, et al. Evaluation of combined valvular prolapse syndrome by two-dimensional echocardiography. Circulation. 1982;65(1):174-180.
25. Tei C, Shah PM, Cherian G, Trim PA, Wong M, Ormiston JA. Echocardiographic evaluation of normal and prolapsed tricuspid valve leaflets. Am J Cardiol. 1983;52(7):796-800.
26. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5(11):685-694. doi: 10.1016/S1473-3099(05)70267-X.
27. Iung B. Epidemiology of valvular heart diseases in the adult. Rev Prat. 2009;59(2):173-7.
28. Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Elsevier Health Sciences; 2014.
29. Orourk R, Alpert J, Dalen R, Ahimtoola S. Syndrome of Mitral valve prolapse. In: Valvular Heart Disease. 3rd ed. Philadelphia: Lippincoti Williams & Wilkins; 1997:157-162.
30. Schlamowitz RA, Gross S, Keating E, Pitt W, Mazur J. Tricuspid valve prolapse: a common occurrence in the click-murmur syndrome. J Clin Ultrasound. 1982;10(9):435-9.
31. Samim H, Hosseini S, Jalalyazdi M. Evaluation of the relationship between mitral valve prolapse (MVP) and body mass index (BMI): a review article. Bali Medical Journal. 2016;5(3):57-63.
32. Hosseinian A, Sadeghieh Ahari S, Dostcami H, Sheikham S. An electrocardiographic changes in mitral valve prolapse (a case-control study). Journal of Ardabil University of Medical Sciences. 2007;7(2):132-136.
33. Michaelides AP, Liakos CI, Antoniades C, et al. ST-segment depression in hyperventilation indicates a false positive exercise test in patients with mitral valve prolapse. Cardiol Res Pract. 2010;2010:541781. doi: 10.4061/2010/541781.
34. Peighambari MM, Alizadehasl A, Totonchi Z. Electrocardiographic changes in mitral valve prolapse syndrome. J Cardiovasc Thorac Res. 2014;6(1):21-23. doi: 10.5681/jcvtr.2014.004.

35. Silventoinen K, Sans S, Tolonen H, et al. Trends in obesity and energy supply in the WHO MONICA Project. Int J Obes Relat Metab Disord. 2004;28(5):710-718. doi: 10.1038/sj.ijo.0802614.
36. Visscher TL, Snijder MB, Seidell JC. Epidemiology: definition and classification of obesity. In: Clinical Obesity in Adults and Children. Wiley; 2010.
37. Kelishadi R, Gharipour M, Sadri GH, Tavasoli AA, Amani A. Cardiovascular disease risk factors, metabolic syndrome and obesity in an Iranian population. East Mediterr Health J. 2008;14(5):1070-9.
38. Hemingway A. Determinants of coronary heart disease risk for women on a low income: literature review. J Adv Nurs. 2007;60(4):359-67.
39. Mion D Jr, Pierin AM, Bambirra AP, et al. Hypertension in employees of a University General Hospital. Rev Hosp Clin Fac Med Sao Paulo. 2004;59(6):329-336.
40. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58(21):2241-7. doi: 10.1016/j.jacc.2011.08.025.