Pattern of acquired heart diseases among children seen in Sokoto, North-Western Nigeria

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Abstract

Background: Acquired heart diseases (AHDs) are serious but largely preventable diseases. They are highly prevalent in developing countries where poverty, illiteracy, and poor socioeconomic conditions still pose a significant challenge. The prevalence and pattern of AHD among children have not been previously documented within the study area.

Objectives: To determine the pattern and outcome of AHDs among children in Sokoto, North-Western Nigeria.

Subjects and Methods: A prospective study conducted at the Pediatric Department of Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria from 1st July 2009 to 30th June 2014. Data from all the subjects with AHD were analyzed using Statistical Package for Social Sciences.

Results: Of the 3810 children, 110 (2.9%) children were diagnosed with AHD over the study period. The mean age of the subjects was 10.4 ± 3.4 years with M: F ratio of 1.2:1. Rheumatic heart disease (RHD) was the most common AHD seen in 47 (42.7%) patients, followed by dilated cardiomyopathy/myocarditis in 36 (32.7%) and pericardial effusion in 12 (10.9%) patients. Endomyocardial fibrosis was seen in 7 (6.4%) patients while infective endocarditis and Kawasaki disease occurred in 6 (5.5%) and 2 (1.8%) patients respectively. Mortality rate was 17.3%. Commonly observed co-morbidities included heart failure, bronchopneumonia, and pulmonary hypertension.

Conclusion: The pattern of AHD is similar to other studies in developing countries, with RHD being the most prevalent. There is a need for increased emphasis on primary prevention to reduce the burden of these diseases in the study area.

Key words: Acquired heart disease, children, Nigeria, outcome, pattern, Sokoto

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Introduction

Acquired heart diseases (AHDs) represent a diverse group of cardiac diseases, which occur after birth. Though known to have global distribution, their relative burden and pattern of distribution vary between regions across the world and even within a particular geographical area.[1,2] In developed countries, for example, Kawasaki disease (KD) is recognized as the leading cause of AHD in children; whereas preventable conditions such as rheumatic heart diseases (RHDs), endomyocardial fibrosis (EMF), tuberculous pericarditis and other infections-related AHDs are quite prevalent in many developing countries.[3] This is due to the endemic poverty, widespread malnutrition, poor living conditions, low immunization coverage for tuberculosis and worsening HIV pandemic in these countries.[4]

Rheumatic heart disease is a particularly serious public health problem, contributing to significant mortality and morbidity in children.[3] Current WHO estimates indicate that globally at least 15.6 million people have RHD.[6] Of the 500,000 people who acquire acute rheumatic fever (ARF) every year, 300,000 go on to develop RHD while over 233,000 deaths occur annually due to either ARF or RHD.[6,7] In Asia and Sub-Saharan Africa including Nigeria, studies have shown that RHD is the most common AHD.[1,8-10] However, a
study among pediatric patients in Lagos, South-Western Nigeria observed RHD to be the second most common AHD after effusive pericarditis\textsuperscript{[11]} while a recent multicenter study involving cohorts of children from Nigerian cities of Benin, Lagos, and Abuja identified RHD as the third most common AHD.\textsuperscript{[12]} Similarly, both Akinwusi et al.\textsuperscript{[13]} and Sadoh et al., \textsuperscript{[14]} had reported low prevalence of RHD in their series (0.16/1000 medical outpatients and 0.57/1000 pupils respectively), which may suggest a declining incidence of the disease.

There is presently no documented study on the types of AHDs prevalent among children within the study area. Most of the aforementioned studies were conducted among patients living in highly cosmopolitan cities of Southern Nigeria.\textsuperscript{[11]-[14]} Since socioeconomic and human development indices as well as access to health care services are not uniform across the country,\textsuperscript{[15]} available data on AHD from other parts of the country may not necessarily represent the true situation in the study area. The present study is, therefore, imperative as it will provide local data on the subject and enable comparison with results of other studies. Information on the relative burden of the various types of AHD may also go a long way in helping to plan and appropriately prioritize strategies for treatment and prevention of AHD in the study area.

**Subjects and Methods**

The study was conducted at the Pediatric Department of Usman Danfodiyo University Teaching Hospital (UDUTH), Sokoto, which is one of the tertiary health institutions located in North-Western Nigeria. The Hospital serves as a referral center for a large number of patients from Sokoto, Zamfara, Kebbi and Katsina States of Nigeria as well as from neighboring countries such as Niger and Benin Republics. The people within the study area are predominantly peasant farmers, with the majority living in rural areas and belonging to low socioeconomic class (SEC).\textsuperscript{[16]}

The study was a descriptive prospective study conducted over a 5-year period (1\textsuperscript{st} July 2009 to 31\textsuperscript{st} June, 2014), with the objective of determining the pattern and outcome of AHDs in Sokoto. Subjects for the study included all children who were seen at the Pediatric Cardiologic Clinic (PCC) or admitted to the Emergency Pediatric Unit and Pediatric Medical Ward of UDUTH for cardiac evaluation and management. Using convenience sampling, study subjects were recruited consecutively as they presented to the PCC and the pediatric wards of the hospital over the study period. Those who already had surgery at the time of presentation were excluded from the study. Children who died before confirmation by echocardiography were also excluded, unless where diagnosis of AHD was confirmed at autopsy. At presentation, demographic and clinical information including age, gender, socioeconomic status as described by Oyedeji,\textsuperscript{[17]} anthropometric indices and oxygen saturation were obtained and entered into a study proforma. Each patient had detailed clinical evaluation including cardiovascular examination, followed by relevant laboratory investigations, chest radiograph, electrocardiography and echocardiographic studies.

Transthoracic echocardiography was performed for all patients with suspected cardiac disease using Sonoscape SSI 5000 echo-machine (Sonoscape Yizhe, Shenzhen, China) mounted with 5PI transducer (3.5-7 MHz). The principal author who had earlier undergone training in pediatric cardiology at the Institute of Cardiovascular Diseases, Madras Medical Mission, Chennai-India conducted the procedure. Cardiac imaging was through apical, parasternal long axis, parasternal short axis, subcostal, and suprasternal notch views.\textsuperscript{[18]} Structural abnormalities were evaluated using two-dimensional-echocardiography whereas; flow direction and pressure gradients were assessed with color flow and continuous wave Doppler respectively. M-mode was used for measurement of ventricular function.\textsuperscript{[18]} Diagnosis of RHD was based on World Heart Federation criteria for echocardiographic diagnosis of RHD\textsuperscript{[19]} while diagnosis of dilated cardiomyopathy (DCM) was made in the presence of dilated left ventricle associated with global hypokinesia and systolic dysfunction.\textsuperscript{[18]}

Kawasaki disease was diagnosed if a patient has fever that persisted for at least 5 days or more in association with at least four of the following principal features: polymorphous rash, nonexudative bilateral conjunctivitis, oral changes (erythematous or dry fissured lips, strawberry tongue, pharyngitis), changes in the extremities (erythema and edema of the hands or feet, desquamation of fingers and toes) and cervical lymphadenopathy of 1.5 cm greater.\textsuperscript{[20]} Presence of coronary artery aneurysm was determined using recommended criteria: An internal diameter of either coronary artery of > 3 mm in children below 5-year or > 4 mm in children above 5-year or if a segment measures 1.5 times the adjacent coronary segment.\textsuperscript{[21]} Infective endocarditis (IE) was diagnosed based on modified Dukes criteria.\textsuperscript{[22]} Ethical approval for the study was obtained from UDUTH Ethics Committee.

**Data analysis**

Data of all the patients with confirmed echocardiographic diagnosis of AHD were entered and analyzed using Statistical Package for Social Sciences version 20 (IBM Corporation, New York). Quantitative data were expressed as means and standard deviations while categorical variables were expressed as proportions. Mean values between two groups were compared using the Student t-test. Chi-square test or, where figures were small, Fisher’s exact test, was used for comparison of proportions. \( P < 0.05 \) was considered as statistically significant.
Results

Demographic characteristics
Of the 3810 patients seen at the Pediatrics Department of UDUTH, a total of 110 (2.9%) children were diagnosed with AHDs over the 5-year study period. There were 61 males and 49 females, giving M: F ratio of 1.2:1. The overall median age of the study cohort at diagnosis was 11 years with a mean ± standard deviation of 10.4 ± 3.4 years (range = 0.58–15 years). Up to 77.3% (85/110) of the children were above the age of 5-year while as high as 65.5% of the patients belonged to low SEC [Table 1].

Types of acquired heart diseases
The distribution of the various types of AHDs among the study subjects is shown in Table 2. RHD was seen in 47 (42.7%) children, followed by DCM/myocarditis in 36 (32.7%).

Comparison of age and gender distributions for specific acquired heart disease types
With respect to the different types of AHDs, the age distribution of the subjects is shown in Table 3. Except for one patient, all the children with RHD were older than 5-years. The patient was a 4-year-9-month-old girl who was referred due to suspicion of congenital heart disease. She had a history of recurrent difficulty in breathing and cough since 1-year prior to presentation. Physical examination revealed hyperactive precordium, heaving and displaced apex with a grade-four pansystolic murmur at the apex, radiating to the axilla. Echocardiography showed severe mitral regurgitation (MR) and mild aortic regurgitation (AR) with normal ventricular function (ejection fraction - 65%, FS - 20%). The patient was managed medically with good response and then commenced on secondary prophylaxis with benzathine penicillin. For children with other AHDs, majority of those that had EMF (67/ or 85.7%) and pericardial effusion (PE) (9/12 or 75%) were above the age of 10 years; whereas 50% (18/36) of those with DCM/myocarditis were below the age of 5-years. The mean ages of children with RHD, DCM and PE were 9.65 ± 2.87 (range = 5–15), 7.56 ± 4.13 (range = 0.58–14) and 11.92 ± 2.97 (range = 6–14) years respectively. It is of note that the mean age of patients with RHD (9.65 ± 2.87 years) was higher than that of children with DCM/myocarditis (7.56 ± 4.13): T = 2.68, P = 0.0089. The two children with KD were aged 2.5 years and 13 years respectively. The male to female ratios were 1:1.4, 1.4:1 and 1.4:1 for patients with RHD, DCM and PE respectively [Table 4].

Echocardiographic and other characteristics of patients with various types of acquired heart disease
Rheumatic heart disease
Mitral valve involvement was present in all 47 patients with RHD. It occurred as an isolated finding in 5 (10.6%) patients and in association with other valve lesions in the remaining 42 (89.4%) patients. Detailed echocardiographic pattern of valve lesions among the children with RHD is shown in Table 5.

One patient, a 12-year-old boy with severe AR and moderate MR, had aortic valve replacement in India and has been on anticoagulant therapy with warfarin since then. He maintained normal coagulation profile (international normalized ratio ranging between 2 and 2.5) and stable cardiovascular status during follow-up at the pediatric cardiology clinic. An 11-year-old girl with RHD, who was on secondary prophylaxis for rheumatic fever, developed anaphylactic hypersensitivity reaction to benzathine penicillin. She presented with sudden collapse/syncope...
and features of shock occurring within seconds of receiving the third prophylactic dose. Fortunately, she responded to resuscitation with saline infusion, adrenaline and steroid (intravenous hydrocortisone) administration. The drug was changed to daily erythromycin. Two patients with rheumatic mitral valve disease presented with arrhythmias: Supraventricular tachycardia in a 15-year-old boy, which responded to treatment with digoxin and atrial fibrillation with persistent heart failure in a 14-year-old girl. The latter patient died despite medical treatment.

**Dilated cardiomyopathy/myocarditis**

Among the 36 patients with DCM/myocarditis, two were children with muscular dystrophies (most probably Duchenne), one with end stage renal failure on chronic hemodialysis and another patient with rhabdomyosarcoma who had prolonged chemotherapy with doxorubicin. For the remaining patients, no specific cause could be identified.

The two patients with muscular dystrophies were siblings aged 8 and 14 years respectively. They were initially being followed-up at the pediatric neurology clinic but were subsequently referred for cardiac evaluation due to the onset of effort intolerance and orthopnea. Echocardiography showed classical features of DCM with ejection fraction of 34% and 22% respectively [Figure 1]. The cardiac function of the 14-year-old boy deteriorated progressively and reportedly died suddenly at home. However, at the time of this study, his younger sibling was still being followed-up at the pediatric cardiology and pediatric neurology clinics. His cardiac function has not significantly improved despite conservative management with digoxin, diuretics, and captopril.

The patient who had doxorubicin chemotherapy was a 5-year-old girl with histology-confirmed embroyonal rhabdomysarcoma of the right forearm. Beside local excision of the tumor, chemotherapy was commenced using a treatment protocol that comprised doxorubicin given at a dose of 40 mg/m². Though there was initial improvement, the tumor recurred after 1-year, which necessitated repeat excision of the tumor and continuation of chemotherapy. However, the patient was noticed to have developed effort dyspnea 6 months later and was consequently referred to the pediatric cardiology unit for cardiac evaluation. At the time of presentation, she had received a total cumulative doxorubicin dose of 720 mg/m². Echocardiographic assessment showed features of mild systolic dysfunction (ejection fraction of 45%). As no other obvious systemic illness or risk factors could be identified to explain her symptom, the cause was presumed to be due to the cardiotoxic effect of doxorubicin chemotherapy.

**Other acquired heart diseases**

Pericardial effusion, EMF, IE, and KD accounted for 24.6% of the patients with AHD. Of the 12 patients with PE, the underlying cause was considered to be tuberculosis in six patients, uremic pericarditis in two patients and as a result of metastasis from a primary malignant abdominal focus in another one patient while the cause was uncertain in the remaining three patients. Cardiac tamponade necessitating emergency pericardiostomy occurred in one of the patients.

Kawasaki disease was diagnosed in two patients. One of the patients was a 14-year-old boy who had associated renal involvement evidenced by proteinuria, hematuria, and impaired renal function. The other patient was a 2.5-year-old...
boy who presented with polymorphous rash, fever, lymphadenopathy, strawberry tongue and desquamative skin changes of the extremities. He also had abnormal hematologic profile (severe thrombocytosis-platelet count of 650 × 10⁹, markedly elevated ESR > 160 mm/h) and right coronary artery aneurysm (coronary artery internal diameter of 5.95 mm) as shown in Figure 2. The two patients belonged to high and middle SECs respectively. Both of them were managed with high-dose aspirin (80 mg/kg), but intravenous immune-globulin could not be used due to nonavailability. There was no mortality.

Similarly, IE was diagnosed in six children all of whom had prolonged high fever (38.5°C-40.0°C) with echocardiographic evidence of vegetation. Five of the patients had underlying ventricular septal defects (VSDs) while one had rheumatic mitral valvular disease. Among the patients, there was a 7-month-old male infant with Down's syndrome who had staphylococcal IE and a 9-month-old male infant whose blood culture repeatedly yielded Escherichia coli. The two patients had prolonged hospital stay (6-7 weeks), but recovered following treatment with antibiotics including intravenous vancomycin. After discharge, definitive surgery for the cardiac defects (VSD closure) was successfully performed in India. The remaining four patients including an 8-year-old boy with VSD and a 2-year-old boy with sickle cell anemia were culture negative, despite echocardiographic evidence of vegetation [Figure 3]. The 8-year-old boy had persistent high fever despite treatment with various antibiotics. Serial echocardiography for the patent showed relatively large vegetation involving the interventricular septum adjacent to the defect and extending to the pulmonary valve as well as the right ventricular outflow tract. Unfortunately, the patient deteriorated and died after prolonged hospital stay.

Outcome of children with acquired heart disease
Of the 110 children in the study, a total of 19 (17.3%) patients died (RHD = 10 (52.6%), DCM/myocarditis = 6 [31.6%]), PE = 2 (10.5) and IE = 1 (5.3%)). However, 42 (38.2%) patients were lost to follow-up, and their outcome is unknown. The remaining 49 (44.5%) patients have been on follow-up at the pediatric cardiology clinic. Observed co-morbidities among the 49 patients on follow-up included heart failure in 37 (75.5%), bronchopneumonia in 28 (57.1%) and pulmonary hypertension in 11 (22.4%) children. As earlier stated, arrhythmias occurred in 2 (4.1%) two (4.1%) patients while right coronary artery aneurysm and anaphylaxis to benzathine penicillin were observed in one (2.0%) patient each.

Discussion
This study highlights the diverse spectrum and epidemiologic characteristics of AHDs within the study area. Unlike congenital heart diseases that usually manifest soon after birth, acquired heart lesions often come to light later in life. This was evident in the present study where more than 70% of the study cohort were older than 5-year at the time of presentation.

Rheumatic heart disease was the most common AHD among the study cohort followed by DCM/myocarditis and pericardial diseases; while IE and KD were less commonly encountered. This pattern of distribution is consistent with some studies in Nigeria and other developing countries. The continuing burden of RF and RHD in many developing nations has been attributed to problems of overcrowding, poverty, illiteracy, poor nutrition and poor access to health care services. These factors are associated with increased transmission of Group A-beta
hemolytic streptococcus, delayed recognition and treatment of streptococcal pharyngitis and poor compliance to secondary prophylaxis. In developed countries, significant improvement in socioeconomic and environmental conditions coupled with efficient preventive measures has been the major reasons responsible for the observed decline in the incidence of RF.[7,24] Though recent studies in Southern Nigeria by Akinwusi et al.[13] and Sadoh et al.[14] have reported low prevalence of RHD, it is difficult to conclude whether such findings reflect a true decline in the incidence of the problem: the former study, being hospital based and among adult population, may underestimate the actual community burden of the disease in pediatric patients; the latter study, which was school-based, might have missed many children with RHD who could not attend school due to ill health.

Patients age and gender are known to be important epidemiologic determinants of diseases. In the present study, the ages of children with RHD ranged between 5 and 15 years. This is the age category known to be at highest risk of Group A streptococcal pharyngitis and hence rheumatic fever.[7,24] RHD is uncommon before the age of 3 years and generally after 21 years.[7,24] Female preponderance was also observed among the study patients with RHD, which is consistent with a previous study in Jos, North-Central Nigeria.[2] In contrast, DCM was most prevalent among under-five children whereas children with EMF and PE were all above the age of 10 years. A recent study by Bode-Thomas et al.[2] has similarly observed that DCM was commoner among children below the age of 5-year and RHD was most prevalent in older children above 5-year.

Like DCM, KD is known to occur predominantly in young children below the age of 5-year.[25] The number of patients with KD in the present study is too small for any in-depth analysis and reliable inference. While one of the patients was within the at-risk-age-group, the other patient was diagnosed at an atypical age of 14 years.[25] The latter case further confirmed the fact that KD can occur even in older age groups.[26] A significant observation in this study is that all the patients with EMF were boys, which is similar to findings from a recent study in Nigeria.[12] Findings from these two studies further confirm earlier report that EMF predominantly affects males.[27] but the reason for this is not clear.

The echocardiographic pattern of valvular lesions among the study cohorts with RHD was consistent with other studies.[12,13,28] The mitral valve was the most frequently affected followed by aortic valve in our series. MR was present in all but two affected patients, and only five patients had evidence of associated mitral stenosis. MR is known to be the dominant cardiac abnormality in patients with rheumatic carditis, occurring in up to 95% of patients; whereas AR occurs in approximately 20-25% of patients, usually in combination with MR.[24] The suggested mechanism of MR is a combination of annular dilatation and chordal elongation, which results in abnormal coaptation and in some cases, prolapse of the tip of mitral leaflet.[7,24] Other valvular lesions such as tricuspid and pulmonary are rare; but when they occur, the mechanism is usually functional.[7]

Unlike RHD, the etiologic factors for DCM are broad and quite heterogeneous.[29,30] They include infectious, metabolic, mitochondrial, arrhythmic, ischemic, toxic, familial and inflammatory diseases.[29-31] Though viral infections and genetic factors are particularly known to play a significant role in the pathogenesis of DCM, many cases of DCM have no identifiable primary cause and are referred to as idiopathic.[29,31] In our series, only four patients had obvious underlying factors that were known to be associated with the development of DCM.[31] These include Duchene muscular dystrophy (DMD) in two patients, end stage chronic kidney disease in one patient and prolonged doxorubucin chemotherapy in another patient with rhabdomyosarcoma. In dystrophinopathies such as DMD, dystrophin gene is lacking not only in skeletal muscle, but also in neurons, smooth muscle, and cardiac muscle.[24] Hence, patients may have additional clinical features, such as cognitive deficits and cardiomyopathy, due to involvement of these tissues.[29]

The suggested mechanism of injury in dystrophin-deficient cells include increased susceptibility to mechanical injury to the sarcolemma during the process of contraction and excess cation permeability that results in increased calcium ion influx and secondary sarcolemma breakdown.[29] On the other hand, the cardiotoxic effect of doxorubucin is related to generation of reactive oxygen species resulting from the reduction of doxorubucin to its semiquinone free radical form, especially within the mitochondria.[29] The risk of doxorubucin-induced cardiomyopathy significantly increased when the total cumulative dose exceeds 350-450 mg/m2.[2,29] It is instructive that the patient in the study cohort had received as high as 720 mg/m2 of doxorubucin. Hence, patients on chemotherapy with doxorubucin should be closely monitored by cardiac evaluation and echocardiographic assessment. The risk of cardiotoxicity can be minimized by not exceeding the recommended cumulative dose. In addition, the use of cardioprotective agents such as dexrazoxane, an iron-chelating agent that prevents free hydroxyl radical generation, is being advocated.[29] The present study is limited by the lack of facilities for molecular and genetic testing for other causes of DCM.

As previously highlighted, the only two cases of KD in this study included an unusual case in a 14-year-old boy that was the first reported case from our center,[25] and a second case in a 2.5-year-old boy who had all the features
of KD in association with abnormal hematologic profile and right coronary artery aneurysm. It has been shown that coronary artery abnormalities occur in 25% of patients with KD and is the most serious sequela that can result in significant morbidity and mortality.\textsuperscript{[2,13,15]} All the patients in the study were managed with high dose acetyl salicylic acid. Intravenous immunoglobulin could not be used due to its nonavailability. Nevertheless, they remained stable after discharge and have been on regular follow-up at the pediatric cardiology clinic with close monitoring of their cardiovascular status. It was noted that the two patients in this study belonged to high and middle SEC respectively. The small number of the patients makes it difficult to make any inference concerning the relationship between SEC and risk for the disease.

Some previous studies reported no cases of KD,\textsuperscript{[10,11]} but the observation of such cases in this study and that of Jos, North-Central Nigeria,\textsuperscript{[13]} as well as from a recent multicenter Nigerian study\textsuperscript{[12]} further indicates that the disease may not be as rare as previously thought.\textsuperscript{[13]} It is of note that the first patient diagnosed with KD in our institution was initially considered to have allergy (urticaria) while the second case was managed initially for measles at the referral hospital before presentation. High index of suspicion is, therefore, necessary to avoid misdiagnosis.

Infective endocarditis is less common in children than adults, with reported incidence ranging from 0.8% to 3.3%.\textsuperscript{[2]} Available studies in Nigeria have reported only a few cases of IE in their series.\textsuperscript{[2,12]} Only six patients were diagnosed with IE in the present study, with VSD being the underlying risk factor in all but one patient. VSD, like some other congenital and acquired heart lesions, is often characterized by steep pressure gradient and high-velocity jet, with resulting turbulence of blood flow, which may traumatize the endothelium.\textsuperscript{[29]} The sequence of events resulting in endocarditis includes formation of nonbacterial thrombotic endocarditis (NBTE) on the surface of damaged endocardium, occurrence of a transient bacteremia, adherence of these bacteria to the NBTE, and subsequent proliferation of the bacteria within vegetation.\textsuperscript{[32]}

The overall mortality among the study cohort was 17.3%, with most of the deaths occurring in children who had RHD and cardiomyopathies. This unacceptable high mortality highlights the need to strengthen preventive measures particularly against rheumatic fever and ensure timely intervention where necessary. The high attrition rate observed during follow-up may be explained either by patient’s death at home or by subsequent resort to traditional healers. The present study had also shown that complications such as heart failure, bronchopneumonia, pulmonary hypertension and arrhythmias are not uncommon especially in patients with RHD and cardiomyopathy. These problems should, therefore, be anticipated early and treated promptly to prevent unnecessary morbidity and mortality. A major challenge is the fact that definitive cardiac surgery is not feasible for many patients in the study area and across other parts of the country due to lack of facilities and expertise. There is, therefore, an urgent need to establish functional cardiac centers across the country and encourage capacity building through both national and international collaboration.

**Conclusion**

The spectrum of AHDs among the study cohort is diverse but similar to the distribution reported in other developing countries.\textsuperscript{[2,13,15]} RHD remains the most prevalent in our environment and accounted for the highest morbidity and mortality in patients with AHD. Hence, the need for increased emphasis on preventive measures in addition to improved diagnostic and curative services.

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**References**

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