Clinical Profile of Rheumatoid Arthritis associated interstitial lung disease at a tertiary hospital in KwaZulu-Natal, South Africa: A retrospective 5 year review.

By

Hosam Mohamed Ghammo

Submitted in partial fulfillment of the academic requirements

for the degree of MMed

in the Department of internal medicine

School of Clinical Medicine

College of Health Sciences

University of KwaZulu-Natal

Durban

2020

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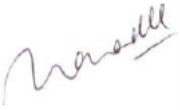
Signed: 

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I Hosam Mohamed Ghammo declare that:

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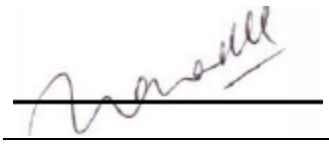
Supervisor Signature:  Date: 11-05-2020

Acknowledgements

I would like to sincerely thank my parents, wife, children, supervisors and Nelson R Mandela School of Medicine, University of Kwazulu-Natal for creating the research environment and completion of this research successfully.

Overview of the Thesis

Back ground of the study

Rheumatoid arthritis (RA) is a multi system inflammatory autoimmune disease affecting approximately 1% of the general population.[1] Interstitial lung disease (ILD) is one of the commonest primary pulmonary manifestations of RA. Rheumatoid arthritis is commoner in females, however males are more affected in RA-ILD with a male to female ratio of 2:1 in some studies.[3] The onset of RA-ILD typically occurs in the fifth decade of life.

Age and smoking have been shown to be risk factors for the development of ILD[4] and high titres of Rheumatoid factor (RF) and Anti citrullinated antibodies (anti-CCP) are a known risk factor for extra-articular manifestations of rheumatoid arthritis, including ILD. Most patients with RA-ILD present with symptoms of dyspnoea or cough.

A restrictive pattern on pulmonary function testing (PFT) is the most common pattern noted on spirometry in the majority of patients with RA-ILD, with or without a decrease in diffusing capacity of the lung for carbon monoxide (DLCO).

In RA a variety of patterns are seen on High Resolution Computerised Tomography (HRCT) scans, with the most common being usual interstitial pneumonia (UIP), which occurs in 40–62% of cases. Non specific interstitial pneumonia (NSIP) is the second most common pattern, occurring in approximately11–32% of patients. Other types of patterns seen in RA-ILD include organising pneumonia, diffuse alveolar damage (DAD), lymphocytic interstitial pneumonia (LIP) and desquamative interstitial pneumonia (DIP). However these are less frequent.

Currently, there have not been enough randomised controlled trials comparing medications for the treatment of RA-ILD. Corticosteroids are still the mainstay of therapy, particularly for cases of NSIP, organizing pneumonia or acute flare up of UIP. Cyclophosphamide, azathioprine and cyclosporine have been used with varying degrees of success.

There is a paucity of literature regarding RA-ILD in sub Saharan Africa and its demographic distribution as well as relationship to HIV. The aim of this study was to review the demographic

data, PFT and HRCT scan pattern and treatment outcomes at a quaternary hospital in Durban, KwaZulu Natal, South Africa.

Methods

This was a retrospective electronic chart review. Patients 18 years and older referred to Inkosi Albert Luthuli Central Hospital pulmonology clinic diagnosed with RA-ILD between January 2010 and December 2015 were included in the study.

Demographic and clinical data, as well as data from special investigations, were captured retrospectively from medical records. Demographic data included age, gender and race. Clinical data captured were presenting symptoms, pre-existing medical conditions, current functional class, date of onset of initial symptoms, and treatment. Special investigations captured included results of HRCT, rheumatoid factor level, anti-CCP levels and PFT.

Ethical approval was granted by the University of KwaZulu-Natal's Human Research Ethics Committee (ref. no. E044/2018).

Statistical analysis

Demographic data with a normal distribution such as age, gender and race are reported as means with standard deviation (SD). Fishers exact test was used for categorical variables. Statistical significance was regarded as a p-value <0.05 unless otherwise stated. Continuous variables are presented as mean SD.

Change in symptoms between initial visit and last visit for cough, dyspnoea, forced expiratory volume in 1 second (FEV1), or forced vital capacity (FVC), was classified as worse or improved/or static. Chi square or Fisher's exact test was used to compare the change by categorical data such as treatment. Initial mean FEV1 and FVC were compared by categories of RF and anti CCP using Mann-Whitney tests. Changes in FEV1 and FVC were coded as worse if the percentage difference change was 10% or more. Changes by treatment medications were analysed using Fisher's exact test. Pairwise comparisons were then done using azathioprine as a reference category using Fisher's exact tests. Data was analysed using Stata V13 statistical software.

Results. There were 61 subjects, the majority being female (90.2%). Approximately 86.9% were 50 years and older. The majority of the subjects were Indian 72.1% (n=44), followed by Black Africans 23% (n=14) and then Whites 4.9% (n=3). All patients were HIV negative. Patients treated with a combination of prednisone and azathioprine had a decline in FVC (p value 0.04). There was no improvements or deterioration in patients treated with either drug alone.

Conclusion.

This is the first study to our knowledge, in South Africa, to study the demographics and treatment of RA-ILD. The majority of patients with RA-ILD at IALCH are of Indian descent, contrary to the population demographics of the country which is greater than 80% Black African. Active treatment of RA-ILD with prednisone, azathioprine or both combination appears to have had no positive impact on symptoms or PFT. However, these results must be interpreted with caution in light of this being a retrospective study with its significant shortcomings.

The management of RA-ILD is still a challenge. The combination of azathioprine and prednisone did not arrest disease progression in our study while either agent alone did not improve clinical and lung function parameters. Large randomised control studies are needed in Sub-Saharan Africa.

Table of Contents

List of Abbreviations

RA-Rheumatoid Arthritis.

ILD-Interstitial Lung Disease.

RA-ILD-Rheumatoid Arthritis associated Interstitial Lung Disease.

RF- Rheumatoid Factor.

PFT- Pulmonary Function Testing.

DLCO-Diffusing Capacity of the Lung for Carbon Monoxide.

HRCT- High Resolution Computerised Tomography Scan.

UIP- Usual Interstitial Pneumonia.

NSIP- Non Specific Interstitial Pneumonia.

LIP- Lymphocytic Interstitial Pneumonia.

DIP -Desquamative Interstitial Pneumonia.

DIP-Diffuse Alveolar Damage.

SD- standard deviation.

FVC-Forced Vital Capacity

FEV1- Forced Expiratory Volume in 1 Second.

BAL- BronchoAlveolar Lavage.

GGOs- Ground Glass Opacities.

BO- Bronchiolitis Obliterans.

MMP-Matrix Metallo Proteases.

OP-Organizing Pneumonia.

IALCH-Inkosi Albert Luthuli Central Hospital.

SA-South Africa.

HIV-Human Immunodeficiency Virus.

List of Tables and Figures

Part 1

Chapter One

Introduction

Rheumatoid arthritis(RA) is a multi system autoimmune disorder that commonly affects the joints, causing progressive, symmetric, erosive destruction of joints and bone, which is usually associated with auto antibody production (1). Rheumatoid arthritis affects approximately 1% of the general population. The incidence and prevalence of rheumatoid arthritis in developing countries is thought to be lower. Although joint disease is the main presentation, there are a variety of extra-articular manifestations including subcutaneous nodules, vasculitis, inflammatory eye disease and lung disease (1, 2). Of these manifestations, lung disease is a major contributor to morbidity and mortality. In some patients, respiratory symptoms may precede joint symptoms. It is critical to assess systemic and articular signs and symptoms of connective tissue disease when evaluating a patient with pulmonary disease of unknown aetiology as patients may initially present with respiratory symptoms (1-3).

Pulmonary manifestations of rheumatoid arthritis are protean, with variable patient presentations, including parenchymal interstitial lung disease (ILD), pleural thickening, and pleural effusion, vasculitis and pulmonary hypertension. These changes may reflect chronic immune activation, increased susceptibility to infection (often secondary to medications) or direct toxicity from disease modifying or

biological therapy(1, 4). Prognosis varies depending on the type and severity of involvement.

Interstitial lung disease:

Interstitial lung disease (ILD) is the most common pulmonary presentation of rheumatoid arthritis lung disease, although the exact prevalence varies depending on the population studied and the diagnostic modality used to define the disease. In an Australian cohort of rheumatoid arthritis patients with a disease duration <2 years, 58% of these patients had changes consistent with ILD on either chest radiograph, high-resolution computed tomography (HRCT), pulmonary function testing (PFT), and bronchoalveolar lavage (BAL) (1, 5, 6). Of these patients, 76% had clinically silent disease. A more recent study of 40 patients, also with <2 years of disease, found that abnormalities on HRCT scans and/or PFTs were present in 45%, with 10% having clinically significant disease. It is currently estimated that approximately 30% of patients with RA have subclinical ILD noted on HRCT scans. While the incidence of some extra-articular manifestations of rheumatoid arthritis have decreased with improvements in therapy, the incidence of ILD has remained fairly stable, if not increased. Whether this reflects an increase in detection or is the result of drug-induced lung disease with more aggressive use of anti-rheumatic agents is not entirely clear (6-8).

Epidemiology and risk factors:

Despite rheumatoid arthritis being more common in females, rheumatoid arthritis associated-ILD (RA-ILD) occurs more frequently in males, with a male to female ratio 2:1 in some studies. Onset of RA-ILD typically occurs in the fifth decade of life

(1, 4). The incidence of RA-ILD may increase as newer agents allow better disease control and increase life expectancy. Age has consistently been shown to be a risk factor for the development of RA-ILD. High levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) are a known risk factor for extra-articular manifestations of rheumatoid arthritis, including ILD. The exact mechanism for this has not been elucidated, but may involve formation of immune complexes (1, 4, 9).

Pathogenesis:

The exact mechanism of pulmonary involvement occurring in RA-ILD is not well understood. Patients with rheumatoid arthritis typically have circulating autoantibodies, the most common being rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) (1, 10, 11). These antibodies may be present in the serum for several years before clinical disease onset. Both rheumatoid factor and anti-CCP have been linked to the development of ILD, particularly when present in high titres (1). Cigarette smoking may play a specific role in RA-ILD by promoting citrullination of lung proteins, thus leading to the development of anti-CCP antibodies (12).

A large case–control study from Sweden demonstrated a 21-fold increased risk of developing rheumatoid arthritis among those who were anti-CCP positive, smoked and had two copies of the shared epitope gene versus non-smokers who did not have the shared epitope gene. It is thought that citrullination increases binding of peptides to HLA-DRB1 shared epitopes, therefore increasing immunogenicity of these proteins (1, 4, 12, 13).

Ascherman *et al* reviewed potential biomarkers implicated in RA-ILD (1). To date, the following cytokines have been considered as potential biomarkers of ILD: platelet

derived growth factor isoforms AB and BB, interferon-alpha, and profibrotic cytokine transforming growth factor-B1. Elevated levels of these cytokines have been observed in BAL (1, 13, 14).

DIAGNOSIS

Clinical features

The clinical presentation of RA-ILD are non-specific. Dyspnea on exertion is the most common symptom, and cough, wheezing, and chest pain have also been reported. However, dyspnea and physical limitations may not be apparent in the early stages of disease (1).

Chest imaging

In RA-ILD patients chest radiographs frequently show reticular, reticulonodular or honeycomb changes in the lung bases. The chest radiograph, however, is insensitive as greater than 50% of patients who have a normal plain chest radiograph will have abnormalities on their HRCT. Therefore, HRCT has replaced plain chest radiography in the initial evaluation of the RA patient with potential lung disease (15, 16, 17).

The incidence of ILD on HRCT depends on the clinical phenotype of the population evaluated. A study screening non-smokers without respiratory symptoms found evidence of ILD on HRCT in 33%. Early RA (2 years duration) patients have evidence of ILD on HRCT in a third of cases, though the extent of disease is mild. In both early and longstanding RA, HRCT changes can precede changes in PFTs. In looking at patients with clinically suspected ILD (symptoms, impaired lung function, or abnormal CXR), 92% have HRCT findings consistent with ILD. The most common

abnormal findings are ground glass opacities (GGOs) and reticulation, seen in over 90% of patients, with reticulation seen in 65%–79% of HRCTs, and seen in isolation in long-standing disease. GGOs are seen in 27% of patients, rarely seen in isolation, and are more common in patients with a shorter duration of disease. Less common findings include honeycombing, traction bronchiectasis, nodules, centrilobular branching lines, and consolidation. In patients with RA referred to an interstitial lung disease centre, patterns of ILD on HRCT include UIP (40%), NSIP (30%), bronchiolitis (17%), and organizing pneumonia (8%).75 Other studies have found similar percentages of UIP and NSIP. Occasionally, patients will have more than one HRCT pattern. HRCT findings are well correlated with underlying histopathology. Reticulation and honeycomb change are associated more frequently with pathologic UIP. GGOs can be found in both UIP and NSIP but are more pronounced and diffuse in the latter. Centrilobular branching is seen with bronchiolitis obliterans and consolidation correlates with organizing pneumonia. There are also associations between HRCT findings and physiology. The degree of parenchymal involvement in RA-ILD is correlated with decreases in FEV1, FVC, and DLCO. Finally, a recent study found that survival is linked to HRCT pattern as patients with a "definite UIP" pattern had a survival that was significantly worse than those with an indeterminate pattern or a pattern suggestive of NSIP (1, 14, 15).

BIOMARKERS FOR RA-ILD

Up to today, the use of RF and anti-CCP as predictive biomarkers for ILD development in patients with RA remains controversial. Some evidence indicates that there is a clear association between high RF and anti- CCP titer levels and RA-ILD.

However, other authors have not identified an association between anti-CCP and RA-ILD (16).

To date, there has been a lack of information about serum ferritin in RA-ILD. However, a cross-sectional study observed significantly increased matrix metalloproteases (MMP)-7 and MMP-1 concentrations in the serum of patients with IPF. Further studies of these metalloproteases in RA-ILD are required (1, 14, 16).

HISTOPATHOLOGY

The main histological patterns of ILD have been characterized, including NSIP, usual interstitial pneumonia (UIP), DAD, organizing pneumonia (OP), and lymphocytic interstitial pneumonia (LIP). The most frequent histological pattern of RA-ILD is UIP, followed by NSIP. In terms of severity the UIP pattern in RA-ILD was associated with worse survival than the non-UIP pattern. In patients with UIP, the mean survival was 3.2 years; in patients with the non-UIP pattern, mean survival time was 6.6 years (1, 2, 4).

Bronchoalveolar lavage

RA-ILD patients have an increase in the total cellular population with increases in neutrophils, lymphocytes, and eosinophils and a decreased CD4/CD8 ratio on bronchoalveolar lavage compared to those without ILD. Abnormal BAL findings can also be seen in patients with RA and subclinical ILD and elevated lymphocyte counts in these patients may help to distinguish them from those with normal physiology and chest radiographs. BAL findings have only a moderate correlation to the lesions found on HRCT, with a higher number of neutrophils found in patients with GGOs (3, 7, 12).

Management

Anti-inflammatory and/or immunosuppressive agents are recommended regardless of the pattern of fibrosis. This is in contrast to IPF, in which use of immunosuppressive therapy has not demonstrated any clinical benefit (17, 18).

Currently there have been no randomised controlled trials comparing medications for the treatment of rheumatoid arthritis lung disease. Corticosteroids are the mainstay of therapy, particularly for cases of NSIP or organising pneumonia where they may lead to regression of consolidation on imaging and potential clinical improvement (15, 16).

Cyclophosphamide and azathioprine have been used with varying success, and there are a few case reports of ILD regression following cyclosporine treatment. More recently, several small studies have demonstrated stabilisation and/ or improvement in symptoms, imaging and PFTs with use of mycophenolate mofetil (18). A review of 125 patients with connective tissue disease associated-ILD (18 of which had rheumatoid arthritis) found that mycophenolate mofetil was associated with improvement in PFTs in patients with non-UIP patterns of ILD, and led to stabilisation among those with UIP (11, 14).

Methotrexate, a first-line agent in the treatment of rheumatoid arthritis joint disease, is known to be associated with drug induced pneumonitis, but fortunately this is rare. However, there is no evidence that this agent leads to progression of ILD. Following 6 weeks of treatment with high-dose steroids, one group found that treatment with methotrexate versus leflunamide or azathoprine was actually associated with an improvement in FVC at 6 months among patients with less fibrosis, although there was no evidence of differences in other outcomes such as mortality. This suggests that

methotrexate use may not be associated with poorer outcomes than other disease modifying anti-rheumatic drugs (1, 4, 7).

There is considerable controversy as to whether anti-tumour necrosis factor (TNF) agents improve or worsen ILD. Studies evaluating this issue tend to be confounded by older age and prior use of methotrexate among participants.

Adjuvant therapy for RA-ILD includes smoking cessation, management of gastro-oesophageal reflux disease, referral to pulmonary rehabilitation, supplemental oxygen, and vaccination against influenza and pneumococcal disease (1, 14, 18).

In the absence of active rheumatoid arthritis, patients with rheumatoid arthritis lung disease who fail to respond to therapy should be considered for lung transplant. In patients with a UIP pattern, work-up for transplant should be considered early. A retrospective review of Canadian patients with advanced lung disease found no difference in outcomes between patients with RA-ILD and those with IPF at 1 year following lung transplant, suggesting that transplant is a reasonable option for these patients (11, 18).

Prognosis

RA-ILD is second only to cardiac disease as a cause of mortality in rheumatoid arthritis. Based on a review of mortality data in the USA from 1988–2004, Olson et al. calculated that RA-ILD contributed to death in 6.8% of females and 9.8% of males with rheumatoid arthritis. Additional risk factors for mortality include advanced age, male sex, UIP pattern and extent of fibrosis on imaging or histopathology, and low DLCO(1,10,18).

Overall, RA-ILD has a better prognosis when compared to identical patterns in non-connective tissue disease-associated idiopathic interstitial pneumonias. The possible exception to this is rheumatoid arthritis associated-UIP, which appears to have poorer prognosis compared to other patterns of RA-ILD and, in fact, may have similar outcomes to IPF. The mean survival for RA-ILD overall has been estimated at 2.6 years from time of diagnosis compared to 9.9 years for rheumatoid arthritis patients without lung involvement. This probably reflects the predominance of the UIP pattern (1, 2, 10, 18).

References;

1. Shaw M, Collins BF, Ho LA, Raghu GJERR. Rheumatoid arthritis-associated lung disease. " *European Respiratory Review* 24.135 (2015): 1-16.
2. Olivas-Flores E, Bonilla-Lara D, Gamez-Nava J, Rocha-Muñoz A, Gonzalez-Lopez LJWJR. Interstitial lung disease in rheumatoid arthritis: current concepts in pathogenesis, diagnosis and therapeutics. 2015;5(1):1e22.." *World J Rheumatol* 5.1 (2015): 1e22.
3. Solomon JJ, Ryu JH, Tazelaar HD, Myers JL, Tuder R, Cool CD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). 2013;107(8): 1247-52." *Respiratory medicine* 107.8 (2013): 1247-1252.
4. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu H-P, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. 2008;168(2):159-66. " *Archives of internal medicine* 168.2 (2008): 159-166.
5. Kim EJ, Collard HR, King Jr TEJC. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. 2009;136(5):1397-405." *Chest* 136.5 (2009): 1397-1405.
6. Rocha-Muñoz AD, Ponce-Guarneros M, Gamez-Nava JI, Olivas-Flores EM, Mejía M, Juárez-Contreras P, et al. Anti-cyclic citrullinated peptide antibodies and severity of interstitial lung disease in women with rheumatoid arthritis. 2015;2015 " *Journal of immunology research* 2015 (2015).
7. Solomon JJ, Brown KKJOarr, reviews. Rheumatoid arthritis-associated interstitial lung disease. 2012;4:21. " *Open access rheumatology: research and reviews* 4 (2012): 21.
8. BIOMDO DIC. Assessment of pulmonary function in rheumatoid arthritis patients attending Rheumatology Clinics in Nairobi: UNIVERSITY OF NAIROBI; 2010.
9. Iqbal K, Kelly CJTaimd. Treatment of rheumatoid arthritis-associated interstitial lung disease : a perspective review. 2015;7(6):247-67." *Therapeutic advances in musculoskeletal disease* 7.6 (2015): 247-267.
10. Hamblin MJ, Horton MRJPm. Rheumatoid arthritis-associated interstitial lung disease: diagnostic dilemma. 2011;2011." *Pulmonary medicine* 2011 (2011).
11. King Jr TEJAjor, medicine cc. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. 2005;172(3):268-79." *American journal of respiratory and critical care medicine* 172.3 (2005): 268-279.
12. Yin Y, Di Liang LZ, Li Y, Liu W, Ren Y, Li Y, et al. Anti-cyclic citrullinated peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. 2014;9(4)." *PLoS One* 9.4 (2014).
13. Gabriel SEJRDCoNA. The epidemiology of rheumatoid arthritis. 2001;27(2):269-81. " *Rheumatic Disease Clinics of North America* 27.2 (2001): 269-281.
14. Silva CIS, Mueller NLJRB. Intrathoracic manifestations of collagen vascular diseases on high-resolution chest computed tomography. 2008;41(3):189-97. Silva, C. Isabela S., and Nestor L. Mueller." *Radiol Bras* 41.3 (2008): 189-197.
15. Adizie T, Moots R, Hodkinson B, French N, Adebajo AJBid. Inflammatory arthritis in HIV positive patients: A practical guide. 2016;16(1):100." *BMC infectious diseases* 16.1 (2016): 100.
16. Ozkaya S, Bilgin S, Hamsici S, Findik SJRMC. The pulmonary radiologic findings of rheumatoid arthritis. 2011;4(4):187-92. ." *Respiratory Medicine CME* 4.4 (2011): 187-192.
17. Medicine IPFCRNJNEJo. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. 2014;370(22):2093-101. ." *New England Journal of Medicine* 370.22 (2014): 2093-2101.
18. Suda TJCMIC, Respiratory, Medicine P. Up-to-date information on rheumatoid arthritis-associated interstitial lung disease. 2015;9:CCRPM. S23289. " *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine*.

Part 2: A submission ready manuscript.

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Clinical Profile of Rheumatoid Arthritis associated interstitial lung disease at a tertiary hospital in KwaZulu-Natal, South Africa: A retrospective 5 year review.

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Abstract

Background: The prevalence, demographic distribution and treatment outcomes in Rheumatoid Arthritis associated interstitial lung disease (RA-ILD) has not been well described in Southern Africa. There is very limited data.

Objective: The aim of the study was to determine the demographic profile of the disease as well as treatments used and their outcomes at Inkosi Albert Luthuli Central Hospital (IALCH), a tertiary hospital in Durban, South Africa.

Methods. This was a retrospective electronic chart review of 61 patients who were diagnosed with RA-ILD between January 2010 and December 2015 at IALCH pulmonology clinic. Demographic and clinical data, symptom presentation, pulmonary function testing (PFT), high resolution computerised tomography (HRCT) features and treatment modalities were analysed as well as outcome based on symptoms, PFT and HRCT.

Results. There were 61 subjects, the majority being female (90.2%). Approximately 86.9% were 50 years and older. The majority of the subjects were Indian 72.1% (n=44), followed by Black Africans 23% (n=14) and then Whites 4.9% (n=3). All patients were HIV negative. Patients treated with a combination of prednisone and azathioprine had a decline in FVC (mean 0.41, p value 0.04). There was no improvements or deterioration in patients treated with either drug alone.

Conclusion. The management of RA-ILD is still a challenge. The combination of azathioprine and prednisone did not arrest disease progression in our study while either agent alone did not improve clinical and lung function parameters. Large randomised control studies are needed in Sub-Saharan Africa.

Introduction

Rheumatoid arthritis (RA) is a multi system inflammatory autoimmune disease affecting approximately 1% of the general population (1). Interstitial lung disease (ILD) is one of the commonest primary pulmonary manifestations of RA (2). Rheumatoid arthritis is commoner in females, however males are more affected in RA-ILD with a male to female ratio of 2:1 in some studies (3). The onset of RA-ILD typically occurs in the fifth decade of life (3, 4).

Age and smoking have been shown to be risk factors for the development of ILD (4) and high titres of Rheumatoid factor (RF) and Anti citrullinated antibodies (anti-CCP) are a known risk factor for extra-articular manifestations of rheumatoid arthritis, including ILD (3-5). Most patients with RA-ILD present with symptoms of dyspnoea or cough (3, 6).

A restrictive pattern on pulmonary function testing (PFT) is the most common pattern noted on spirometry in the majority of patients with RA-ILD, with or without a decrease in diffusing capacity of the lung for carbon monoxide (DLCO) (7). An obstructive pattern may coexist on PFT and can be seen in patients manifesting airway involvement, such as bronchiolitis obliterans (BO) (3).

In RA a variety of patterns are seen on High Resolution Computerised Tomography (HRCT) scans, with the most common being usual interstitial pneumonia (UIP),

which occurs in 40–62% of cases. Non specific interstitial pneumonia (NSIP) is the second most common pattern, occurring in approximately11–32% of patients. Other types of patterns seen in RA-ILD include organising pneumonia, diffuse alveolar damage (DAD), lymphocytic interstitial pneumonia (LIP) and desquamative interstitial pneumonia (DIP). However these are less frequent (3).

Once a diagnosis of RA-ILD has been confirmed, treatment is generally directed to control the systemic disease with immunosuppressive agents while tailoring therapy to the underlying histopathological subtype (8, 9).

Currently, there have not been enough randomised controlled trials comparing medications for the treatment of RA-ILD (8). Corticosteroids are still the mainstay of therapy, particularly for cases of NSIP, organizing pneumonia or acute flare up of UIP (3, 10). Cyclophosphamide, azathioprine and cyclosporine have been used with varying digress of success (3).

There is a paucity of literature regarding RA-ILD in sub Saharan Africa and its demographic distribution as well as relationship to HIV. The aim of this study was to review the demographic data, PFT and HRCT scan pattern and treatment outcomes at a tertiary hospital in Durban, KwaZulu Natal, South Africa.

Methods

This was a retrospective electronic chart review. Patients 18 years and older referred to Inkosi Albert Luthuli Central Hospital pulmonology clinic diagnosed with RA-ILD between January 2010 and December 2015 were included in the study.

Demographic and clinical data, as well as data from special investigations, were captured retrospectively from medical records. Demographic data included age, gender and race. Clinical data captured were presenting symptoms, pre-existing medical conditions, current functional class, date of onset of initial symptoms, and treatment. Special investigations captured included results of HRCT, rheumatoid factor level, anti-CCP levels and PFT.

Ethical approval was granted by the University of KwaZulu Natal's Human Research Ethics Committee (ref. no. E044/2018).

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Demographic data with a normal distribution such as age, gender and race are reported as means with standard deviation (SD). Fishers exact test was used for categorical variables. Statistical significance was regarded as a p-value <0.05 unless otherwise stated. Continuous variables are presented as mean SD.

Change in symptoms between initial visit and last visit for cough, dyspnoea, forced expiratory volume in 1 second (FEV1), or forced vital capacity (FVC), was classified as worse or improved/ static. Chi square or Fisher's exact test was used to compare the change by categorical data such as treatment. Initial mean FEV1 and FVC were compared by categories of RF and anti CCP using Mann-Whitney tests. Changes in FEV1 and FVC were coded as worse if the percentage difference change was 10% or more. Changes by treatment medications were analysed using Fisher's exact test. Pairwise comparisons were then done using azathioprine as a reference category using Fisher's exact tests. Data was analysed using Stata V13 statistical software.

Results

Demographics

There were 61 subjects who met the inclusion criteria with the majority being female by far at 90.2%. The majority of patients were above the age of 50 (86.9%). Most of the subjects were Indian 72.1% (n=44), followed by Black Africans 23% (n=14) and then Whites 4.9% (n=3) (table .1).

Table 1: Demographic details of the study population.

Age	Number	%
40-50	8	13.1%
50-60	15	24.6%
60-70	21	34.4%
70-80	17	27.9%
Sex		
Male	6	9.8%
Female	55	90.2%
Race		
Black African	14	23.0%
Indian	44	72.1%
White	3	4.9%

Presenting symptoms and functional status

Presenting symptoms were recorded at initial visit. The majority of patients had exertional dyspnoea as one of their initial symptoms followed by chronic cough. The New York Heart Association (NYHA) functional class at enrolment was recorded and 8 patients (13.1%) were class I disabled, 29 (47.5%) class II, 3 (3.3%) class III and none class IV. Twenty two patients (36.1%) had no dyspnoea at initial visit.

Pulmonary function tests

FEV1 and FVC were recorded in 58 patients with 3 patients having missing data. The median FEV1 was 1.54 L with IQR (0.87 – 2.34) . The median FVC was 1.87 L (0.75 – 3.02) IQR.

The majority of patients in our study had a restrictive pattern, 6 patients (9.8%) presented with obstructive pattern on PFT and 3 patients had missing data.

A transfer factor for carbon monoxide was recorded for some patients but the majority were not recorded due to lack of data.

There was a significant difference in percentage change in FVC by weight change, Patients who gained weight have greater percentage increase in FVC (p = 0.005, mean =21.61, sd=46.28).

HRCT analysis showed the following RA-ILD patterns: UIP 36.1% (n=22), followed by NSIP pattern 19.7 % (n=12), BO pattern 9.8% (n=6) and others 34.4% (n=21) (figure.1).

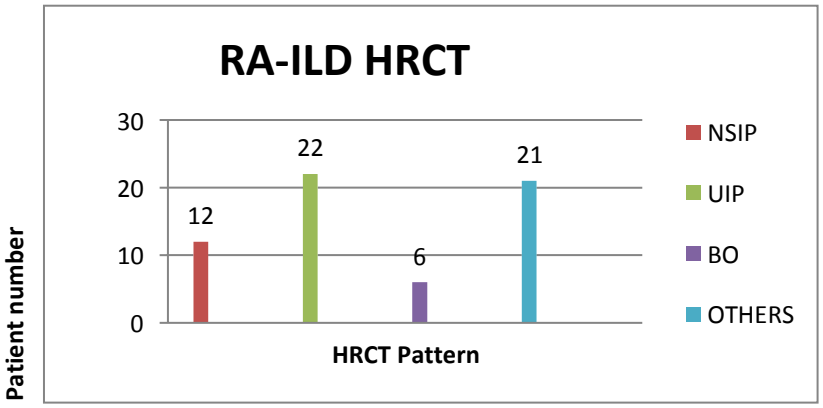

Figure2 High Resolution Computed Scan Pattern.

Associations between anti-CCP, RF titres with initial ILD presentation, initial lung function test, initial HRCT.

Thirty five patients (57.4%) had a positive anti-CCP titre with a median of 94 IU, (30.9-300). Forty one patients (67.2%) had an elevated RF antibody with a median of 116.5 IU, (46.5-207). There was no association between anti-CCP antibodies or RF antibodies with the presenting lung function or HRCT pattern.

Treatment outcomes

Therapy was categorised into 4 groups: azathioprine alone (n=3, 4.9%), prednisone alone (n=10, 16.4%), azathioprine combined with prednisone (n=13, 21.3%), and no therapy (n=35, 57.4%). Subjective responses with change in cough and dyspnoea were analysed before and after treatment as assessed by first and last visit. HRCT and PFT were used as objective responses to treatment before and after therapy.

The patients were classified as either disease progression or improved or static. There was no statistically significant differences in cough, dyspnoea, change in PFT or change in HRCT. However patients on prednisone and azathioprine combined had significant worsening of the FVC (mean 0.41, IQR (-0.5 to -0.2), p value 0.04).

All 61 patients were HIV negative.

Discussion

RA-ILD is often subtle in onset, slowly progressive and of uncertain response to immune modulating agents (11). This study aimed to clarify the current clinical, radiographic and pathologic status of RA-ILD and treatment and outcomes of patients seen at our tertiary hospital, IALCH, in Durban KwaZulu Natal.

RA-ILD has been recognised as the most common extra articular complication in RA patients. In this retrospective study, we evaluated ILD in RA patients referred to our clinic. We found that 86.9% of the patients (n=53) with RA-ILD are between the ages of fifty to eighty years. About 13.1 % of the patients (n=8) were less than 50 years of age. This is similar to findings in most studies (3, 12). The likely explanation for the higher proportion of patients above age of 50 with ILD may be due to long duration of disease in the majority of RA patients or late diagnosis. Most patients were females (90.2%) as reported in many studies. The study done by Gabriel *et al* states that RA occurs 2–3 times more commonly in women with onset generally in adulthood, peaking in the 4th and 5th decade (13). However male gender has been shown to be a

risk factor for RA-ILD in a number of studies (12). This gender imbalance has been observed across different ethnic populations, as well as in familial studies (12). In our study we found that most of the patients are Indian followed by Black African and then White. This finding in is not in line with the demographics of KwaZulu Natal and South Africa in which Black Africans comprise more than 80% of the total population of both the province and the country. It may be that the Indian race group may be more prone to ILD due to RA compared to Black Africans or more prone to RA as a disease. Referral patterns in the different race groups may also be a factor.

Of particular interest are the differential associations observed between immunodeficiency secondary to HIV and RA-ILD, which we were unable to establish in our cohort. All our patients were HIV negative. Several reports have suggested that patients with established rheumatoid arthritis experience clinical improvement after the development of immunodeficiency secondary to HIV (14). Tarr *et al* observed that most HIV positive RA patients in their cohort had lower joint counts and composite disease activity scores despite stopping immune modulating therapy compared to HIV negative controls, supporting the suggestion that HIV infection improves RA disease activity (15). There have been no studies thus far in sub-Saharan Africa addressing the correlation between HIV and RA-ILD activity.

The majority of patients in our study had a restrictive pattern on PFT which is similar to most studies (3, 6). We identified 6 patients (9.8%) who presented with an obstructive pattern. Airflow obstruction may coexist and be seen in patients manifesting airway involvement such as bronchiolitis obliterans (3).

The present study confirms current knowledge from other parts of the world: for example Silva *et al* showed that the predominant pattern of ILD in RA is UIP (14). In our study UIP accounted for more than one-third of patients (36.1%, n=22), followed by NSIP pattern (19.7 %, n=12), bronchiolitis obliterans (9.8%, n=6) and others (34.4%, n=21). The UIP pattern is independently associated with a poorer prognosis and an increase in all-cause mortality (11).

The differential associations observed between anti-CCP antibodies and rheumatoid factor in relation to initial symptoms such as cough, dyspnoea, initial PFT, HRCT outcome and HRCT abnormalities are of particular interest. Anti-CCP antibodies are highly specific for RA and are associated with poor articular prognosis (16).

Consistent with most other studies in RA, we have not identified a relationship between anti-CCP antibodies or rheumatoid factor and initial symptoms such as cough and dyspnoea or initial PFT, nor HRCT patterns. However a study from New Zealand demonstrated an association between anti-CCP antibodies and both physiologic abnormalities and bronchial wall thickening on HRCT (16). This may suggest an association between the antibody and the interstitial lung disease.

The management of patients with RA-ILD remains unclear. It is not known whether treatment will delay or stop progression of the disease activity. The mainstay of treatment in RA-ILD is immune suppressive agents. First line therapy is steroids such as prednisone, for prolonged duration especially for non UIP patterns such as NSIP and OP. In this retrospective study we found 16.4% of patients had been treated with prednisone alone, 4.9% with azathioprine alone, and 21.1% with both prednisone and azathioprine. More than half the patients (57.4%) had no specific treatment for the RA-ILD. There were no differences in symptoms or PFT outcome between first and last visit. However we found that, patients who were on both prednisone and azathioprine had a significant decline in FVC. It is very likely that this subgroup of patients had both drugs administered because they had the most aggressive disease. It is highly unlikely that the associated decline was due to the treatment. It is possible that the rate of decline could have been worse if both treatments had not been given.

The PANTHER study revealed an increased rate of death and hospitalisation in the combination therapy group (prednsione, azathioprine and NAC) compared with placebo. More serious adverse events were noted in the combination therapy group with no improvement in lung function. Due to these findings, the combination regimen arm was stopped and the study terminated prematurely (17).

Several studies have raised the possibility that the response to therapy correlates with the histological patterns in RA-ILD. RA-ILD with the NSIP pattern has a more favourable response to therapy than that with the UIP pattern, resulting in a better prognosis. Patients with the OP pattern typically show rapid improvements in response to corticosteroid therapy (18).

Limitations of this study

This was a retrospective review of electronic data and only data captured and available could be analysed. It was a small sample size at a single centre with missing data, which made it very difficult to determine any associations or lack thereof. There is the possibility of overestimation as the study was conducted at a tertiary hospital in a specialised clinic, which may have resulted in referral bias. There may also have been patients with interstitial lung disease at the rheumatology clinic, who may have been missed because they were asymptomatic.

Conclusion

This is the first study to our knowledge, in South Africa, to study the demographics and treatment of RA-ILD. The majority of patients with RA-ILD at IALCH are of Indian descent, contrary to the population demographics of the country which is greater than 80% Black African. None of our patients were HIV infected which may attest to previous reports of a protective effect of HIV on RA.

Active treatment of RA-ILD with prednisone, azathioprine or both combination appears to have had no positive impact on symptoms or PFT. However, these results must be interpreted with caution in light of this being a retrospective study with its significant shortcomings.

Further prospective multi centre randomised controlled trials are required in this field to determine the optimal drug treatment to manage RA-ILD in sub-Saharan Africa as well as the impact of HIV infection.

REFRENCES:

1. Solomon, Joshua J., et al. "Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)." *Respiratory medicine* 107.8 (2013): 1247-1252.
2. Gochuico, Bernadette R., et al. "Progressive preclinical interstitial lung disease in rheumatoid arthritis." *Archives of internal medicine* 168.2 (2008): 159-166. http://dx.doi.org/10.1016/j.rmed.2013.05.002.
3. Shaw, Megan, et al. "Rheumatoid arthritis-associated lung disease." *European Respiratory Review* 24.135 (2015): 1-16. http://dx.doi.org/10.1183/09059180.00008014.

4. Assayag, Deborah, Joyce S. Lee, and Talmadge E. King Jr. "Rheumatoid arthritis associated interstitial lung disease: a review." *Medicina (Buenos Aires)* 74.2 (2014).http://www.medicinabuenosaires.com/PMID/24736263.pdf.
5. Rocha-Muñoz, Alberto Daniel, et al. "Anti-cyclic citrullinated peptide antibodies and severity of interstitial lung disease in women with rheumatoid arthritis." *Journal of immunology research* 2015 (2015). http://dx.doi.org/10.1155/2015/151626.
6. Solomon, Joshua J., and Kevin K. Brown. "Rheumatoid arthritis-associated interstitial lung disease." *Open access rheumatology: research and reviews* 4 (2012): 21.http://dx.doi.org/10.2147/oarrr.s14723.
7. BIOMDO, DR IRENE C. *Assessment of pulmonary function in rheumatoid arthritis patients attending Rheumatology Clinics in Nairobi*. Diss. UNIVERSITY OF NAIROBI, 2010.
8. Iqbal, Kundan, and Clive Kelly. "Treatment of rheumatoid arthritis-associated interstitial lung disease: a perspective review." *Therapeutic advances in musculoskeletal disease* 7.6 (2015): 247-267. http://dx.doi.org/10.1177/1759720x15612250.
9. Hamblin MJ, Horton MRJPm. Rheumatoid arthritis-associated interstitial lung disease: diagnostic dilemma. 2011;2011. " *Pulmonary medicine* 2011 (2011). http://dx.doi.org/10.1155/2011/872120.
10. King Jr TEJAjor, medicine cc. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. 2005;172(3):268-279. " *American journal of respiratory and critical care medicine* 172.3 (2005): 268-279 http://dx.doi.org/10.1164/rccm.200503-483oe.
11. Horton, Maureen R. "Rheumatoid arthritis associated interstitial lung disease." *Critical reviews in computed tomography* 45.5-6 (2004): 429-440.http://dx.doi.org/10.1080/10408370490905325.
12. Yin Y, Liang D, Zhao L, Li Y, Liu W, Ren Y, et al. Anti-cyclic citrullinated peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. 2014;9(4):e92449. " *PLoS One* 9.4 (2014). http://dx.doi.org/10.1371/journal.pone.0092449.
13. Gabriel SEJRDCoNA. The epidemiology of rheumatoid arthritis. 2001;27(2):269- 281. " *Rheumatic Disease Clinics of North America* 27.2 (2001): 269-281. http://dx.doi.org/10.1016/s0889-857x(05)70201-5.
14. Silva CIS, Müller NLJRB. Intrathoracic manifestations of collagen vascular diseases on high-resolution chest computed tomography. 2008;41(3):189-197. " *Radiol Bras* 41.3 (2008): 189-197. http://dx.doi.org/10.1007/978-1-4614-9194-1_511.
15. Adizie T, Moots R, Hodkinson B, French N, Adebajo AJBid. Inflammatory arthritis in HIV positive patients: A practical guide. 2016;16(1):100." *BMC infectious diseases* 16.1 http://dx.doi.org/10.1186/s12879-016-1389-2.
16. Ozkaya S, Bilgin S, Hamsici S, Findik SJRMC. The pulmonary radiologic findings of rheumatoid arthritis. 2011;4(4):187-192. " *Respiratory Medicine CME* 4.4 (2011): 187-192.
17. Medicine IPFCRNJNEJo. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. 2014;370(22):2093-101. http://dx.doi.org/10.1016/j.rmedc.2011.03.003. " *New England Journal of Medicine* 370.22 (2014): 2093-2101.

18. Suda, Takafumi. "Up-to-date information on rheumatoid arthritis-associated interstitial lung disease." *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 9 (2015): CCRPM-S23289.
htt://dx.doi.org/10.4137//ccrpm.s23389.

Appendix 1: The final Study Protocol:

The final Study Protocol

Title of study

Prevalence and outcomes of Rheumatoid Arthritis associated Interstitial lung disease at a tertiary level hospital in KwaZulu Natal, South Africa: A retrospective 5-year review.

2.2 Identify the problem that is motivating your research.

Substantiate this claim by anecdotal evidence that derives from your practice or clinical experience, specifying the observed factors contributing to the problem and the potential outcome.

Interstitial lung disease (ILD) has been recognized as an important co-morbidity in rheumatoid arthritis (RA). We aimed to assess incidence, prevalence, risk factors, morbidity and mortality of RA associated ILD.

2.3 What is the research question or the hypothesis?

Pulmonary involvement is common among patients with rheumatoid arthritis and has a variety of manifestations, with ILD, pleural disease and pulmonary drug toxicity being the most common. Mechanisms of lung injury have been attributed to genetics, environmental exposure and medications. Pulmonary disease may precede the development of other rheumatoid arthritis manifestations, such as articular involvement, but patients with pulmonary disease may also be asymptomatic. Overall, morbidity and mortality from rheumatoid arthritis associated-lung disease are high. To date, there are no prospective randomised clinical trials for RA-ILD and, thus, treatment for RA-ILD is essentially immunomodulating agents that are used for rheumatoid arthritis in general. Further research is needed to determine specific risk factors and

appropriate therapy. There is very limited data regarding this disease entity in Sub Saharan Africa

The aim of this study?

To determine the patient profile and treatment outcomes of patients that develop Interstitial lung disease associated with RA in the south African context.

The objectives of the study.

a. To determine the incidence and prevalence of patients that develop Interstitial lung disease associated with RA.
b. To describe the demographic profile of the study participants
c. To examine the specific patterns of ILD on HRCT scan
d. To examine the management options that patients were placed on for ILD and treatment specific outcomes .
e. To assess the Rheumtoid factor level, CCP level and development of ILD.
f. To assess PFT parameters before and after treatment
g. To assess chest radiograph finding of patients with ILD
h.To determine if there is any increased risk with HIV.

Background and Literature review

Besides the joints, the inflammatory process that underlies rheumatoid arthritis (RA) also affects other parts of the body, including lungs, skin, eyes, digestive system, heart and blood vessels. RA-related lung complications are the most common extra-articular manifestations of RA and include pulmonary nodules pleural effusion; bronchiectasis and interstitial lung disease (ILD)[1] .

In fact, it is estimated that 1 in 10 people with rheumatoid arthritis will develop ILD over the course of their disease, making it as deadly among people with RA as congestive heart failure[2].

Interstitial lung disease refers to a group of disorders characterized by inflammation and scarring of the lung tissue. In the case of RA-associated ILD, the scarring is caused when the over-active immune system attacks the lungs. When the scarring builds up over time, breathing becomes difficult, and patients may need lung transplants to regain function[3,4], .

The risk of developing lung disease is eight times higher in people with RA than in the general population. However, most people with RA are not affected. Risk factors for ILD include:

Smoking. People with RA who smoke are more likely to develop ILD.

Higher RA disease activity. High levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptides (antiCCP) antibodies – substances that are indicative of more active disease – increase the risk for development of ILD,Older age at diagnosis [1]. People who are diagnosed with rheumatoid arthritis after age 60 are more likely to develop ILD[1]. Male Gender. Men with RA have a two-to-three times higher risk of developing ILD than women[2]

Treatment with methotrexate and other DMARDs. Several DMARDs, including methotrexate, leflunomide and azathioprine, as well as biologics, particularly tumor necrosis factor (TNF) inhibitors, have been associated with RA-ILD, according to a literature review published in the April 2014 issue of Seminars in Arthritis and Rheumatism, says the risk of methotrexate-induced lung injury is less than 1 percent and is reversible once the drug is stopped[2]. However, methotrexate is not recommended for people with existing ILD or RA-ILD by the American College of Rheumatology in their 2012 guidelines [3,4].

It is challenging to catch ILD early because it doesn't cause any specific symptoms. Once shortness of breath and dry cough develop, the disease has probably already progressed [3,4].

The diagnostic process includes a comprehensive clinical exam, X-rays and lung function tests. If there are risk factors for ILD or abnormal X-ray findings, then doctors will likely perform a high resolution CT[5].

Interstitial lung disease is hard to treat and has a high mortality rate. According to a 2010 study published in the journal Arthritis & Rheumatism, once ILD was diagnosed, the average survival in patients with RA was 2.6 years [3,4].

People diagnosed with ILD in its early stages can be helped with medication such as corticosteroids and immunosuppressants and put on the waiting list for a lung transplant sooner.[5]However, these treatments don't work for everyone. The best approach is to treat the underlying RA, although ILD may get worse despite well controlled arthritis[3,4].

REFERENCEs

1-O'Dwyer DN, Armstrong ME, Cooke G, et al. Rheumatoid arthritis (RA) associated interstitial lung disease (ILD).

2-Eur J Intern Med 2013; 24: 597–603. Olson AL, Swigris JJ, Sprunger DB, et al.Rheumatoid arthritis-interstitial lung disease-associated mortality.Am J Respir Crit Care Med 2011; 183: 372–378.

3-↲Doyle TJ, Lee JS, Dellaripa PF, et al. A roadmap to promote clinical and translational research in rheumatoid arthritis-associated interstitial lung disease. Chest 2014; 145: 454–463.

4-↲Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997; 156: 528–53.

Research design: retrospective observational descriptive study.

Study population: Adults (age >18yrs) diagnosed with rheumatoid arthritis with interstitial lung disease at Inkosi Albert Luthuli Central Hospital

6. Study sample: patients (age 12 years) who are diagnosed with rheumatoid arthritis with interstitial lung disease during the period between January 2010 and December 2015.

Sampling technique: electronic chart review

Aim for a sample of 50 patients

Sampling strategy

The study population will include patients (age 18 years) who diagnosed with rheumatoid arthritis with interstitial lung disease in the period between January 2010 and December 2015.

Variables

Variables that will be recorded include:

1.Age

2.gender

3.race,

5. Rheumatoid factor titre

6. Anti CCP level

7.Clinical presentation and duration of symptoms.

8.Radiological findings including CXR and HRCT

9.Histological findings if done

10.Pulmonary Function testing

11.Medications

12. Outcomes after treatment

13. HIV status including CD4 count and Viral Load

14. CRP and ESR level

Inclusion Criteria:

All ADULTS (age > 18 years) diagnosed with rheumatoid arthritis with interstitial lung disease at the Department of pulmonology and rheumatology clinics at Inkosi Albert Luthuli Central Hospital between 01/01/2010 to 31/12/2015.

Exclusion criteria:

-Cases where electronic data sets can not be retrieved.

-Patients with other connective tissue diseases.

-Patient in whom the diagnosis of RA or ILD is doubtful.

Data Collection Methods and Tools:

Research method: data collection sheet.

Retrospective electronic chart review between January 2010 to December 2015 in the Department of pulomonolgy and rheumatology at Inkosi Albert Luthuli Central Hospital,Durban,South Africa.

Data analysis techniques:

Sample Size Determination:

This project aims to determine the difference between males and females in terms of response to rheumatoid arthritis (RA) and interstitial lung disease (ILD). The response variables in this study are CT pattern and response to treatment, blood investigation and histology. The inclusion criteria is that all participants should be adults (age > 12

years), diagnosed with RA with ILD at the Department of Pulmonology at Inkosi Albert Luthuli Central Hospital between the 1st of January 2010 and 31st of December 2014.

The null hypothesis is that there is no statistically significant difference between males and females in terms of response to RA and ILD. The following statistical parameters were used to arrive the appropriate sample size with a statistical power of 80%; effect size of 0.99 (magnitude or size of an effect, type 1 (α) error = 0.05 (this is the probability of falsely rejecting null hypothesis), type 2 (β) error equal = 0.2 (this is the probability of falsely failing to reject null hypothesis). On the base of the above statistical parameters, a minimum sample size of 36 was determined. This means that 36/2 equal to 18 males and 18 females will be included in the study . This condition RA/ILD is not common in literature, it's stated that it affects 1% of all general population.

Statistical analysis:

Research data will be primarily be analyzed within a quantitative framework. Data will be entered into IBM SPSS, version 24 (Statistical Packages for the Social Sciences). A p-value <0.05 will be considered as statistically significant. Continuous variables will be expressed as mean ± standard deviation or medians (interquartile range) and compared using Student's t-test or Wilcoxon-Mann-Whitney test as appropriate. Proportions and categorical variables will be compared using Pearson's chi-square test or Fisher's exact test as appropriate.

Study location:

The study location will include patients (age 12 years) who diagnosed with rheumatoid arthritis with interstitial lung disease at the at Inkosi Albert Luthuli Central Hospital.

Study period:

The study population will include patients (age 12 years) who diagnosed with rheumatoid arthritis with interstitial lung disease in the period between January 2010 and December 2015.

Limitations of the study:

The study is limited to one center. This may not be truly representative of the general population, but as this is the only centre that provides this service for the population of Kwazulu-Natal, it is reflective of the state of care for interstial lung disease.

Due to a retrospective of the study , incomplete data and lack of follow-up may affect the findings of this study.. Inconsistencies in capturing of clinical and laboratory data.

Ethical considerations:

As this is a retrospective study with no patient contact informed consent will not be necessary. There will be no direct impact on patient care. No patient identifier will be used and subjects will be allocated study numbers. A data sheet these with allocations will be kept separating , Confidentiality with all data captured from records will be ensured entering by password protect to the data set.

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

Manuscript preparation
Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

AJTCCM is a medical journal covering all aspects of respiratory health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 – 25 references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Click Here for an example of a good abstract.

Case reports/Scientific letters/Short reports

These include side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Contributors are encouraged to write to the Editor about possible papers to be considered for review, and where appropriate a review outline will be submitted to experts in the field for consideration before a full review is commissioned. It is expected that an author or authors have substantial experience and track record in the field that the review is about.

*Guideline word limit: 3 500 words (*unless an alternative word limit has been arranged with the Chief Editor)

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important

- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Contributors are encouraged to include tables and figures in their reviews to keep to the maximum word count.

Guidelines

Must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

- A structured abstract not exceeding 250 words
- Recommended sub-headings: Background, Recommendations, Conclusion is required.
- Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents.
- References, appendices, figures and tables must be kept to a minimum.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the AJTCCM or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.

- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.

- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

  South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

  Rex v Jopp and Another 1949 (4) SA 11 (N)
  Rex v Jopp and Another: Name of the parties concerned
  1949: Date of decision (or when the case was heard)
  (4): Volume number
  SA: SA Law Reports
  11: Page or section number
  (N) : In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
  NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

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- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Author Agreement form [forthcoming]
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
  - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

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8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
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Appendix 3: Ethical approvals

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

20 February 2019

Dr H Ghammo (214585524)
School of Clinical Medicine
College of Health Sciences
Hosam.Ghammo@yahoo.com

Dear Dr Ghammo

Protocol: Prevalence and outcomes of Rheumatoid Arthritis associated interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective 5 year-review
Degree: MMed **BREC Ref No: BE044/18**

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	26 March 2019
Expiration of Ethical Approval:	25 March 2020

I wish to advise you that your application for Recertification received on 04 February 2019 for the above protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 12 March 2019.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

Postgraduate administrator: SCMpgrad@ukzn.ac.za
Supervisor: mohmitha@gmail.com

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Office of The Medical Manager
IALCH

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

15 February 2018

Dr H Ghammo
School of Clinical Medicine
College of Health Sciences

Dear Dr Ghammo

Re: Approved Research: Ref No: BE 044/18: Prevalence and outcomes of Rheumatoid Arthritis associated interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective 5 year-review degree.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

Dr N Tathwali

Dr L P Mtshali pp
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

Reference: BF 657/17
Enquiries: Medical Management

15 February 2018

Dr H Ghammo
School of Clinical Medicine
College of Health Sciences

Dear Dr Ghammo

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Prevalence and outcomes of Rheumatoid Arthritis associated interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective 5 year-review degree.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

Dr N. Tathali

Dr L P Mtshali /pp
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

330 Langalibalele street,
Private Bag X9051 PMB, 3200
Tel: 033 395 2805/3189/3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management (HKRM)

Reference: HRKM111/18
KZ_201803_018

05 April 2018

Dear Dr H M Ghammo
(UKZN)

Subject: Approval of a Research Proposal

1. The research proposal titled **'Prevalence and outcomes of Rheumatoid Arthritis associated Interstitial lung disease at a tertiary level hospital in KwaZulu-Natal, South Africa: A retrospective 5-year review.'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facilities before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 06/04/18

Appendix 4: Data collection tools:

Appendix 5: Raw data:

PATIENT KZ NUMBER	AGE GROUP 1.(40-50) 2.(50-60) 3.(60-70) 4.(70-80)	SEX GROUP MALE(1) .FEMALE (2)	RACE GROUP BLACK(1) INDIAN(2) WHITE(3) COLOURED(4)	PULMONARY HYPERTENSION ,NO (1) .YES (2)	
KZ00001883	2	2	1	2	
KZ00002180	2	2	2	1	
KZ00003964	1	2	1	2	
KZ00004029	3	2	2	1	
KZ00006448	3	2	2	1	
KZ00011978	4	2	2	1	
KZ00016316	4	2	2	1	
KZ00016414	4	2	2	1	
KZ00016697	4	2	2	1	
KZ00020015	4	2	3	2	
KZ00021472	3	2	2	2	
KZ00022943	3	2	2	1	
KZ00025140	3	2	1	2	
KZ00027010	4	2	2	1	
KZ00037490	4	2	2	1	
KZ00046318	3	2	1	1	
KZ00046347	4	2	2	1	
KZ00055801	3	2	2	1	
KZ00061935	1	2	2	1	
KZ00062163	2	2	1	2	
KZ00063373	2	2	2	2	
KZ00066491	2	2	2	1	
KZ00107313	2	2	2	2	
KZ00110761	2	2	2	1	
KZ00117745	3	2	1	1	
KZ00119457	1	2	2	1	
KZ00119527	3	2	1	1	
KZ00129659	4	2	2	1	
KZ00135461	3	2	1	1	
KZ00135478	2	2	2	1	
KZ00139434	3	2	2	1	
KZ00140403	3	2	2	1	
KZ00143480	2	1	2	1	
KZ00146419	2	2	2	1	
KZ00149931	3	2	2	1	
KZ00159859	2	2	1	1	
KZ00164215	3	2	2	1	
KZ00172859	1	2	1	1	
KZ00180578	3	1	3	1	
KZ00182714	3	1	3	2	
KZ00185228	1	1	2	1	
KZ00188846	2	2	2	1	
KZ00196156	3	2	2	1	
KZ00205375	2	2	2	1	
KZ00218234	4	2	2	1	
KZ00218573	3	2	2	1	

KZ00223529	4	2	2	1
KZ00225855	2	2	1	1
KZ00233036	4	2	2	1
KZ00233044	3	1	2	1
KZ00254374	4	2	1	1
KZ00261505	4	1	2	1
KZ00264115	3	2	2	2
KZ00267210	4	2	2	1
KZ00267226	4	2	2	1
KZ00273771	3	2	2	1
KZ00279659	4	2	2	1
KZ00281319	1	2	1	1
KZ00283454	1	2	1	1
KZ00284490	2	2	2	1
KZ00290219	1	2	2	2

Comorbidity	RA with other connective tissue SLE (1) . OTHERS (2).NIL (3) ,SCLERODWEMA(4).	DYSNEA GRADE (0)(1-2-3 frist clinic
HPN/PHTN	3	
T2DM/HPN/PSORISIS	3	
SCLERODERMA/T2DM/HPN/PHTN/OSTEOPROSIS	4	
COPD /HPN/DEPRESSION /HYPOTHYRODISM	3	
ASTHMA/T2DM /CRONS DISEASE/HYPOTHRODISM	3	
HPN/OA	3	
OSTEOPROSIS	3	
T2DM/IHD/HPN	3	
HPN /AF/GASTRITIS	3	
MIXED CONNECTIVE TISSUE DISEASE /OSTEOPROSIS	2	
SLE / RA overlap/HPN/CKD/CQ MACULOPATHY	1	
SLE/ HPN/OSTEOPROSIS/OA/IHD	1	
HPN/OSTEOPROSIS/PHN	3	
HPN/T2DM/OSTEOPROSIS/CKD	3	
HPN/OSTEOPROSIS	3	
SLE	1	
Scleroderma / PM/ OSTEOPROSIS	4	
SLE/ RA/ prev myositis/OSTEOPROSIS	1	
SLE	1	
SLE overlap/Hep B/HPN	1	
Asthma/Allergic Rhinitis/HPN/PTB/HYPOTHYRODISM	3	
HPN/OSTEOPROSIS	3	
HPN/T2DM/HEP B/PTB	3	
T2DM/AORTIC SCLEROSIS	3	
HEP B	3	
SLE/Shogrens/T2DM/HPN/CKD	1	
MCTD / Scleroderma / Polymyositis	2	
OA/IHD/OSTEOPROSIS	3	
Hypothyroid /Hiatus hernia	3	
T2DM/IHD/HPN/OSTEOPROSIS/ALLERGHIC RHINITIS	3	
OA/OSTEOPROSIS	3	
Scleroderma overlap/Lichenoid Photodermatitis	4	
OSA/T2DM/HPN/TKR	3	
OA/HPN/T2DM/DYSLIPIDEMIA	3	
OA/OSTEOPROSIS/IHD /T2DM/HPN/IDA	3	
OA/HPN	3	

OSTEOPROSIS/MDR TB /T2DM/TIA	3
Diffuse cutaneous systemic sclerosis / MCTD /Myositis	4
COPD/OSTEOPROSIS/HPN	3
ASTHMA/HPN /OA/OSTEOPROSIS/pHPN/HYPOTHYRODISM	3
HPN/COPD	3
OA	3
HPN/T2DM/OA/PSORAISIS	3
HPN	3
ASYHMA/HPN/T2DM	3
OA/TKR/THYROID CA	3
IHD/HPN /T2DM	3
HPN /T2DM /HYPOTHYRODISM	3
T2DM/OA/IDA/OSTEOPROSIS/HYPOTHYRODISM	3
HPN/GOUT/CKD/OA	2
HPN/SJOGREN/BACKER CYST/RA	2
COPD/HPN/osteoporosis	3
SCLERODERMA/T2DM/HPN/PHTN/OSTEOPROSIS/SLE	4
OA/OSTEOPROSIS/IHD /T2DM/HPN	3
OA/OS/HYPERTHYRODISM/T2DM/HPN/IHD	3
OA/HPN/T2DM /HYPOTHYRODISM	3
ASTHMA/HPN /OA/OSTEOPROSIS/HPN/OSA	2
MCTD/OA/OS	3
OS/OA	3
T2DM/HPN/OS/OA	3
HPN/PHTN/OA	3

COUGH at frist clinic NO(1) .YES (2)	DYSNEA GRADES at last clinic NIL(0) (1-2-3-4)	COUGH clinic N YES(2)
1	0	1
2	2	2
2	2	2
1	3	2
1	0	1
1	2	1
1	0	1
1	3	1
1	2	1
1	1	1
1	0	1
1	3	1
1	0	1
1	0	1
1	0	1
1	0	1
2	2	2
1	0	1
2	2	2
1	3	1
2	2	1
2	2	2
2	2	1
1	1	1
2	2	2
2	2	1

2	2	2
1	1	1
1	0	1
2	2	2
1	0	1
2	2	2
1	2	1
2	2	2
1	0	1
2	2	2
1	0	1
2	2	2
2	3	2
2	3	2
2	2	2
2	2	2
1	0	1
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1	1	2
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2	2	2
1	0	1
2	0	1
1	0	1
1	3	1
1	0	1
1	2	1
1	0	1
1	0	1
2	0	1
2	2	2
1	0	1
2	2	2
2	2	1

DIFFUSION CAPACITY OF CARBON MONOXIDE (DLCO)	CT 1-USUAL INTERSTITIAL PNEUMONIA .2 NON SPECIFIC INTERSTITIAL PNE 4.OTHER TYPES
40%	
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HIGH RESOLUTION CT SCAN OUTCOME 1.NO PORGRESSION ,2-DECLINED 3.IMPROVED .5 NOT DONE

fev1 1st	fev1 last	last -initail	change	percentage of change
1.52	1.06	-0.46	-0.30263	-30.26315789
1.36	1.06	-0.3	-0.22059	-22.05882353
1.51	1.21	-0.3	-0.19868	-19.86754967
2.21	1.77	-0.44	-0.1991	-19.90950226
1.64	1.43	-0.21	-0.12805	-12.80487805
1.77	1.57	-0.2	-0.11299	-11.29943503
1.31	1.24	-0.07	-0.05344	-5.34351145
1.48	1.34	-0.14	-0.09459	-9.459459459
1.67	1.28	-0.39	-0.23353	-23.35329341
1.6	1.46	-0.14	-0.0875	-8.75
0.87	0.78	-0.09	-0.10345	-10.34482759
1.12	NOT DONE	not done	not done	not done
1.53	1.71	0.18	0.117647	11.76470588
1.16	1	-0.16	-0.13793	-13.79310345
1.12	1.11	-0.01	-0.00893	-0.892857143
2.03	1.74	-0.29	-0.14286	-14.28571429
0.98	1.05	0.07	0.071429	7.142857143
1.31	1.18	-0.13	-0.09924	-9.923664122
1.75	1.23	-0.52	-0.29714	-29.71428571
2.34	2.05	-0.29	-0.12393	-12.39316239
1.71	1.18	-0.53	-0.30994	-30.99415205
2.23	1.3	-0.93	-0.41704	-41.70403587
1.28	1.09	-0.19	-0.14844	-14.84375
1.41	1.4	-0.01	-0.00709	-0.709219858
1.72	1.98	0.26	0.151163	15.11627907
1.61	1.56	-0.05	-0.03106	-3.105590062
1.48	1.09	-0.39	-0.26351	-26.35135135
1.26	1.43	0.17	0.134921	13.49206349
1.48	1.04	-0.44	-0.2973	-29.72972973
1.69	1.55	-0.14	-0.08284	-8.284023669
NOT DONE	NOT DONE	not done	not done	not done
NOT DONE	NOT DONE	not done	not done	not done
1.81	1.1	-0.71	-0.39227	-39.22651934
1.21	0.85	-0.36	-0.29752	-29.75206612
1.42	1.36	-0.06	-0.04225	-4.225352113
0.94	1.42	0.48	0.510638	51.06382979
1.21	1.2	-0.01	-0.00826	-0.826446281
0.78	1.34	0.56	0.717949	71.79487179
3.31	3.72	0.41	0.123867	12.38670695
0.87	0.93	0.06	0.068966	6.896551724
2.09	1.33	-0.76	-0.36364	-36.36363636
0.65	0.94	0.29	0.446154	44.61538462
1.92	1.91	-0.01	-0.00521	-0.520833333

1.26	1.79	0.53	0.420635	42.06349206
0.86	0.49	-0.37	-0.43023	-43.02325581
1.59	1.3	-0.29	-0.18239	-18.23899371
1.47	1.42	-0.05	-0.03401	-3.401360544
1.28	1.16	-0.12	-0.09375	-9.375
1.42	1.28	-0.14	-0.09859	-9.85915493
2.01	1.91	-0.1	-0.04975	-4.975124378
1.81	2	0.19	0.104972	10.49723757
2.23	1.67	-0.56	-0.25112	-25.11210762
1.31	1.2	-0.11	-0.08397	-8.396946565
1.24	1.13	-0.11	-0.08871	-8.870967742
1.43	0.88	-0.55	-0.38462	-38.46153846
1.21	0.98	-0.23	-0.19008	-19.00826446
1.11	1.41	0.3	0.27027	27.02702703
1.85	2.21	0.36	0.194595	19.45945946
1.65	1.65	0	0	0
2.18	1.91	-0.27	-0.12385	-12.3853211
2	2.1	0.1	0.05	5

LUNG FUNCTION TEST OUTCOME Fev1 (1)static ,(2)-DECLINED (3).NOT DONE (4).IMPROVED

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fvc 1st	fvc last	last - initial	change	percentage
1.77	1.31	-0.46	-0.25989	-25.9887006
1.65	1.41	-0.24	-0.14545	-14.5454545
1.76	1.5	-0.26	-0.14773	-14.7727273
2.88	2.5	-0.38	-0.13194	-13.1944444
2.18	1.89	-0.29	-0.13303	-13.3027523
2.07	2	-0.07	-0.03382	-3.38164251
1.82	1.71	-0.11	-0.06044	-6.04395604
1.7	1.57	-0.13	-0.07647	-7.64705882
2.35	1.85	-0.5	-0.21277	-21.2765957
1.84	1.77	-0.07	-0.03804	-3.80434783
1.02	0.99	-0.03	-0.02941	-2.94117647
2.37	NOT DONE	NOT D	NOT DON	NOT D
1.71	2	0.29	0.169591	16.9590643
1.36	1.22	-0.14	-0.10294	-10.2941176
1.75	1.77	0.02	0.011429	1.14285714

2.41	2.13	-0.28	-0.11618	-11.6182573
1.17	1.21	0.04	0.034188	3.41880342
1.42	1.51	0.09	0.06338	6.33802817
1.86	1.86	0	0	0
2.61	2.4	-0.21	-0.08046	-8.04597701
2.43	1.84	-0.59	-0.2428	-24.2798354
2.66	1.62	-1.04	-0.39098	-39.0977444
1.66	1.49	-0.17	-0.10241	-10.2409639
1.77	1.71	-0.06	-0.0339	-3.38983051
1.89	2.39	0.5	0.26455	26.4550265
1.79	1.76	-0.03	-0.01676	-1.67597765
1.92	1.82	-0.1	-0.05208	-5.20833333
1.28	1.5	0.22	0.171875	17.1875
1.86	1.74	-0.12	-0.06452	-6.4516129
2.11	2.07	-0.04	-0.01896	-1.8957346
NOT DONE	NOT DONE	NOT D	NOT DON	NOT D
NOT DONE	NOT DONE	NOT D	NOT DON	NOT D
2.2	1.48	-0.72	-0.32727	-32.7272727
1.56	1.06	-0.5	-0.32051	-32.0512821
2.06	1.96	-0.1	-0.04854	-4.85436893
1.23	2.02	0.79	0.642276	64.2276423
1.23	1.23	0	0	0
0.75	1.67	0.92	1.226667	122.666667
3.42	4.09	0.67	0.195906	19.5906433
1.43	1.59	0.16	0.111888	11.1888112
2.49	1.95	-0.54	-0.21687	-21.686747
0.79	0.71	-0.08	-0.10127	-10.1265823
2.2	2.36	0.16	0.072727	7.27272727
1.86	2.49	0.63	0.33871	33.8709677
1.33	0.8	-0.53	-0.3985	-39.8496241
1.67	1.47	-0.2	-0.11976	-11.9760479
1.73	1.72	-0.01	-0.00578	-0.57803468
1.41	1.36	-0.05	-0.03546	-3.54609929
1.77	1.76	-0.01	-0.00565	-0.56497175
2.47	2.47	0	0	0
2.26	2.6	0.34	0.150442	15.0442478
3.02	2.49	-0.53	-0.1755	-17.5496689
1.61	1.55	-0.06	-0.03727	-

				3.72670807
1.63	1.48	-0.15	-0.09202	-9.20245399
1.51	1.18	-0.33	-0.21854	-21.8543046
1.65	1.61	-0.04	-0.02424	-2.42424242
1.68	2.02	0.34	0.202381	20.2380952
1.97	2.6	0.63	0.319797	31.9796954
1.68	1.84	0.16	0.095238	9.52380952
2.44	2.22	-0.22	-0.09016	-9.01639344
2.44	2.41	-0.03	-0.0123	-1.2295082

LUNG FUNCTION TEST OUTCOME FVC 1:(1)STATIC. (2)DECLINED (3).NOT DONE (4).IMPROVED

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fev1/fvc last		6MINUTE WALK TEST	DIFFUSION CAPACITY OF CARBON MONOXIDE (DLCO)		
	81%	NOT DONE			40%
	75%	580M			50%
	81%	400M			30%
	71%	380M			45%
	76%	470M			50%
	79%	360M			40%
	73%	480M			60%
	85%	NOT DONE	NOT DONE		
	69%	NOT DONE	NOT DONE		
	82%	380M			30%
	79%	360M			35%
NOT DONE		NOT DONE			30%
	86%	600M	NOT DONE		
	82%	480M			50%
	63%	380M			55%
	82%	390M			45%
	87%	NOT DONE	NOT DONE		
	78%	NOT DONE	NOT DONE		
	66%	368M			40%
	85%	320M			30%
	64%	390M			45%
	80%	400M			41%
	73%	380M			30%
	82%	NOT DONE	NOT DONE		
	83%		NOT DONE	NOT DONE	
	89%	600M			40%
	60%	300M			30%
	95%	NOT DONE	NOT DONE		
	60%	NOT DONE	NOT DONE		
	75%	300M			60%
NOT DONE		NOT DONE	NOT DONE		
NOT DONE		NOT DONE	NOT DONE		

74%	300M		41%
80%	360M		39%
69%	NOT DONE	NOT DONE	
70%	NOT DONE		38.30%
98%	NOT DONE	NOT DONE	
80%	400M		35%
91%	NOT DONE	NOT DONE	
58%	NOT DONE	NOT DONE	
68%	NOT DONE		33%
132%	NOT DONE	NOT DONE	
81%	390M		70%
72%	NOT DONE	NOT DONE	
61%	NOT DONE	NOT DONE	
88%	NOT DONE		33%
83%	285M		44%
85%	320M	33,5%	
73%	NOT DONE	NOT DONE	
77%	NOT DONE	NOT DONE	
77%	NOT DONE	NOT DONE	
67%	228m		25%
77%	NOT DONE		36%
76%	320M		40%
75%	175M		28.50%
61%	NOT DONE	NOT DONE	
70%	NOT DONE		55.50%
85%	NOT DONE	NOT DONE	
90%	460M		49%
86%	600M		74%
87%	331M	NOT DONE	

RF LEVEL	RF(1).POSITIVE (2).NEGATIVE 3.NOT DONE	ANTI CCP LEVEL(1).POSITIVE (2).NEGATIVE 3 NOT
200		1
20		1
0.1		2
147		1
180		1
not done		3
not done		3
not done		3
not done		3
16		1
401		1
not done		3
84		1
not done		3
not done		3
180		1
0		2
206		1

54	1
208	1
164	1
116	1
0	2
103	1
not done	3
72	1
221	1
35	1
0	2
62	1
not done	3
191	1
81	1
496	1
160	1
160	1
51	1
381	1
not done	3
0	2
163	1
307	1
not done	3
0	2
not done	3
81	1
not done	3
34	1
0	2
395	1
107	1
117	1
518	1
305	1
93	1
340	1
73	1
42	1
267	1
206	1
566	1

HIV N NEGATIVE P POSITIVE
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