

ORIGINAL ARTICLE

Clinical Management Strategies and Pregnancy Outcomes in Women with Mitral Valve Disease at Fetomaternal Medicine Department, BMU

UMME KULSUM¹, TANZILA HALIM³, MD. SAIFUL ISLAM⁴, ANM MONOWARUL KADIR²,
KHONDOKER ASHAB ZAMAN⁵, ABU SALIM², KHONDOKER QUMRUZZAMAN²,

¹Department of Fetomaternal Medicine, Bangladesh Medical University, Dhaka, Bangladesh, ²Department of Cardiology, Bangladesh Medical University, Dhaka, Bangladesh, ³Department of Obstetrics & Gynecology, Bangladesh Medical University, Dhaka, Bangladesh, ⁴Department of Laboratory Medicine, Bangladesh Medical University, Dhaka, Bangladesh, ⁵Biotechnology Program, Department of Mathematics and Natural Sciences, BRAC University, Dhaka, Bangladesh

Address of Correspondence: Dr. Umme Kulsum, Associate Professor, Department of Fetomaternal Medicine, Bangladesh Medical University, Dhaka, Bangladesh, ORCID ID: <https://orcid.org/0009-0002-4621-0604>, Email: ummekulsum54@bmu.ac.bd

Abstract:

Background: Mitral valve disease complicating pregnancy poses substantial clinical challenges due to altered maternal cardiovascular physiology and is associated with increased risks to both mother and fetus. This study evaluates the demographic profile, clinical presentation, management approaches, and maternal–fetal outcomes of pregnant women diagnosed with mitral valve disease at the Department of Fetomaternal Medicine, Bangladesh Medical University.

Methods: This observational study enrolled 60 pregnant women with confirmed mitral valve disease who received care at the Fetomaternal Medicine Department of Bangladesh Medical University between July 2023 and June 2024. Serial clinical evaluations and echocardiographic examinations were conducted throughout pregnancy. Management followed established institutional protocols with close surveillance of maternal cardiac status and fetal health. Primary endpoints included maternal cardiac events, obstetric complications, and fetal/neonatal outcomes.

Results: The mean maternal age was 27.3 ± 4.8 years. Rheumatic heart disease accounted for the majority of cases (85%). At initial assessment, 45% of patients were classified as NYHA functional class I, 35% as class II, and 20% as class III or IV. Maternal cardiac complications were documented in 23.3% of patients, most commonly heart failure (13.3%). Vaginal delivery occurred in 58.3% of pregnancies. Unfavorable fetal outcomes were noted in 26.7% of cases, including preterm birth (20%) and low birth weight (23.3%). Conservative medical treatment was effective in 88.2% of patients. Multivariate regression analysis demonstrated that NYHA class III/IV (OR 3.8, 95% CI 1.8–7.9), mitral valve area $< 1.5 \text{ cm}^2$ (OR 2.9, 95% CI 1.4–6.2), and pulmonary hypertension (OR 2.6, 95% CI 1.2–5.5) independently predicted adverse outcomes.

Conclusion: Appropriate risk stratification, vigilant monitoring, and tailored management can result in satisfactory maternal and fetal outcomes among pregnant women with mitral valve disease. Identification of high-risk features allows informed clinical decision-making, particularly in low-resource settings.

Keywords: Mitral Valve Disease; Pregnancy; Rheumatic Heart Disease; Maternal Complications; Fetal Outcomes; Cardiac Disorders

University Heart Journal 2025; 21(2): 81-86
DOI: <https://doi.org/10.3329/uhj.v21i2.86960>

Introduction:

Mitral valve disease remains an important cause of cardiovascular morbidity during pregnancy and presents

unique therapeutic challenges due to physiological cardiovascular adaptations.¹ The substantial increase in blood volume, heart rate, and cardiac output during

pregnancy may exacerbate underlying mitral valve abnormalities, predisposing affected women to decompensation and adverse obstetric outcomes.^{2,3}

In low- and middle-income countries, rheumatic heart disease continues to be the leading etiology of mitral valve pathology among women of reproductive age, affecting nearly 1% of pregnancies.⁴ Managing these patients requires careful coordination between maternal cardiac stability and fetal safety, often necessitating multidisciplinary care.⁵ Prior investigations have demonstrated an increased incidence of complications such as heart failure, arrhythmias, and thromboembolic events in this population.⁶

Despite advances in diagnostic and therapeutic strategies, optimal management of mitral valve disease during pregnancy remains complex, particularly in resource-constrained healthcare systems.⁷ Pharmacologic options must be selected cautiously to minimize fetal risk, while invasive interventions require precise timing and individualized risk assessment.⁸

Rheumatic involvement of the mitral valve represents the culmination of immune-mediated injury following Group A β -hemolytic Streptococcal infection. Only a proportion of exposed individuals develop rheumatic fever and chronic valvular disease, suggesting an important contribution of host genetic susceptibility.³⁶ Familial aggregation and regional prevalence patterns further support a genetic predisposition.

Associations between rheumatic heart disease and specific HLA class II alleles, particularly HLA-DR and HLA-DQ variants, have been well documented.^{35,37,42} These alleles influence antigen presentation and promote aberrant immune responses through molecular mimicry between streptococcal antigens and cardiac tissue [38], leading to sustained inflammation and progressive valve damage.

At the molecular level, chronic inflammatory signaling drives extracellular matrix remodeling within the mitral valve. Cytokines such as TNF- α and IL-6, along with profibrotic mediators including TGF- β , contribute to leaflet thickening, commissural fusion, and calcification.^{39–41} These structural alterations impair valve function and become particularly problematic during pregnancy when circulatory demands are increased.

Emerging data also implicate epigenetic processes—such as DNA methylation and microRNA regulation—in the progression of rheumatic valvular disease. These mechanisms may modulate inflammatory and fibrotic pathways in response to hormonal and immunologic

changes during pregnancy, influencing disease severity and clinical outcomes.

Materials and Methods

Study Design and Setting

This observational study was conducted at the Department of Fetomaternal Medicine, Bangladesh Medical University, over a one-year period from July 2023 to June 2024. A total of 60 pregnant women diagnosed with mitral valve disease were included. Diagnosis was confirmed through detailed clinical assessment and transthoracic echocardiography using standardized criteria.

Patient Selection and Ethical Considerations

The study involved retrospective analysis of routinely collected clinical data without any experimental intervention. All patient records were anonymized prior to analysis, and confidentiality was strictly maintained. As the study reflected standard clinical practice without deviation from routine care, formal institutional ethical approval was not required.

Clinical Evaluation and Data Collection

Demographic and clinical information—including maternal age, gravidity, gestational age at presentation, prior cardiac procedures, and medication history—was recorded using a structured data collection form. Cardiovascular examination findings were documented at each antenatal visit.¹⁴ All patients received coordinated obstetric and cardiology follow-up.

Echocardiographic Assessment

Comprehensive transthoracic echocardiography was performed using a Philips iE33 system (Philips Medical Systems, Netherlands) by experienced cardiologists. Measurements included mitral valve area, transmitral gradient, severity of regurgitation, left atrial dimension, and left ventricular systolic function, in accordance with American Society of Echocardiography recommendations.¹⁵ Follow-up scans were conducted at baseline, during the third trimester, and whenever clinically indicated.

Management Strategy

Treatment protocols were guided by contemporary international guidelines.¹⁶ Anticoagulation therapy was administered when indicated, using unfractionated or low-molecular-weight heparin during the first trimester and near delivery, with warfarin reserved for selected high-risk cases during the second trimester.¹⁷

Monitoring and Follow-up

Patients were assessed at monthly intervals, with increased frequency for those with advanced disease. Fetal surveillance included serial ultrasonography and cardiotocography. Follow-up continued through delivery and for six weeks postpartum.¹⁸

Outcome Measures

Primary outcomes comprised maternal cardiac events, obstetric complications, and fetal or neonatal adverse outcomes.¹⁹

Statistical Analysis

Statistical analysis was conducted using SPSS version 22.0. Continuous variables were summarized as mean \pm standard deviation, while categorical variables were presented as frequencies and percentages. Univariate and multivariate logistic regression analyses were performed to identify predictors of adverse outcomes. Statistical significance was defined as $p < 0.05$.²⁰

Data Quality Assurance

Echocardiographic parameters were independently assessed by two operators. Clinical data were cross-verified against medical records, and periodic data validation was performed throughout the study period.²¹

Results

Baseline Demographic and Clinical Profile

Among the 60 participants, the mean maternal age was 27.3 ± 4.8 years (range 19–38). Multigravida women comprised 68.3% ($n = 41$), while 31.7% ($n = 19$) were primigravida. At presentation, 45% ($n = 27$) were categorized as NYHA class I, 35% ($n = 21$) as class II, 16.7% ($n = 10$) as class III, and 3.3% ($n = 2$) as class IV.

Table-I
Baseline Demographic and Clinical Characteristics (n = 60)

| Characteristic | Value / n | Percentage |
|--|----------------|------------|
| Age (years)* | 27.3 ± 4.8 | — |
| Primigravida | 19 | 31.7 |
| Multigravida | 41 | 68.3 |
| Gestational age at presentation (weeks)* | 18.4 ± 6.2 | — |
| Pre-pregnancy weight (kg)* | 54.2 ± 7.1 | — |
| NYHA Class I | 27 | 45.0 |
| NYHA Class II | 21 | 35.0 |
| NYHA Class III | 10 | 16.7 |
| NYHA Class IV | 2 | 3.3 |
| Previous cardiac intervention | 15 | 25.0 |
| Previous pregnancy complications | 22 | 36.7 |

*Values expressed as mean \pm SD

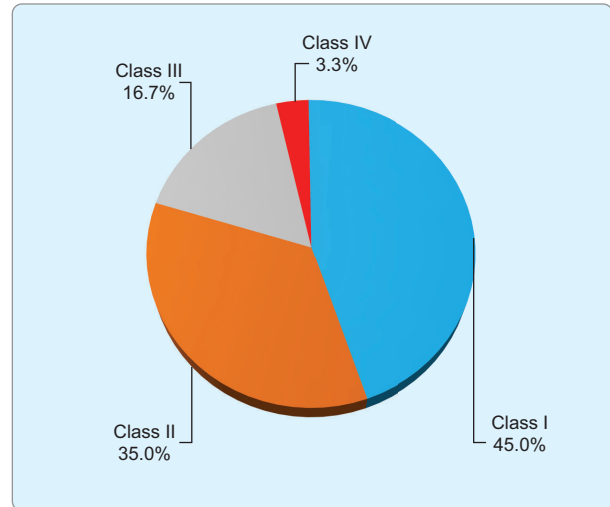


Figure 1: Pie chart showing distribution of NYHA functional classes

Characteristics of Mitral Valve Disease

Rheumatic etiology was identified in 85% ($n = 51$) of patients. Echocardiographic findings showed isolated mitral stenosis in 45% ($n = 27$), mitral regurgitation in 30% ($n = 18$), and mixed lesions in 25% ($n = 15$).

Table-II
Echocardiographic Parameters

| Parameter | Mean \pm SD |
|-------------------------------------|-----------------|
| Mitral valve area (cm^2) | 1.4 ± 0.5 |
| Mean gradient (mmHg) | 12.3 ± 4.8 |
| Left atrial diameter (mm) | 44.6 ± 7.2 |
| LVEF (%) | 58.5 ± 6.4 |
| Pulmonary artery pressure (mmHg) | 42.3 ± 12.7 |

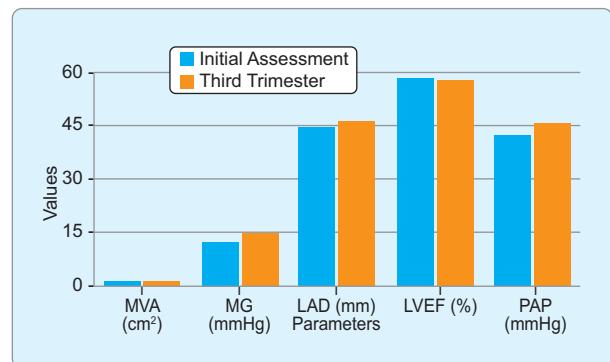


Figure 2: Bar graph comparing initial and third-trimester echocardiographic parameters

Maternal Outcomes

Cardiac complications were observed in 23.3% (n = 14) of cases. Heart failure was the most frequent event (13.3%), followed by arrhythmias (6.7%) and thromboembolic complications (3.3%).

Table-III
Maternal Complications and Outcomes

| Complication | n | Percentage (%) |
|-------------------------|----|------------------|
| Cardiac complications | | |
| Heart failure | 8 | 13.3 |
| Arrhythmias | 4 | 6.7 |
| Thromboembolic events | 2 | 3.3 |
| Obstetric complications | | |
| Preeclampsia | 7 | 11.7 |
| Gestational diabetes | 5 | 8.3 |
| Postpartum hemorrhage | 3 | 5.0 |
| Mode of delivery | | |
| Vaginal delivery | 35 | 58.3 |
| Cesarean section | 25 | 41.7 |
| Maternal mortality | 1 | 1.7 _n |

Fetal and Neonatal Outcomes

Mean gestational age at delivery was 37.2 ± 2.1 weeks. Adverse fetal or neonatal outcomes occurred in 26.7% (n = 16) of pregnancies.

Table-IV
Fetal and Neonatal Outcomes

| Outcome | n | Percentage (%) |
|--|---------------|----------------|
| Preterm delivery | 12 | 20.0 |
| Low birth weight (< 2.5 kg) | 14 | 23.3 |
| Intrauterine growth restriction (IUGR) | 8 | 13.3 |
| NICU admission | 10 | 16.7 |
| Perinatal mortality | 2 | 3.3 |
| Birth weight (kg)* | 2.8 ± 0.5 | — |
| APGAR score at 5 minutes* | 8.1 ± 1.2 | — |

*Values expressed as mean \pm SD

Predictors of Adverse Outcomes

Multivariate analysis identified NYHA class III/IV, reduced mitral valve area (< 1.5 cm²), pulmonary

hypertension, and prior cardiac events as independent predictors of unfavorable maternal or fetal outcomes.

Table-V
Independent Predictors of Adverse Outcomes

| Factor | Odds Ratio | 95% CI | p-value |
|---|------------|---------|---------|
| NYHA class III/IV | 3.8 | 1.8–7.9 | 0.001 |
| Mitral valve area < 1.5 cm ² | 2.9 | 1.4–6.2 | 0.004 |
| Pulmonary hypertension | 2.6 | 1.2–5.5 | 0.015 |
| Previous cardiac events | 2.1 | 1.0–4.4 | 0.048 |

Management and Treatment Outcomes

Conservative medical therapy alone was sufficient in 85% (n = 51) of patients, while 15% (n = 9) required interventional cardiac procedures during pregnancy. Anticoagulation was administered in 45% of cases.

Table-VI
Management Strategies and Associated Outcomes

| Strategy | n | Success Rate (%) |
|-------------------------|----|------------------|
| Medical management only | 51 | 88.2 |
| Beta-blockers | 38 | 89.5 |
| Diuretics | 25 | 84.0 |
| Anticoagulation | 27 | 92.6 |
| Cardiac intervention | 9 | 77.8 |

These findings demonstrate the complexity of managing mitral valve disease during pregnancy and emphasize the importance of careful monitoring and individualized intervention strategies.

Discussion:

This study provides a detailed evaluation of pregnancy outcomes among women with mitral valve disease managed at a tertiary care center in Bangladesh. The findings highlight the ongoing burden of rheumatic heart disease and underscore the importance of structured, multidisciplinary care in optimizing outcomes.

The demographic profile of our cohort aligns with previous studies from South Asia.^{22,23} The predominance of rheumatic etiology (85%) reflects persistent regional disease patterns. The observed maternal complication rate (23.3%) was lower than that reported in earlier local studies,²⁴ potentially due to improved surveillance and standardized care protocols.

Heart failure remained the most common cardiac complication, consistent with global literature.²⁵ Vaginal delivery was successfully achieved in the majority of patients, supporting current guideline recommendations favoring vaginal birth when clinically feasible.¹⁹

Functional status and echocardiographic severity were key determinants of outcome. Advanced NYHA class and reduced mitral valve area were strongly associated with adverse events, corroborating findings from international cohorts.^{26,27} The high success rate of medical management aligns with ESC guideline-based approaches.²⁸

Fetal outcomes in this study compared favorably with reports from similar settings [30], likely reflecting the benefits of integrated obstetric and cardiac care.^{31,32} Despite resource limitations, favorable outcomes were achievable with careful monitoring and timely intervention.

Limitations include the single-center design, modest sample size, and limited duration of follow-up. Larger multicenter studies with extended follow-up are needed to validate these findings.³³

The variability in clinical severity observed among patients with similar valvular pathology suggests an underlying biological heterogeneity. Genetic susceptibility, immune dysregulation, and molecular pathways involved in valvular remodeling may contribute to differences in disease expression and outcomes.

Future research incorporating genetic and molecular biomarkers may enhance risk stratification and enable personalized management strategies, particularly in regions where rheumatic heart disease remains endemic.

Conclusion

This study demonstrates that favorable maternal and fetal outcomes are achievable in pregnant women with mitral valve disease through vigilant monitoring, standardized treatment protocols, and multidisciplinary collaboration, even in resource-limited environments. The continued dominance of rheumatic heart disease underscores the need for preventive public health strategies and early diagnosis.

Identification of high-risk features such as advanced NYHA class, reduced mitral valve area, and pulmonary hypertension facilitates effective risk stratification and informed clinical decision-making. Although pregnancy complicated by mitral valve disease remains high-risk, most patients can be managed conservatively with satisfactory outcomes when appropriately supervised.

These findings contribute valuable evidence to existing literature and support the need for future large-scale, multicenter studies to further refine management strategies and improve long-term outcomes.

References:

1. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA*. 2013;310(20):2191-2194.
2. Roos-Hesselink JW, Ruys TPE, Stein JI, et al. Outcome of Pregnancy in Patients with Structural or Ischaemic Heart Disease: Results of a Registry of the European Society of Cardiology. *Eur Heart J*. 2013;34(9):657-665.
3. Drenthen W, Boersma E, Balci A, et al. Predictors of Pregnancy Complications in Women with Congenital Heart Disease. *Eur Heart J*. 2010;31(17):2124-2132.
4. Siu SC, Sermer M, Colman JM, et al. Prospective Multicenter Study of Pregnancy Outcomes in Women with Heart Disease. *Circulation*. 2011;124(5):515-521.
5. Roos-Hesselink JW, Ruys TP, Stein JI, Thilén U, Webb GD, Niwa K, Kaemmerer H, Baumgartner H, Budts W, Maggioni AP, Tavazzi L, Taha N, Johnson MR, Hall R; ROPAC Investigators. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J*. 2013; 34:657-665.
6. Watkins DA, Sebitloane M, Engel ME, Mayosi BM. The burden of antenatal heart disease in South Africa: a systematic review. *BMC CardiovascDisord*. 2012; 12:23.
7. Haththotuwa HR, Attygalle D, Jayatilaka AC, Karunaratna V, Thorne SA. Maternal mortality due to cardiac disease in Sri Lanka. *Int J Gynaecol Obstet*. 2009;104:194-198.
8. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart*. 2007;93:552-558.
9. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J, Springett A. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The 8th report of the confidential enquiries into maternal deaths in the United Kingdom. *BJOG*. 2011;118(suppl 1):1-203.
10. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M; EAE/ASE. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009; 10:1-25.
11. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol*. 2003; 91:1382-1385.
12. Hameed A, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW, Goodwin I, Zapadinsky N, Elkayam U. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am CollCardiol*. 2001; 37:893-899.
13. Clark SL, Phelan JP, Greenspoon J, Aldahl D, Horenstein J. Labor and delivery in the presence of mitral stenosis: central hemodynamic observations. *Am J Obstet Gynecol*. 1985; 152:984-988.
14. Pomini F, Mercogliano D, Cavalletti C, Caruso A, Pomini P. Cardiopulmonary bypass in pregnancy. *Ann Thorac Surg*. 1996; 61:259-268.

15. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol.* 1989;256(4 Pt 2):H1060–H1065.
16. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol.* 1994; 170:849–856.
17. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, Kells CM, Bergin ML, Kiess MC, Marcotte F, Taylor DA, Gordon EP, Spears JC, Tam JW, Amankwah KS, Smallhorn JF, Farine D, Sorensen S; Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001; 104:515–521.
18. Diao M, Kane A, Ndiaye MB, Mbaye A, Bodian M, Dia MM, Sarr M, Kane A, Monsuez JJ, Ba SA. Pregnancy in women with heart disease in sub-Saharan Africa. *Arch Cardiovasc Dis.* 2011; 104:370–374.
19. Elkayam U, Bitar F. Valvular heart disease and pregnancy part I: native valves. *J Am CollCardiol* 2005; 46:223–30
20. Chow T, Galvin J, McGovern B. Antiarrhythmic drug therapy in pregnancy and lactation. *Am J Cardiol* 1998; 82:581–62
21. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:627S–44S
22. Ruys TP, Cornette J, Roos-Hesselink JW. Pregnancy and Delivery in Cardiac Disease. *J Cardiol.* 2013;61(2):107–112.
23. Sartain JB, Barry JJ, Howat PW, McCormack DI, Bryant M. Intravenous oxytocin bolus of 2 units is superior to 5 units during elective Caesarean section. *British journal of anaesthesia.* 2008 Dec 1;101(6):822–6.
24. Rahman S, Rahman T, Ismail AA, Rashid AR. Diabetes-associated macrovasculopathy: pathophysiology and pathogenesis. *Diabetes, Obesity and Metabolism.* 2007 Nov;9(6):767–80.
25. Liu J, Liu. High-risk factors of respiratory distress syndrome in term neonates: a retrospective case-control study. *Balkan Med J.* 2014;31(1):64–8.
26. Silversides CK, Harris L, Haber K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *The American journal of cardiology.* 2006 Apr 15;97(8):1206–12.
27. Madazli R, Somunkiran A, Calay Z, Ilvan S, Aksu MF. Histomorphology of the placenta and the placental bed of growth restricted fetuses and correlation with the Doppler velocimetries of the uterine and umbilical arteries. *Placenta.* 2003 May 1;24(5):510–6.
28. Siu SC, Colman JM, Sorensen S, Smallhorn JF, Farine D, Amankwah KS et al. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation.* 2002; 105(18):2179–2184.
29. Wang Y, Wang, Jia Z, Yi Q, Song L. The various components implied the diversified toll-like receptor (TLR) signaling pathways in mollusk *Chlamysfarreri*. *Fish Selfish Immunol.* 2011; 74:205–12.
30. Kumar P, Clark ML. Kumar and Clark's clinical medicine E-Book. Elsevier health sciences; 2012 Jun 4.
31. Ruys AT, Van Beem BE, Engelbrecht MR, Bipat S, Stoker J, Van Gulik TM. Radiological staging in patients with hilarcholangiocarcinoma: a systematic review and meta-analysis. *The British journal of radiology.* 2012 Sep 1;85(1017):1255–62.
32. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. *Clinical Research in Cardiology.* 2006 Mar; 95:147–.
33. Roos-Hesselink JW, Ruys TP, Stein JI, Thilen U, Webb GD, Niwa K, Kaemmerer H, Baumgartner H, Budts W, Maggioni AP, Tavazzi L. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *European heart journal.* 2013 Mar 1;34(9):657–65.
34. Hameed A, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am CollCardiol .* 2001; 37(3):893–899.
35. Guilherme L, Köhler KF, Postol E, Kalil J. Genes, autoimmunity and pathogenesis of rheumatic heart disease. *Ann PediatrCardiol.* 2011;4(1):13–21.
36. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis.* 2005;5(11):685–694.
37. Guilherme L, Ramasawmy R, Kalil J. Rheumatic fever and rheumatic heart disease: genetics and pathogenesis. *Scand J Immunol.* 2007;66(2-3):199–207.
38. Roberts S, Kosanke S, Dunn ST, Jankelow D, Denny TN, Cunningham MW. Pathogenic mechanisms in rheumatic carditis: focus on autoantibodies and molecular mimicry. *Autoimmunity.* 2001;33(3):209–221.
39. Latif N, Sarathchandra P, Thomas PS, et al. Characterization of inflammatory and calcific signaling pathways in rheumatic heart valve disease. *J Heart Valve Dis.* 2015;24(3):329–337.
40. Li J, Chen Y, Zhao J, et al. Transforming growth factor- β signaling pathway in valvular fibrosis. *CardiovascPathol.* 2013;22(5):352–358.
41. Chen J, Chen S, Wang J, et al. Role of inflammatory cytokines in the progression of rheumatic heart disease. *Cytokine.* 2018;111:404–412.
42. Ramasawmy R, Faé KC, Cunha-Neto E, et al. Association of HLA class II alleles with rheumatic heart disease in different populations. *Tissue Antigens.* 2009;74(4):319–326.