

**ECHOCARDIOGRAPHIC ABNORMALITIES IN PATIENTS WITH
RHEUMATOID ARTHRITIS ATTENDING THE RHEUMATOLOGY
CLINIC AT THE KENYATTA NATIONAL HOSPITAL.**

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**A RESEARCH FOR DISSERTATION SUBMITTED AS PART OF
FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER IN MEDICINE (INTERNAL MEDICINE), UNIVERSITY OF
NAIROBI.**

DECLARATION

I declare that this dissertation is my original work and to the best of my knowledge, it has not been presented for a degree in any other university.

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DEDICATION

In memory of my father

Your words of inspiration and encouragement in the pursuit of excellence, still linger on.

To my mother

With love and eternal appreciation

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First and foremost, I would like to thank God whose many blessings have made me who I am today. You have given me the power to believe in my passion and pursue my dreams. I could never have done this without the faith I have in you. This document summarizes three years' worth of effort, frustration and achievement and I have only you to thank, Almighty.

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LIST OF ABBREVIATIONS

1. A	Late mitral flow
2. A'	Late myocardial velocity
3. ACL	Anticardiolipin
4. Anti CCP	Anti-cyclic citrullinated peptide.
5. ACR	American College of Rheumatology
6. ANA	Antinuclear antibody
7. aPL	Antiphospholipid
8. CDAI	Clinical disease activity index
9. CI	Confidence Interval
10. CVD	Cardiovascular disease
11. CW	Continuous wave Doppler
12. 2D	Two dimension
13. DAS 28	Disease activity score in 28 joints
14. Dct	Mitral deceleration time
15. E	Early Mitral flow
16. E'	Early myocardial velocity
17. EULAR	European League Against Rheumatism
18. KNH	Kenyatta National Hospital
19. LA	Left atrium
20. LV	Left ventricle
21. MOPC	Medical outpatient clinic
22. MV	Mitral valve
23. PAH	Pulmonary arterial hypertension
24. PAP	Pulmonary arterial pressure
25. P _{1/2}	Pressure half time
26. RA	Rheumatoid Arthritis
27. RF	Rheumatoid Factor
28. SDAI	Simple disease activity index
29. SLE	Systemic lupus erythematosus
30. sPAP	Systolic pulmonary arterial pressure
31. TLR	Toll like receptor

ABSTRACT

Background: The risk for cardiovascular disease (CVD) in Rheumatoid arthritis (RA) is not related primarily to traditional atherosclerosis risk factors or to drugs but rather has a complex multifactorial interaction. Traditional management of RA has been directed against joint inflammation and damage and not against increased cardiac abnormalities, however, the detection and/or prevention of cardiac abnormalities in RA merits as much attention as the reduction of joint inflammation and disability.

Objectives: To determine the prevalence of echocardiographically detected cardiac abnormalities in patients with RA at Kenyatta National Hospital (KNH). Secondary objectives were to determine associations between cardiac abnormalities in RA with disease activity using the clinical disease activity index (CDAI) and to determine associations between cardiac abnormalities in RA and duration of disease.

Materials and Methods: A cross-sectional descriptive study of 104 RA patients consecutively sampled over 3 months. Clinical examination and transthoracic 2D echocardiography were done for all patients. The echocardiogram outcome variables included pericardial disease, cardiomyopathy/myocarditis, valvular disease and pulmonary hypertension. Clinical outcome variables included CDAI and duration of illness. The study population was described using demographic and clinical characteristics. Continuous data were presented as means and medians, categorical data as percentages and the prevalence of cardiac abnormalities was presented as proportions with a corresponding 95% CI.

Results: One hundred and four RA patients fulfilled the inclusion criteria with a mean age of 51 years and a female to male ratio of 25:1. The prevalence of echocardiographic abnormalities was found to be 62.5% and was unrelated to CDAI and duration of disease. The most common cardiac lesion was pericardial effusion at 39.4%. The tricuspid valve was the most commonly affected valve with 15.4% having tricuspid regurgitation (TR). Pulmonary hypertension was found in 5.5% of patients.

Conclusion: This study shows a high prevalence of cardiac abnormalities among RA patients despite these patients being on disease modifying medications and being diagnosed relatively earlier. Majority of the patients were in remission with duration of illness less than 5 years.

1.0 INTRODUCTION

Rheumatoid arthritis (RA) is a progressive, multi-systemic autoimmune disease characterized by chronic inflammation of multiple joints with associated systemic manifestations. This inflammation causes joint pain, stiffness and swelling, resulting in joint dysfunction due to damage of the bone and cartilage, often leading to progressive disability. RA is a multifactorial chronic condition, resulting from the interaction of both genetic and environmental factors (1). RA has an estimated worldwide prevalence of 1% of the adult population and is a leading cause of chronic morbidity in the industrialized world, but little is known about the disease burden in Africa (2). There is a female preponderance with a ratio of about 3:1 in younger populations, however, the ratio approximates in the older age groups (3). RA remains the most important form of arthritis seen in rheumatology practice in the developed world and the geographical distribution of the disease is remarkably homogeneous (4).

Historically, RA in Africa has been seen as a rare disease compared to Europe and America (5). Recent evidence shows RA to be increasing in most parts of Africa excluding West Africa (6). In Uganda initial studies reported the occurrence of RA as a rare entity, but over the decades, studies have shown a gradual rise in the number of patients seen with the disease. In 1979 Bagg et al reported 76 patients with RA over an 18 month period at the KNH, MOPC (6). In 2011, a survey of the outpatient rheumatology clinic at KNH found that 37.3% of patients attending the clinic had RA (7). The increasing number of patients diagnosed with RA in Kenya may be attributed to improved diagnostic capabilities (serology and radiological) and refined classification criteria (ACR/EULAR 2010 criteria) which identifies RA patients early. Increased physician awareness and easier access to health facilities also has helped in diagnosing the disease early.

RA is associated with many extra-articular clinical including the skin, eye, heart, lung, hematopoietic tissue, renal, nervous and gastrointestinal systems (8). Extra-articular manifestations of RA occur in about 40% of patients, either at the beginning or during the course of their disease (9). The presence of extra articular manifestations in RA is associated with severe active disease and increased mortality (9). The disease is associated with a high

risk for morbidity and premature death related to cardiovascular, lung diseases and malignancies (11). A systematic analysis of 127 hospitalized patients with RA showed 76% had one or more extra-articular feature including subcutaneous nodules, pulmonary fibrosis, digital vasculitis, skin ulceration, lymphadenopathy, non-compressive neuropathy, splenomegaly, episcleritis or pericarditis. On follow-up of the total group of patients after five years a mortality of 20% was found (12). Patients with RA with high titers of RF are more likely to have extra-articular manifestations during their course of the disease (9,13,14). RA patients with extra-articular manifestations should be aggressively treated and monitored closely (15). The prevalence of extra-articular manifestations of RA has been declining over the past few years, indicating that disease-modifying RA treatments may be changing the natural course of the disease (16,17).

The only study done locally by Kirui F, et al on the prevalence of cardiovascular risk factors in patients with RA at KNH showed hypertension (41.3%), diabetes (6.3%), dyslipidemia (71.3%), obesity (22.5%), and abnormal waist hip ratio (33.8%) as the cardiovascular risk factors amongst RA patients (18). A study by Schorn et al showed 73% overall cardiac abnormalities in RA with pericardial effusion in 32% and pericardial thickening in 11% (19). Merz et al looked for etiologies of pericardial effusion in 204 patients with RA and only 3.43% of the cases had a specific diagnosis (20). Heart failure may be one of the main causes of increased cardiac mortality in RA, particularly in men with RA (24). Left ventricular diastolic dysfunction in RA on Echo-Doppler was found to be greater in RA patients than in the general population (24). A study done in Spain by Gonzalez et al confirms a high frequency of left ventricular diastolic dysfunction and pulmonary hypertension in patients with RA without evident CVD (25). Echocardiographic and autopsy studies show valvular disease in almost 30% of patients with extra-articular RA. As compared to non-RA populations, mitral regurgitation may be more common in RA patients (26). Aortic root abnormalities, including aortitis, have been reported in association with RA (26,27). The risk of sudden death and myocardial infarction appears to be increased in patients with RA and this increase is independent of traditional CV risk factors (28,29). Coronary vasculitis is an uncommon complication of RA even though patients with RA have an increased risk of premature CAD and death from atherosclerotic disease (27).

2.0 LITERATURE REVIEW

The precise cause of RA is unknown, and the prognosis is guarded, especially in those with high disease activity states. Better understanding of the pathogenesis of RA has stimulated the development of new biologic therapies, with better outcomes, all in pursuit of clinical remission. Prolonged remission is rarely fully achieved and requires ongoing pharmacological therapy.

2.1 PATHOPHYSIOLOGY OF RA

An interaction between genetics, environmental factors, and chance exists in RA. RA is characterized by synovial joint inflammation and hyperplasia, autoantibody production (RF and anti-CCP), cartilage and bone destruction, and multi-systemic features, including cardiovascular, pulmonary, hepato-biliary, haematological, and psychological (17).

2.2 GENETIC AND ENVIRONMENTAL FACTORS

Twin studies allude to genetic factors in RA with concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins (30). Genome wide analyses offer evidence that immune regulatory factors underlie the disease (31). The relationship between the human leukocyte antigen (HLA) –DRB1 locus in patients who are positive for RF or anti CCP; alleles that contain a common amino acid motif (QKRAA) in the HLA-DRB1 region, called the shared epitope, confers an actual susceptibility for these patients to develop RA (32). These findings suggest that some predisposing T-cells, antigen presentation or alteration in peptide affinity has a role in stimulating the adaptive immune responses. Another explanation for the interplay between RA and the shared epitope implicates molecular mimicry of the shared epitope by microbial proteins, increased T-cell senescence caused by shared epitope containing HLA molecules, and a pro-inflammatory signalling function that is not related to the function of the shared epitope in antigen recognition (33,34). Gene–gene interactions that increase the risk of disease, as described between HLA-DRB1 and PTPN22, reveal the complexity of the net risk caused by any given gene (35).

Smoking and exposure to other forms of bronchial stressors (e.g. Exposure to silica) increase the risk of RA among persons with susceptibility HLA– DR4 alleles (36). Moreover,

smoking and HLA-DRB1 alleles synergistically increase the risk of having anti CCP (37). Unifying these observations gives the result that environmental stressors of pulmonary and other barrier tissues may stimulate posttranslational re-arrangements, through peptidyl arginine deiminase and type IV (PADI4), that result in quantitative and/or qualitative changes in citrullination of specific proteins. Absent tolerance to neoepitopes elicits an anti CCP response which can be detected with a diagnostic anti-CCP assay (38,39). Several citrullinated self-proteins are recognized in anti-CCP assays, such as α -enolase, keratin, fibrinogen, fibronectin, collagen, and vimentin. An estimated 43 to 63% of patients with anti CCP-positive RA are seropositive for citrullinated α -enolase, which is strongly associated with HLA-DRB1*04, PTPN22, and smoking (40). Infectious agents (e.g., Epstein-Barr virus, cytomegalovirus, proteus species and Escherichia coli) and their by-products (e.g. Heat-shock proteins) have been linked with RA, and although the common mechanisms remain obscure, the formation of immune complexes and molecular mimicry has been postulated (41,42). Autoantibodies, such as RF and anti CCP, are often (but not always) detected in patients before the development of arthritis (pre-articular phase of RA); in some series, autoantibody levels have increased and there has been evidence of epitope spreading as the onset of disease approaches (43).

2.3 CYTOKINES AND THE IMPACT ON EFFECTOR CELLS

It is well known that pro-inflammatory cytokines (e.g. IL-6 and TNF- α) play a pivotal role in the pathogenesis of RA (44,45). TNF- α and IL-6 play dominant roles in the pathophysiology of RA; however, IL-1, VEGF and IL-17 also have a major influence on the disease process. Through complex signal pathways, these cytokines activate genes associated with inflammatory responses, including additional pro inflammatory cytokines and MMPs involved in tissue degradation (46). The presence of IL-17-secreting subset of CD4+ cells (TH17) in the synovial fluid and peripheral blood of patients with RA suggests the involvement of pro-inflammatory cytokines in RA pathogenesis (47,48). Furthermore, the widespread expression of the IL-17 receptor (IL-17R) on fibroblasts, endothelial cells, epithelial cells and neutrophils suggests that this cytokine has the potential to affect a number of pathways and effector cells involved in RA (49).

IL-6 is of special interest because although many cytokines show a paracrine effect, IL-6 can also exert its effects on distant target cells by way of trans-signalling through abundantly expressed receptors and is a major factor in RA pathogenesis (50,51). The classic signalling mechanism involves a protein complex that comprises a membrane-bound, non-signalling α -receptor unit (IL-6R) plus two signal-transducing glycoprotein 130 (gp130) subunits. As IL-6R is expressed on few cell types, trans-signalling increases the range of IL-6-responsive cells (51). Trans-signalling also controls the manifestation of pre-B-cell colony-enhancing factor, a cytokine-like factor contributing to B-cell development and has a major function in various inflammatory conditions (52). IL-6 in combination with TGF- β in mice and by different other combinations of TGF- β , IL-21, IL-6, IL-23, IL-1 β and TNF- α in humans are responsible for the differentiation of naïve T cells into TH17 cells (53). IL-6 has the greatest effect on acute-phase protein levels (CRP, hepcidin, serum amyloid A, haptoglobin and fibrinogen) although IL-1, TNF- α , TGF- β 1 and IFN- γ are also contributory.

3.0 CARDIAC ABNORMALITIES IN RA

Cardiac manifestations are observed in RA patients and echocardiography is the method of choice to detect pathologies in the morphology and function of the heart. A wide range of spectrum of cardiac abnormalities has been described in various cohorts of RA

3.1 PERICARDIAL DISEASE IN RA

Morphologically pericardial disease is common in RA, but is usually clinically silent (54). Thustochowicz et al reported about one third of patients with RA had pericardial effusion, in which half of them revealed signs of chronic pericarditis (55). A study in South Africa done by Mody et al using 2D echocardiogram to determine the presence of pericardial effusion revealed a 6% prevalence in the RA cohort that was studied (5). Pericardial disease was detected in 5.5% of RA patients in a study done in Turkey using standard echocardiographic findings (61).

The associations of RA with constrictive pericarditis were thought to be present in 4 of 32 patients studied over 25 years in Dublin (58). It affects males more frequently than females and the relation with subcutaneous rheumatoid nodules has been noted. The most common

cardiac involvement in RA is pericarditis and various studies have reported an increase in the prevalence in patients with seropositive RA (59–61). While higher incidences are found on echocardiographic or postmortem studies, clinically pericarditis is lower, i.e. <10% in patients with severe RA have a clinically significant pericardial effusion (62–65). Echocardiography has been held to be the most useful investigative modality in diagnosing pericardial involvement in RA (66).

3.2 MYOCARDIAL DISEASE IN RA

Myocardial disease in RA is typically clinically silent and only manifests as myocardial dysfunction after a prolonged preclinical phase (67). An updated evaluation of myocardial disease is justified in RA, preferably using a non-invasive technique to serially monitor patient's progression over time and potentially identifying patients at the greatest risk of cardiac-related morbidity and mortality. Doppler echocardiography is a non-invasive means for detecting myocardial function, but cannot distinguish specific aetiologies of dysfunction with accuracy (24,68–71).

The underlying pathophysiology is uncertain, but it is suggested that multifactorial aetiologies contribute to its development, including myocarditis, coronary arterial disease and drug induced cardiomyopathy.

Lebowitz in a study of 62 subjects, found 19% of rheumatoid subjects showing inflammatory lesions consisting of focal infiltration of the myocardium with plasma cells, lymphocytes, and histiocytes (72). Manuela Di Franco et al studied 32 patients with RA in Italy and found left ventricular filling abnormalities characterized by a reduced E/A ratio versus controls. They concluded that RA patients with no clinical evidence of cardiac disease, show diastolic dysfunction characterized by impaired E/A and S/D ratio (73).

3.3 VALVULAR HEART DISEASE

Cardiac tissues, especially valve leaflets are extremely vulnerable to the process of inflammation and autoimmunity. In the study by Maksimowicz-McKinnon and Mandell cardiac valvular diseases were investigated in patients with systemic autoimmune disorders of RA, SLE, aPL syndrome, seronegative arthropathies, systemic vasculitis and scleroderma.

Different valvular disorders were shown in a study by Kaminski et al, and the results indicated that RA leads to valve degeneration (74). In a study by Beckhauser et al, valve involvements in RA patients were investigated and 15.2% were found to have valvular disease. Damages to valves were common in patients with disease duration of more than 15 years and the aortic valve was most commonly involved (75). There was no relationship between valve involvement and gender, age, exposure to tobacco, positive RF, presence of ANA, rheumatoid nodules and anti-cardiolipin antibodies (75). Valvular disease was the most common cardiac abnormality in a study conducted by Claudie Guedes et al using echocardiography amongst 30 patients and single-valve disease was predominant (76). A number of cases with involvement of multiple valves or pancarditis have been reported. The study conducted by Claudie Guedes et al reported that the number of valves involved increased with increasing age, but was not related to the duration of disease (76–78). Regurgitation is the most common form of valve disease, although stenosis has been reported (77,78). The mitral valve was selectively involved in the RA patients studied by Guedes et al, and mitral valve disease was significantly more common in the RA group than in the control group. Cases of pulmonary and tricuspid valve disease were identified, but were few (79). The literature suggests that AR may be more likely to cause a functional derangement than MR and that some cases of AR progress to acute decompensation requiring emergency valve replacement (80–83). Several studies have reported risk factors such as disease severity, disease duration, presence of subcutaneous nodules, male sex, or extent of inflammation (84–87). Other studies have failed to detect correlations linking valvular diseases to the clinical and/or laboratory features of RA (27,77,78,84,88–91)

3.4 PULMONARY HYPERTENSION IN RA

Pulmonary involvement is common among patients with RA and has a variety of manifestations including pulmonary hypertension. Dawson et al in the United Kingdom studied, raised pulmonary artery pressures measured by doppler echocardiography in 146 RA patients. Twenty one percent RA patients had pulmonary hypertension without clinically significant cardiac abnormalities or an underlying lung disease evident on pulmonary function testing (92). A correlation linking pulmonary arterial pressure and the disease duration ($r=0.68$, $p<0.0001$) exists, proposing a subclinical involvement of the pulmonary

vasculature with disease progression and it may be a relevant contributor to the high incidence of cardiovascular deaths observed in patients with RA (93).

3.5 CONGESTIVE HEART FAILURE IN RA

Gabriel et al estimated the incidence of CHF among all RA patients in Minnesota, from data retrieved from medical records (21,22,94–96). Between 1955 and 1985, 78 CHF patients were identified among 450 prevalent cases of RA compared to 54 cases among the same number of non-RA controls matched for age, sex, and baseline comorbidities, yielding a relative risk of 1.60. A follow-up retrospective review of the same cohort extended to 1995, now using the Framingham diagnostic criteria for CHF, Nicola et al confirmed an increased risk of incident CHF in both RF negative and positive RA patients (hazards ratio 1.34 and 2.29, respectively) compared to non RA controls. CHF risk remained elevated after adjustment for comorbid ischemic heart disease (hazard ratio 1.28 and 2.59 in RF negative and positive RA patients, respectively).

Between 30% and 50% of patients with CHF have a preserved systolic function (LV ejection fraction (LVEF) \geq 45-50% (97,98). Patients with CHF and normal LVEF have an increase in mortality compared to the normal population (97). In asymptomatic individuals, with preserved systolic function there is also a prediction of subsequent development of overt CHF (99).

A number of Doppler echocardiographic studies have been conducted amongst RA patients without clinical evidence of CHF (25,73,100–106). Although limited by small numbers of RA patients and, in some cases, failure to provide a non-RA comparator group, these studies are consistent in representing a high prevalence of asymptomatic diastolic dysfunction in patients with preserved systolic function. A relationship between the degree of diastolic dysfunction and RA disease duration has been shown in several investigations (105,106). Without longitudinal assessments, however, few conclusions can be drawn with regards the long-term effects of RA disease activity on cardiac abnormalities or, more importantly, factors inducing the evolution of asymptomatic cardiac disease to clinical CHF in RA.

Some traditional risk factors for CHF are exemplified in RA patients, they do not account for all of the increased CHF risk observed (69). Other associated factors, particularly the chronic elevation of pro-inflammatory cytokines, are likely contributors to myocardial dysfunction in RA patients.

3.6 CLINICAL DISEASE ACTIVITY INDEX (CDAI)

A variety of instruments is used to measure disease activity in RA. The American College of Rheumatology (ACR), the European League against Rheumatism (EULAR), and the World Health Organization /International League against Rheumatism (WHO/ILAR) have suggested “core” sets of variables to be used in the assessment RA disease activity. These variables comprise swollen and tender joint counts, patient assessment of pain, patient and evaluator's global assessment of disease activity, a measure of the acute phase response, and assessment of functional aspects. The currently available composite disease activity tools used are the Disease Activity Score (DAS), the DAS using 28 joint counts (DAS- 28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). CDAI is the only composite index that does not include an acute phase response and can therefore be used to conduct a disease activity evaluation on the spot.

A study in Austria in 2009 showed that DAS-28, SDAI and CDAI were significantly correlated to one another on a group level ($p < 0.001$) (113). Ndirangu et al compared three disease activity tools amongst RA patients attending the KNH rheumatology clinic and concluded all three, CDAI, SDAI and DAS 28 disease activity tools were comparable in this cohort (10).

4.0 2-D ECHOCARDIOGRAPH

2D echocardiography is a non-invasive procedure capable of displaying a cross-sectional view of the heart, including the four chambers, left and right sided valves and the major blood vessels that exit from the left and right ventricle. It is particularly useful in detecting various valvular lesions, measuring the left ventricular ejection fractions, determining myocardial wall abnormalities and also measuring the pulmonary pressures and detecting the presence of pericardial effusions. It is accessible even in resource limited settings and for the purpose of this study; 2D echocardiograph was the diagnostic method of choice in achieving the objectives of this study.

The limitations of standard echocardiography, which include poor endo-cardial definition, lack of inter-observer reproducibility of ejection fraction estimates and lack of standardization of diagnostic criteria for diastolic dysfunction, often make it difficult to be precise about the diagnosis of diastolic dysfunction.

5.0 STUDY JUSTIFICATION

RA diagnosis is increasing in our setting and various related complications contribute to the high mortality and morbidity. Cardiac abnormalities are important causes of morbidity and mortality in RA and current management strategies are directed towards joint inflammation and not against the cardiac lesion. The burden of cardiac abnormalities in RA has not been evaluated in this setting using 2D echocardiogram. In many resource limited settings, non-invasive 2D echocardiographic studies are not routinely done for patients with RA to evaluate for these abnormalities. This study aimed at providing information about the burden and overall prevalence of cardiac abnormalities in RA at KNH. Current data on this topic has been lacking in our local setting and the results of this study have contributed in filling that knowledge gap.

6.0 RESEARCH QUESTION

What is the prevalence of cardiac abnormalities detected by 2D echocardiograph in RA patients attending the KNH rheumatology clinic?

7.0 OBJECTIVE OF THE STUDY

7.1 PRIMARY OBJECTIVE:

To determine the prevalence of echocardiographically detected cardiac abnormalities in patients with Rheumatoid Arthritis at Kenyatta National Hospital.

7.2 SECONDARY OBJECTIVES

- 1) To determine associations between cardiac abnormalities in RA with disease activity using the clinical disease activity index (CDAI)
- 2) To determine associations between cardiac abnormalities in RA and duration of disease.

8.0 METHODOLOGY

8.1 STUDY DESIGN

The study was a cross sectional descriptive study of RA patients attending the rheumatology clinic at KNH.

8.2 STUDY SETTING

The study was conducted at KNH which is the national referral and teaching hospital located within an urban environment in Nairobi.

Currently at KNH, there is no specialized ward designated for rheumatology patients, however, there is a rheumatology outpatient clinic held once a week (Thursdays afternoon) and which is operated by rheumatologists and registrars in the department of clinical medicine and therapeutics.

The echocardiography department within KNH has four echocardiograph machines and operates daily; it is operated by Echocardiographic technicians and cardiologists and is accredited to perform diagnostic echocardiogram.

8.3 STUDY POPULATION

The study population was RA patients on follow up at KNH. Current hospital records show that there are 146 RA patients attending the rheumatology clinic. A cohort of RA patients derived from this finite population was subjected to a non-invasive 2D echocardiograph for the determination of cardiac abnormalities.

9.0 CASE DEFINITION

Patients who fulfilled the ACR/EULAR 2010 criteria for diagnosis of RA and who are to follow up at KNH (Appendix III).

9.1 INCLUSION CRITERIA

1. Patients who fulfilled the case definition.
2. Patients 13 years of age and above.
3. Patients who consented or provided assents.

9.2 EXCLUSION CRITERIA

1. Patients with mixed connective tissue diseases
2. Patients with cardiac abnormalities from alternative causes previously documented in hospital files or from clinical examination.

10.0 SAMPLE SIZE DETERMINATION

A prevalence of cardiac abnormalities detected by echocardiogram among RA patients of 37% as reported by Mody G M et al, in a similar study done in Cape Town, South Africa was used in the calculation of the desired sample size. An estimated number of 146 RA patients are on follow up at the Rheumatology clinic, KNH. Using the formula for finite population (less than 10,000, Daniel 1999). The calculation was as follows:

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1) + Z^2P(1-P)}$$

Where; n = sample size required

N = Size of target population = 146

Z = z score for 95% confidence interval = 1.96

p = Proportion of RA patients with any cardiac abnormality = 37% (Mody et al 1987)

d = Margin of error = 5%

This calculation resulted in a minimum sample size of 104 that was needed to estimate the true population proportion with a margin of error of 5% at 95% CI.

11.0 SAMPLING METHOD

Consecutive sampling was used to recruit patients with RA who visited the KNH Rheumatology clinic till a sample size of 104 was attained. This clinic operates once a week, every Thursday afternoon at 2 pm except on public holidays. An average of 10 RA patients were seen per clinic visit.

12.0 PATIENT RECRUITMENT

Two registered clinical officers were enrolled, trained and worked in the capacity of a research assistant alongside the principal investigator to recruit RA patients into the study from the Rheumatology clinic at KNH. The principal investigator and trained research assistants perused the files before the start of the Rheumatology clinic on the designated clinic day and identified RA patients. Those who satisfied the ACR/EULAR diagnostic criteria were informed about the study and requested to sign consent forms if willing to participate in the study. Specific information about age, duration of disease and current medications was obtained from the patients and their respective files. A targeted history was obtained by the principal investigator and the research assistants in either English or Kiswahili. Patients that fulfilled the inclusion criteria were recruited into the study without interference with their medical care. Physical examination was performed by the principal investigator for all patients after consent was signed. Each participant included in the study had a 2D echocardiograph by a study dedicated echocardiograph technician and read by two

independent cardiologists at the department of cardiology KNH. Those who declined consent were allowed standard medical care at the Rheumatology clinic KNH.

13.0 ECHOCARDIOGRAPHY METHODS

Each patient included in this study had a complete 2D transthoracic echocardiography study performed in accordance with the recommendations of the American Society of Echocardiography (ASE) (108). A study dedicated technician at the cardiology unit undertook a complete 2D, M-mode and Doppler analyses using a Phillips iE 33 ultrasound system equipped with a 2.5Hz multifrequency transducer. Standard parasternal long and short axis, apical and subcostal views were obtained. All echocardiographs reports were read by two independent cardiologists.

13.1 PERICARDIAL ASSESSMENT

The pericardial space was evaluated in the parasternal longitudinal axis and subcostal views and dimensions assessed using 2D echocardiograph. Pericardial effusion was measured as the echo free separation between the visceral and parietal pericardium on M-mode. Pericardial separation that disappears during the diastolic phase was considered inconsequential and not documented. Pericardial thickening was measured in parasternal long axis M mode, in diastole and defined as thickening more than 3mm.

13.2 ASSESSMENT OF MYOCARDIAL FUNCTION

13.2.1 SYSTOLIC FUNCTION

Systolic function was determined by calculating the left ventricular fractional shortening and ejection fractions according to standard ASE guidelines. In M-mode, LV diameter in end diastole and end systole was determined. From these measurements LV fractional shortening was calculated and documented. LV diastolic and systolic volumes and LV ejection fraction were measured using the two chamber views (the difference between end-diastolic and end systolic volumes divided by end-diastolic volume) (109).

13.2.2 DIASTOLIC FUNCTION

Diastolic function indices were determined by pulsed Doppler recording across the anterior leaflet of the mitral valve; with the sample volume located between the tips of the mitral valve leaflets. Primary measurements of mitral inflow included the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the Isovolumetric relaxation time (IVRT). Mild diastolic dysfunction (grade 1) was determined when the mitral E/A ratio is < 0.8 , DT is > 200 ms, IVRT is ≥ 100 ms. Moderate diastolic dysfunction (grade II) was determined when the mitral E/A ratio is 0.8 to 1.5 (pseudonormal) and decreases by $> 50\%$ during the valsalva maneuver, the E/e' (average) ratio is 9 to 12, and e' is < 8 cm/s. Severe diastolic dysfunction (grade III) was determined when restrictive LV filling occurs with an E/A ratio ≥ 2 , DT < 160 ms, IVRT ≤ 60 ms.

13.3 VALVE ASSESSMENT

13.3.1 MITRAL VALVE

The mitral valve (MV) was assessed by 2D and M-mode in the parasternal and apical views to assess for valve thickness, leaflet mobility and presence of vegetations. Colour flow doppler in multiple planes was used to detect mitral regurgitation. The pressure gradient across the mitral valve was obtained using continuous wave Doppler (CW) by placing the sample volume across the mitral orifice in the apical four chamber view. The mean gradient was calculated from the velocity time integral across the MV as measured by CW Doppler. In cases of mitral stenosis the MV pressure half time ($P_{1/2}$) was estimated from which the MV area was calculated using the Hatle equation (116).

13.3.2 AORTIC VALVE

The aortic valve was evaluated in the parasternal long and short axis views to assess opening of the cusps, number of cusps, thickness and the presence of vegetation. Colour flow doppler was applied in the parasternal long axis and apical five chamber views to detect regurgitation. If aortic regurgitation is detected CW Doppler was applied along the regurgitant jet in the apical five chamber view to estimate the pressure half time across the aortic valve and determine the rate of deceleration of the jet i.e. the time taken for pressure across the aortic

valve to fall by half. Aortic valve area was measured to determine aortic stenosis and categorized into mild, moderate and severe AS depending on the area of the valve.

13.3.3 TRICUSPID AND PULMONRY VALVES

Two dimensional Doppler assessment of the tricuspid and pulmonary valve was done in the parasternal and apical views to assess morphology and detect regurgitation.

13.4 PULMONNARY HYPERTENSION

Noninvasive Doppler echocardiography is a well-established and useful screening tool for PH. Systolic pulmonary arterial pressure (sPAP) can be unreliable because overestimation by 10 mmHg is common, as is an underestimation in severe tricuspid regurgitation when calculated from tricuspid regurgitation jet alone (49). This is an inherent limitation of this tool, but however it is still recommended. Doppler echocardiogram was used to approximate sPAP using the tricuspid valve velocity gradient and the estimated RA pressure.

14.0 ECHOCARDIOGRAM OUTCOME VARIABLE DEFINITION

Pericardial Effusion: Echo free space surrounding the heart

- Small Effusion: Less than 5mm in maximum dimension and visualized throughout the cardiac cycle.
- Moderate Effusion: 5 to 10mm in dimension
- Large Effusion: greater than 10mm in dimension

Pericardial Thickening: Pericardial thickness greater 3mm.

Pericardial Calcification: Echo bright area around the heart.

Systolic Dysfunction: Fractional shortening less than 29% and/or ejection fraction less than 50%.

Diastolic Dysfunction:

- Grade 1: Impaired relaxation; mitral E/A < 1m/s
- Grade 2: Pseudonormal pattern; E/A 0.8 – 1.5m/s
- Grade 3: Restrictive reversible; E/A > 2m/s

- Grade 4: Restrictive irreversible; same as Grade 3 but irreversible on Valsalva maneuver
- Deceleration time (DT): The deceleration time taken from the maximum E point to baseline.
- Isovolumetric relaxation time (IVRT): time between the closure of the aortic valve and the opening of the mitral valve

Mitral Valve Thickening: Mitral valve dimension greater than 3mm in the parasternal long axis in diastole measured at the mid portion by M-mode.

Mitral Regurgitation: Backward flow into the LA on color flow Doppler across the mitral valve.

- Grade 1+: Regurgitant jet extending up to the proximal ¼ of the left atrium (LA)
- Grade 2+: Regurgitant jet detected halfway up the LA
- Grade 3+: Regurgitant jet detected up to ¾ of the LA
- Grade 4+: Regurgitant jet extending beyond ¾ of the LA

Mitral Stenosis: Mitral valve area less than 2cm²

- Mild MS – Mitral valve area >1.5cm²
- Moderate MS – Mitral valve area 1.0-1.5cm²
- Severe MS – Mitral valve area <1.0cm²

Aortic Valve thickening: Thickness greater than 2mm measured during systole by M-mode in the parasternal long axis view.

Aortic Regurgitation: Back flow into the LV on color flow Doppler through the aortic valve

- Mild AR – Pressure half time > 500msec
- Moderate AR – Pressure half time 200-500msec
- Severe AR – Pressure half time <200msec

Aortic Stenosis: Aortic valve area less than 2cm²

- Mild AS – Mean gradient < 20mmHg
- Moderate AS – Mean gradient 20-40 mmHg
- Severe AS – Mean gradient >40mmHg

Assessment of Pulmonary Pressure

The European Society of Cardiology and European Respiratory Society guidelines have proposed arbitrary criteria for PH diagnosis by echocardiography, using tricuspid regurgitation peak velocity, Doppler calculated sPAP, assumption of right atrial pressure of 5mmHg and additional right heart variables suggestive of PH (49). The right heart variables suggestive of PH are tricuspid annular systolic plane excursion (TAPE), increased velocity of pulmonary regurgitation and short acceleration time of right ventricular ejection into the pulmonary artery. Right chamber enlargement, increased right ventricular wall thickness, abnormal shape and function of the interventricular septum and dilated main pulmonary artery are variable suggestive of advanced PH (50).

15.0 CLINICAL METHODS

The principal investigator and trained research assistants administered the study proforma for collecting demographic data from all patients. The data included age, gender, duration of disease (time of diagnosis) and current medications. Data on clinical variables for each patient were obtained through a standard and comprehensive clinical evaluation with emphasis on signs and symptoms of RA

16.0 CLINICAL VARIABLE DEFINITION

16.1 RHEUMATOID ARTHRITIS

Arthritis was defined by history and/or examination findings, according to the ACR/EULAR 2010 criteria for diagnosing RA (Appendix III) (117).

17.0 QUALITY ASSURANCE

All echocardiography studies were carried out at the department of cardiology KNH and interpreted by two independent cardiologists. In cases of discrepancies, the two cardiologists reviewed the images together and came to a consensus.

18.0 ETHICAL CONSIDERATION

The study was conducted after approval from the department of Clinical Medicine and Therapeutics, University of Nairobi and the KNH/UON joint ethics and research committee. Only patients who signed consent were included in the study. Patients were recruited strictly on a voluntary basis and had the liberty to withdraw from the study at any time without discrimination. The results of the echocardiography studies were printed and communicated to all patients at the time of the procedure and were made available in their files for use by their attending physicians. Patients found to have cardiac abnormalities that required treatment, were referred to the cardiac clinic or the accident and emergency department in cases that requirement was deemed urgent.

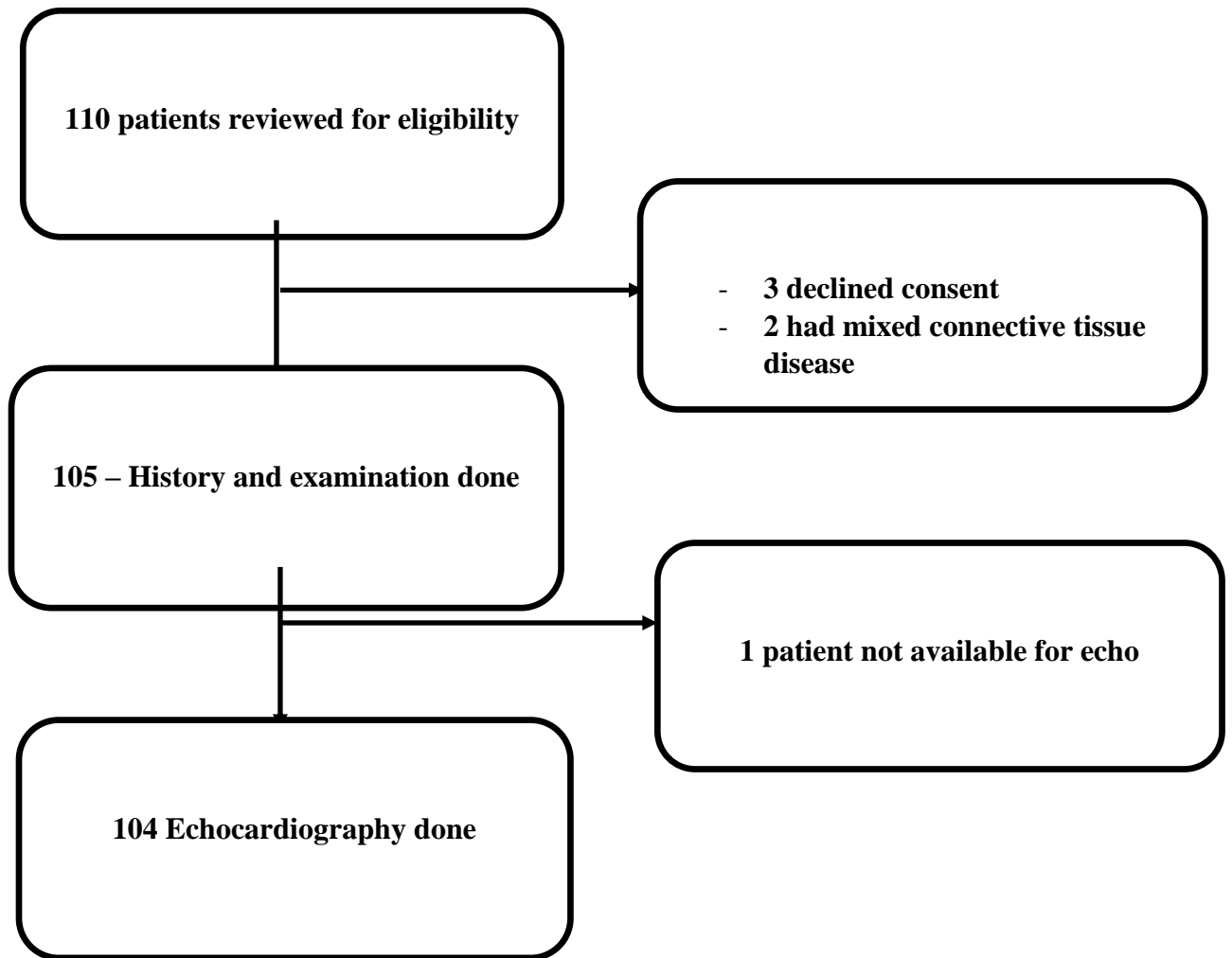
19.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

All data from study pro forma and echocardiography study were encoded, entered and managed in a Microsoft access database. Data cleaning and verification was performed at the end of data collection and statistical analysis performed using statistical package for social sciences, version 21.0 for windows. The study population has been described using demographic and clinical characteristics. Continuous data (duration of disease) has been analyzed into means and medians while categorical data (CDAI) analyzed using percentages. The prevalence of cardiac abnormalities has been analyzed as a proportion with corresponding 95% confidence interval. Specific cardiac lesions have been analyzed and presented as proportions. Demographic and clinical factors are associated with various cardiac abnormalities and analyzed using Student's t test to compare means and chi square test for categorical data associations. Criteria for statistical significance was set as a $p \leq 0.05$. The findings of this research are presented using tables and graphs.

20.0 RESULTS

Between 16th December 2015 and 17th March 2016, 110 patients being managed for RA at KNH were screened for study eligibility, of these 104 subjects underwent a targeted history and examination and were booked for echocardiography either the same day or another day during the course of the week with 6 patients excluded. All 104 subjects had echocardiography studies done and were included in the analysis as depicted in figure 1.

FIGURE 1: Flow Chart of Patient screening and enrollment process



20.1 DEMOGRAPHICS AND DURATION OF DISEASE

The mean age of the study sample was 51.0 years with a female to male ratio of 25:1. The majority of the patients had a RA disease duration of more than 1 year (84.6%) (Table1).

Table 1: Patients demographic characteristic and duration of disease

Variable	Frequency (%) n = 104
Age (years) Mean age (SD) Min-Max	 51.0 (16.4) 13-88
Gender Male Female	 4 (3.8) 100 (96.2)
Duration of disease Less than 1 year 1 to 5 years 6 to 10 years >10 years	 16 (15.4) 48 (46.2) 31 (29.8) 9 (8.6)

20.2 CLINICAL VARIABLES

Fifty one percent of all patients were on at least 2 combination disease modifying anti rheumatic drugs (DMARD's) (45.2% on 2 and 5.8% on 3 DMARDs respectively). Forty nine percent of patients were on a single DMARD and the most frequently used DMARD was hydroxychloroquine. The frequency of patients on methotrexate was 22.2% and 18.3% on leflunomide as the other DMARDs used by this population (Table 2).

Table 2: Frequency of DMARDS used by patients

Number of drugs	Frequency (%) n=104
1	51 (49.0)
2	47 (45.2)
3	6 (5.8)
DMARDS	
Hydroxychloroquine	39 (37.5)
Methotrexate	8 (7.7)
Leflunomide	4 (3.8)
Hydroxychloroquine+ Methotrexate	9 (8.7)
Hydroxychloroquine+ Leflunomide	38 (36.5)
Hydroxychloroquine+ Methotrexate+ Leflunomide	6 (5.8)

20.3 ECHOCARDIOGRAPHIC FINDINGS

The overall prevalence of cardiac abnormalities detected by echocardiography was 62.5% (CI 52.9 – 72.1) with the major contributors to this high prevalence being pericardial effusion and Type 1 diastolic dysfunction. However, both the pericardial effusion and Type 1 dysfunction were regarded to as clinically insignificant because there were no associated features or echocardiographic feature of constrictive pericarditis or tamponade associated with the pericardial effusion and all the patients with type 1 diastolic failure were at NYHA grade 1 with no other features of decompensation (Table 3)

Table 3: Frequency of cardiac abnormalities

Variable	Frequency (%)	95% CI
Cardiac abnormalities		
Abnormal	65 (62.5)	52.9-72.1
Normal	39 (37.5)	27.9-47.1

20.3.1 Pericardial Assessment

Pericardial effusion was the most common abnormality detected among patients in the study with a prevalence of 39.4%. The pericardial effusion in this subset of patients was graded as mild effusion (<5mm) as it was not associated with clinical or echocardiographic feature suggestive of constrictive pericarditis. No pericardial thickening was observed in the study and none of the patients was found to have pericardial calcification on echocardiography.

Table 4: Pericardial abnormalities

Variable	Frequency (%) n =104	95% CI
Pericardial effusion	41 (39.4)	34.0-53.2
Pericardial effusion size		
<5mm	102 (98.1)	95.2-100.0
>10mm	2	0-4.8

20.3.2 Myocardial Function

There was generally good systolic function among patients with only 2.9% of patients having systolic dysfunction characterized by an ejection fraction of less than 50%. Diastolic

dysfunction on the other hand was more prevalent in this population of RA patients, with a prevalence of 22.1%, of which type 1 diastolic dysfunction was predominant (20.2%).

20.3.3 Valvular Assessment

The overall prevalence of valvular abnormalities detected in the study population was 30.8%. The valvular abnormalities found in this cohort of RA patients were predominantly tricuspid valve regurgitation at 15.4%. All patients found to have tricuspid regurgitation had a mild regurgitation as it was not necessarily associated high pulmonary pressure. Mitral valve regurgitation was found in 5.8% and mitral stenosis in 1.9% of study patients. Among patients with mitral insufficiency, 66.7% had grade I mitral insufficiency and 33.3% had grade 2 insufficiency. 6.7% of patients were found to have aortic valve regurgitation and all were graded as mild regurgitation as it was not associated with LV dilatation (Table 5)

Table 5: Valvular abnormalities

Variable	n =28
Valvular abnormalities	28
Mitral regurgitation Grade I Grade II	6 4 2
Mitral stenosis Mild	2 2
Aortic regurgitation Mild Aortic stenosis	7 7 0
Tricuspid regurgitation Mild Moderate Stenosis	12 9 3 0
Pulmonary regurgitation Mild Pulmonary stenosis	1 1 0

20.3.4 Pulmonary Pressure

Of the 104 patients in the study, 5.5% had pulmonary hypertension of which only one patient was associated with pulmonary regurgitation.

20.3.5 Number of cardiac lesions

55.4 % of patients with cardiac abnormalities were found to have more than one abnormality (35.4% with 2 cardiac abnormalities and 13.0% with 3 cardiac abnormalities). 44.6% of the patients had only one abnormality detected on echocardiograph.

Table 6: Number of cardiac abnormalities

Number of cardiac abnormalities	Frequency (%)
1	29 (44.6)
2	23 (35.4)
3	13 (20.0)

21.0 CLINICAL DISEASE ACTIVITY INDEX (CDAI)

Using the tool to determine the clinical activity 60.5% of all patients were in remission, 30.8% had low activity and only 8.7% had moderate activity.

22.0 ASSOCIATIONS

The mean age at diagnosis was comparable between those who had cardiac abnormalities and those who do not have any cardiac abnormality at 51.5 and 50.2 respectively. This explorative study was not powered to make any associations between cardiac abnormalities, CDAI and duration of disease due to a small sample size. There was no association of overall cardiac abnormalities with the other variables in this study. More numbers of patients having duration of disease less than one year had cardiac abnormalities compared to normal echocardiographic findings for the same duration, however, there is a trend toward developing cardiac abnormalities for those with a longer disease duration more than 10 years and those with a higher disease activity (OR 1.6 and 2.2 respectively) (Table 7). The results of this study also did not show any association between cardiac abnormalities and the various drug combinations use in this cohort. Mild pericardial effusion being the most common

abnormality detected in this cohort had no significant associations with both demographic and clinical variables.

Table 7: Associations of demographic and clinical variables with cardiac abnormalities

Variable	Cardiac abnormality		OR (95% CI)	P value
	Abnormal	Normal		
Age at diagnosis, mean (SD)	51.5 (16.7)	50.2 (15.1)	-	0.701
CDAI				
Remission	39 (61.9)	24 (38.1)	1.0	
Low activity	19 (59.4)	13 (40.6)	0.9 (0.4-2.1)	0.811
Moderate activity	7 (77.8)	2 (22.2)	2.2 (0.4-11.2)	0.354
Duration of disease				
< 1 year	11 (68.8)	5 (31.2)	1.0	0.551
1 to 5 years	29 (60.4)	19 (39.6)	0.7 (0.2-2.3)	0.475
6 to 10 years	18 (58.1)	13 (41.9)	0.6 (0.2-2.3)	0.629
>10 years	7 (77.8)	2 (22.2)	1.6 (0.2-10.6)	

CDAI – Clinical Disease Activity Index

23.0 DISCUSSION

The overall prevalence of echocardiographic abnormalities amongst 104 RA patients was 62.5%. This represents a composite of pericardial, myocardial, valvular abnormalities and pulmonary hypertension. The whole spectrum of structural and functional cardiac abnormalities that could be evaluated by echocardiography was included in the study, as to provide data that could serve as the basis for future research on cardiac abnormalities in this cohort. The prevalence of cardiac abnormalities in our study is similar to a study done in South Africa by Schorn et al who performed echocardiograph in 44 rheumatoid arthritis patients and showed a 73% overall cardiac abnormalities (22). A large number of patients in this study (55.4%) had more than one cardiac abnormality and this is also in keeping with the natural history of the chronic inflammatory state of the disease affecting all structures of the heart and the combination DMARD's used amongst these patients.

The high prevalence was mostly driven by clinically insignificant pericardial effusion and type 1 diastolic dysfunction. The pericardial effusion was graded as mild effusion as the size was less than 5mm. Type 1 diastolic dysfunction is a nonspecific echocardiographic finding 20.2% of the study population with no associated clinical features suggestive of overt heart failure. Schorn et al found pericardial effusion in 32% of RA patients studying a similar spectrum of structural and functional cardiac abnormalities (22). Macdonald et al in California performed echocardiographic studies on 51 RA patients in a cross sectional study and reported 31% mild pericardial effusion. Pericardial disease was detected in 5.5% of RA patients in a study done in Turkey using standard echocardiographic findings (61). Our study reports a high prevalence of subclinical pericardial effusion at 39.4%, which could be explained by both the natural history of the disease and the various combinations of disease modifying agents used for these patients (Hydroxychloroquine, Methotrexate, etc.). No pericardial thickening or calcification was noted in any of the patients.

Myocardial dysfunction in RA is a consequence of several factors, including direct inflammatory process of RA on the myocardium, premature atherosclerosis and side effects of some of the medications used to treat the condition, specifically cardiotoxicity related to hydroxychloroquine use. Literature suggests that myocardial dysfunction in RA patients presents predominantly as diastolic dysfunction and in the majority of patients it is asymptomatic. In our study a generally good LV function among RA patients is reported by only 2.9% having mild LV dysfunction. 20.2% of RA patients at KNH had a type 1 diastolic dysfunction and this is much lower compared to a study done by Gabriele S, et al in the USA who did a cross sectional community based study comparing adults with and without RA and without clinical evidence of heart failure using 2D echocardiography. Their study included 244 subjects with RA with a mean age of 60.5 years wherein they reported a 31% diastolic dysfunction, which had a positive association with duration of disease (13). Diastolic dysfunction in our study was not found to be associated with a prolonged duration of RA even though the natural course of diastolic function is known to deteriorate with time. Furthermore, there are no associations found between diastolic dysfunction and use of disease modifying drugs. In this study confounders such as hypertension were not assessed for but the relatively high prevalence of diastolic dysfunction should be a cause for concern because

of the potential to progress to overt diastolic heart failure. Diastolic heart failure, preferably denoted as heart failure with preserved ejection fraction is frequently encountered in older patients with multiple comorbidities and associated with similar mortality rates as heart failure with reduced ejection fraction.

In a study by Beckhauser et al, valve involvements in RA patients were investigated and 15.2% were recognized with valve disease. Valve damages were more common in patients whose disease was of more than 15 years duration and the aortic valve was most commonly involved. Valvular involvement reflects the chronic inflammatory state of the disease. There was no relationship between valve involvement and gender, age, exposure to tobacco, positive RF, presence of ANA, rheumatoid nodules, and anti-cardiolipin antibodies (75). Our study found a high prevalence of valvular involvement compared to other studies at 30.8%. The valvular abnormalities found in this cohort of RA patients were predominantly tricuspid valve regurgitation at 15. Tricuspid regurgitation in this cohort was mild as determined by the echo criteria, it was not associated with pulmonary hypertension hence it may be considered to be due to the effect of RA on the valves. From our study, we cannot determine the exact reason for this high prevalence of tricuspid valvular regurgitation in this population. We did not find any association between valvular abnormality and disease duration, age at diagnosis or clinical features; however, our study was not powered to assess for these associations.

Dawson et al in the United Kingdom studied, raised pulmonary artery pressures measured by Doppler echocardiography in 146 RA patients and 21% of all the RA patients had pulmonary hypertension without significant cardiac disease or lung disease evident on pulmonary function testing (92). We report a much lower prevalence of pulmonary hypertension at 5.5% with no significant association between raised pulmonary pressure and any of the demographic or clinical variables evaluated. This was graded as mild pulmonary hypertension as it was not associated with echocardiographic and clinical evidence of an associated right ventricular enlargement or right valvular lesions. Our study population was recruited at an outpatient basis and may therefore have been skewed toward the less severe end of the disease spectrum as compared with the overall population of RA patients thus explaining the above mild and clinically insignificant findings.

24.0 CONCLUSION

The study demonstrates a high prevalence of cardiac abnormalities among RA patients despite being diagnosed reasonably earlier and on disease modifying medications. Even though the majority of these abnormalities comprised of clinically insignificant pericardial effusion and type 1 diastolic failure, the prevalence of pericardial effusion is substantially higher than the prevalence seen in other studies evaluating cardiac abnormalities in RA. The majority of patients in this study had a disease duration of less than 5 years and even though these cardiac abnormalities may be subclinical at the time of performing echocardiography the long term impact on morbidity and mortality can only be predicted as unfavorable.

25.0 IMPLICATIONS

Baseline echocardiography should not be routinely done for all RA patients rather those with a high disease activity should have an evaluation of cardiac abnormalities.

25.0 RECOMMENDATIONS

The lack of a unifying explanation for the various cardiac abnormalities in rheumatoid arthritis is reflected by the confusion that still exists regarding possible preventive measures aimed at decreasing cardiovascular risk.

We recommend longitudinal studies to be undertaken using larger numbers to properly determine a cause and effect relationship between RA and the various cardiac abnormalities and to determine the progression and outcome of cardiac abnormalities seen in RA patients in our setting.

We also recommend studies determining echocardiographic abnormalities using a non RA cohort so as to clearly delineate the spectrum of cardiac abnormalities between the two groups.

26.0 LIMITATIONS

This study was limited by using a small number of patients with RA and hence it was not powered to make associations between cardiac abnormalities in RA, demographic and clinical variables.

A non RA comparative group was not used hence some of the abnormalities may have been of normal variation

A high prevalence of diastolic dysfunction may have also been reflected by the fact that the calculation of the E/A ratio was used and tissue Doppler was not used in this study

Echocardiographic studies are user dependent and may have overestimated or underestimated some echocardiographic variables.

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APPENDIX I

Statement of Information for Patients Participating In the Study

Introduction

I, Dr. Emmanuel Alieu Ibrahim-Sayo, a post graduate student in the department of clinical medicine and therapeutics at the University of Nairobi, would like to introduce you to a study that will determine the cardiac abnormalities using a non-invasive 2D echocardiogram amongst Rheumatoid arthritis patients at Kenyatta National Hospital.

RA is a multisystem inflammatory disease that has both articular and extra articular features. The cardiovascular system is mostly affected resulting in premature death in this cohort of patients. Early diagnosis will help doctors initiate treatment and institute preventive measures to halt or delay progression of heart disease.

What is the study about?

The study seeks to document how frequent is the heart involved and to document the various types of cardiac abnormalities among RA patients in our population.

What does the study entails?

You will be required to give history about your condition and undergo a physical examination. Thereafter you will undergo an echocardiography study by a cardiologist, which will help identify abnormalities caused by RA. All findings will be explained to you by the cardiologist after the study. In case of any detected abnormality requiring immediate treatment, you will be referred to the appropriate clinic.

What will I benefit from the study?

The information gathered from the study will help your doctors to treat or prevent progression of any heart disease found during the test. The cost of the echocardiogram will be incurred by the principal investigator.

Are there any risks involved?

There is no risk involved; echocardiography is a routine non-invasive heart assessment. It is painless and has no short or long term harmful effects on your body.

Voluntary participation

Your participation in this study will be voluntary. If you choose to participate, you will be required to sign a consent form to give us permission to include you in the study. You are free to withdraw from the study and this shall not affect your care or treatment.

Confidentiality

All information gathered during the study will be kept confidential. A report of the echocardiography will be made available to your attending physician to aid in your management.

You are free to ask questions before signing the consent form.

For any further queries that you or your health care giver have, you can contact the principal investigator Emmanuel A. Ibrahim-Sayo on +254 726 504 676. OR

Professor Omondi Oyoo at +254 722522359 OR

The Chairman of Ethical and Review Committee

Kenyatta National Hospital

Tel:254 020 2726300, Ext 44355, 726300-9

APPENDIX II

CONSENT FORM

I..... the study participant

Age.....

Tel.....

Has been requested to take part in the study evaluating echocardiographic abnormalities in rheumatoid arthritis study patients attending Kenyatta National Hospital. This will involve taking a history, doing a physical examination and heart evaluation by a noninvasive 2D echocardiography. I also understand that my consent is voluntary and that I can withdraw from the study at any time without any penalty.

I therefore consent to be recruited into the study

Sign.....

Date.....

Thumb Print.....

Date.....

TAFSIRI YA KISWAHILI

Mimi.....

Umri.....NambariyaSimu.....

NaombwakushirikikatikautafitikutathminiMadharayamoyokatikamaumivuyaviungovyawago njwawanaohudhuriaHospitaliyaTaifaya Kenyatta.

Hiiitakuwakuhusishakuchukuahistoria ,kufanyauchunguziwamwilinamoyotathmininakipimo cha kuangaliandaniyamoyo

.Nimeelezwakwambakipimohichohakinamadharayoyotemwilinimwangu. Mimi

pianaelezwakwambaridhaayanguniyahiarinakwambanawezakujitoakwenyeutafitiwakatiwowot ebilaadhabuyoyote .

Kwahiyokukubaliananawataajiriwakatikautafiti.

Sahihi.....

Tarehe.....

APPENDIX III

ASSENT FORM (AGE 13-17)

I, **Dr. Emmanuel A Ibrahim-Sayo**, a postgraduate student in the department of Clinical Medicine and Therapeutics of the University Of Nairobi am conducting a study on

Echocardiographic abnormalities in patients with rheumatoid arthritis attending the rheumatology Clinic at the Kenyatta National Hospital. Basis of participation

Your child's participation will be purely voluntary. You are free to withdraw the child from the study at any time during the course of the study period. Your refusal to allow the child to participate or withdrawal at any time during the study period will not in any way affect the quality of his/her treatment.

Confidentiality

All information obtained in the study will be treated with utmost confidentiality.

I shall NOT use your child's name in any of my reports.

Benefits

The results of this study may be published in a medical book or journal or for teaching purposes and will be given to the community for better understanding of this topic. Once the echocardiogram reports are ready, we will inform your child's doctor, who will then inform you about his/her structural cardiac abnormalities if any and advice you accordingly.

Risks and discomfort

Echocardiographic studies are non-invasive and pose no harm to your child. Some of the questions asked may be personal but privacy and confidentiality will be assured at all time.

Request for information

You may ask more questions about the study at any time or at this moment. You will be informed of any significant findings discovered during or after the study.

Cost

Participating in this study will not have any added cost to the patient.

Having read this consent form, all my questions have been answered, my signature below indicates my willingness to allow my child to participate in this study and my authorization to use and share with others.

I.....parent/guardian to.....understand the
above and voluntarily accept to allow my child to participate in the study.

Signed.....Date.....

I confirm I have explained to the parent/guardian the above

Signed.....Date.....(Interviewer)

Telephone Contacts (of parent/guardian).....

APPENDIX IV
INVESTIGATOR'S STATEMENT

I the investigator have educated the research participant on the purpose and applications of this study.

Signed.....

Date.....

For further enquiries during the course of the study, contact the following:

Principal Investigator

Lead Supervisor

Dr. Emmanuel Alieu Ibrahim-Sayo

Prof. O. Oyoo

Mobile: +254 726 504 676

Dept. of Clinical Medicine, UON

Mobile: +254 722 522 359

The Secretary

KNH/UON Ethics and Review Committee

Tel: 2726300, Ext: 44102

APPENDIX V

The ACR 2010 criteria for Rheumatoid arthritis

Symptom Duration (as reported by patient)	Points
▪ < 6 weeks	0
▪ > 6 weeks	1
Joint Distribution	Points
▪ 1 large joint	0
▪ 2-10 large joints	1
▪ 1-3 small joints (with or without involvement of large joints)	2
▪ 4-10 small joints (with or without involvement of large joints)	4
▪ > 10 joints (at least 1 small joint)	5
Serology	Points
▪ RF- and CCP-	0
▪ Low RF+ or CCP+	2
▪ High RF+ or CCP+	3
Acute Phase Reactants	Points
▪ Normal ESR or CRP	0
▪ Abnormal ESR or CRP	1

RF: rheumatoid factor. CCP: anti-citrullinated citric peptide. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. Low: < 3 x upper limit of normal (ULN). High: > 3 x ULN

Requirements: patients who have at least 1 swollen joint, and not better explained by another disease to be applied. A score ≥ 6 points is required for classification as definite RA.

APPENDIX VI
STUDY PROFOMA
Clinical Data Collection Form

1. DEMOGRAPHIC

Patient Code.....

Case No.....

Hospital No.....

Gender: Male

Age..... Date of RA diagnosis.....

Duration of illness: Less than 1 yr 1-5 yrs 5-10 yrs >10 yrs

Date of enrolment/...../.....

2. MEDICATIONS

Steroids		Leflunomide	
Methotrexate		NSAID	
Hydroxychloroquine		Azathioprine	

3. CLINICAL FEATURES

Feature	History	Examination
Arthritis		
Kerato conjunctivitis sicca		
Subcutaneous Rheumatoid nodules		

APPENDIX VIII

Echocardiography Report Form

- **Pericardial Effusion**

If present: Mild <5mm Moderate 5-10mm severe >10mm
Pericardial Thickness: <3mm >3mm

Systolic Function

Fractional shortening % Ejection fraction %

- **Diastolic Function**

E velocity A velocity E/A ratio m/s
Grade 1 Grade 2 Grade 3 Grade 4

- **Mitral valve (MV)**

MV thickness mm MS MR Orifice area cm²
MS: mild moderate severe
MR: Grade 1 Grade 2 Grade 3 Grade 4

- **Aortic Valve (AV)**

AV thickness mm AS AR Orifice area cm²
AS: mild moderate severe
AR: mild moderate severe

- **Tricuspid Valve (TV)**

TV thickness mm TS TR Orifice area cm²
TS: mild moderate severe
TR: mild moderate severe

- **Pulmonary Valve (PV)**

PV thickness mm TS TR Orifice area
cm²
PS: mild moderate severe
PR: mild moderate severe

Pul Pressure

Mild Pul Htn Moderate Pul Htn Severe Pul Htn

APPENDIX IX: ETHICAL APPROVAL FOR STUDY

For more details consult the KNH- UoN ERC website <http://www.erc.uonbi.ac.ke>


Yours sincerely,



PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

- c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chair, KNH-UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
Supervisors: Dr. G. Omondi Oyoo, Dr. Elijah Ogola, Dr. Ilovi Syokau

APPENDIX X: KNH APPROVAL LETTER TO CONDUCT STUDY

 KENYATTA NATIONAL HOSPITAL
P.O. BOX 20723, 00202 Nairobi

Tel.: 2726300/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

Ref: KNH/AD-MED/42B/VOL.1 Date: 16th December, 2015

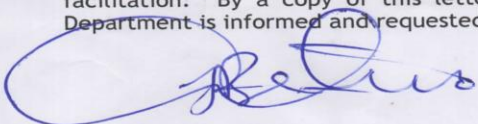
Dr. Emmanuel Alieu Ibrahim-Sayo
Department of Clinical Medicine & Therapeutics
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Sayo

RE: APPROVAL TO CONDUCT STUDY IN KNH, MEDICINE DEPARTMENT

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration form, permission is hereby granted for you to collect data from Medicine Department, Cardiology Unit to enable you complete your research on study titled: *"Echocardiographic Abnormalities in Patients with Rheumatoid Arthritis attending the Rheumatology Clinic at the Kenyatta National Hospital"*.

Kindly liaise with the Senior Assistant Chief Nurse, Medicine Department for facilitation. By a copy of this letter, the Senior Assistant Chief Nurse, Medicine Department is informed and requested to facilitate.



DR. BERNARD GITURA
AG. ASSISTANT DIRECTOR, MEDICINE

Cc. Senior Assistant Chief Nurse, Medicine

IBRAHIM-SAYO E A. Echocardiographic abnormalities in patients with Rheumatoid Arthritis attending the Rheumatology Clinic at the Kenyatta National Hospital, Nairobi, Kenya.