ASSESSMENT OF PULMONARY FUNCTION IN RHEUMATOID ARTHRITIS PATIENTS ATTENDING RHEUMATOLOGY CLINICS IN NAIROBI

A dissertation submitted in part fulfillment of the requirements for the degree of MASTER OF MEDICINE IN INTERNAL MEDICINE OF THE UNIVERSITY OF NAIROBI

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This dissertation is my original work and has not been presented for a degree at any university.

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LIST OF ABBREVIATIONS

ACR: American college of Rheumatology

Anti-CCP: Anti-cyclic citrullinated protein

ATS: American Thoracic Society

COPD: Chronic Obstructive Pulmonary Disease

DAS: Disease activity score

DAS 28: Disease activity score 28 joints

DMARDS: Disease modifying anti-rheumatic drugs

DLCO: Diffusion Capacity of Carbon Monoxide

ESR: Erythrocyte Sedimentation Rate

FEF 25-75: Forced Expiratory Flow at 25% to 75% of vital capacity

FEV1: Forced Expiratory Volume in one Second

FVC: Forced Vital Capacity

FEV1/FVC: Ratio that shows Restriction and Obstruction of the airways

FRC: Functional Residual Capacity

GOLD: Global Initiative on Obstructive Lung Disease

HRCT: High Resolution Computed Tomography of the Chest

ILD: Interstitial Lung Disease

IP: Interstitial Pneumonia

KNH: Kenyatta National Hospital

LTRC: Lung Tissue Research Consortium

MTX: Methotrexate

NSAID: Non steroidal anti-inflammatory drugs

NSIP: Non specific interstitial pneumonia

OP: Organising pneumonia

PFTS: Pulmonary Function Tests

RV: Residual Volume

RA: Rheumatoid arthritis

RF: Rheumatoid factor

ROC: Receiver Operating Characteristic Curve

ROPC: Rheumatology Outpatient Clinics

TLC: Total Lung Capacity

TNF: Tumor Necrosis Factor

UIP: Usual interstitial pneumonia

UON: University of Nairobi

ABSTRACT

Background: Pulmonary involvement is frequent and among the most severe extra-articular manifestations of Rheumatoid arthritis (RA) ranking as the second cause of mortality in this patient population. Rheumatoid arthritis can affect the lung parenchyma, airways and pleura. Pulmonary complications are directly responsible for 10-20% of all mortality in RA patients. Spirometry is becoming increasingly available in Kenya and could be used in peripheral areas to screen and monitor for pulmonary function abnormalities in well characterized patient populations such as those with RA. Abnormalities detected by pulmonary function tests may precede symptoms by years and lead to early diagnosis of pulmonary fibrosis in rheumatoid arthritis and hence intervention.

Objective: To determine the prevalence of pulmonary function abnormalities in Rheumatoid arthritis patients attending Rheumatology Clinics in Nairobi.

Study Design: Cross sectional descriptive Study.

Study population: Rheumatoid arthritis patients who have met the American College of Rheumatology Criteria (ACR) 2010 age 16 to 65 years.

Study site: Rheumatology Clinics in Nairobi as follows; Kenyatta National Hospital, Aga Khan University hospital and Mater hospital.

Methods: Rheumatoid arthritis patients who fulfilled the study inclusion criteria were recruited. Sociodemographic characterictics and respiratory symptoms were assessed using Lung Tissue Research Consortium questionnaire (LTRC) and RA disease activity was established by Disease Activity Score (DAS28). Pulmonary function tests were then done using Spirolab 111 according to the American thoracic society recommendations.

Results: One hundred and sixty six RA patients were recruited; the male to female ratio was 1:9.3, with a median age of 47 years. The overall 6 month prevalence of pulmonary function abnormalities was 38.5% as measured by Spirometry and all our patients did not carry any prior pulmonary disease diagnosis. The predominant ventilatory defect was Obstructive pattern at 20.4%, followed by Restrictive pattern at 16.8% and least common being a mixed picture at 1.2%. Factors that were shown to be independently associated with pulmonary function abnormalities were age and RA disease activity. Respiratory symptoms that were predictive of PFTs abnormalities were cough, increased frequency of chest colds and illnesses and phlegm.

Conclusion: High prevalence of pulmonary function abnormalities was observed. Respiratory symptoms, older age and ongoing disease activity can identify patients in greatest need of further pulmonary evaluation.

1.0 BACKGROUND

Rheumatoid arthritis (RA) is the most commonly encountered connective tissue disease [**1**]. It is a chronic inflammatory and systemic disease which mostly affects the synovial tissues with a prevalence ranging from 0.5% to 2%. It is a progressive autoimmune process characterized by symmetrical erosive synovitis. Although the central pathology of RA develops within the synovium of diarthrodial joints, many nonarticular organs become involved, particularly in patients with severe joint disease. The female to male ratio of RA is 2.5:1 most frequently seen in the 25-55 yr age group **[1,2].**

The prevalence of widely disseminated lesions in other regions of the body has been highlighted with clinical observation and studies, thus pointing out the systemic nature of the disease. The strongest predictors of premature mortality appear to be the presence of RA-related complications and associated co morbidities, specifically, cardiovascular disease and pulmonary disease **[2].** In recent cohort studies, nearly 40% of patients with RA suffered from some type of extra-articular manifestations **[2,3,4]**. Extra-articular manifestations can be detected in almost all organ systems as cutaneous, ocular, hematological, cardiovascular, and **pulmonary lesions [4]**.

Pulmonary involvement is a frequent and among the most severe extra-articular manifestation of RA **[5]**. It is a leading cause of excess death in patients with RA and the second cause of death in this patient population **[6,7]**. Pulmonary complications are directly responsible for **10 to 20%** of all mortality **[8,9,]**. When compared with control populations, patients with RA and with a respiratory disease have an estimated standardized mortality ratio that ranges from 2.5 to 5.0 **[6,9]**. The majority of lung disease occurs within the first 5 years after the initial diagnosis, and may be a presenting manifestation in 9 to 20% of patients. The onset of respiratory manifestation may even precede the onset of symptoms of arthritis [**5**].

Lung disease directly associated with the underlying RA is more common, even though pulmonary infection and drug toxicity are frequent complications of RA. The lung is involved in rheumatoid disease because of the abundant vasculature and connective tissue which is involved in collagen vascular diseases. RA can affect the lung parenchyma, airways, and the pleura, with

variable amounts of pathological inflammation and fibrosis. The well-characterized pulmonary disorders in RA include: RA-associated interstitial lung disease, pleural effusions and pleuritis, rheumatoid nodules, Caplans syndrome, pulmonary vasculitis and pulmonary airway involvement. Bronchiectasis and an increased incidence of chest infections have also been reported **[10,11,12]**.

The prevalence of a particular complication varies based on: The characteristics of the population studied, the definition of lung disease used and the sensitivity of the clinical investigations employed. However, all studies concur in that a high prevalence of abnormality can be found. Furthermore, while the prevalence of other serious extra-articular manifestations is declining, RA-associated lung disease is increasing **[13]** both pulmonary infection and drug-induced lung disease included **[14,15]**.

There is significant heterogeneity between study results in terms of the type of abnormality detected. Whereas in some cases, the predominant defect was volume restriction with impaired gas transfer, in others airway obstruction, both large and small, predominated. This heterogeneity could reflect differences in study design. The diagnostic modality used (radiology or physiology) will clearly have a large impact on the range of lesions detected **[16]**.

Recently, attention has been drawn to the higher prevalence of Chronic obstructive pulmonary disease (COPD) in patients with RA. COPD has been reported to occur more frequently in patients with RA than in general population even after adjusting for smoking, and is believed to have a more pronounced impact on survival compared to COPD in patients without RA **[17]**. Thus, both restrictive and obstructive lung disease produce clinically important effects in patients with RA. However, their diagnosis is often delayed as the early signs and symptoms may be indolent, non-specific and masked by reduced physical activity due to articular disease.

Respiratory complaints may be under-reported and/or unrecognized in RA patients with lung disease as individuals with RA are generally less physically active due to joint pain and chronic fatigue and thus less likely to experience symptoms such as dyspnea on exertion. In addition the nature of the symptoms of lung involvement overlap with symptoms of cardiac disease, another common co morbidity in RA, thus potentially constituting the diagnosis of respiratory disease even more prodigious.

The pulmonary manifestations associated with RA have been evaluated through; histopathological, radiological and functional approaches. This study examines the role of lung disease in RA from a clinical, epidemiological and functional/physiological perspective with the use of pulmonary function tests (Spirometry) and a standardized questionnaire.

2.0 LITERATURE REVIEW

2.1 INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) is a frequent manifestation of rheumatoid lung disease and often asymptomatic. Estimates of the prevalence of interstitial lung disease in RA range between **19% and 44% [18,19]** . Among patients with early rheumatoid disease (joint symptoms <2 years) who were surveyed with a range of investigations including pulmonary function tests, radiographs, and bronchoalveolar lavage, 21 of 36 patients (58 percent) had abnormal findings on at least one modality that were consistent with ILD **[20]**. Pulmonary involvement was clinically apparent in 14 percent and clinically silent in 44 percent of this population.

The reported prevalence of ILD in patients with RA is highly variable and depends on the methods of detection e.g high-resolution chest tomography (HRCT) scan, chest radiograph, or pulmonary function testing and the population selected for study i.e symptomatic or asymptomatic and autopsy series. Through chest radiography, the diagnosis of rheumatoid lung disease is made in 1 - 5% of RA patients **[13].** In most cases it may be normal even in the presence of disease. The estimated prevalence of rheumatoid arthritis associated interstitial lung disease (RA-ILD) using HRCT is 20–44% **[21]** and is a highly sensitive modality to use although expensive investigation in resource limited centres.

However, a relatively cheaper modality may be used. It has been shown that 40% of patients may have restrictive abnormalities when pulmonary function tests (PFTS) - Spirometry and reduction in diffusion capacity of carbon monoxide (DLCO) – are used as diagnostic measures [**21**]. Asymptomatic ILD often precedes the articular manifestations of RA by months or years. ILD typically becomes symptomatic late in its course when fibrosis is present. Presentation is more common at 50 to 60 years of age, in men, and in association with seropositive and erosive joint disease **[22].** Radiographic changes and changes on pulmonary function testing may precede overt symptoms by years. Once clinically apparent, ILD is associated with significant mortality.

2.1.1 PATHOGENESIS

Clinical, genetic, and environmental factors have been used to predict the development of lung disease in RA. In contrast to most connective tissue diseases, RA-ILD is three times more common in males than in females, in individuals with late-onset disease, high titre rheumatoid factor and in smokers **[23,24].** High-titre rheumatoid factor (RF) has been associated with the presence of RA-ILD and decreased diffusion capacity for carbon monoxide (DLCO) **[25,26,27]**

One hypothesis for the development of lung fibrosis in RA is that a cellular inflammatory process is required for and initiates a secondary fibroproliferative process, and that the fibroproliferative process may become progressive and independent of its initiating cause. The initial insult is an injury to the epithelial surface causing inflammation in the air spaces and alveolar walls. If the disease becomes chronic, inflammation spreads to adjacent portions of the interstitium and vasculature and eventually causes interstitial fibrosis. The development of irreversible scarring (fibrosis) leads to significant derangement of ventilatory function and gas exchange. **[28,29]**

2.1.2 PATHOLOGY

A wide variety of histopathology features have been observed in RA. Various types of interstitial pneumonia are observed with associated airway diseases. There is also frequent overlap between different patterns of interstitial pneumonia in the same patient, making the pathological diagnosis more complicated **[30,31].** These disorders affect not only the interstitium (space between endothelial and epithelial basement membranes) but also the adjacent airspaces, the peripheral airways, and the vessels.

Currently available data show that among RA-ILD patients, there is a higher proportion of a patient with usual interstitial pneumonia (UIP) pattern compared to patients with other connective tissue diseases. Lee et al. **[32]** found UIP to be the most common histopathologic pattern in RA-ILD patients (56%). This was followed by nonspecific interstitial pneumonia (NSIP) pattern in 33% and organizing pneumonia (OP) in 11%.

Flaherty et al **[33]** demonstrated that patients with collagen vascular disease-associated UIP pattern had fewer fibroblastic foci and better survival compared to patients with the idiopathic type, which may be related to better prognosis of UIP associated with collagen vascular diseases.

2.1.3 DIAGNOSIS

The diagnosis of RA-ILD is generally based on the combination of clinical presentation, pulmonary function testing, HRCT, and in some cases, lung biopsy **[34]**. A careful exposure history (including occupational, environmental and pharmaceutical) should be conducted to evaluate potential alternative causes.

Pulmonary function tests frequently demonstrate reduced lung volumes and DLCO, even in the absence of symptoms [**20**]. Reduced DLCO was suggested to be the most sensitive marker for interstitial pneumonia on HRCT **[35].** Progressive dyspnea as measured by a standardized questionnaire is a strong predictor of shortened survival **[36]**.The declining size of the lung as measured by plain chest radiographic study as well as the extent of disease seen on HRCT are powerful predictors of disease **[37,38]**.

Serial changes in pulmonary physiology with declines in forced vital capacity can be used both in detection, prediction and as follow up tool of disease progression **[39,40]**.These changes over time are stronger prognostic markers than baseline measure **[41].**

2.1.4 TREATMENT

In general, more aggressive treatment is justified in patients with evidence of inflammation on HRCT, lymphocytes on bronchoalveolar lavage, or a non-UIP pattern on biopsy. Glucocorticoid therapy is the treatment of choice with variable subjective and objective improvement in the treatment of RA-ILD **[34,42,43]**. Other drugs reported to be beneficial include cyclophosphamide, azathioprine, hydroxychloroquine, D-penicillamine, and cyclosporine **[44]**.

Effective treatment of the joint disease should not be used as a surrogate for beneficial or even adequate treatment of the ILD. Just as clinically important diffuse lung disease can precede the development of active joint disease in RA, progressive ILD can occur despite the absence of synovitis **[34]**.This strongly argues for continued regular pulmonary follow-up of known lung disease in patients with even excellent control of their joint disease as well as early pulmonary referral when respiratory symptoms develop or progress in patients with RA, regardless of the activity of their joint disease.

Despite the absence of effective treatments for advanced respiratory disease it is possible that therapeutic intervention at an early stage may be beneficial. It has been suggested that early diagnosis and treatment with antifibrotic agents may alter the prognosis of pulmonary fibrosis **[34].**

2.2 PULMONARY AIRWAY DISEASE

Rheumatoid arthritis is known to cause both upper and lower airway disease.

Major manifestations of large airways involvement are the Cricoarytenoid arthritis and Bronchiectasis. Major manifestations of small airway disease encompass Bronchiolitis; Follicular bronchiolitis, Constrictive bronchiolitis/obliterative bronchiolitis among others.

2.2.1 UPPER AIRWAY OBSTRUCTION

Jurik and Pedersen found arthritis of the cricoarytenoid joints in 55% of 150 patients with RA The incidence was higher in females (65%) than in males (20%) **[45]**. Though not disabling, the cricoarytenoid joints may become inflamed and immobilized with the vocal cords adducted to midline, causing inspiratory stridor and upper airway obstruction. Pulmonary function tests may reveal blunting of the inspiratory loop in patients with variable extrathoracic obstruction.

2.2.2 BRONCHIOLITIS

These include bronchiolar diseases such as Follicular bronchiolitis and Constrictive bronchiolitis (Bronchiolitis obliterans). These diseases are usually seen in patients with positive rheumatoid factor and active joint disease.

Follicular bronchiolitis is characterized by the presence of abundant lymphoid tissue, situated in the walls of the bronchioles and, to some extent, in larger bronchi. In RA, it probably represents lymphoid hyperplasia in response to an extrinsic immune stimulus or altered systemic immune response.

Constrictive bronchiolitis is characterized by progressive concentric narrowing of membranous bronchioles due to inflammation and fibrosis. The symptoms are characterized by dyspnea and nonproductive cough. Although chest radiograph is generally normal, PFTs reveal airflow obstruction with reduced ratio of Forced Expiratory Volume in one second to the Forced Vital

Capacity (FEV1/FVC) and this is due to air trapping, small nodular opacities in centrilobular distribution, patchy areas of low attenuation and peribronchial thickening; all depicted in HRCT, DLCO is usually normal **[46,47].**

The reported prevalence of obstructive dysfunction in small airways in RA patients, estimated on the basis of decreases in Forced Expiratory Flow at 25% to 75% of vital capacity (FEF 25-75) values and the ratio of FEV1/FVC, varies among studies, ranging from **8% to 65%.** This variation may be explained by the different criteria used in different studies to assess small-airway disease as well as by variation in the patient populations examined.

Davidson et al (1974) **[48]** in London studied 42 RA patients with normal chest radiography and found that 10 out of these, had impaired gas transfer. The evidence from the study suggested that abnormal lung function may occur fairly commonly in asymptomatic patients with RA with normal chest x-rays.

Schernthaner et al (1976) **[49]** in Vienna, Austria reported on 62 patients and found a negative correlation between DLCO and rheumatoid factor. Their results also showed that 42% of their patients had high residual volumes, 21% had reduced FEV1/FVC ratios, and 18% had increased airway resistance.
He commented that the reduced lung compliance found frequently in RA was probably due to inflammatory changes of interstitial tissues which could develop into interstitial fibrosis. Restriction of lung volumes could have possibly been due to pleurisy, reduction in thoracic rigidity and to rheumatoid myopathy. Bronchial obstruction (increased airway resistance and reduction in FEV1) if smoking was excluded, may serve as an early sign. He concluded that because interstitial, vascular, and alveolar changes can develop independently of each other, and may not occur to a similar extent in a given patient, lung compliance and DLCO are not necessarily decreased in the same way.

Geddes et al (1979) **[50]** reported the prevalence of airflow obstruction in RA patients in Westminster London to be 38%**.** Owing to the report of an association between rheumatoid arthritis (RA) and obliterative bronchiolitis, Spirometry was performed on 100 patients with RA

and 84 control subjects matched for age, sex, and smoking habits. Patients with RA had significantly lower values for FEV1, FVC, FEV1/FVC ratios, when compared with the control. He commented that the prevalence of airflow obstruction is remarkably high, previous studies of lung function in RA had tended to concentrate on evidence of pulmonary interstitial disease and to ignore the airways.

The study showed strong evidence that neither smoking itself nor an increased susceptibility to its effects was the sole cause of airflow obstruction. He concluded that airway disease may be the commonest form of lung involvement in rheumatoid arthritis.

These laid a foundation for other studies. Recent studies done:

Thierry et al (1998) **[51]** studied 50 RA patients in Lille France without radiographic evidence of RA-related lung changes, the study sought to assess the prevalence and characteristics of airway involvement in RA patients in the absence of interstitial lung disease. He found an obstructive pattern in 18% of patients using PFTs and HRCT features of airway disease were found in 34% of the same cases, the study suggests a high prevalence of airways involvement by RA in the absence of interstitial lung disease. Among the 15 patients with normal CT scans, PFTs depicted a moderate obstructive pattern in two cases. This apparent discordance can be explained by the well-known limitations of CT in depicting mild changes in bronchial-wall thickness and/or diameter.

With regard to functional impairment, their findings are in agreement with the 16% frequency of airway obstruction reported in a population of 81 unselected RA patients (versus 0% in matched controls) by Vergnenègre et al (1997) **[52]** in an earlier study in France.

Shunsuke et al (2010)**[53]** in Japan obtained evidence suggesting that obstructive dysfunction of small airways is common among 155 RA patients, even among those without a diagnosis of Interstitial pneumonia(IP) or bronchiolitis pattern on HRCT. Prevalence of obstructive small-airway disease in RA patients without the IP or bronchiolitis pattern was 30.3%.

The presence of respiratory symptoms, positive smoking history, and disease duration >10 years were predictive factors for the presence of abnormal FEF25–75 values.

These findings may suggest that small-airway disease has a long-term clinical significance as a manifestation of RA. In its early stages, obstructive changes in small airways are subtle, which makes it difficult to definitively diagnose the bronchiolitis pattern in HRCT images. Among these cases, some subset may subsequently develop clinically evident and HRCT-confirmed bronchiolitis during the course of RA.
Pulmonary Function Tests (PFTS) may be useful in such cases for earlier detection.

In the USA,a study done in John Hopkins University by Pappas et al (2010) [**54**] on 159 RA patients, found a 28% prevalence of pulmonary function abnormalities on Spirometry. The most common ventilatory defect was obstructive at 11.3%, restrictive pattern was observed in 7.6% and an isolated impaired DLCO in 9.6%. He identified factors such as seropositivity to rheumatoid factor, high titres of Anti-CCP antibodies and ongoing corticosteroid use as predictive of abnormalities on PFTs. Chronic cough, phlegm and breathlessness were the respiratory symptoms that were found to associate with this abnormalities. His was the first study to exclude patients with clinically apparent cardiovascular disease, thus increasing the likelihood that the reported respiratory symptoms truly reflected lung disease, rather than cardiac disease.

In Africa, a study done by Amir et al (2011) **[55]** on Egyptian patients with rheumatoid arthritis (non smokers) revealed that out of the 36 patients studied 23 (64%) demonstrated abnormalities in PFTs and 47% in HRCT. Mixed restrictive and obstructive pattern was the commonest and reported in nearly 31% followed by restrictive pattern at 22.2% and finally obstructive pattern at 11.1% on spirometry. ILD was the commonest pulmonary affection detected by HRCT at 39%. Nearly two-thirds of the patients reported one or more pulmonary symptom whether dyspnea, cough, wheezing or phlegm. Dyspnea was the most frequent symptom.
Advanced age, high radiological score, and severity of rheumatoid disease were found to be predictive of lung involvement. When specific pulmonary abnormalities were considered, only dyspnea was identified as predictor for restriction. For obstructive abnormality, both cough and wheezing provided valid prediction.

Avnon et al. (2009) **[56]** in Israel showed that 13.2% of 82 RA patients with no symptoms or evidence of respiratory disease, participating in a 5-year follow-up study recently developed small-airway defect, defined as reduced FEF25–75. He recommended that serial PFTs among

patients with RA is indicated and allows for earlier identification of various ventilatory defects. It also identifies silent clinically relevant conditions that require follow-up and perhaps even intervention.

2.2.2.3 PATHOGENESIS

The reason for the high incidence of small-airway obstruction in RA patients remains unclear. One of the most attractive explanations is that the obstructive changes are due to frequent and recurrent infections in the small airways. Colonization of the small airways by pathogenic microorganisms has been reported in patients with clinically stable bronchiectasis **[57].** The evidence indicates that RA patients may have an increased susceptibility to airway infections or a reduced ability to eradicate these infections [**58**].

Chronic colonization, secondary persistent inflammation, and progressive lung injury may contribute to the frequent development of airway obstruction during the disease course. As an alternative explanation, several studies have proposed that bronchi/bronchioles are one of the main targets of autoimmunity in RA patients. Bronchiolar inflammation may secondarily induce mucosal edema, which eventually leads to development of small-airway obstruction **[59]**. Such pulmonary lesions may create a favorable environment for persistent infections. It is uncertain whether microbial colonization may precede bronchiolar obstructive changes or not. Regardless of which came first, a vicious spiral of infections and obstructive changes in the small airways can develop in the lungs of RA patients.

2.2.2.4 DIAGNOSIS

The diagnosis of RA-associated pulmonary disease should be supported by clinical features (signs, symptoms and laboratory tests), abnormal PFTs, and either a compatible HRCT or a lung biopsy **[60].**

Pulmonary function testing has proved valuable in detection and follow up of RA-associated lung disease. High resolution computed tomography is highly sensitive for detecting the presence of ILD. When used together the variable incidence of reported abnormalities may reach up to 60% of the patients in some studies **[35].**

Given the impact of lung disease on morbidity and mortality in RA, screening of asymptomatic RA patients for pulmonary involvement has been recommended by some. Unfortunately, the cost of screening all asymptomatic RA patients with HRCT and/or PFT techniques limits their suitability for screening of asymptomatic individuals **[55].**

The precise characterization of obstructive changes in small airways that is enabled by both PFT and HRCT appears to be helpful in evaluating not only their long-term significance as pulmonary complications of RA but also their implication in RA pathogenesis.

2.2.3 BROCHIECTASIS

An association between bronchiectasis and RA has been noted and bronchiectasis may result from recurrent infections, retraction in interstitial lung diseases (traction bronchiectasis) or the progression of lymphocytic/constrictive bronchiolitis **[61]**

Walker et al (1967) **[62]** has shown that patients with RA are more prone to respiratory tract infections than patients with osteoarthrosis, and that bronchiectasis is also more common.

2.3 INFECTIONS

Patients with RA have been shown to have an increased risk of infections compared with the general population, even after adjustment for age, sex, smoking status, leukopenia, corticosteroid use, and diabetes mellitus **[63,64].** Several treatment modalities for RA may induce infections, including corticosteroids, disease-modifying anti-rheumatic drugs (DMARDS), Tumour necrosis factor (TNF) antagonist, and new biotherapies. Opportunistic infections may also appear.

Pneumonia is a major cause of mortality in patients with RA and is probably the most common respiratory cause of death **[9].** The relative risk for pneumonia and lower respiratory tract

infections is 1.68 and 1.88 respectively **[63]**.

Treatment of RA and other autoimmune disorders with anti-TNF agents is associated with an increased risk of reactivation of latent Mycobacterium tuberculosis **[65, 66].** The rate of tuberculosis in patients with RA treated with anti-TNF therapy is three to four times higher in patients receiving infliximab and adalimumab than in those receiving etanercept [**67].**

Geddes et al (1979)**[52]** attributed the high prevalence of obstructive airway disease in RA patients may be due to due to frequent respiratory tract infections.

2.4 PLEURAL INVOLVEMENT

Pleural involvement is a common manifestation of lung disease in RA. Although its prevalence has been estimated to be less than 5%, 20% of RA patients have symptoms related to pleural disease [**68]** and a high frequency (40–75%) of pleural involvement is noted in autopsy reports **[30].**

The annual incidence of rheumatoid pleural effusion in the RA population is 0.34% in women and 1.54% in men **[69].** Many pleural effusions are found incidentally on chest radiography, with overt clinical evidence of pleural disease in less than 5% **[70,71].** Sequelae of pleurisy (pleural thickening and/or effusion) were found in 24% of men and 16% of women in 309 chest radiographs of RA patients **[72].**

Unresolved rheumatoid effusion may result in marked pleural thickening, a trapped lung with progressive restriction of lung volume. PFTs usually detect a restrictive picture; FEV_1/FVC ratios that are normal in the setting of reduced lung volumes **[73].**

2.5 DRUG-INDUCED LUNG DISEASE

Several of the medications used to treat RA can be associated with lung injury. The incidence of pulmonary toxicity in patients treated with methotrexate (MTX) for RA is 1–5%. Toxicity is rare with doses less than 20 mg per week, although more recent studies have reported that methotrexate pneumonitis occurs with a dose of 5 mg per week **[74].**

2.5.1 METHOTREXATE

MTX lung injury is most often a subacute process, in which symptoms are present for several weeks before diagnosis. Approximately 50% of cases are diagnosed within 32 weeks of initiation of MTX treatment**.** Predominant clinical features of MTX lung injury include shortness of breath,

cough, and fever. Hypoxemia and a restrictive pattern on pulmonary function testing are observed. Chest x-rays and CT demonstrate diffuse infiltrates **[75].**

The pathogenesis of this entity is not known. It probably has a hypersensitivity mechanism suggested by the frequent finding of peripheral eosinophilia and lymphocytosis on bronchoalveolar lavage. It may be an idiosyncratic immune reaction.

Earlier recognition and drug withdrawal may avoid the serious and sometimes fatal outcomes that have been observed. Patients generally respond to withdrawal of methotrexate and the prognosis is usually good. Uncontrolled studies suggest that glucocorticoids can hasten recovery and may be important for severely ill patients. Rechallenge with methotrexate has been reported without recurrence of lung disease, and can be tried with caution **[76].**

2.5.2 LEFLUNOMIDE

Interstitial pneumonia as an adverse reaction of leflunomide is rare. The incidence of such cases is reported to be 0.02% in Western countries. In Japan in 2003, 16 cases (0.48%) of ILD, including five fatal cases (0.15%), were associated with leflunomide therapy among 3360 registered patients **[77].**

Leflunomide has been reported to induce interstitial lung disease and cases of new or accelerated pulmonary nodule formation, which stabilized after cessation of the drug **[78,79,80].** Risk factors for the development of lung injury included preexisting lung disease (the most significant risk factor), smoking, low body weight, and use of a loading dose **[81,82].** In patients with known ILD, leflunomide treatment in RA patients with pulmonary involvement is not recommended due to the possibility of causing accelerating ILD in these patients.

2.6 THORACIC CAGE ABNORMALITY

Abnormalities of thoracic cage mobility can be present in RA and is associated with pleurisy, myopathy, and thoracic rigidity. Restrictive patterns with reduced lung volumes with a low or normal DLCO have been reported **[9].**

3.0 MONITORING FOR LUNG DISEASE

The role of surveillance for lung disease in patients with RA is clear and necessary. Early diagnosis is important before the pathology progresses to irreversible lung fibrosis with established interstitial lung disease. Pulmonary related drug reaction should also be detected and monitored.

Thus, a thorough history and examination for pulmonary symptoms and signs should be performed in all patients. When abnormalities are found, further investigations are likely to be required to define the process. Lung function tests can be used as the baseline tests to detect those who will need more expensive and/or invasive investigations such as HRCT, bronchoscopy with bronchoalveolar lavage, and transbronchial or surgical lung biopsy, when indicated.

Given the impact of lung disease on morbidity and mortality in RA, screening of asymptomatic RA patients for pulmonary involvement has been recommended by some experts. It has been suggested that early identification and timely therapeutic intervention with antifibrotic agents may alter the prognosis of pulmonary fibrosis. Similarly, early intervention in patients with RA and COPD might improve quality of life and performance status. A practical, cost effective way of identifying early pulmonary disease in patients with RA could yield significant benefit in patient outcomes.

The most sensitive method for detecting ILD is high-resolution computed tomography of the chest, but this technique is expensive and associated with significant radiation exposure, limiting its suitability for screening of asymptomatic individuals. Another limitation is in depicting mild changes in bronchial wall thickness and or diameter which pulmonary function testing has proved valuable. PFTS can be used serially to detect and monitor disease progression. These measures include among others, serial changes in vital capacity as depicted by the FEV_1 and FVC ratios and DLCO.

3.1 PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) are performed in order to diagnose and classify disease processes that impair lung function. Impairments in lung function can be broadly classified as those resulting in airflow obstruction, volume restriction, or a combination of obstructive and restrictive defects**[49]** It is indicated for evaluation of respiratory symptoms (eg, cough, wheezing, dyspnea, and chest pain), bronchodilator therapy, effect of workplace exposure to dust or chemicals, and disability. It can also be used to assess severity and progression of lung diseases, such as asthma, chronic obstructive lung disease, and various restrictive diseases.

The major types of PFTs include spirometry, lung volumes, and diffusing capacity of carbon monoxide. Other PFTs include flow-volume loops (which record forced inspiratory and expiratory flow rates) and measurements of maximal respiratory pressures. Spirometry is the measurement of the movement of air into and out of the lungs during various breathing maneuvers.

Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are the primary measurements obtained by spirometry. Their ratio (FEV1/FVC) is important for distinguishing obstructive airways disease and restrictive disease. A reduced ratio suggests obstructive airway disease and a normal ratio suggests restrictive disease, if accompanied by reduced lung volumes. Measurement of lung volumes complements spirometry. Common measurements include total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV).

Decreased lung volumes suggest restrictive disease if accompanied by a normal FEV1/FVC ratio. Increased lung volumes suggest static hyperinflation due to obstructive airways disease if accompanied by decreased FEV1/FVC ratio. Coexisting restriction and obstruction can be detected, but requires spirometry and lung volumes. Typically, airflow obstruction can be diagnosed using spirometry alone by demonstrating a lower-than-predicted FEV_1/FVC ratio. Since affordable hand-held spirometers are now widely available, diagnosis of obstructive and restrictive lung disease can easily be made in an outpatient setting.

Pulmonary function testing has proved valuable in early detection of RA-associated lung disease. Pulmonary disease in RA patients may not be routinely sought by rheumatologists and internists in the absence of cost-effective, accurate and time-efficient means of screening. Spirolab 111 is a portable spirometry machine that has been used in the periphery clinics and has been endorsed by the Global initiative in Obstructive Lung disease (GOLD), to have a sensitivity of 84% and a specificity of 89%.

In summary, the approach to patients with rheumatoid arthritis presenting with respiratory symptoms needs to take into account multiple possible causes, including interstitial lung disease, airway disease, drug-related lung toxicity and infection secondary to immunosuppression. Careful history and physical examination, including a search for extrapulmonary signs of disease in concert with pulmonary function tests and HRCT may suggest the underlying diagnosis. Lung biopsy may be needed before treatment is administered.

4.0 STUDY JUSTIFICATION

Respiratory illness is a significant contributor to morbidity and mortality in patients with RA, ranking as the second major cause of death in this patient population. In Kenya RA patients present with already advanced stage of lung disease having lost the opportunity for early recognition and management with anti inflammatory drugs and DMARDs. The burden of lung disease in RA patients in Kenya, though present is unknown as there is paucity of data.

In establishing the prevalence of abnormalities detected by spirometric pulmonary function tests (PFTs), this study will highlight the need for screening and monitoring for pulmonary involvement in RA patients by use of an adequate screening tool that could easily be integrated into clinical care and represent a critical step in early detection.

5.0 RESEARCH QUESTION

What is the prevalence, pattern and associated factors of pulmonary function abnormalities in Rheumatoid arthritis patients?

6.0 STUDY OBJECTIVES

6.1 Broad Objective

To determine the prevalence of pulmonary function abnormalities and certain correlates (clinical and demographic) in Rheumatoid Arthritis patients attending Rheumatology clinics in Nairobi.

6.2 Specific objectives

1. To determine the prevalence of pulmonary function abnormalities in RA patients using Spirometry.

2. To describe the demographic and clinical characteristics of RA patients with pulmonary function abnormalities.

3. To determine demographic and clinical characteristics associated with pulmonary function abnormalities in RA patients.

7.0 METHODOLOGY

7.1 STUDY SITE

Study took place in three Nairobi rheumatology outpatients' clinics as follows:

- Kenyatta National Hospital rheumatology clinic; takes place on Thursday.
- Aga Khan University Hospital rheumatology Clinic; takes place on Friday.
- Mater hospital rheumatology clinic; takes place on Wednesday.

These three sites were chosen so as to achieve the Sample size of 165. KNH has 130 registered rheumatoid arthritis patients on follow up, AKU has 30 registered patients and Mater has 20. The plan was to recruit all eligible patients into the study because of their few numbers.

These are the three clinics in Nairobi which cater for rheumatoid arthritis patients and the health care is standardized. This study population was taken to be homogenous with similar characteristics hence no stratification of the patients was be done, however in the final analysis the number of patients recruited from the three sites was included.

All clinics run on different days on the depicted days as above. The principal investigator had two trained research assistants who helped in collection of data.

Permission was sought and granted from the participating hospitals once KNH/UON Ethics committee approved the study.

7.2 STUDY POPULATION

These were Rheumatoid arthritis patients, between 16 to 65 years of age.

7.3 STUDY DESIGN

This was a Cross sectional descriptive study

7.4 INCLUSION CRITERIA

RA patients who met the American College for Rheumatology (ACR 2010) criteria with informed consent/assent were recruited.

7.5 EXCLUSION CRITERIA

Those excluded were:

-Patients who had other connective tissue diseases e.g Systemic Lupus Erythematosus (SLE), Osteoarthritis

-Patients who had documented active pulmonary lesions e.g Pulmonary tuberculosis, Pneumonia, Asthma, COPD.

-Patients who had documented Cardiac disease.

-Contraindications to spirometry including:

- > 65yrs of age
- Recent haemoptisis (3 months)
- Recent surgery of thorax, abdomen, eye surgery.

7.6 SAMPLING METHOD

Consecutive sampling procedure was carried out. The RA pts were screened as they sought outpatient services at the clinics; those who met the inclusion criteria and gave consent were recruited. Enrollment was done until desired sample size was achieved.

7.7 SAMPLE SIZE

Sample size was obtained using the Fishers formula for prevalence studies:

$n = t^2 \times p (1- p) / m^2$

Where: n = required sample size, t=confidence interval at 95% (standard value of 1.96), p=estimated Prevalence of pulmonary function abnormalities in RA (average of 30% from Shunsuke's study), m=margin of error at 7% (standard value of 0.07)

The calculated sample size was:

$n= 1.96^2 \times 0.3(1-0.3) /0.07^2$

= 165

8.0 RECRUITMENT AND CONSENTING PROCEDURES

The Principal investigator was responsible for enrolment which included getting informed consent from the patients. Enrolment of patients involved screening to identify the ones who met the eligibility criteria. The eligible patients were then taken through a consenting process which included giving the patient general information on the study, the risks and benefits associated with the study, confidentiality and their freedom to refuse to participate in the study. The eligible patients who agreed to participate in the study were recruited after signing a consent form.

9.0 DATA COLLECTION PROCEDURES

The patients enrolled into the study were interviewed using a structured questionnaire to seek information on their socio-demographic and the disease characteristics. Respiratory symptoms were evaluated using the Lung Research Tissue Consortium Questionnaire (LRTC).
Rheumatoid arthritis disease activity was measured by use of Disease Activity Score (DAS 28).

Finally, pulmonary function was assessed using Spirometry. This was done by trained research assistants in accordance to the American Thoracic Society (ATC) recommendations.

10.0 DATA COLLECTION INSTRUMENTS

Data collection was done by two instruments:

1. Questionnaire - Proforma
    - Lung Tissue Research Consortium (LRTC)
    - Disease activity score of Rheumatoid arthritis (DAS 28)
2. Spirolab 111 – Spirometry tool which measures Pulmonary function: FEV_1, FVC and calculates ratio of the two. Ventilator defects such as Obstructive and Restrictive are identified from the values of these ratios.

10.1 Study Proforma: This included:

- Sociodemographic factors such as Age, sex, marital status, occupation.
- Rheumatoid arthritis disease history such as Duration of illness, Seropositivity to rheumatoid factor, DMARDs use.
- Cigarette smoking exposure such as history of, whether active, passive (spousal) smoker.

10.2 Lung Tissue Research Consortium Questionnaire (LRTC)

This assessed respiratory symptoms such as cough, phlegm, wheezing, breathlessessness and increased frequency of chest colds and illnesses as answered by the patient. This questionnaire meets American Thoracic Society (ATS) criteria for epidemiologic surveys in chronic respiratory diseases and is considered reproducible, valid, and free of bias

10.3 Disease Activity Score of Rheumatoid Arthritis - (DAS 28)

This measured disease activity of Rheumatoid Arthritis. It is a clinical index of RA disease activity that combines information from swollen joints, tender joints and acute phase response. It is calculated using a formula that includes the number of tender joints and swollen joints (28 joints maximum) and ESR thus depicting the severity of the disease. The DAS28 high and low disease activity thresholds have been validated in clinical trials and practice.

The relevance of DAS 28 in the study is to determine whether disease activity of rheumatoid arthritis correlates with Ventilator defects identified (obstructive, restrictive or combined) and respiratory symptoms reported.

10.4 PULMONARY FUNCTION TESTS (PFTS)

PFTS measurements were performed at the end of the interviews (on site) according to the American Thoracic Society recommendations, for subject maneuver, techniques, and quality control using Spirolab III – a portable spirometer machine. These were performed by a trained research assistant. Three tests with values within 5% were defined as acceptable, and the best of the three values were used for comparisons. Forced expiratory volume in one minute (FEV1), Forced Vital Capacity (FVC), Ratio of the two- FEV1/FVC ratio and their respective % predicted values were recorded.

10.4 .1 DEFINITION OF PULMONARY FUNCTION ABNORMALITIES

Clinical diagnosis was based on Spirometric tests alone. This test was used to evaluate if the pulmonary function was normal or abnormal. If abnormal, the interpretations of the parameters used to identify the ventilatory defects were as follows:

- Airway obstruction was defined as FEV_1/FVC ratio of <70% and an FVC of >80% of predicted values for age, sex, height and weight of the individual.
- Restrictive defects was defined as FEV_1/FVC ratio of >70% with an FVC of <80% predicted
- Combined defects was defined as FVC of <80% predicted and an FEV1/FVC ratio of <70%.

The degree of severity of functional impairment was defined according to American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines based on FEV1 (for obstructive defects) and FVC (for restrictive defects) as follows:

Degree of Severity	**FEV1 (Obstructive) or FVC (Restrictive) (% of predicted)**
Mild	60-69
Moderate	50-59
Moderately severe	35-39
Severe	< 35

11.0 OUTCOME VARIABLES

The Primary outcome was:

- Presence or absence of a ventilatory defect.

The Secondary outcomes were:

- Relationship of above to age, gender, duration of illness, use of DMARDS and disease activity (DAS 28).

-Relationship of the above to respiratory symptoms assessed by LTRC

11.1 INDEPENDENT VARIABLES

- Age
- Sex
- Occupation
- History of Cigarette Smoking
- Rheumatoid Factor
- Duration of Disease
- Disease Activity of Rheumatoid Arthritis (DAS 28)
- Respiratory symptoms

12.0 DATA MANAGEMENT

Data was cleaned, entered and analyzed using SPSS version 17.0. The study population was described by summarizing the demographic and clinical characteristics into proportions and means/medians for categorical and continuous variables respectively. Prevalence of PFTs abnormalities and their respective patterns whether obstructive, restrictive or mixed were analyzed and presented as proportions with 95% confidence interval. Age, duration of illness, respiratory symptoms and RA disease activity (DAS28) were compared between patients with pulmonary function abnormalities and those with normal function using Student's t-test and

Mann Whitney U test. Gender, occupation, smoking history and use of DMARDS were associated with pulmonary function abnormalities using Chi square test or Fisher's exact test. Factors independently associated with pulmonary function abnormalities were determined using logistic regression model. All the statistical tests were performed at 5% level of significance (95% confidence interval).

12.2 QUALITY ASSUARANCE

The Research Assistants were trained personnel in spirometry. The Spirolab III is a Portable spirometry machine used in Primary care peripheral facilities. It has a Sensitivity of 84%, Specificity of 89%, diagnostic as per the Global Initiative in Obstructive lung disease (GOLD). For quality control the spirometer machine was calibrated as per the manufacturer's recommendations regularly. The results were automatically adjusted for age, sex, height, weight and race. Infection control practices including use of disposable mouth pieces, bacterial filters, cleaning/ disinfection of spirometer parts on manufacturer's recommendations and appropriate disposal of used mouth pieces were adhered to.

The Lung Tissue Research Consortium (LTRC) questionnaire is approved for use in evaluation of chronic respiratory diseases in epidemiological surveys, reproducible, valid and no bias.

The Disease activity Score (DAS 28) is used as a clinical index for assessment of rheumatoid disease activity in the clinical setting.

13.0 STUDY FEASIBILITY

Kenyatta National Hospital Rheumatology clinic (Thursday) has 130 registered RA patients, Aga Khan University Hospital (Friday) has 30 registered patients and Mater hospital (Wednesday) has 20 patients. All eligible patients were recruited so as to achieve sample size of 165.

All the clinics run on different days of the week, the Principal investigator together with the research assistants were able to cover the three clinics in a week. There are records of the patients and where need be, patients were called to the clinics to participate in the study and transport costs reimbursed.

14.0 ETHICAL CONSIDERATION

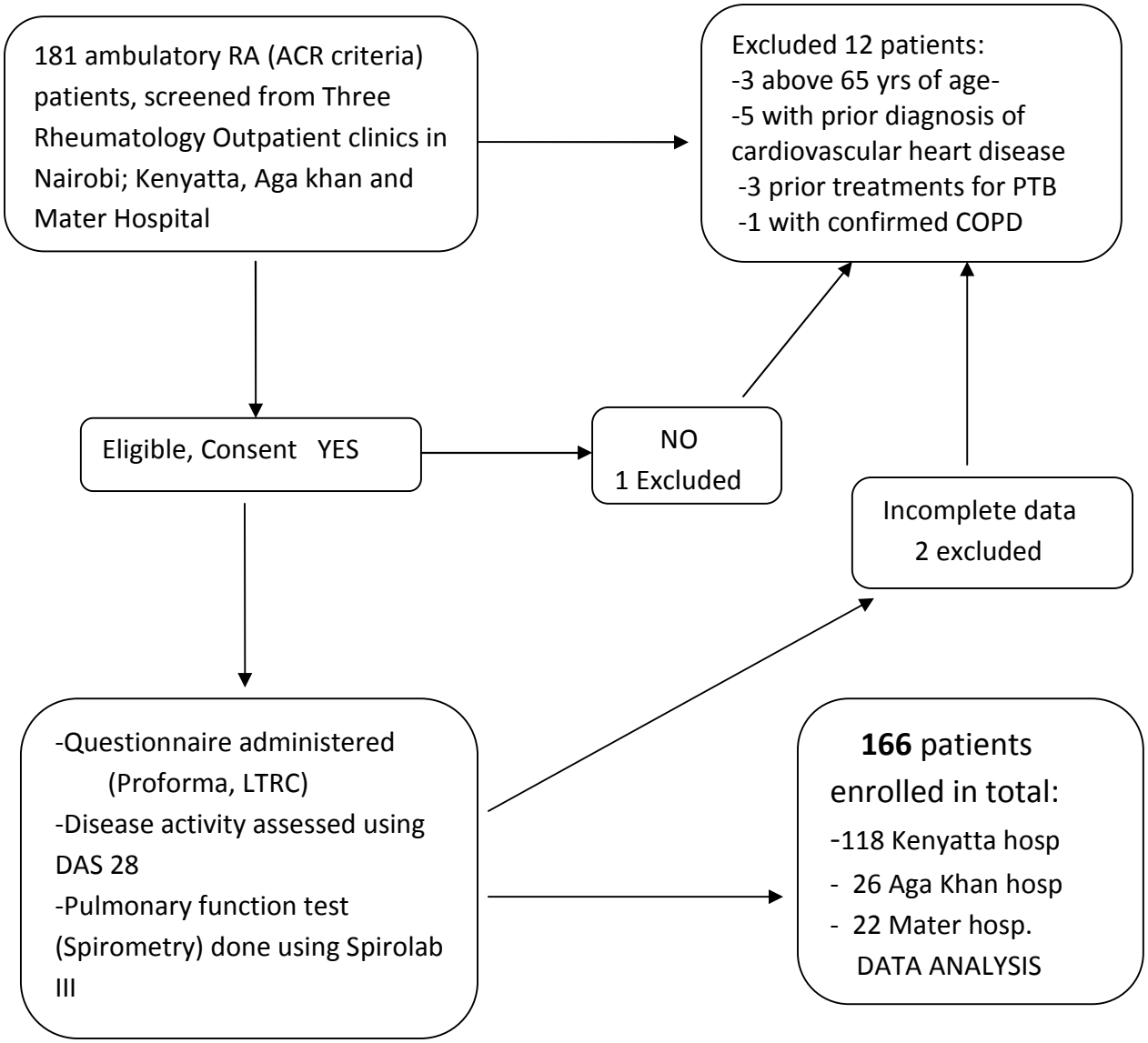
The study was approved by UON and the KNH Scientific and Ethical Review Committee. Only patients who gave informed consent and were eligible were recruited. Confidentiality was maintained.

Permission was sought and granted from the respective hospitals to carry out the study in their Rheumatology Clinics.

15.0 RESULTS

Flow diagram illustrating the data collection process

Figure 1: Patient's flow diagram



KEY:

RA- Rheumatoid Arthritis
ACR- American College of Rheumatology
LRTC- Lung Research Tissue Consortium
DAS 28- Disease Activity Score 28 joints
COPD- Chronic Obstructive Lung Disease
PTB- Pulmonary Tuberculosis

A total of 181 ambulatory rheumatoid arthritis patients from three Nairobi hospitals met the American College of Rheumatology classification criteria (2010) for RA and were screened for eligibility during the months of September 2012 to February 2013. This was done in the Rheumatology outpatient's clinics that took place on different days of the week. Consecutive sampling was done and 166 were recruited. One hundred and eighteen patients were recruited from Kenyatta National Hospital, twenty six from Aga Khan and twenty two from Mater hospital. Fifteen individuals were excluded: 3 above the age of 65years, 5 had prior history and a diagnosis of cardiovascular heart disease, 3 had been treated previously for Pulmonary TB and one already had a diagnosis of COPD. One declined to participate in the study and 2 were later on excluded due to incomplete data.

15.1 DEMOGRAPHIC CHARACTERISTICS

Out of the 166 patients recruited, 150 (90.4%) were female and 16 (9.6%) were male. Their ages ranged from 16 to 65 years with a mean of 47±13years. The patients who were married were 133 and those Single; including Widowed and Divorced were 33. Of these 64 (38.6%) were unemployed, 56 (33.7%) were in formal employment, 22 (13.3%) were farmers and 24 (14.4%) were in business.

A history of cigarette smoking was reported in 24 patients (14.4%) in which 6 (3.6%) were ex smokers, the rest, 18 (10.8%) were either exposed to cigarette smoking as current/active smokers; 3 (16.7%) or through spousal smoking; 15 (83.3%)

15.2 CLINICAL CHARACTERISTICS

15.2.1 RA DISEASE

Rheumatoid factor was positive in 104 (62.7%) and negative in 62 (37.3%). The median duration of RA illness was 5 years, ranging from 4 to 10. Patients who were on DMARDs were 129 (78%), 36 (21.7%) were on Steroids, while 27 (16.2%) patients on NSAIDS. Disease activity of the Rheumatoid Arthritis was evaluated using the DAS 28 score. The mean DAS28 score was 3.68 ± 1.5 with a range of 1.5-7.6. Majority of the patients 84 (50.6%) had mild disease activity (score of >2.6 - 3.2) while only 20 (12.0%) had their disease in remission (score of <2.6). Those with moderate disease activity were 41 (24.6%) patients, score of 3.2-5.1 and the ones with high

disease activity were 21 (12.6) with a score >5.1 as shown in figure 4. Erythrocyte Sedimentation Rate (ESR) had a median of 15 with a range of 5-40.

Table 1: Selected Demographic and Clinical characteristics of the study participants

Variables	N=166	%
Sex		
Male	16	9.6
Female	150	90.4
Age in years		
<30	21	12.6
30 - 39 years	37	22.2
40 - 49 years	39	23.4
50 – 59 years	49	29.5
60 – 65 years	20	12.0
Duration of disease		
<1 year	25	15.0
1 - 5 years	64	38.5
>5 years	77	46.3
Type of medication		
DMARDs	129	78.1
Steroids	36	21.6
NSAIDs	27	16.2
Type of DMARDS		
Methotrexate	96	57.8
HCQ + MTX	27	15.6
Eternecept	2	1.2
Leflunomide	4	2.4
Rheumatoid Factor		
Positive	104	62.6
Negative	62	37.4

15.2.2 RESPIRATORY SYMPTOMS

Respiratory symptoms were assessed using the LTRC questionnaire. The commonest symptom reported was Increased frequency of chest colds and chest illnesses in a year at 36.7%, followed by Cough at 33.7% and then production of Phlegm 15.7% while few reported Wheeze 10.7% and Breathlessness 2.4%.

Figure 2: Frequency of reported Respiratory symptoms

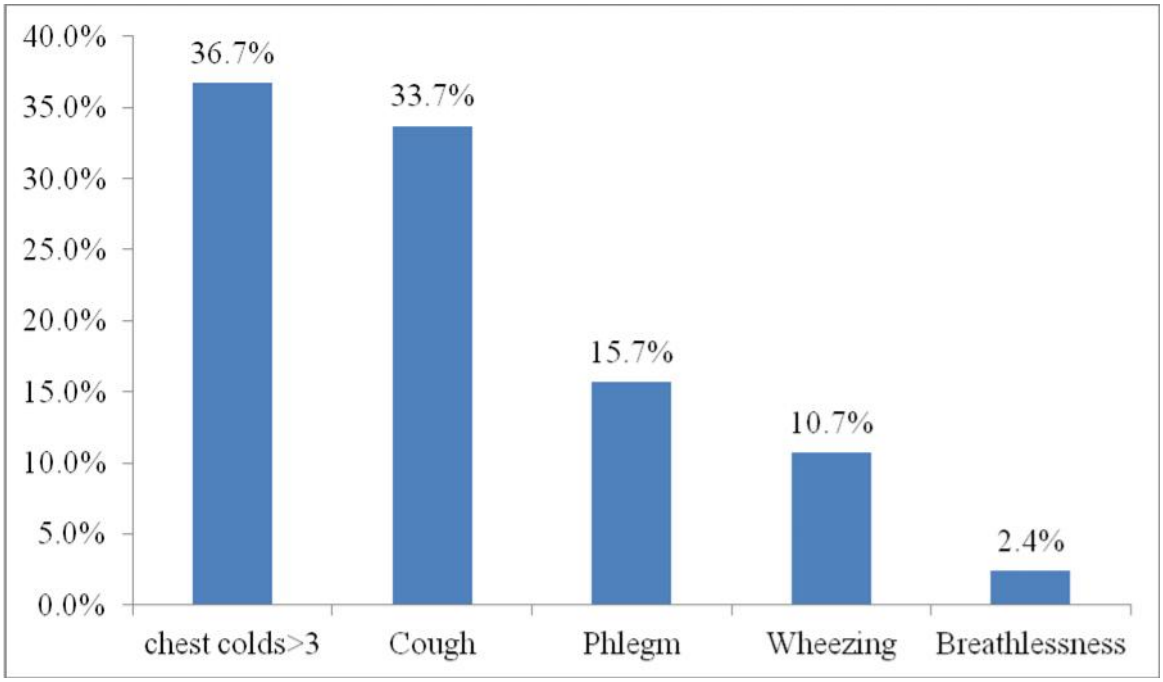
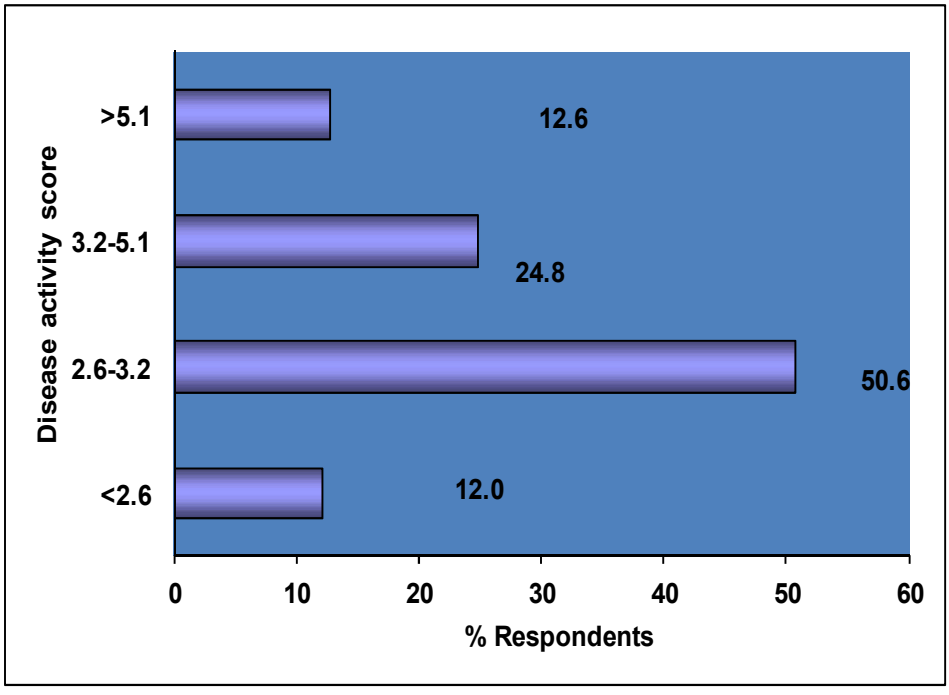


Figure 3: Distribution of RA disease activity (DAS 28)



15.3 PREVALENCE OF PULMONARY FUNCTION ABNORMALITIES

Pulmonary function tests were performed using the Spirolab 111 machine, of the 166 patients who underwent this test 64 (38.5%) were found to have abnormalities while 102 (61.4 %) were normal. Out of the 64 patients with abnormalities, 34 (20.4%) had Obstructive ventilatory defects, 28 (16.8%) had Restrictive defects, and 2 (1.2%) had a mixed obstructive and restrictive ventilatory defect as shown in Figure 4. Confidence intervals with median measurements in Table 2.

In terms of severity, majority of patients had mild ventilatory defects, in the patients who showed an Obstructive pattern, 28 (83.3%) had mild defects and only 6 (16.7%) had moderately severe defects, none had severe. While the ones with a Restrictive pattern, 17(60.7%) had mild defects, 10 (35.7%) moderately severe and 1(3.6%) had severe; Figure 5.

Table 2: Prevalence of PFTs abnormalities with confidence intervals.

Prevalence	**n (%)**	**95% CI of %**	**Median measurements**
Normal	102 (61.4)	53.0-68.1	-
Pulmonary function abnormalities	64 (38.5)	31.9- 47.0	-
Obstructive	34 (20.4)	15.7- 28.3	FEV_1/FVC 65%
Restrictive	28 (16.9)	11.4- 22.9	FVC 71%
Mixed	2 (1.2)	0.0- 2.4	-

Figure 4: Prevalence of PFTs abnormalities and patterns in RA patients

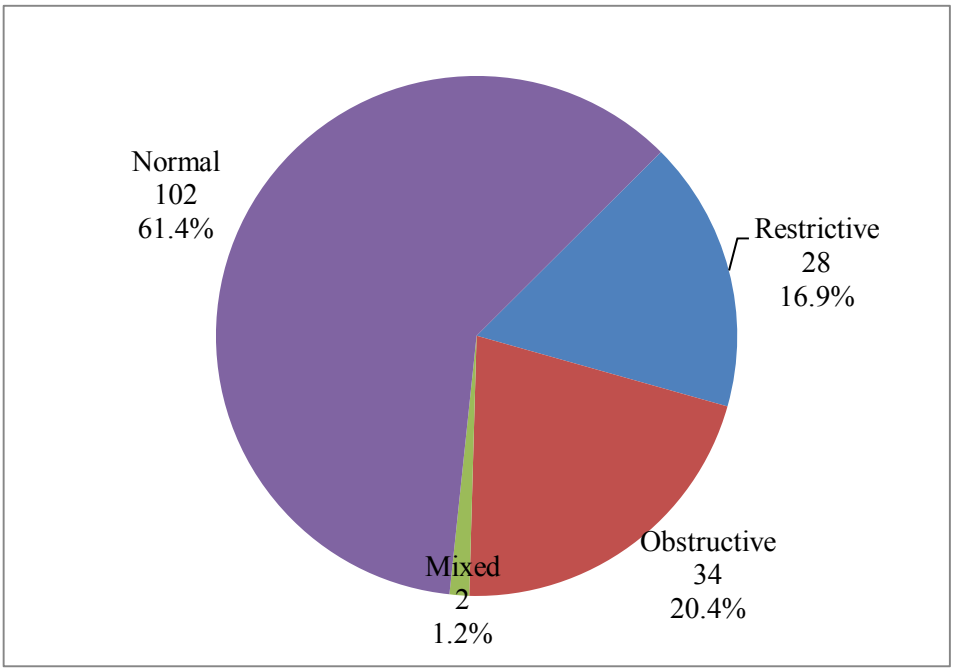
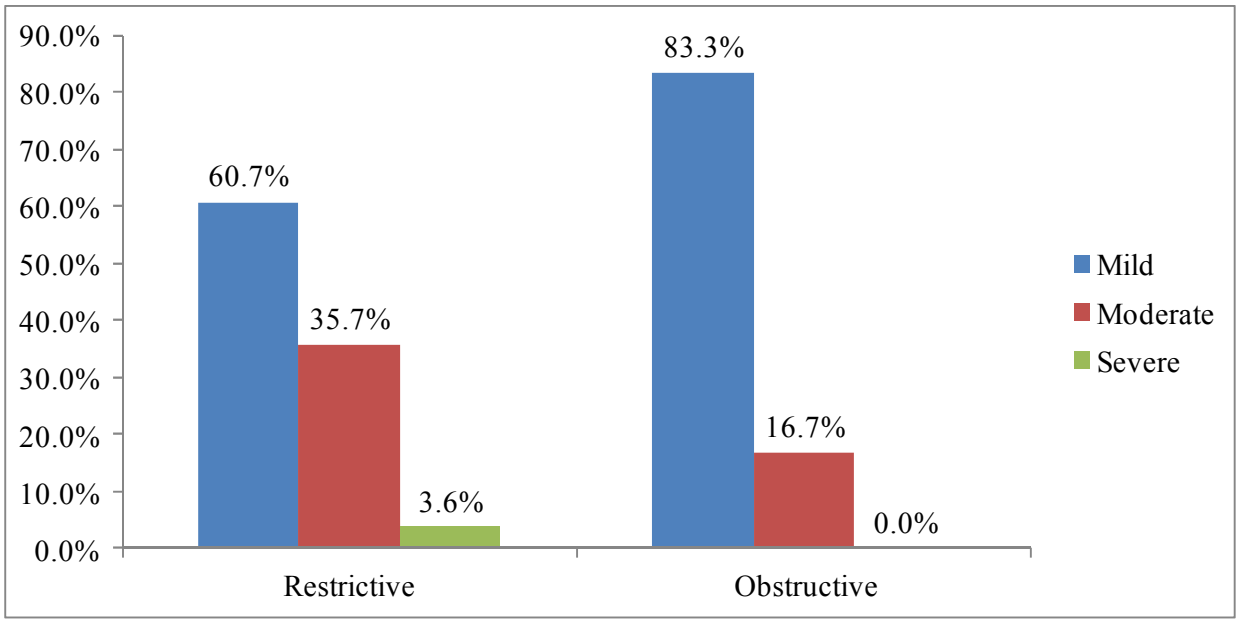


Figure 5: Severity of Restrictive and Obstructive Patterns identified.



15.4 DEMOGRAPHIC AND CLINICAL FACTORS ASSOCIATED WITH PFT ABNORMALITIES

Certain demographic and clinical factors were observed to be associated with pulmonary function abnormalities in this patient population. Those who showed abnormalities on PFT were significantly older in age; a mean age of 51 years for those who had pulmonary function abnormalities compared with 44.5 years with normal spirometry (p=0.003). No other differences were noted as regards demographic characteristics between patients with and without PFT abnormalities. Smoking history, though reported by few, 24 patients, had no relationship to the outcome (p=0.626). Among RA features, the variables shown to be associated with pulmonary involvement were seropositivity to rheumatoid factor, 47 out of the 64 patients with PFT abnormalities had positive rheumatoid factors (p= 0.03).

Fifty six patients with DAS 28 score of 3.2 to 7.6, depicting moderate to high disease activity, were observed to have abnormalities compared to 25 who had mild disease activity (p=0.001) . The ESR median value of 36.1 had abnormal spirometry compared with those at 11 who had normal (p=0.001). DMARDs or Steroids medications did not show any relationship to the outcome (p= 0.907, p=0.970 respectively). Therefore older age, positive rheumatoid factor, those with high to moderate disease activity score when evaluated with DAS 28 and those with a high ESR were more likely to have abnormalities in their pulmonary function testing as shown in Table 3.

Table 3: Factors associated with Pulmonary Function abnormalities

Variable	PF abnormalities	Normal	OR (95% CI)	P value
Sex				
Male	5 (7.7)	12 (10.9)	0.65 (0.2-2.1)	0.495
Female	59 (92.3)	90 (89.1)	1.0	
Age	51.0 (12.6)	44.5 (14.2)	-	**0.003**
Duration of illness (years)	5.0 (4.0-10.0)	5.0 (3.0-10.0)	-	0.168
Rheumatoid factor				
Positive	47 (72.3)	57 (56.4)	2.0 (1.0-3.9)	**0.039**
Negative	18 (27.7)	44 (43.6)	1.0	
Smoking				
Yes	8 (12.3)	10 (9.9)	1.3 (0.5-3.4)	0.626
No	56 (87.7)	92 (90.1)	1.0	
Smoking history				
Yes	4 (6.2)	2 (2.0)	3.3 (0.6-18.3)	0.211
No	60 (93.8)	100 (98.0)	1.0	
Disease activity				
Moderate to High dse activity (3.2-7.6)	56 (69.2)	6 (7.0)	29.5(11.9-76.7)	**<0.001**
Mild to No disease activity (1.5-3.1)	25 (30.8)	79 (92.9)	1.0	
ESR	36.1 (19.8)	11.0 (9.2)	-	**<0.001**
Medications				
Methotrexate				
Yes	34(52.3%)	62(61.4%)	0.7 (0.4-1.30)	0.248
No	30(47.7%)	38(38.6%)		
HCQ+MTX				
Yes	10(15.6%)	15(14.7%)	1.0 (0.5-1.8)	0.907
No	54(84.4%)	87(85.2%)		
Prednisolone				
Yes	14(21.5%)	22(21.8%)	1.0 (0.5-2.1)	0.970
No	50(78.5%)	80(78.2%)		
Occupation				
Unemployed	33 (50.8)	31 (30.7)	2.4 (1.2-5.2)	**0.020**
Formal employment	17 (26.2)	39 (38.6)	1.0	
Business	6 (9.2)	18 (12.9)	1.1 (0.3-3.3)	0.921
Farming	8 (12.3)	14 (13.9)	1.3 (0.5-3.7)	0.609

15.5 RESPIRATORY SYMPTOMS ASSOCIATED WITH PULMONARY FUNCTION ABNORMALITIES

As regards respiratory symptoms, Cough was reported in 36 (56.3%) patients with abnormal spirometry compared with 19 who had normal (p= 0.001), Phlegm was reported by 20 (31.0%) such patients compared with 6 patients (p= 0.001). A history of increased frequency of chest colds and chest illnesses (> 2 times in a year) was reported by 32 (50%) patients with pulmonary involvement compared with 20 who had normal test.((p=0.001) Hence respiratory symptoms observed to be associated with PFTs abnormalities were cough, production of phlegm and frequency of chest colds and illnesses as depicted in table 4.

Table 4: Associations between respiratory symptoms and pulmonary abnormalities

Variable	PFT	Normal	OR (95% CI)	P value
Cough				
Yes	36 (56.3%)	19 (18.7%)	5.6 (2.8-11.5)	**<0.001**
No	28 (43.7%)	83 (81.3%)	1.0	
Phlegm				
Yes	20 (31.0%)	6 (6.8%)	7.1 (2.6-18.7)	**<0.001**
No	44 (69.0%)	96 (93.2%)	1.0	
Wheeze				
Yes	3 (4.6%)	3 (2.9%)	1.6 (0.5-5.2)	0.352
No	61 (95.4%)	99 (97.1%)	1.0	
Breathlessness				
Yes	1 (1.5%)	3 (3.0%)	0.5 (0.1-5.0)	1.000
No	63 (98.5%)	99 (97.0%)	1.0	
Frequency of chest colds and illnesses				
Less than once a year	11 (17.2%)	43 (41.2%)	1.0	
Once a year	11 (17.2%)	24 (22.7%)	1.8 (0.7-4.9)	0.234
02-04 times per year	32 (50.0%)	29 (29.9%)	4.0 (1.7-9.3)	**0.001**
05 or more times per year	10 (15.6%)	6 (6.2%)	6.1 (1.8-20.4)	**0.004**

Figure 6 : Prediction of Respiratory Symptoms and PFT abnormalities

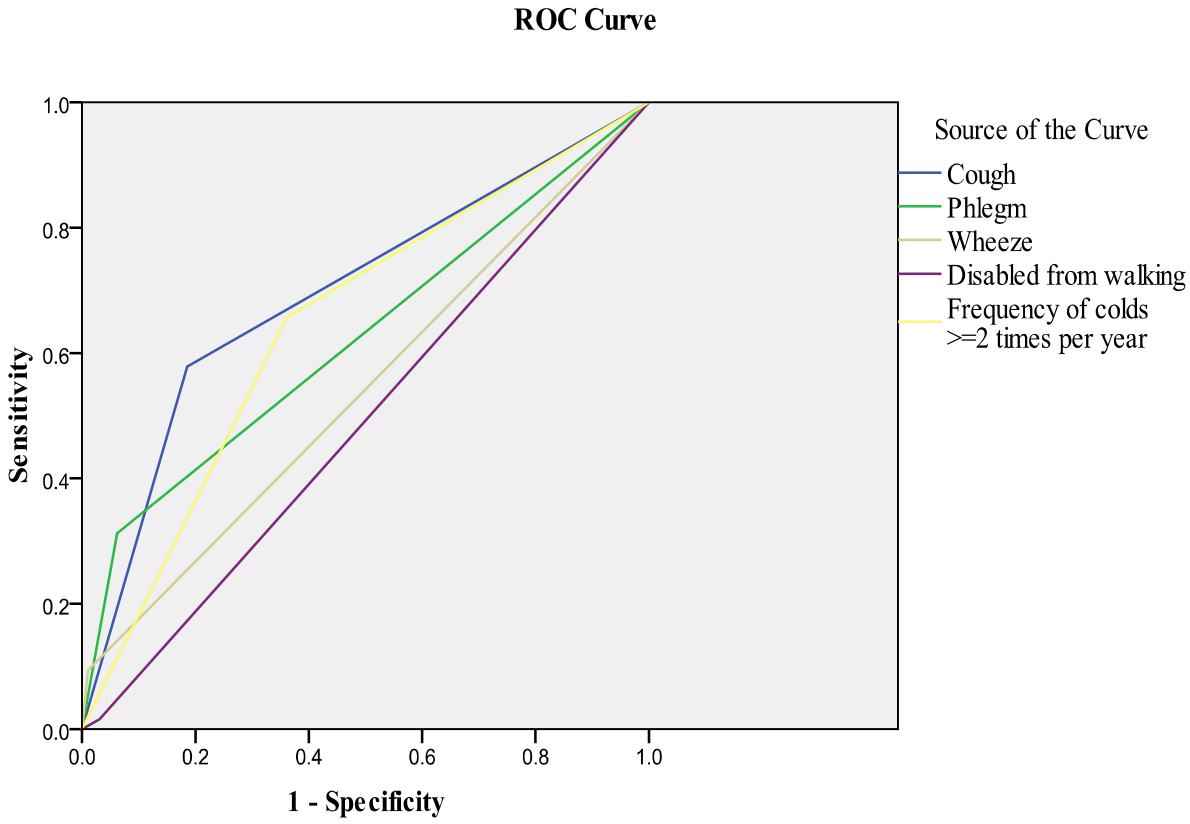
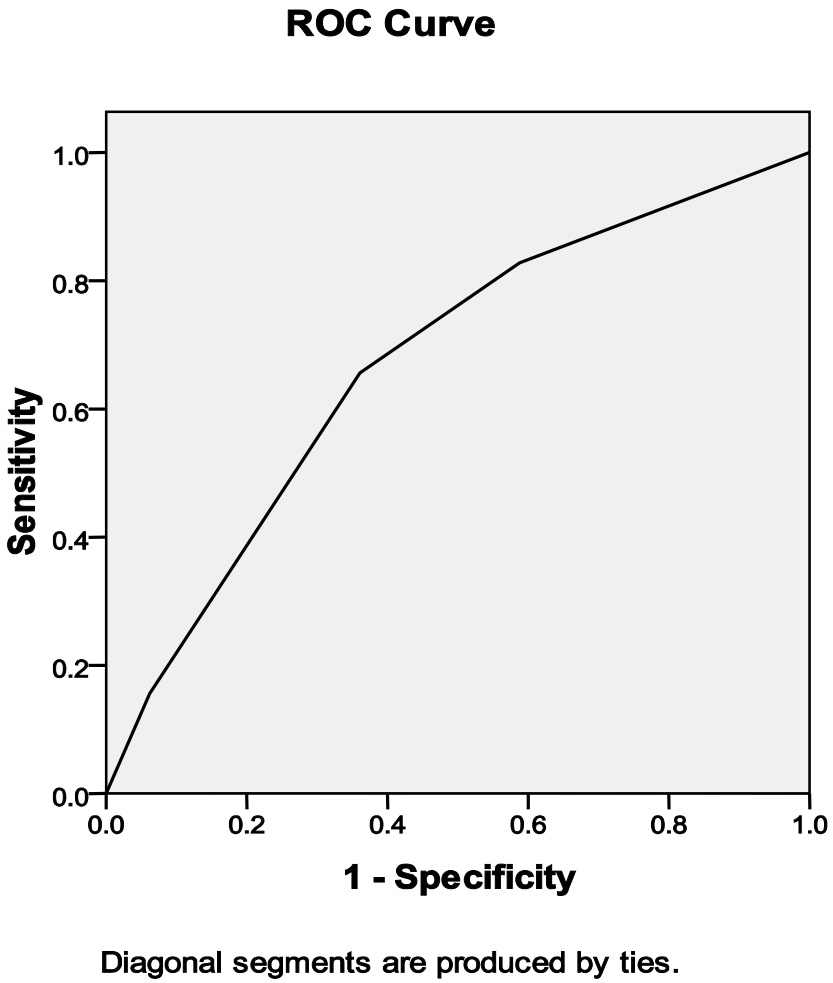


Table 5 : Respiratory symptoms and prediction for Pulmonary involvement.

Symptoms	**Sensitivity**	**Specificity**	**Area under the Curve**
Cough	57%	81%	0.70
Frequency of chest colds and illnesses >= 2 times per year	67%	64%	0.67
Phlegm	30.8%	94%	0.63
Wheeze	10%	99%	0.54
Disabled from walking by any condition	2%	97%	0.49

Figure 7: Frequency of chest colds and illnesses in a year and prediction for PFT abnormalities



AUC – 0.672

Table 6: Frequency of chest colds and illnesses and prediction for Pulmonary involvement

Category	Sensitivity	Specificity
Once a year	82%	41%
02-04 times per year	66%	64%
05 or more times per year	16%	94%

15.6 MULTIVARIATE ANALYSIS

On logistic regression analysis, the factors independently associated with pulmonary function abnormalities were age of patient (p= 0.010) and moderate to high disease activity; score of 3.2-7.6 (p= 0.025), as shown in Table 5.

Table 7: Factors independently associated with pulmonary function abnormalities

Variable	Crude OR (95% CI)		Adjusted OR	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	-	0.003	1.07 (1.02-1.12)	**0.010**
Positive Rheumatoid Factor	2.0 (1.0-3.9)	0.039	1.9 (0.6-5.8)	0.273
Moderate to High disease activity	29.4 (11.9-76.7)	<0.001	10.3 (1.3-78.9)	**0.025**
ESR	-	<0.001	1.16 (1.00-1.12)	0.051
Unemployment	2.4 (1.2-5.2)	0.020	1.28 (0.8- 4.9)	0.065

16.0 DISCUSSION

The aim of this study was to determine the prevalence of pulmonary function abnormalities in RA patients and certain correlates (clinical and demographic) in Rheumatoid arthritis patients attending Rheumatology clinics in Nairobi.

Our study took place in three Rheumatology Outpatient clinics in Nairobi that is in Kenyatta National hospital, Aga khan University and Mater hospital. All patients met the American College of Rheumatology criteria (2010) for RA, and were receiving standardized medical care. The total number of patients who were recruited into the study was 166; this is larger than the numbers recruited from previous local studies. This is because when using the ACR 2010 criteria for diagnosis of RA, more patients are diagnosed as compared to using the ACR 1987 criteria, which these studies did. Recruiting patients from three hospitals who run Rheumatology outpatient clinics, also helped to achieve the sample size.

The mean age of the study population was 47 years. This is expected because RA is a disease with onset from the third to fifth decades of life. Women were predominantly affected by the disease at 90.4% with a male to female ratio of 1: 9.3. Though this was higher than commonly reported (usually 1: 2.5), RA, like majority of other connective tissue diseases predominantly affects females. A local study done by Owino et al (2009) **[83]** found 86.7% were females with a male to female ratio of 1:6.5,which was slightly lower than what we observed possibly because our study was recruiting patients from the age of 16 years as compared to his at 18 years. RA has been shown to be common in younger women compared to younger males, but the difference diminishes as the age increases **[1].**

Majority of the patients 78.6 % were on DMARDs while 21.7% were on steroid therapy. Those patients not on DMARDS or steroids were mostly new referrals to the ROPC and diagnosed with RA during the study period while some were on NSAIDS alone. Most of our patients were on 1 DMARD at 60.2%, 15.6 % on 2 DMARDs and 1.2% were on biological DMARDs. This is comparable to a recent study by Kirui et al (2013) **[84]** which found 80% of RA patients in KNH on DMARDs, 61.3% of whom were on 1 DMARD, 17.5% on 2 DMARDs, 1.3% on 3 DMARDs, none on biologics. In contrast Owino et al observed that 46.7% of RA patients were on treatment with at least 1 DMARD, but this was a much earlier study, reflecting improvement

in the knowledge of healthcare workers in use of DMARDs hence prescribing them or probably the increased availability and affordability of the drugs.

The overall 6 month prevalence of pulmonary function abnormalities was 38.5% as measured by Spirometry and all our patients did not carry any prior pulmonary disease diagnosis. The predominant ventilatory defect was Obstructive pattern at 20.4%, followed by Restrictive pattern at 16.8% and least common being a mixed picture at 1.2%. When evaluation of severity was done majority of these patients had mild defects (83.3% in the obstructive pattern and 60.7% in the restrictive).

A study done by Pappas et al (2010) **[54]** in John Hopkins university in the United States of America found a prevalence of pulmonary function abnormalities at 28%, nearly a third of the patients he studied, commonest being obstructive pattern at 11.3%, followed by restrictive at 7.6%. He also identified 9.6% with an impaired DLCO. Notably is that the patients studied had a lower disease activity score at a median of 3.1 compared to our study which was at 3.68, depicting that our patients were symptomatic for RA and still had active disease. It has been shown pulmonary involvement is higher in the setting of severe RA disease [**4**].

In Africa Amir et al (2011) **[55]** studied 36 RA Egyptian patients and 64% of them demonstrated abnormalities in their pulmonary function tests, Mixed restrictive and obstructive pattern was commonest and reported in 11(30.6%), restrictive pattern at 8(22.2%) and obstructive pattern in 4 (11.1%). The mean Disease activity score in his study was 3.63, almost similar to ours, hence the high prevalence of pulmonary impairment but differed in the patterns observed. His study excluded patients who had been exposed to cigarette smoking, since smoking has been shown to be the most consistent independent risk factor predicting the development of ILD in RA in most studies [**31**]. This could explain the lower incidence of obstructive pattern in his study as compared to our study which included 24 patients exposed to cigarette smoking.

The present study found the prevalence of obstructive ventilatory defect to be the most common at 20.4%. This was an important finding since other studies have solely set out to find the prevalence of obstructive dysfunction in small airways in RA.

In France,Thierry et al (1998) **[51]** found an obstructive pattern of lung changes in 18% of RA patients using spirometry, He found no significant difference in the proportion of airflow obstruction among smokers and non smokers suggesting a minor role of tobacco smoke in such

manifestations. This was also observed in our study where exposure to cigarette smoke had no relationship with the outcome (p=0.626), though we only had a small number of our patients exposed to cigarette smoking. A case control study by Vergnenegre et al **[52]** reported a 16% prevalence of airway obstruction (verses 0% in matched controls). A recent one by Shunsuke et al (2010) **[53]** found this to be 30.3%, after excluding 18% of the patients who had abnormalities in their HRCT indicative of interstitial lung disease. However, he included a significant number of smokers.

The reason for the high prevalence of PFTs abnormalities in our study is possibly due to ongoing RA disease activity. However the study took place in Sub-saharan Africa where environmental pollution and the use of biomass as fuel is common. These are known to cause deterioration in the physiological lung function and though not assessed in our study, may have contributed to our results [**85,86**].

From this study, older age was shown to be associated with pulmonary abnormalities (p = 0.010), the mean age of those affected was 51yrs compare to 44 with normal tests. On the other hand, we could not get any conclusion regarding sex of the patients since we only included 16 male patients. Exposure to cigarette smoking, though depicted, showed no relationship to outcome, possibly due to the small numbers. Other factors that were shown to associate with pulmonary function abnormalities were seropositivity to Rheumatoid factor (p=0.039), unemployment (p=0.02), moderate to high score on disease activity (p=<0.001) and ESR (p=0.001). These potentially significant parameters were tested for possible interrelationship by logistic regression analysis. Age remained an independent factor, the older the patient the more likely she had pulmonary involvement (p=0.010). Presence of disease activity as measured by DAS 28; clinical index of joint tenderness and swelling, also remained an independent factor. Patients who had a high and moderate score were more likely to have abnormalities in their tests (P = 0.025).

These findings are comparable to Amir et al **[55]** who observed that pulmonary abnormalities by PFT or HRCT were associated with older age and the RA clinical features that proved to associate with pulmonary involvement were joint tenderness index, duration of morning stiffness, and clinical disease severity. Pappas et al **[54]** did not find any age correlation, but observed that seropositivity to rheumatoid factor, presence of high titres of anti CCP antibodies

and ongoing steroid therapy were associated with abnormalities in pulmonary function and identified patients in need of further pulmonary evaluation. These could well infer that symptomatic RA disease and/or disease severity was associated with pulmonary involvement because these are serological markers of disease activity hence supporting our findings. We did not evaluate for disease severity with the use of radiological score (hand and feet x-rays) or serology markers such as anti-CCP as these studies did, instead we used the disease activity score and ESR. As regards the higher pulmonary abnormalities in the older age group, possible explanation could be longer duration of exposure to symptomatic RA disease with late diagnosis. In this study duration of RA disease was not clinically significant (p=0.168), this was from the time the patients were diagnosed to have RA. It could well be that they were symptomatic much earlier but were treated for various other diseases hence a late diagnosis.

As might be expected, respiratory symptoms were statistically more significant in patients with abnormal PFTs. Presence of cough in 56.9% (P=0.001), increased number of chest colds and illnesses in a year (2-4times a year) reported by 50% (p=0.001) and production of phlegm by 30.8% were found to be significant. Receiver operator characteristic (ROC) curve was constructed to examine the ability of pulmonary symptoms to predict PFTs abnormalities. Area under the curve values for cough was 0.70, frequency of chest colds in a year 0.67, and production of phlegm 0.63 hence these symptoms were found to be predictive.

Our findings were in contrast with Amir et al **[55]** who reported that among respiratory symptoms, dyspnea and cough were associated with any pulmonary abnormalities. He went further to elucidate that when specific pulmonary abnormalities were considered, dyspnoea was identified as predictor for restrictive pattern and for obstructive, both cough and wheezing provided valid prediction. Pappas et al **[54]** found chronic cough was predictive of obstructive pattern, breathlessness for restrictive and chronic phlegm for impaired gas transfer.

Our study did not look at these predicitions individualy, we however went further to characterize the increased frequency of chest colds and illnesses in a year, which was found to be significant in the present study compared to the ones mentioned. The different environments where each study took place could explain these findings. Our study was in the African tropics where the climatic conditions, environmental pollution and presence of communicable diseases may predispose the patients to experience frequent chest colds and illnesses in a year. Micro injuries to the alveoli caused by these factors initially leads to inflammation that may be self limiting in

normal individuals but may proceeds to fibrosis if unchecked in RA patients [**28,29**]. From this finding, a possible preventive role of the influenza and pneumococcal vaccine could be incooperated into patient care. This has already been endorsed by the British rheumatology society but can be strengthened by our study. The possibility of already existing pulmonary disease from childhood as a risk factor was ruled out since none of our patients reported this.

Although some anti-rheumatic drugs can cause lung damage, we did not find any significant correlation between the use of any drug and the presence or severity of lung affection. The drugs were as follows, Methotrexate($p=0.248$), Methotrexate in combination with Hydroxychloroquine (0.607) and Steroid therapy ($p=0.670$). This may be due to the dosing of the drugs; all the patients on methotrexate did not exceed 20mg per week. Doses higher than this are known to cause pulmonary toxicity [**74**].

19.1 CONCLUSION

We observed a high prevalence of pulmonary function abnormalities as measured by spirometry in this RA population. The commonest ventilator defect pattern was obstructive followed by restrictive. In terms of severerity most of the ventilatory defects were mild. There was an increased frequency of reported respiratory symptoms in RA patients with abnormal tests. Rheumatoid disease activity, older age and respiratory symptoms were identified as predictors of physiological pulmonary impairment as determined by Spirometry.

19.2 LIMITATIONS

1. PFTs are not the gold standard for detecting respiratory disease. We chose to use PFTs as our marker of lung disease in this analysis as they provide a common and low-risk diagnostic modality that often precedes radiographic evaluation in clinical practice. Using a more sensitive imaging modality e.g High resolution chest computed tomography might strengthen our associations by identifying parenchymal abnormalities in patients who reported symptoms but were found to have normal PFTs.
2. Recruitment of patients from a university hospital rheumatology department could introduce some bias through selection of patients with more severe articular involvement than that in the overall RA population.

19.3 RECOMMENDATIONS

Pulmonary involvement is an important part of the systemic affection of RA.
The role of surveillance for lung disease in patients with RA is clear and necessary. Rheumatologists and internists should routinely screen patients for pulmonary involvement to aid in early detection and intervention.
Respiratory symptoms, older age and ongoing disease activity can identify patients in greatest need of further pulmonary evaluation.

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Appendix 1

RHEUMATOID ARTHRITIS DIAGNOSIS CRITERIA

In 2010 the *2010 ACR / EULAR Rheumatoid Arthritis Classification Criteria* were introduced.

The "new" classification criteria, jointly published by the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) establish a point value between 0 and 10. Every patient with a point total of 6 or higher is unequivocally classified as an RA patient, provided he has synovitis in at least one joint and given that there is no other diagnosis better explaining the synovitis. Four areas are covered in the diagnosis:

- Joint involvement, designating the metacarpophalangeal joints, proximal interphalangeal joints, the interphalangeal joint of the thumb, second through third metatarsophalangeal joint and wrist as *small joints*, and elbows, hip joints and knees as *large joints*:
    - Involvement of 1 large joint gives 0 points
    - Involvement of 2-10 large joints gives 1 point
    - Involvement of 1-3 small joints (with or without involvement of large joints) gives 2 points
    - Involvement of 4-10 small joints (with or without involvement of large joints) gives 3 points
    - Involvement of more than 10 joints (with involvement of at least 1 small joint) gives 5 points
- Serological parameters – including the rheumatoid factor as well as ACPA – "ACPA" stands for "anti-citrullinated protein antibody":
    - Negative RF *and* negative ACPA gives 0 points
    - Low-positive RF *or* low-positive ACPA gives 2 points
    - High-positive RF *or* high-positive ACPA gives 3 points
    -
- Acute phase reactants: 1 point for elevated erythrocyte sedimentation rate, ESR, or elevated CRP value (c-reactive protein)
- Duration of arthritis: 1 point for symptoms lasting six weeks or longer

Appendix 2: Consent Form *: **Consent Explanation before Recruitment***

I am Dr. Irene Biomdo a postgraduate student in Internal Medicine at the University Of Nairobi. I would like to inform you that I am conducting a study on 'Assessment of Pulmonary Function in Rheumatoid Arthritis Patients". The study aims at determining the prevalence and type of pulmonary function abnormalities in RA. If significant, the instruments used here will be integrated into the routine clinical management of Rheumatoid Arthritis for early recognition and intervention of lung disease. I would also like to inform you that:

Joining the study is voluntary and no payments will be charged to you for any investigations done due to participation in the study.

Participation in the study will not delay your treatment in any way and will be beneficial to you because this study will detect if you have any lung involvement due to your rheumatoid illness and hence alert the treating consultant on need for further evaluation and management of the chest condition.

You may decline to participate in the study or drop out at will and this will not lead to any denial of treatment or any form of care in the hospital.

Once you agree to participate in the study, you will answer questions of personal nature as laid in the study questionnaire; I will carry out a full physical examination and then perform Spirometry on you. This is a procedure where you are to inhale deeply and then blow the air from your lungs into the disposable mouth pieces. Any results obtained will be communicated to your primary physician and in case of any abnormality in your lung function, appropriate further investigations and possible referrals to a chest physician will be done.

If you have not yet had any blood workup to check disease activity e.g Rheumatoid Factor and ESR, with your consent I will perform them. You will feel a little pain as is normal with standard phlebotomy and the amount of blood drawn will not affect your health.

During the physical examination, depending on the clinical findings you may be requested to have certain radiological tests e.g chest x-ray and bone x-ray done. These will be beneficial in excluding certain pulmonary diseases. You will not be required to pay for these additional tests.

The information obtained from you will be treated with utmost confidentiality. Any publications arising out of the study will not identify you. If you have understood the information that we have given you and you are willing to participate in the study, you will be required to sign a form indicating your willingness to be recruited.

If you have any questions about this study, you may contact

Dr. Irene Biomdo Tel: 0722 978 550

Dr. Omondi Oyoo. Dept of Internal Medicine. Tel: 020-2725452

The Chairman, KNH/UoN Ethics Research Committee. Tel: 020-2726300 Ext 44355

STATEMENT OF CONSENT BY THE PATIENT

The purposes of this study, procedure, study benefits and my rights have been fully explained to me. I hereby give my written consent to allow myself …… to participate in the study.

NAME:…… SIGNATURE: ……

DATE: …….

WITNESS …… SIGNATURE: ……

DATE: ……..

INTERVIEWER'S STATEMENT

I have explained the purpose and benefits of this study to the respondent. To the best of my knowledge and conviction, he / she has understood and has given consent.

INTERVIEWER: …… SIGNATURE: ……..DATE: ……

Appendix 3：　　QUESTIONNARE

Part 1

1. STUDY PARTICIPANT NUMBER: …….

2. SOCIAL DEMOGRAPHIC STATUS:

SEX:

AGE:

OCCUPATION:

2. RHEUMATOID ARTHRITIS DISEASE:

- Duration of illness:

- Rheumatoid Factor:

- Cigarette smoking: 1. Active smoker

2. Passive smoker - Husbands smokes

- History of smoking; If Yes, How many months ago-

How many years ago-

- Medication used (DMARDS):

LUNG TISSUE RESEARCH CONSORTIUM (LTRC)

SYMPTOM QUESTIONNAIRE

ID Number:	0	0		-					-	
Letter Code:										
Form Type:	S	Q	0	1						

1. Date of Interview: __ __ - __ __ - 2_ _ _ _ (Month, Day, Year) vis_dt

I. COUGH

These questions pertain mainly to your chest. Please answer YES or NO. If you are in doubt about whether your answer is YES or NO, then answer NO.

		Yes	No	
1.	Do you usually have a cough? (Count a cough with first smoke or on first going out-of-doors). Exclude clearing your throat.	(1)	(2) **If NO, go to Question 3.**	cough
2.	Do you usually cough as much as 4 to 6 times a day, 4 or more days out of the week?	(1)	(2)	coughdy
3.	Do you usually cough at all on getting up, or first thing in the morning?	(1)	(2)	cougham
4.	Do you usually cough at all during the rest of the day or night?	(1)	(2)	coughpm
	If YES to any of questions 1-4, go to Question 5. If NO to all questions, go to Part II.			
5.	Do you usually cough like this on most days for three consecutive months during the year?	(1)	(2)	coughmo
6.	For how many years have you had this cough?	__ __ Years		coughyrs

ID Number:	0	0		-					-	
Letter Code:										
Form Type:	S	Q	0	1						

II. PHLEGM

		Yes	No	
1.	Do you usually bring up phlegm from your chest?	(1)	(2) ↓	phlegm

Count phlegm with the first smoke or on first going out-of-doors. Exclude phlegm from the nose. Count swallowed phlegm.

If NO, go to Question 3.

2.	Do you usually bring up phlegm like this as much as twice a day, 4 or more days out of the week?	(1)	(2)	phlegmdy
3.	Do you usually bring up phlegm at all on getting up, or first thing in the morning?	(1)	(2)	phlegmam
4.	Do you usually bring up phlegm at all during the rest of the day or at night?	(1) ↓	(2) ↓	phlegmpm

If YES to any of questions 1-4, go to Question 5. If NO to all, go to Part III.

5.	Do you bring up phlegm like this on most days for three consecutive months or more during the year?	(1)	(2)	phlegmmo
6.	For how many years have you had trouble with phlegm?	__ __ Years		phlegmyr

III. EPISODES OF COUGH AND PHLEGM

If question 1 in Part I was answered NO, go to Part IV.

		Yes	No	
1.	Have you had periods or episodes of increased cough and phlegm lasting for three weeks or more each year?	(1)	(2) ↓	epiwks

If NO, go to Part IV.

		epiyrs	epiyr_dk	
2.	For how long have you had at least one such episode per year?	__ __ Years	Don't Know (1)	

ID Number:	0	0		-					-	
Letter Code:										
Form Type:	S	Q	0	1						

IV. WHEEZING

		Yes	No	
1.	Does your chest ever sound wheezy or whistling?			
	A. When you have a cold?	(1)	(2)	cold
	B. Occasionally, apart from colds?	(1)	(2)	nocold
	C. Most days or nights?	(1)	(2)	wheeze

If NO, to all of the above, go to Question 3.

2.	For how many years has this been present?	__ __ Years	wheezyrs
3.	Have you ever had an attack of wheezing that has made you feel short of breath? (1) (2)		shrtbr

If NO, go to Part V.

4.	How old were you when you had your first attack?	__ __ Years	shrtbrag
5.	Have you had two or more such episodes? (1) (2)		shrtbr2
6.	Have you ever required medicine or treatment for the(se) attack(s)? (1) (2)		shrtbrrx
7.	Have you had an attack of wheezing that has made you feel short of breath in the past year? (1) (2)		shrtbryr

If NO, go to Part V.

8.	Have you had two or more such episodes in the past year? (1) (2)		shrbryr2
9.	Have you required medicine or a treatment for the(se) attack(s) in the past year? (1) (2)		shrbrrx2

V. BREATHLESSNESS

		Yes	No	
1.	Are you disabled from walking by any condition OTHER than heart or lung disease?	(1)	(2)	cantwalk
	If YES, please describe the nature of the condition(s):			walk_sp
	A. _____			
	_____			
	_____			
	_____			

ID Number:	0	0		-					-	
Letter Code:										
Form Type:	S	Q	0	1						

2. The following questions are designed to determine how much work would make you short of breath. Please answer each question. If you use supplemental oxygen please answer each question as though you are NOT using your oxygen.

		Yes	No	
A.	Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?	(1)	(2)	shrbrhil

If NO to A, go to Part VI.

		Yes	No	
B.	Do you have to walk slower than people of your age on the level because of breathlessness?	(1)	(2)	walkslow
C.	Do you ever have to stop for breath when walking at your own pace on the level?	(1)	(2)	walkstop
D.	Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level?	(1)	(2)	walkdist
E.	Are you too breathless to leave the house or breathless on dressing or undressing?	(1)	(2)	cantleav

VI. CHEST COLDS AND CHEST ILLNESSES

1. How often do you get colds? oftcold

   Less often than once a year (1)
   Once a year (2)
   2-4 times per year (3)
   5 or more times per year (4)

If LESS THAN ONCE A YEAR, go to Question 5.

		Yes	No	
2.	Do your colds usually go to your chest? ("Usually" means more than half the time).	(1)	(2)	chstcold

3. How often did you get colds in the past 12 months? oftcold2

   Not at all (1)
   Once (2)
   2-4 times (3)
   5 or more times (4)

If NOT AT ALL, go to Question 5.

ID Number:	0	0		-					-	
Letter Code:										
Form Type:	S	Q	0	1						

4. Did your colds in the past 12 months usually go to your chest? ('Usually' means more than half the time).

Yes (1) No (2) chstoft

5. During the past 12 months, have you had any chest illnesses that have kept you off work, indoors at home, or in bed?

Yes (1) No (2) chstyr

If NO, go to Question 8.

6. Did you produce phlegm with any of these chest illnesses? (1) (2) chstphlm

7. In the past 12 months, how many such illnesses, with (increased*) phlegm, did you have which lasted a week or more? chstnbr

*(for persons who usually have phlegm)

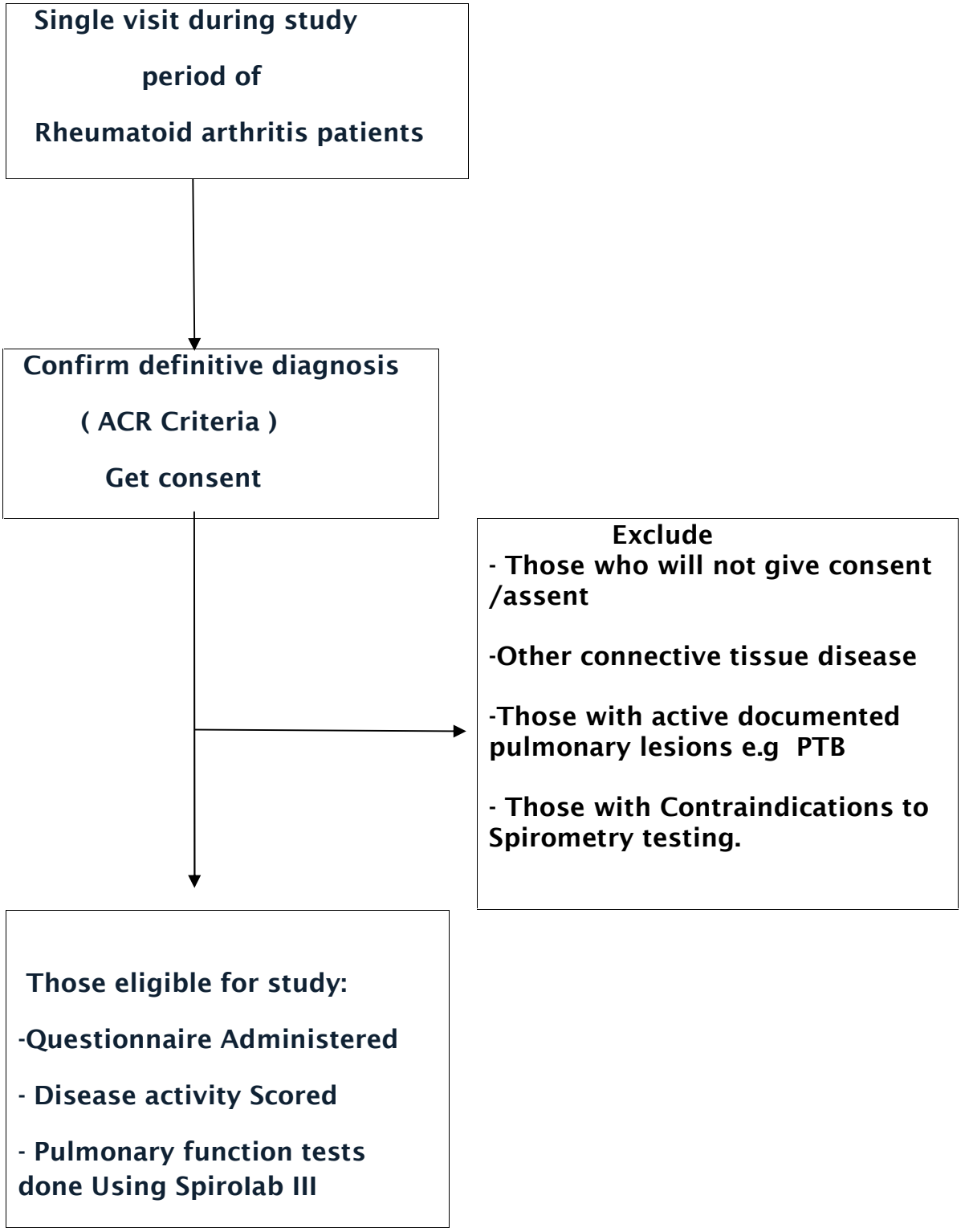
___ ___
No. of illnesses

8. Did you have any lung trouble before the age of 16? Yes (1) No (2) lungl6

9. Did you have any chest illness before the past 12 months? (1) (2) chsill12

A. If YES to question 9, specify: _____ chill_sp

Appendix 4: FLOW CHART OF DATA COLLECTION



Appendix 5*:* Das28 Form

Study participant no…….. ***Date of Birth ……-……-……..*** ***Gender*** …….

Date ……-…

	Left		***Right***	
	Swollen	tender	Swollen	Tender
Shoulder				
Elbow				
Wrist				
MCP 1				
2				
3				
4				
5				
PIP 1				
2				
3				
4				
5				
Knee				
Subtotal				

Total	swollen		Tender	

No disease activity high disease activity

Swollen (0-28)	
Tender (0-28)	
ESR	
VAS disease activity (0-100mm)	

DAS28 = 0.56*√(t28) + 0.28*√(sw28) + 0.70*Ln(ESR) + 0.014*VAS