Abnormal Spirometry in Patients with Rheumatoid Arthritis Attending a Quaternary Clinic in Durban, South Africa

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A. Declaration

I hereby declare that this research project is my own original work, and to the best of my knowledge and belief, it contains no material previously published or written by any other person, nor material that has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgement has been made in the text.

Anisa Parasram	14 November 2021
_____	_____
Student's Full Names (first, middle, and last name)	Date

B. Dedication

This thesis is dedicated to my loving parents, brother and sister. Thank you for the support and encouragement throughout this educational journey.

C. Acknowledgement

I would like to acknowledge and give my warmest thanks to my clinical supervisors Dr. Fakey-Khan and Mrs. K. Naidoo who made this work possible. Your guidance and sound advice carried me through all the stages of writing this project.

I would also like to thank Dr. R. Prakaschandra, my research methodology lecturer and 4th year clinical co-ordinator for your endless encouragement and advice which contributed tremendously to the completion of this mini-dissertation.

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H. List of abbreviations

- ATS-ERS : American Thoracic Society and European Thoracic Society
- COPD : Chronic Obstructive Pulmonary Diseases
- CT : Computed Tomography
- DOH : Department of Health
- DRC : Departmental Research Committee
- FEV_1 : Forced Expiratory Volume in One Second
- FEV1/FVC ratio : Tiffeneau-Pinelli Index
- FVC : Forced Vital Capacity
- GPA : Granulomatosis with Polyangitis
- HRCT : High Resolution Chest Tomography
- IALCH : Inkosi Albert Luthuli Central Hospital
- ILD : Interstitial Lung Disease
- IREC : Institutional Research Ethics Committee
- KZN : Kwa-Zulu Natal
- PFL : Pulmonary Function Laboratory
- PFT(s) : Pulmonary Function Test(s)
- PTB : Pulmonary Tuberculosis
- RA : Rheumatoid Arthritis
- RV : Residual Volume
- SLE : Systemic Lupus Erythematosus
- TLC : Total Lung Capacity

I. Abstract

Introduction: Rheumatoid arthritis (RA) is described as a chronic inflammatory autoimmune disease that predominantly affects the joints. Extra-articular manifestations include a multitude of other bodily organs such as the heart, blood vessels, and peripheral nerves; however, pulmonary involvement is most commonly seen in these diseased patients. The objectives of the present research aimed to determine the prevalence of abnormal spirometry in patients with RA and to measure the association between abnormal spirometry patterns and abnormal high resolution computed tomography (HRCT) findings within this population.

Materials and Methods: A retrospective, cross-sectional study conducted on 140 [117 (83.6%) female and 23 (16.4%)] rheumatoid arthritis patients were evaluated for lung involvement by spirometry and HRCT scan. Information was obtained via electronic chart review. Measured forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the FEV_1/FVC ratio were considered as the parameters in this study.

Results: A high prevalence of pulmonary function abnormalities (52.9%) was seen in rheumatoid arthritis patients. An obstructive pattern was observed in 32.9% of the cases. A restrictive pattern was found in 17.9% and 2.1% revealed a mixed obstructive-restrictive pattern. On HRCT, majority of the patients revealed to have interstitial lung disease as the common finding. There was no significant association ($p=0.921$) between abnormal spirometry and abnormal HRCT. The most common respiratory symptom experienced was dyspnoea.

Conclusion: Different patterns of pulmonary function abnormalities can be manifested in RA patients and obstruction represents the most common feature in this study. Spirometry should not be used as a sole screening tool, HRCT scans should be incorporated into practice since it is sensitive enough to detect lung alterations.

1. Chapter One: Introduction

1.1. Introduction and Background

Rheumatoid arthritis (RA) is described as a chronic inflammatory autoimmune disease that predominantly affects the joints thus leading to eventual joint deformity. It frequently occurs more in females, by at least three times as more than in males with age related differences (Khadhum *et al.* 2017: 110; Divya: 2015: 2). The global prevalence of RA is roughly 0.5-1% but there is some variability among several populations (Khadhum 2017: 110).

Extra-articular manifestations include a multitude of other bodily organs such as the heart, blood vessels, peripheral nerves, however, pulmonary involvement is most commonly seen in these diseased patients (Khadhum *et al.* 2017:110; Yunt and Solomon 2015: 1). Within the confines of the lungs, manifestations differ and may involve the airways (bronchiectasis), parenchyma (interstitial lung disease – ILD), vascular compartments (pulmonary hypertension), and/or the pleura (pleural effusion) (Yunt and Solomon 2015: 1). This may be a reason why many of the RA diagnosed patients reveal an abnormal pattern such as restrictive, obstructive or mixed upon performing the pulmonary function tests (PFTs). In saying this, these patients can also reveal a normal lung function.

1.2. Study Aims and Objectives

1.2.1. Problem Statement

Various regions around the world have conducted pulmonary function based studies on individuals diagnosed with RA and many of them revealed to have abnormal lung functions. A study done by Madhavan (2017: 2000) on 30 RA patients had mentioned that through spirometry testing 36.6% of them showed an abnormal pattern of which 26.6% were obstructive and 10% were restrictive. However, this was not the case in two other studies, the two sources, (Kadhum *et al.* (2017: 111); Chattopadhyay *et al.* (2015: 29)) contrasted the result and revealed that there were more RA patients who showed a restrictive pattern rather than an obstructive one, which was 22.5% and 28.3%, respectfully. A fourth study by Bilgici *et al.* (2004: 431) found that a mixed pattern was the most prevalent among RA patients.

It has been noted that the region of the study along with the particular characteristics of the study population will also play a role in the results obtained (Chattopadhyay *et*

al. 2015: 29). Many of these studies have been conducted overseas and there is very limited amount of data available in South Africa particularly of the Kwa-Zulu Natal province. Thus the present research aims to fill that paucity of data by providing valid information on our country's particular population since we encompass of various races and ethnicities.

Another gap that was identified across many studies as a limitation was a small sample size. Smaller samples sizes may lead to a type II error. A very large sample size is not recommended as well. If a study has an appropriate sample size then more precise and accurate conclusions can then be drawn. The sample size for the present study is 224.

From existing literature it has been noted that pulmonary involvement is common in patients who are diagnosed with RA as mentioned in the study by (Yunt and Solomon 2015: 1) however; the uncertainty lies with which spirometric abnormality is most the prevalent and this is likely due to the various types of pulmonary manifestations associated with RA. Hence, the research question arises, which spirometric abnormality is the most prevalent among RA patients. The present study hypothesizes that the prevalent pattern to be seen will be a restrictive one since ILD is the most common pulmonary manifestation of RA (Shaw *et al.* 2015: 1) as it is regarded as a parenchymal disease.

1.3. Aims and objectives

1.3.1. The Aim of the Study

To determine which spirometry pattern was prevalent among RA patients who presented to the Pulmonary Function Laboratory at Inkosi Albert Luthuli Central Hospital (IALCH) between the time periods 2017 to 2019.

1.3.2. The Objectives of this Research are as follows:

- To describe the demographic profile of the study population.
- To determine the prevalence of abnormal spirometry in patients with RA.
- To measure the association between abnormal spirometry patterns and abnormal high resolution computed tomography (HRCT) findings as well as the demographic profile in patients diagnosed with RA.

1.4. Rationale

Respiratory illnesses are a significant contributor to the mortality and morbidity in patients with RA – ranking as the second major cause of death in this particular population. However, the rationale for the present study arises from the varying spirometric patterns seen on the PFT which may be due to the geographic location of the study as well as the particular characteristics of the population being studied. In addition, there is a paucity of data among the South African population and by pursuing this study it will help to shed light on the pattern of pulmonary dysfunction in the established country's scenario.

1.5. Methodology and Data Analysis

1.5.1. Sample Population

The present study was conducted in the Pulmonology Department AT IALCH which is a quaternary care referral hospital, encompassing both public and private partnerships. It is located on Vusi Mzimela Road, Mayville, Durban, KZN, South Africa. As a central hospital it provides highly specialized care for the entire population of KZN. No sampling strategy was necessary since the researcher will collect data from an electronic system and intends to use all of the available records.

A power analysis calculation was used to determine the minimum sample size that should be maintained in order to provide valid statistical conclusions. The main statistical analysis method in the present study included testing the independent associations between two categorical variables – using the Chi-square test. In the application of the Chi-square test, sample sizes usually detect effect sizes between 0.1-0.5. Using Gpower software version 3.1.9.7 for sample size calculation, it is estimated that a sample size of least 224 participants is required to detect a medium effect size of 0.3 about 80% of the time.

1.5.2. Selection Criteria

1.5.2.1. Inclusion Criteria:

- Patients who are already diagnosed with RA.
- Adults of all races and both genders (18 years and older).
- Patients who are also on medication that are used to treat RA such as methotrexate.

- Patients who have at least one PFT performed any time between the years of 2017 and 2019.
- RA patients who also have respiratory diseases such as chronic obstructive pulmonary diseases (COPD), asthma and/or past pulmonary tuberculosis (PTB).

1.5.2.2. Exclusion Criteria:

- Patients with flow-volume loops that show artefacts.
- Patients who have other connective tissue diseases that overlaps with RA such as scleroderma, granulomatosis with polyangitis (GPA), Churg-Strauss syndrome, Systemic Lupus Erythematosus (SLE), polymyositis/dermatomyositis and Marfan syndrome.

1.6. Data Collection

The relevant permissions of approval have been sought from the appropriate committees [Departmental research committee (DRC), Institutional Research Ethics Committee (IREC), Department of Health (DoH), the Head of Department of the Pulmonology Department and Hospital management/CEO] which allowed data collection to proceed. All data that was collected were secondary data (via electronic chart review) thus making this study a retrospective one.

The researcher developed a list of rheumatology patients who had visited the laboratory between the years 2017 and 2019 by manually sifting through the log book kept at the pulmonary function laboratory (PFL). Once the list with patient identification numbers was compiled, the researcher manually went through patient files that are found on IALCH's database called MEDITECH in search of those who met the inclusion criteria. Of those who have, they were recruited as participants in the present study. All information obtained was recorded on an MS Excel spread sheet and all patient data was kept strictly confidential by having it cleaned and coded as necessary before analysis could take place.

In other words, the process of data collection was conducted and undertaken in a professional manner. All information was collected only by the researcher to ensure that there were no leakages of any patient information. All data collected and captured as electronic format was password protected (encryption) and was only

accessible by the researcher. Any hardcopies of captured data was safely stored in a secure cabinet, once again, that was only accessible to the researcher.

Patient's personal details (name, surname and hospital identity numbers) were only known to the researcher for the purpose of sorting, cleaning and coding of the data. Coding of the data allowed each patients information to be anonymised by allocating each of them a study number thus ensuring a strict level of confidentiality. All documents will be stored for a maximum of 5 years after the conclusion of the study. Thereafter, those documents will be appropriately disposed of; hardcopies will be shredded and soft copies stored on password encrypted devices will be permanently deleted.

1.7. Statistical Methods

Both descriptive and inferential statistics was used to present the data. Descriptive statistics is typically used to organise, describe or summarise a set of numerical data (Grand-Clement *et al.* 2018: 57). In this study, the patient's demographic profile as well as the prevalence of abnormal spirometry in patients diagnosed with RA was computed using univariate descriptive statistics. Numerical variables was presented using box plots whereas categorical variables was shown on bar and pie charts.

Inferential statistics, by contrast uses the laws of probability to predict or make inferences about the sample data in order to draw statistical conclusions (Johnson and Christensen: 2012). The third objective in this study was analysed using the chi-square test. This statistical analysis method includes testing for the independent associations between two categorical variables, i.e., spirometry patterns and HRCT findings. In the same objective, the demographic profile of the HRCT findings had been described as well. A p-value < 0.05 was considered statistically significant.

1.8. Potential Contributions of the Study

• Support the research information done by previous researchers by proving the present studies hypothesis as well as showing that spirometry is a good predictor for what would be expected to be seen on the HRCT chest scan.

• Contribute to the body of knowledge in South Africa by providing a local view on the lung function and the prevalent abnormality found in RA patients in Durban, KZN.

2. Chapter Two: Literature review

2.1. Introduction

Rheumatoid Arthritis (RA) is a chronic systematic autoimmune disease that mainly affects the joints, causing progressive, symmetric, erosive obliteration of the joints and bone (Ghammo 2020: 15) resulting in joint deformity (Divya 2015: 14). The characteristic feature of RA as described by Madhavan (2017: 2000) is persistent inflammatory synovitis, which usually involves the peripheral joints, more commonly the small joints such as the hands and feet, before affecting the larger joints. The development of RA can occur at any age with a greater incidence between the ages of 35 and 55 years, and the worldwide prevalence is roughly about 0.5-1% but there is some variability among several populations (Kadhum 2017: 110). It is further stated that RA occurs more frequently in females than in men but extra-articular manifestations of RA seem to be more frequent in men. Hence, the present study aims to investigate the pulmonary involvement in RA patients.

Extra-articular manifestations include a multitude of other bodily organs such as the heart, blood vessels, peripheral nerves or the pulmonary system (Kadhum *et al.* 2017: 110). The pulmonary system is a frequent site for the development of extra-articular disease, with an incidence ranging from 20% in some studies to as high as 67% in others (Yunt and Solomon 2015: 1; Kadhum *et al.* 2017: 110) and it may be the second most common cause of death after infections (Bilgici 2004: 429). It is explained by Yunt and Solomon (2015: 1) that within the confines of the lungs, manifestations differ and may involve the airways, parenchyma, vascular compartments, and/or the pleura. In most cases pulmonary involvement is usually the primary manifestation of RA and it may be the most aggressive attribute of the disease.

This literature review aims to discuss the context of RA, including brief discussions on extra-articular manifestations of the established disease, details on spirometry and its components and a review of past literature that is related to the present study in order to outline a rationale.

2.1.1. Historical context of Rheumatoid Arthritis

Rheumatoid arthritis was initially expressed in the year 1800 by Augustin Jacob Landre-Beauvais (Divya 2015: 13). Nine female patients presented with a sore, inflammatory arthritis which affected their hand joints by causing it to swell and eventually become deformed. He regarded it as being related to gout because of the similarities in symptoms and thus referred to it as *Primary Asthenic Gout* (ANRF: 2019) purely based on the premise of female predominance, polyarticular inflammation, pattern of joint involvement and the chronic nature of its progression. Alas, his calculation of RA being the relative of gout had been inaccurate however, in the later years it helped to refine the clinical description of RA (Divya 2015: 13).

In the mid-19th century, Alfred Garrod clearly distinguished gout from rheumatic conditions. He had described the diagnosis of gout in great detail and characterized RA as an independent entity and thus renamed it as *Rheumatic Gout.* However, Archibald Garrod, the fourth son of Alfred Garrod, gave the condition a new name; *Rheumatoid Arthritis* in the year 1890 and that name stuck throughout all these years (Divya 2015.: 13). It was also explained by Archibald that RA is not a modern age illness as it affected our ancestors and went on to note that skeletal damage was noted in the remains of human beings from ancient Egypt.

2.2. Prevalence of Rheumatoid Arthritis

Development of RA can occur at any age with an increased incidence between the ages of 35 and 55 years. The worldwide prevalence of RA is around 0.5-1%, however, there is some variability among various populations (Kadhum *et al.* 2017: 110). In developed countries such as China, the United States of America and Japan, the prevalence is about 0.42%, 0.6% and 0.75%, respectively (Jin *et al*. 2017: 2; Divya n.d.: 16 and Kojima *et al.* 2020: 1). Ghammo (2020: 15) stated that developing countries tend to have a considerably lower prevalence rate however, that did not seem to be the case as Kadhum *et al.* (2017: 110) mentioned that both Iraq and India's prevalence are 1%. Furthermore, in a systematic review and meta-analysis study carried out by Usebo *et al.* (2015: 1) it was revealed that the complete prevalence in South Africa was 2.5%. But, most of the studies included in the meta-analysis were conducted in a rural context with the African population being the main focus.

2.3. Pathophysiology of Rheumatoid Arthritis

The cause of RA is still a mystery however, numerous hypotheses have been proposed, some of which involve the super antigen-driven disease, autoimmune mechanism and infectious stimulus. Furthermore, the pathogenesis of RA remains poorly understood despite the number of investigations over the past 40 years. Though it is not fully understood, emphasis has been placed on the cellular and molecular mechanisms of the disease (Rathore, Rathore and Singh: 2019: 1).

The inflammation and stimulation of different cell populations and the release of many inflammatory and destructive mediators, including prostaglandins, cytokines and metalloproteinase are all involved in the pathogenesis of RA. Feltmann (1996 cited in Ratore, Ratore and Singh 2019: 1) stated that the pathology encompasses throughout the synovial joint and comprises of (i) tissue destruction/fibrosis, (ii) acute and chronic inflammation, and (iii) cell proliferation. In an ordinary synovium, the tissue coating the capsule of the joint is fragile, however in RA the synovium is altered into an aggressive, tumour-like structure known as the pannus, which attacks and wears away the joint.

2.3.1. T-Cells and B-Cells

T-cells (lymphocytes) and B-cells together with the cooperation of a few cytokines (pro-inflammatory substances) assume an imperative part in the pathophysiology of RA as well, and the primary event is the initiation of innate immune response following an unidentified antigenic stimulus that could either be exogenous or autologous (Divya 2015: 17). The adaptive immune system is also involved and together they lead to complex autoimmune and inflammatory processes that typify RA with the features of synovitis, swelling and joint harm (Rathore, Rathore and Singh: 2019: 2).

Knowledge on the participation of T-cells in RA has been studied by several researchers and it has been shown that there is some correlation between the two variables. The lymphocytes account for the mononuclear infiltrate within synovial sub-lining. The hereditary evidence involving the Human Leukocytes antigens (HLA-DR) alleles suggests T lymphocytes play a role as well. It also suggests that HLA-DR alleles are involved in a pathogenic course at the level of antigen presentation by the major histocompatibility complex (MHC) (Rathore, Rathore and Singh: 2019: 2). Divya (2015: 17) has noted that most RA patients carry a peculiar epitope, which is a

piece of an antigen to which an antibody binds, of HLA-DRB1*04 cluster. This disease related HLA-DR alleles present the arthritis-related peptides, subsequently resulting in the simulation and development of auto-antigen specific T-cells in the lymph node.

Within a vulnerable person, the interaction of the environment and the genes results in a loss of tolerance of self-protein that contains a citrulline residue. The enzyme peptidylarginine deiminase induces the generation of citrulline residue via post translational alteration of arginine (Gibofsky 2014: S129). It is further mentioned that in individuals with shared epitope alleles, there tends to be a generation of citrullinated peptides that is not recognisable as 'self' by the immune system. Therefore, it subsequently produces Anti-Citrullinated Protein Antibodies (ACPAs). Divya (2015: 17) has reported that HLA-DR and HLA-DR4 shared epitope alleles are related to an increased sensitivity to RA and apart from these alleles there are at least 30 which increase the susceptibility of the disease as well.

B-cells have a vital role in the pathogenesis of autoimmune diseases and therefore in RA. It plays a dual role in the established disease, one as antigen presenting cells in which they aid in developing autoimmunity, and the second being the creation of cytokines and autoantibodies that intervene the inflammatory cascade. Significant biomarkers for evaluating disease activity in RA are the autoantibodies anti-CCP and Rheumatoid Factor (RF) and because of these autoantibodies, there is formation of immune-complexes that further animates the creation of pro-inflammatory cytokines such as TFN-alpha (Rathore, Rathore and Singh: 2019: 2; Divya 2015: 18). RF antibody is present in roughly 75-80% of RA patients and is now commonly used as a diagnostic indicator for the disease. RF autoantibodies are directed to the crystallisable fragment of immunoglobulin G (IgG) molecules. It has a self-binding capacity that can lead to the development of very large immune complexes (Rathore, Rathore and Singh 2019: 2).

2.3.2. Cytokines

The inflammatory response comprises of the serial release of mediators as well as the recruitment of circulating leukocytes, which are initiated at the inflammatory site and thus further mediators are released. The main task of the cytokines are to regulate the progression and upkeep of autoimmunity: obstructing their action with

antibodies can either reduce or aggravate RA. Cytokines are local protein mediators that partake in most of the biological cycles, such as cell development and activation, inflammation, immunity and differentiation. Though cytokines secreted by both T-cells and non T-cells are present, macrophage derived cytokines like TNF-alpha IL-6 and IL-1 are more plentiful than those of T-cell origin such as IFN-g, IL-4 and IL-2. The inflammatory cytokines are more abundant in the tissue and synovial fluid and they are both potent triggers of synovial tissue functions, mainly adhesion molecule expression, proliferation and prostaglandin production within the inflamed joint (Rathore, Rathore and Singh: 2019: 2)

2.4. Extra-articular manifestations of Rheumatoid Arthritis

2.4.1. Dermatological manifestations

The most common skin manifestation is rheumatoid nodules but it can also appear within the heart, lung and the upper airway. It is frequently found in the extensor aspect of the forearm and in patients that have a positive RA factor. These nodules are pulmonary lesions that are comprised of central fibrinoid necrotic region surrounded by granulation tissue, lymphocytes, fibroblasts mononuclear cells and plasma cells. Nodules in the lung can present in either single or several nodules and are classically found in the pleural or sub pleural regions (Yunt and Solomon 2015: 5). Due to the sub pleural distribution, these nodules can cause complications such as pleural effusions, empyema and pneumothorax (Divya 2015: 35).

Other manifestations that affect the skin are digital gangrene, periungual infarcts and leg ulcers among others. They appear in areas where the skin is exposed as well as the lower appendages. Dermatological manifestations are often connected with pericardial and pleural effusions and episcleritis (Divya 2015: 29)

2.4.2. Ocular manifestations

Common ocular manifestations like episcleritis, keratoconjunctivitissicca and scleritis are seen in about 10% of RA affected patients. It is often accompanied with xerostomia in secondary Sjogren's syndrome. Episcleritis is a self-restricting condition that involves the superficial layer of the sclera. Scleritis is characterised by painful inflammation of the sclera and is an aggressive form of an ocular involvement (Divya 2015: 29).

2.4.3. Cardiac manifestations

Forms of cardiac involvement in RA include: valvular endocarditis, pericarditis and myocarditis or atherosclerotic coronary occlusions. Clinically evident pericardial involvement is infrequent however; in autopsy up to 50% of patients had pericardial inflammation and most had a positive RF. There is a higher risk of the development of atherosclerotic plague in the coronary vessels, and in individuals with RA, the risk of myocardial infarction is twice as high as compared to non RA patients but if the duration of the illness has exceeded ten years then the risk is tripled (Divya 2015: 29).

2.4.4. Haematological manifestations

Manifestations such as neutropenia, anaemia, thrombocytopenia and thrombocytosis, eosinophilia and haematological malignancies are often seen in RA patients but the most common abnormality is anaemia. Various reasons can induce anaemia such as bone marrow suppression and feeble erythropoiesis, drugs, chronic gastro-intestinal bleed and nutritional causes. Thrombocytosis is frequently seen all through the disease activity and is associated with the amount of joints that are actively inflamed (Divya 2015: 29).

2.4.5. Pulmonary manifestations

Lung involvement is frequent in RA patients and it contributes significantly to the morbidity and mortality rate. Pulmonary manifestations may precede the joint symptoms and may frequently happen when there is active disease progression. The manifestations could be caused in view of the inflammatory cascade and its effect on the lung parenchyma or it could be drug-actuated by medication used to treat RA.

Common clinical manifestations on the onset of RA include joint pain, stiffness, swelling, fatigue, musculoskeletal symptoms, anorexia and generalised weakness. Joint inflammation, in most cases leads to destruction and disfigurement ultimately causing significant disability, which hinders the patients' quality of life. Some of the lung diseases involved in RA is (Box 1): (i) rheumatoid nodules, (ii) ILD, (iii) diseases of the airways and, (iv) pleural disease (Divya 2015: 29).

2.4.5.1. Interstitial Lung Disease

Interstitial Lung Disease (ILD) refers to a varied group of parenchymal lung disorders categorised by distinct clinical, pathological and radiographic features (Yunt and

Solomon 2015: 2). The established disease is a common manifestation of RA and the prevalence of the illness ranges between 19% and 44% (Biomdo 2010: 15). In a study conducted by Ghammo (2020: 26) on 61 RA-ILD patients it was revealed that 52 (85.5%) of the 61 showed a restrictive defect on spirometry whereas 6 (9.8%) had an obstructive pattern and 3 had missing data. Therefore the prevalent abnormality seen in this specific study was restriction.

The common forms of RA-ILD are nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) however, other forms like organising pneumonia (OP), diffuse alveolar damage and lymphocytic interstitial pneumonia among others, have been described but are less common (Yunt and Solomon 2015: 2). In the aforementioned study by Ghammo (2020: 26) the most common feature on HRCT was UIP (36.1%), NSIP (19.7%) and bronchial obliterans (BO) (9.8%). In a study by Cortet *et al.* (1997: 598), HRCT was abnormal in 55 (80.9%) out of 68 patients. Bronchiectasis was detected to be the most frequent abnormality seen on HRCT (18 patients – 30.5%) followed by pulmonary nodules (28%) and air trapping (25%).

Risk factors are associated with old age, history of smoking, alcohol consumption, patients who are already diagnosed with RA, those who have a family background of the disease or the male sex (Yunt and Solomon 2015: 2; Biomdo 2010: 15). Even though it has been established that men have a higher prevalence of developing extra-articular manifestations of RA such as RA-ILD, in the study by Ghammo (2020: 25), it has been proven otherwise since more females, 90.2% were included in the study than men (9.8%). This indicates that more females than males presented with this specific extra-articular manifestation.

The earliest and predominant clinical symptoms include progressive dyspnoea and a cough of gradual onset. This is in-keeping with the studies conducted by Cortet *et al.* (1997: 598) and Bilgici (2004:431). Other frequent symptoms are fatigue and generalised weakness (Yunt and Solomon 2015: 2). Irreparable fibrosis, increasing pulmonary hypertension and cor pulmonale may develop as well (Biomdo 2010: 32).

The preliminary diagnostic evaluation for RA patients who present with respiratory signs include assessments of lung physiology through radiographic imaging with HRCT and PFTs as well as the assessment of the patient's oxygenation both during movement and rest. The PFTs ought to include measurements of lung volumes,

airflow with reversibility testing, and diffusion capacity for carbon monoxide (DLCO) measurements (Yunt and Solomon 2015: 2).

The pathophysiology remains unclear, however environmental and genetic factors are suggested to play a critical part in the development of RA associated ILD (Biomdo 2010: 16). According to Yunt and Solomon (2015: 2) specific HLA variants HLA-B54, HLA-B40, HLA-DQBI*0601, and HLA-DR4 have been reported to be associated with RA. Another factor that is linked to RA is cigarette smoking. In individuals with a smoking history, the risk of developing RA is at least 1.3 to 2.5 times greater (Divya 2015: 3).

Circulating autoantibodies are normally present in patients with RA with the most common ones being RF and anti-cyclic citrullinated peptide (anti-CCP), and they can be present in the serum some years before clinical disease onset (Ghammo 2020: 13).

The treatment of choice is glucocorticoid therapy but other drugs that have been reported to be valuable include azathioprine, cyclophosphamide, cyclosporine, D-penicillamine and hydroxychloroquine (Biomdo 2010: 17).

2.4.5.2. Pulmonary airway disease

The prevalence of airway disease in RA is high and it has been established that any part of the airway may be affected by it. The most common manifestations include both the large (upper and lower) airways and the distal small airways (Yunt and Solomon 2015: 5). In a study by Madhavan (2017: 2001) the commonality of airway disease was depicted. From the 30 RA patients who participated in the study 11 (36.6%) of them had PFT abnormalities from which 20% had small airway disease, 6.6% had large airway disease and 10% showed a restrictive pattern.

The most common manifestations of large airway diseases have been distinguished as cricoarytenoid arthritis and bronchiectasis (Yunt and Solomon 2015: 5). Bronchiolitis falls under the category of small airway diseases which predominantly affects the distal airways (2mm in diameter or less) and it can be present in two forms, either as follicular bronchiolitis or constrictive bronchiolitis (Biomdo 2010: 18). PFTs and HRCTs are useful in the detection of airway involvement; however HRCT

has a greater sensitivity for detecting small airway disease than PFTs (Yunt and Solomon 2015: 5).

Cricoarytenoid arthritis occurs in up to 75% of patients and can lead to midline adduction of the vocal cords thus causing hoarseness as well as inspiratory stridor in a number of cases. Bronchiectasis, described as the destruction and widening of the large airways occurs in as many as 16% to 58% of RA patients (Yunt and Solomon 2015: 5). It can occur as a result of recurrent infections, traction bronchiectasis or progression of constrictive bronchiolitis (Biomdo 2010: 23). Yunt and Solomon (2015: 5) also mentioned that when cases of bronchiectasis are present, symptoms often include cough, sore throat as well as sputum production.

Follicle bronchiolitis is pathologically recognised by the occurrence of hyperplastic lymphoid follicles with reactive germ cell centres found in the bronchial walls. Whereas, constrictive bronchiolitis is recognised by constriction of the membranous as well as the respiratory bronchioles, which may be as a result of scarring and peribronchiolar inflammation without evidence of lymphoid hyperplasia (Yunt and Solomon 2015: 5; Divya 2015: 33). Featured symptoms include dyspnoea and non-productive cough. In these diseased patients, the chest radiographs are generally normal but the PFTs depict airflow obstruction with a decreased ratio of Forced Expiratory Volume in one second to the Forced Vital Capacity (FEV_1/FVC), owing to air trapping. In addition, results of DLCO are normal (Biomdo 2010: 18-19).

Table 1 Showing the pulmonary manifestations of Rheumatoid Arthritis

Interstitial lung disease	• Usual interstitial pneumonia • Nonspecific interstitial pneumonia • Organizing pneumonia • Lymphocytic interstitial pneumonia • Acute interstitial pneumonia
Airways disease	• Follicular bronchiolitis • Constrictive bronchiolitis (obliterative bronchiolitis) • Bronchiectasis

	• Cricoarytenoid arthritis
Pleural disease	• Pleuritis • Pleural effusion • Pneumothorax • Empyema
Vascular disease	• Pulmonary hypertension • Vasculitis
Rheumatoid nodules	
Rheumatoid pneumoconiosis (Caplan syndrome)	
Drug toxicity	
Infection	
Amyloidosis	
Fibrobullous disease	

2.5. Pulmonary function tests (PFTs) – spirometry and High Resolution Computed Tomography (HRCT)

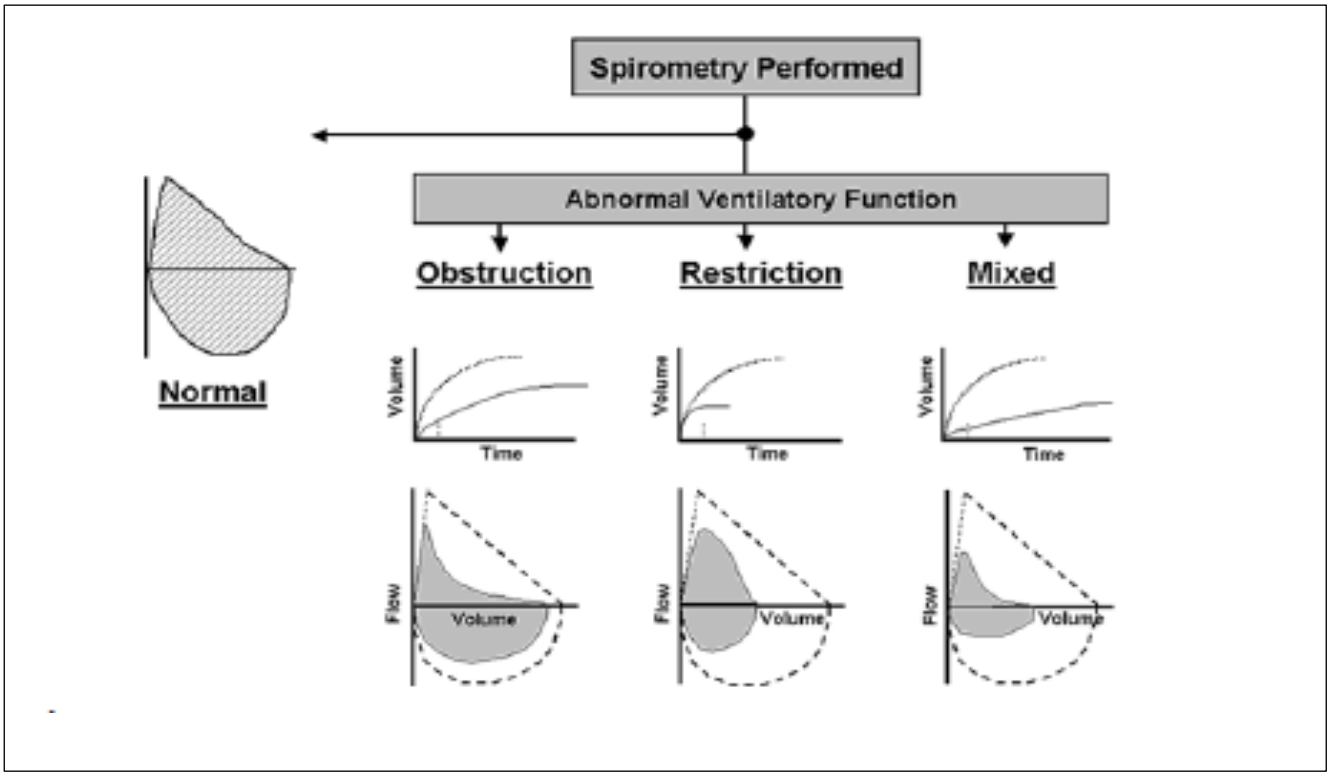
PFTs (spirometry, lung volumes and DLCO) are often performed to diagnose and categorise disease processes that cause pulmonary impairment. Volume restriction, airflow obstruction or the combination of obstructive and restrictive defects can be categorised as pulmonary abnormalities. Other PFTs include flow-volume loops which records forced expiratory and inspiratory flow rates (Biomdo 2010: 27) (BOX 2). It is used to measure the movement of air into and out of the lungs during various breathing manoeuvres (Divya 2015: 36). Some of the indications include evaluation of respiratory symptoms, bronchodilator therapy, and occupational exposure or to evaluate the severity and progression of lung diseases like asthma, COPD and multiple restrictive diseases (Biomdo 2010: 27).

The primary measurements of spirometry are the FEV_1, which is defined as the measure of the volume expired over the first second of an FVC manoeuvre (Mottram 2018: 1117), FVC is the total volume of air expired with maximal effort after a maximum inspiration and the ratio of the two volumes which is critical in distinguishing obstructive airway and restrictive diseases (Divya 2015: 38; Biomdo 2010: 27).

Mottram (2018: 1127) defines obstruction as any process that interferes with the airflow into or out of the lungs. Examples include asthma, COPD, bronchiectasis among others. Restrictive diseases such as pulmonary fibrosis or ILD are characterised by reductions of lung volumes, and processes that affect the bellows action of the lungs and chest wall usually cause restriction (Mottram 2018: 71). Box 2 illustrates the obstructive and restrictive patterns that can be detected using spirometry.

According to Biomdo (2010: 27) a normal ratio indicates a restrictive defect, if it is accompanied by decreased lung volumes but, a reduced ratio could indicate an obstructive airway disease. Coexisting obstruction and restriction can also be identified but requires both spirometry and lung volumes. This guideline will help achieve the aim of the present study which seeks to determine which abnormal spirometry pattern is the most prevalent among RA patients.

BOX 2. The diagram below illustrates the normal and abnormal shapes of the flow-volume curves as well as the spirograms for obstructive, restrictive and mixed ventilatory defects (Pierce and John 2008: 11).



BOX 3. Illustrating normal and abnormal spirometry parameters (Neill and Nolan, 2015:17; Chattophadyay 2015: 28).

Parameters	Normal	Obstructive	Restrictive	Mixed (obstructive and restrictive)
FEV_1	More than or equal to 80% of predicted value (≥80%)	<80% of predicted value.	Normal to <80% of predicted value.	<80% of predicted value.
FVC	≥80% of the predicted value.	Normal to <80% of predicted value.	<80% of predicted value.	<80% of predicted value.
FEV_1/FVC ratio	≥70% of the predicted value.	Normal to <70% of predicted value.	Normal to >70% of predicted value.	<70% of predicted value.

High Resolution Computed Tomography imaging of the lungs is useful for diagnosing and managing a variety of pulmonary diseases. It has been noted by HRCT Lungs

(2020: 1) that the key objective of HRCT is to detect, characterize and determine the extent of diseases that involve the lung parenchyma and airways. HRCT images are normally acquired at suspended full inspiration with the patient in a supine position.

2.6. Review of literature

A clinical survey conducted by Davidson *et al.* (1974 cited in Divya 2015.: 38) was regarded as a landmark study. The particular reason for that circumstance was that it was one of the very first reports based on pulmonary function abnormalities in RA patients. The results concluded that significant airway obstruction was present in the vast majority of RA participants.

A prospective study was conducted by Cortet *et al.* (1997: 596) on 68 (54 female, 14 male) RA patients. In the study population, 52 were non-smokers and 16 were current smokers. Large airway obstruction was present in 6 patients (9%), small airway involvement was noted in 8 of the 59 cases (14%) – small airway involvement was not evaluated in 9 cases due to history of radiation therapy for breast carcinoma, and 8 patients (12%) revealed to have a restrictive pattern. From this study it can be noted that airway disease was the prevalent spirometry pattern, matching the outcome of the landmark study, previously mentioned. The PFT results regarding the non-smokers and current or past smokers depicted no significant difference. The most common pattern seen on the HRCT was: bronchiectasis, pulmonary nodules and air trapping.

A study piloted by Bilgici (2004: 431) yielded a greater variability in the spirometry pattern seen in RA patients. Fifty two patients (8 males, 44 females) with RA were prospectively evaluated with a mean age of 53.6 years. The PFT results revealed to be restrictive in 3 patients; airway obstruction was present in 12, 13 had normal spirometry results and a combination of both defects (mixed pattern) was present in 14 cases, thus making it the prevalent abnormality. It was revealed that 2 out of the 12 patients present with airway obstruction were smokers. Thirty nine of the patients partaking in the study were lifelong non-smokers, and 13 were current or past smokers. Among the 13 smokers, 4 showed a combination pattern on spirometry and 3 had shown an obstructive defect. Though, there was a difference in the outcome of the prevalent spirometry pattern between this study and Cortet *et al.*, a similarity was still drawn. The results of the PFTs were also not different between the

39 non-smokers and former/current smokers. This study also included HRCT findings in RA where it was found that 17 patients out of 52 revealed normal HRCT images and the remaining had abnormal HRCT with the most frequent abnormality detected as a reticulonodular pattern. In contrast, Cortet *et al,* (1997: 598) concluded that bronchiectasis was the most common feature detected on HRCT.

In another comparative, pilot study conducted by Chattophadyay (2015: 26) a total of 106 RA diagnosed patients of Indian background were selected and 50 health subjects were used as the control group. Of the 106 cases, 82 (77.36%) were females and the remaining 24 (22.64%) were males with a mean age of 42.5 ± 7.5. The control group consisted of 70% females and 30% male (mean age: 45.8 ± 6.5). Using Chi-square test, it was established that there was no significant difference in the sex between both groups. The results of the study revealed that 56.6% of RA patients had a normal lung function, 15.09% had obstructive lung disease and 28.3% presented with a restrictive defect. All participants in the control group yielded normal results. This study differs from the three reviewed studies as the dominant abnormality was restriction. The weakness of this study was that it was a pilot study thus it may not be a true representation of the population at large.

Kadhum *et al.* (2017: 109) evaluated the extent and pattern of pulmonary involvement in RA patients by using spirometry in a case control study. A total of 40 (33 (82.5%) females and 7 (17.5%) men) RA diagnosed patients was included in the study. Of the 40, 30 (75%) revealed to have normal lung functions, 9 (22.5%) showed restrictive and the remaining 1 (2.5%) had an obstructive defect. In this study the control also revealed to have normal lung functions.

In a study by Madhavan (2017: 2000) which was discussed previously, it was revealed that more RA patients presented with an obstructive defect (30% small airway disease and 6.6% large airway disease) than with a restrictive defect (10%). It was also noted that there was no correlation between age of the patient and pulmonary dysfunction (Madhavan 2017: 2002). This study concluded that a high prevalence of lung function abnormalities is often seen in RA and that males have an association with an increased risk of developing RA related pulmonary disease. This study was conducted on only the Indian population in India.

These studies have reported that significant lung function abnormalities occur in RA patients however; they have yielded varying results in terms of which spirometric abnormality was the prevalent defect.

2.7. Research problem, aims and justifications

From the reviewed literature it has been established that pulmonary involvement is common among RA patients, however varying results of the prevalent spirometric defect remain in question; since in one study a mixed pattern prevailed but in other studies the predominant defect was either restriction or airway obstruction (of both small and large airways). The causes of these variations have been hypothesised as a result of geographical variation and characteristics of the population that is being studied (Chattopadhyay *et al.* 2017: 29; Biomdo 2010: 13).

The prevalence of RA in various populations has been noted in multiple studies. In a meta-analysis study conducted by Usenbo *et al.* (2015: 1) based on the prevalence of six types of arthritis in Africa. Twenty seven cross-sectional studies were included in the analysis but of the 27 only 12 were conducted in South Africa. From the 12 studies, 6 were based on RA, however, of the 6, 3 were piloted in both a rural and urban context, and the remaining 3 were rural based. In all of these studies, the population looked at were all of African race only. The total prevalence was reported as 2.5% in South Africa.

An extensive web search for South African based studies on the prevalence of spirometry abnormalities have been undertaken by the researcher and the resultant was that there may be a lack of adequate data in the South African population. Hence, the present study will attempt to fill the paucity of knowledge in the established country's scenario. The context of the study will take place in Kwa-Zulu Natal at the Inkosi Albert Luthuli Central Hospital.

The present study differs from the previous studies conducted since it will include all races that have attended the quaternary clinic between the years 2017 to 2019 as opposed to just a single race. The inclusion of flow-volume loops together with the appropriate parameters will be looked at to identify the normal, obstructive or restrictive defect. There will be no control group; as all studies reviewed have revealed that the control groups had all yielded normal lung functions. Hence, the present study aims to investigate only RA affected patients in order to establish

which pulmonary defect is prevalent among them as well as which age and gender was most affected. In addition to this, this study will attempt to prove that spirometry testing is a good indicator for predicting the type of pulmonary disease, whether obstructive or restrictive that may be seen on the HRCT scan.

3. Chapter Three: Methods and Methodology

3.1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that predominantly affects the joints thus leading to eventual joint deformity. It frequently occurs more in females than in males with age related differences (Khadhum *et al.* 2017:110). Extra-articular manifestations involving the pulmonary system are often seen in these diseased patients (Yunt and Solomon 2015: 1). On PFTs, many RA patients reveal a normal pattern and even abnormal patterns such as restrictive, obstructive or mixed may also be seen.

The rationale of the study stems from the differing prevalent patterns reviewed from the literature which outlines that abnormal spirometry is common among patients, however, the types of abnormal patterns seen are not consistent and this may largely be due to the geographic regions and there is also a paucity of data based on lung function abnormalities in individuals from KZN, South Africa. Thus, the aim of the present study is to determine which spirometry pattern was prevalent among RA patients who presented to the PFL at IALCH between the time periods of 2017 to 2019.

The objectives are to (1) describe the demographic profile of the study population, (2) determine the prevalence of abnormal spirometry in patients with RA, and (3) to measure the association between abnormal spirometry patterns and abnormal HRCT findings as well as the demographic profile in patients diagnosed with RA.

3.2. Methodology Plan

3.2.1. Study Area

The study will be conducted in the Pulmonology Department at IALCH which is a quaternary care referral hospital, encompassing both public and private partnerships. It is located on Vusi Mzimela Road, Mayville, Durban, Kwa-Zulu Natal, South Africa. As a central hospital it provides highly specialized care for the entire population of KZN. This institution accepts referrals from all provincial regional hospitals and referrals from the Eastern Cape.

3.2.2. Study Population

The participants of the study will include adults (18 years and older) of both sexes (male and female) who are diagnosed with Rheumatoid Arthritis (RA) and has

presented to the Pulmonary Function Laboratory at IALCH between the years of 2017 to 2019. These patients will include both referred (from other hospitals) and known patients.

3.2.3. Sample Size and Sampling Strategy (Calculated as per the biostatistician P. Tinarwo – APPENDIX C)

A list of Rheumatology clinic patients who have visited the PFL between the years 2017 and 2019 have been extracted from the laboratory's book of logs. Data was then collected electronically with the intention of using all the available records hence no sampling strategy will be necessary. However, it is understood that there is a likelihood of losing power should there be elimination of some of the patient records during the data preparation process. Hence, the power analysis calculation will be to determine the minimum sample size that should be maintained in order to provide valid statistical conclusions.

The present study's main statistical analysis methods have included testing the independent associations between two categorical variables. It is assumed that the most complex contingency table to be involved will be a cross tabulation of 7-levels categorical variable (HRCT chest scan) and 4-levels categorical variable (spirometry patterns). This will give rise to a 7x4 table structure resulting in (7-1)(4-1) = 18 degrees of freedom (df).

The null hypothesis (H_0) to be tested is that there is no association between the two independent variables. The Chi-square test or Fisher's exact test depending on the frequency distribution will be used to evaluate this null hypothesis. It is assumed that should the test reject this null hypothesis when it is actually true, Type I error has been set not to exceed 5% ($\alpha = 0.05$) and this translates to a 95% confidence in the conclusions to be reached.

On the other hand, should the test fail to reject the null hypothesis when it is actually false, this Type II error has been set not to exceed 20% ($\beta = 0.20$), translating to 80% power of test. In the application of the Chi-Square test, sample sizes usually detect effect sizes between 0.1-0.5 with 0.1 considered small and desirable, 0.3 (medium) and 0.5 (large). Using Gpower software version 3.1.9.7 for sample size calculation, it is estimated that a sample size of least 224 participants is required to detect a medium effect size of 0.3 about 80% of the time. In the event that the

expected sample size becomes difficult to reach, the smaller sample sizes than the 224 will only detect higher effect sizes than 0.3 at the same 80% power of test and 5% level of significance (see figure 3).

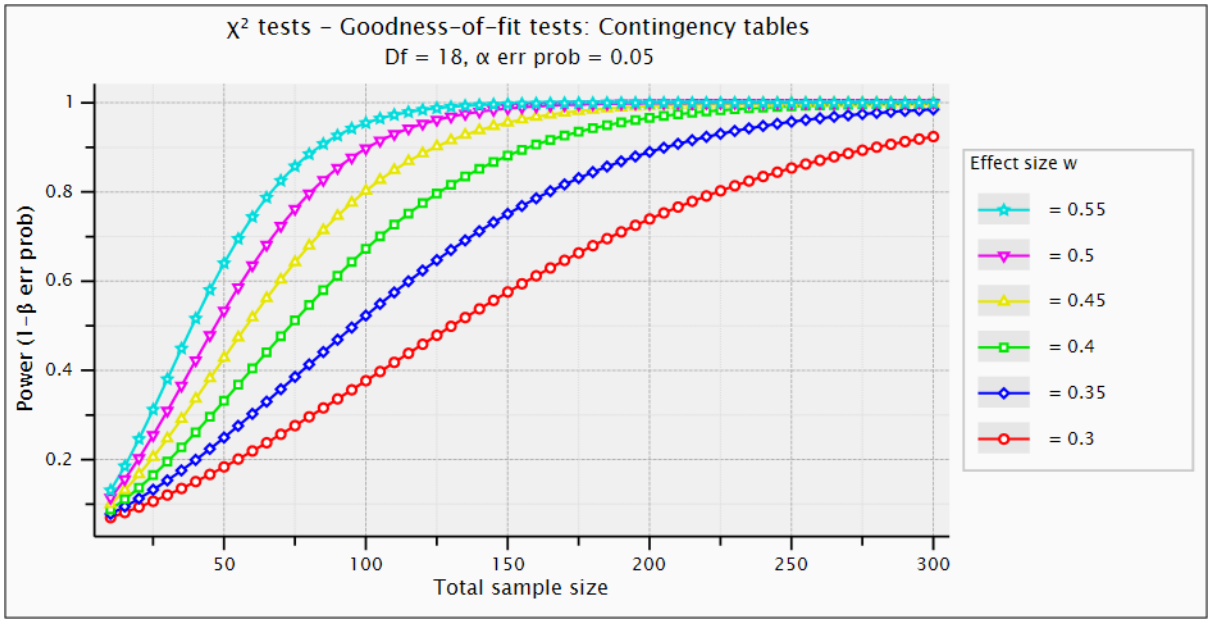


Figure 1 Sample size

3.2.3.1. Variables that will be recorded include:

1. Age
2. Sex
3. Race
4. Clinical respiratory symptoms.
5. Spirometry Parameters
    a. Forced Expiratory Volume in One Second (FEV_1)
    b. Forced Vital Capacity (FVC)
    c. FEV_1/FVC ratio
    d. Shape of the Flow-Volume curve
6. High Resolution Chest Tomography (HRCT) findings
    a. Pleural effusion/thickening
    b. Interstitial Lung Disease (ILD)
    c. Nodules
    d. Bronchiectasis
    e. Obliterans bronchiolitis
    f. Normal

g. Organising pneumonia

3.2.3.2. Inclusion Criteria

a. Patients who are already diagnosed with RA.
b. Adults of all races and both genders (18 years and older).
c. Patients who are also on medication that are used to treat RA such as methotrexate.
d. Patients who have at least one PFT performed anytime between the years of 2017 and 2019.
e. RA patients who also have respiratory diseases such as COPD, asthma and/or past PTB.

3.2.3.3. Exclusion Criteria

a. Patients with flow-volume loops that show artefacts (Appendix D).
b. Patients who have other connective tissue diseases that overlaps with RA such as scleroderma, granulomatosis with polyangitis (GPA), Churg-Strauss syndrome, Systemic Lupus Erythematosus (SLE), polymyositis/dermatomyositis and Marfan syndrome.

3.2.4. Data Collection

Full ethical approval for data collection has been granted by the IREC, IALCH's CEO/manager and the DOH. It was obtained through a formal letter directed to those of which it may have concerned.

All data that was collected are secondary data (via electronic chart review) which made this study a retrospective one. The researcher has developed a list of rheumatology clinic patients who had visited the laboratory between the years 2017 and 2019 by manually sifting the log book kept at the PFL. From that list the researcher has manually gone through the patient files present on IALCH's database called MEDITECH. Those who met the inclusion criteria were sought out. Of those who meet the criteria, they were recruited as participants in the present study. All information obtained was recorded on an MS Excel spread sheet (figure 2) and all patient data has been kept strictly confidential by having it cleaned and coded as necessary before analysis took place.

SPREADSHEET
(consultina).xlsx

Figure 2 Document of spread sheet for data collection. Kindly double click to view the document

Spirometric data (FVC manoeuvre) was measured using the spirometer brand Jaeger Masterscreen PFT and was performed by a qualified Pulmonary Function Technologist as per the American Thoracic Society and European Thoracic Society (ATS-ERS) guidelines. All measurements recorded were converted to a PDF format and uploaded on the MEDITECH system. The technique for the FVC manoeuvre according to the ATS-ERS (2005: 327) guideline is as follows:

- Anthropometric measurements are taken (height, weight, sex, age, and race).
- The procedure is explained and demonstrated by the technologist to ensure patient is aware of what is expected of them.
- The subject assumes the correct position and inserts the mouthpiece (in the mouth). Patient is then asked to breathe normally (tidal breathing).
- Then, in one continuous sequence the following should be done; a slow inspiration to total lung capacity (TLC), followed by a rapid full expiration with maximal effort to residual volume (RV) which should last for at least 6 seconds. A rapid full inspiration with maximal effort back to TLC should be performed immediately in sequence.
- Instructions should be repeated as necessary with adequate coaching.
- The parameters to be obtained from performing this manoeuvres are the FEV_1, FVC and FEV_1/FVC ratio as well as the spirogram (flow-volume curves) since the three parameters and the flow-volume curve are most commonly used in determining the type of spirometric pattern seen.
- Three tests with the FEV_1 values within 5% or 150mL of each other were defined as acceptable.

Table 2 Showing normal and abnormal spirometry parameters (Neill and Nolan, 2015:17; Chattophadyay 2015: 28)

Parameters	Normal	Obstructive	Restrictive	Mixed (obstructive and restrictive)
FEV_1	More than or equal to 80% of predicted value (≥80%)	<80% of predicted value.	Normal to <80% of predicted value.	<80% of predicted value.
FVC	≥80% of the predicted value.	Normal to <80% of predicted value.	<80% of predicted value.	<80% of predicted value.
FEV_1/FVC ratio	≥70% of the predicted value.	Normal to <70% of predicted value.	Normal to >70% of predicted value.	<70% of predicted value.

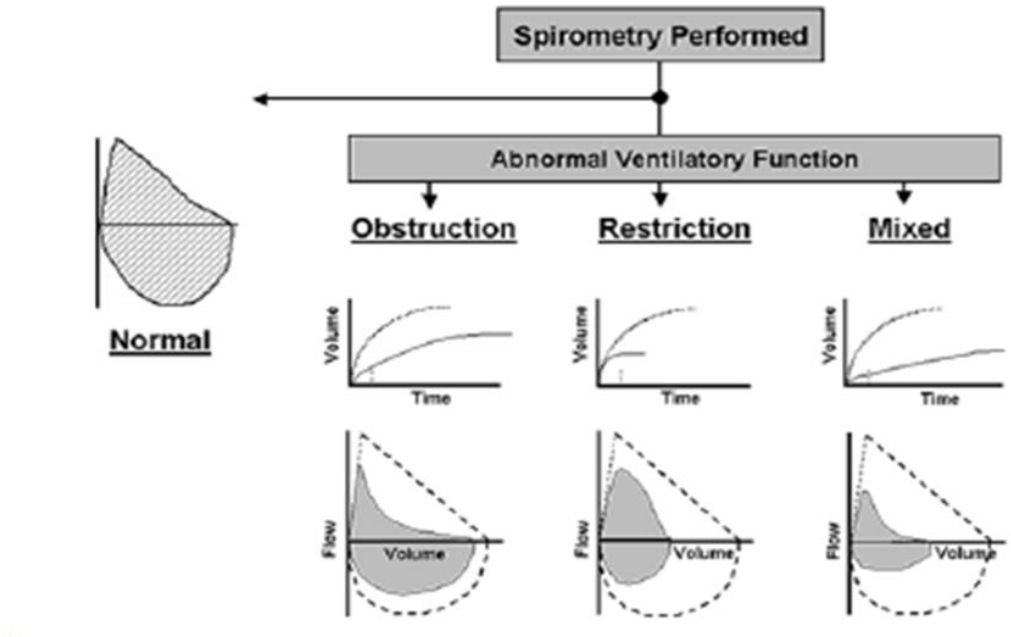


Figure 3 The diagram below illustrates the normal and abnormal shapes of the flow-volume curves as well as the spirograms for obstructive, restrictive and mixed ventilator defects (Pierce and John 2008: 11)

A short explanation of the HRCT scan based on Table 2 (below) is outlined below according to the article *Computed Tomography (CT) – Chest (2018):*

- The patient is positioned on the CT scan table, supinely. Straps or pillows may also be used to help maintain the appropriate position and allow them to remain still during the procedure.
- A special dye called contrast material may be needed for some CT scans. It is used to highlight the areas of the body that is being examined and it may be administered intravenously or via the mouth.
- The CT table moves slowly through the machine as the actual CT scan is performed.
- The patient is asked to hold their breath as to avoid any sort of motion that could potentially cause artefacts.
- Once the scan is complete and the radiologist is pleased with the quality of the image for interpretation then the procedure is concluded.
- The test usually lasts up to 30 minutes, including exam preparations.

Table 3 Shows the (High Resolution Computed Tomography (HRCT) technique as per (Lake Smit Partners 2016)

PROTOCOL	**CT HIGH RESOLUTION CHEST**
DESCRIPTION	**CT LUNG, TRACHEA, LEFT ANO RIGHT BRONCHUS, BRONCHIOLE**
TARIFF CODE	**30350 CT CHEST - HIGH RES – COMPLETE**
INDICATIONS	• Interstitial lung Disease • Diffuse Parenchymal Lung Disease • Interstitial Pneumonitis • Idiopathic Pulmonary Fibrosis • Cystic Fibrosis • Pneumocvstis pneumonia • Sarcoidosis • Emphysema • Bronchiectasis/ Bronchitis

	• Bronchiolitis Obliterans Organizing Pneumonia • Pneumonia • Lung transplant • Granulomatosis • Lung Nodule Assessment • Extrinsic allergic alveolitis • small airway disease
POSITION/LANDMARK	SUPINE, FEET FIRST, STERNAL NOTCH
SCAN TYPE	HELICAL
SPECIAL PREP	**PLEASE PRACTISE BREATHING TECHNIQUE AND ASSESS PATIENT BREATHOLD CAPABILITY PRIOR TO SCANNING.**
RESPIRATION TECHNIQUE	**HYPERVENTILATION PRIOR SCOUT SCANS** **HYPERVENTILATION PRIOR TO MAIN ACQUISITION**
SCAN PHASE/PARAMETERS	START AT APEX OF CHEST TO INCLUDE LUNG FIELDS AND END AT BASES
PACS	• AXIALS (LUNG) – 1mm × 5mm • AXIALS (STANDARD) 5mm × 5mm • CORONALS – 1mm × 5mm • SAGITTALS – 1mm × 5mm
SCAN TECHNIQUE MODIFICATIONS	**PARAMETERS TO ADJUST:** • Decrease rotation time — faster scan • Increase pitch factor — faster scan • MA if must be adjusted accordingly if rotation and pitch changed

3.2.5. Ethics Consideration

The process of data collection was conducted and undertaken in a professional manner. All information was collected only by the researcher which guaranteed no leakages of any patient information. The information collected from IALCH's database has been kept strictly confidential so to avoid any harm to the patient in any form such as discrimination. All data collected and captured as electronic format was password protected (encryption) and was only accessible to the researcher. Any hardcopies of captured data was safely stored in a secure cabinet, once again, that was only accessible to the researcher.

Patient's personal details (name, surname and hospital identity numbers) were known only to the researcher for the purpose of sorting, cleaning and coding of the data. Coding of the data allowed each patients information to be anonymised by allocating each of them a study number which ensured a strict level of confidentiality. All documents will be stored for a maximum of 5 years after the conclusion of the study. Thereafter, those documents will be appropriately disposed of; hardcopies will be shredded and soft copies stored on password encrypted devices will be permanently deleted.

3.3. Research Tool/ Data Measurement Instruments

The present study is retrospective however; the process of gathering information is one of primary data collection. Ethical approval has been granted and the researcher has sourced the information required from the MEDITECH system (electronic chart review) using a compiled list of rheumatology clinic patients who visited the laboratory between the years 2017 to 2019. That list was extracted from the PFL's book of logs. Hence, the data collection instrument used is electronic chart review/retrieval. Information collected was transferred onto a data collection sheet (figure 2) to later be cleaned and coded for analysis (see table 3). Variables that were collected included an individual's age, sex, race, lung function parameters and diagnoses on the HRCT scan.

3.4. Data Analysis Plan

All results obtained from the data collection process has been captured on a Microsoft Excel spread sheet (figure 2). An Excel spread sheet is recognised as a collection of rows and columns that form a table. Numbers are allocated to rows and

alphabetical letters are given to columns; and the cell is referred to the point where the column and the row meet (Guru99 2021).

Assistance from a professional statistician was sought and analysis was performed using Statistical Package R (version 3.6.3) at a 0.05 confidence interval. This is a statistical software program which includes a broad range of statistical analysis, graphics and data management programs that will be used to assist in categorising, sorting and summarising the collected data into logical and appropriate sets of information that is easy to interpret and work with. The present study's variables to be recorded will be coded as seen in Table 3 below.

Table 4 Data Codes

Patient Number		Each patient will be allocated a number starting from 1
Sex	Male	M
	Female	F
Race	Indian	1
	Caucasian	2
	African	3
	Coloured	4
Respiratory symptoms	Cough	C
	Shortness of Breath	SOB
	Fatigue	F
	Chest Pain	CP
Spirometry patterns	Normal	N
	Obstructive	O
	Restrictive	R
	Mixed	M
HRCT chest scan	Normal	1
	Pleural effusion/thickening	2
	Interstitial lung disease (ILD)	3

	Nodules	4
	Bronchiectasis	5
	Obliterans bronchiolitis	6
	Organising pneumonia	7

3.4.1. Data Preparation

In order to prevent the possibility of false conclusions from incorrect or inconsistent data, the data was therefore be cleaned. Data that had been duplicated or irrelevant was removed from the dataset. This included fixing errors made during data transfer such as typographical and grammatical errors; long headings such as the ones that may appear on a graph will be avoided by renaming the variables. Missing data after the data collection and capturing process have been dropped using row wise deletion or they may be imputed. The latter was considered as it may yield a more accurate conclusion (Formplus: 2021). Wherever necessary, numerical variables were binned into categorical variables for better presentation of the results. All the data entered as codes has been decoded prior to the actual analysis.

3.4.2. Statistical Methods

Both descriptive and inferential statistics were used to present the data. Descriptive statistics is typically used to organise, describe or summarise a set of numerical data (Grand-Clement *et al.* 2018: 57). In this study, the patient's demographic profile as well as the prevalence of abnormal spirometry in patients diagnosed with RA has been computed using univariate descriptive statistics. Numerical variables have been presented using box plots whereas categorical variables are shown on bar, pareto and pie charts. See Table 4.

Inferential statistics, by contrast uses the laws of probability to predict or make inferences about the sample data in order to draw statistical conclusions (Johnson and Christensen 2012). The third objective in this study has been analysed using the chi-square test. This statistical analysis method includes testing for the independent associations between two categorical variables, i.e., spirometry patterns and HRCT findings. In the same objective, the demographic profiles of the HRCT findings were described as well. A p-value of < 0.05 was considered statistically significant.

Table 5 Showing the type of statistics to be used for each objective.

Objective	Test used	Parameters
1. To describe the demographic profile of the study population.	Univariate descriptive statistics such as the minimum, maximum, quartiles, standard deviation and standard deviation will be used to summarise numerical variables such as age. In addition, a boxplot will be used to visually display the summaries. On the other hand, counts and percentage frequencies will be used to summarise categorical variables such sex, race and respiratory symptoms. Simple bar and pie charts will also be used. The prevalence of symptoms may be presented on a pareto chart.	Age (year), sex, race and respiratory symptoms.
2. To determine the prevalence of abnormal spirometry in patients with RA.	Univariate descriptive statistics such as counts and percentage frequencies will be used together with Chi-	Normal, obstructive, restrictive and mixed.

	Square goodness of fit for pairwise comparison of the prevalence of the patterns. A bar chart will be used to further visualise the proportions.	
3. To measure the association between abnormal spirometry patterns and abnormal HRCT findings in patients diagnosed with RA.	Chi-square test for independence. The results will be visualised in the form of multiple bar chart.	To determine if the HRCT findings (normal, pleural effusion/thickening, ILD, nodules, bronchiectasis, obliterans bronchiolitis and organising pneumonia) depend on the Spirometry patterns (normal, obstructive, restrictive and mixed).

3.5. Ethics

The design of the study is retrospective in nature hence informed consent from patients will not be required since data has been collected from secondary sources. The data collected were all found on IALCH's computers/database that could only be accessed by staff members through login credentials. However, before accessing or extracting any information the appropriate permissions were acquired as a prerequisite.

All gatekeeper permissions have been sought from the Departmental Research Committee (DRC), Institutional Research Ethics Committee (IREC) (Appendix G), Kwa-Zulu Natal Department of Health (DOH) (Appendix A/F), IALCH's CEO/manager (Appendix B) and the Head of Department of Pulmonology (Appendix E). Hence, the study could commence.

4. Chapter Four: Analysis and findings

4.1. Introduction

This section presents the findings from the statistical data analysis. The demographic profile of the patients is outlined followed by the clinical findings. This study had adopted a positivist paradigm since data was quantitative, and it sought to approve or disapprove a hypothesis. It was also a cross-sectional, retrospective study, making it observational in nature. The first objective of this research intended to determine the demographic profiles of rheumatoid arthritis patients, second was to find out which spirometric abnormality was most prevalent among them. The third aimed to measure the association between abnormal spirometry patterns and abnormal HRCT patterns. It was hypothesised that a restrictive defect would be the most common pattern observed on spirometry.

The data captured was inclusive of patients diagnosed with RA who had attended the pulmonary function laboratory (PFL) at Inkosi Albert Luthuli Central Hospital (IALCH) between the years 2017 to 2019. Data was captured via electronic chart review and thereafter cleaned and coded by the researcher. Data was cleaned using Microsoft Excel version 2010. The coded data was statistically analysed by a biostatistician using R statistical computing software of the R Core Team 2020, version 3.6.3.

Both descriptive and inferential statistics were used to present the data. Descriptive statistics is typically used to organise, describe or summarise a set of numerical data (Grand-Clement *et al.* 2018: 57). In this study, the patient's demographic profile (objective 1) as well as the prevalence of abnormal spirometry in patients diagnosed with RA (objective 2) has been computed using univariate descriptive statistics.

Inferential statistics, by contrast uses the laws of probability to predict or make inferences about the sample data in order to draw statistical conclusions (Johnson and Christensen 2012). The third objective in this study has been analysed using the chi-square test. This statistical analysis method included testing for the independent associations between two categorical variables, i.e., spirometry patterns and HRCT findings. The data was represented using pie charts, horizontal bar graphs, tables, box and whisker plots and parallel plots.

4.2. Demographics

Of the 140 patients, majority ($p<0.001$) were females (n= 117, 83.9%) and this proportion was significantly higher than that of males (n= 23, 16.4%), Figure 4. Further, V_{Cramer} = 0.7 is an indication of how the one group tends to be dominant. In this cohort, women were more commonly affected by RA than men.

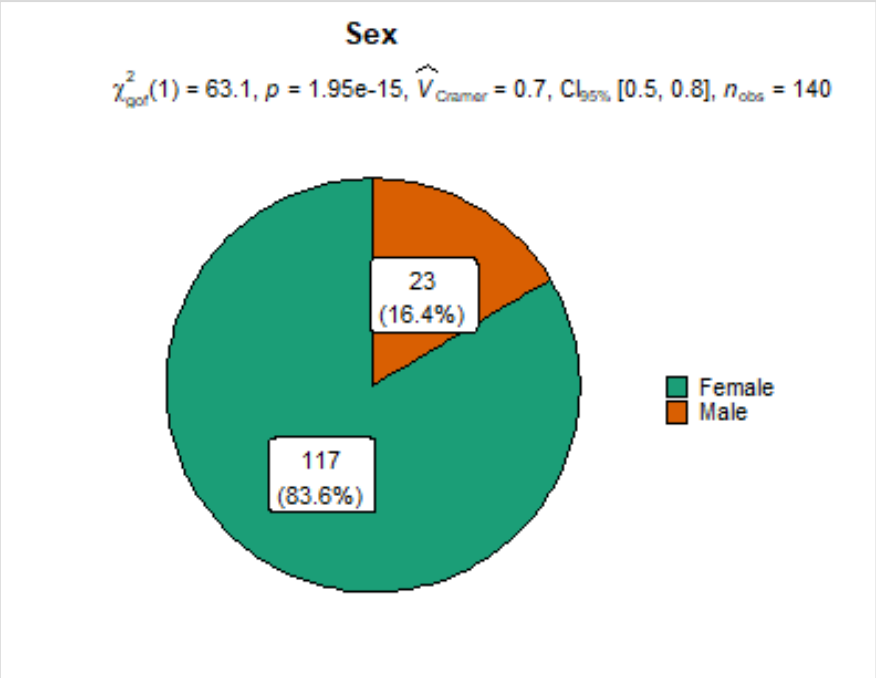


Figure 4 Sex

Most, 49.3% (n=69) of the study participants were of the Black ethnic group, Figure 5. This was followed by Indians, 36.4% (n=51). The proportions of Coloured and Caucasian ethnic groups were similar and constituting 7.9% (n=11) and 6.4% (n=9) respectively.

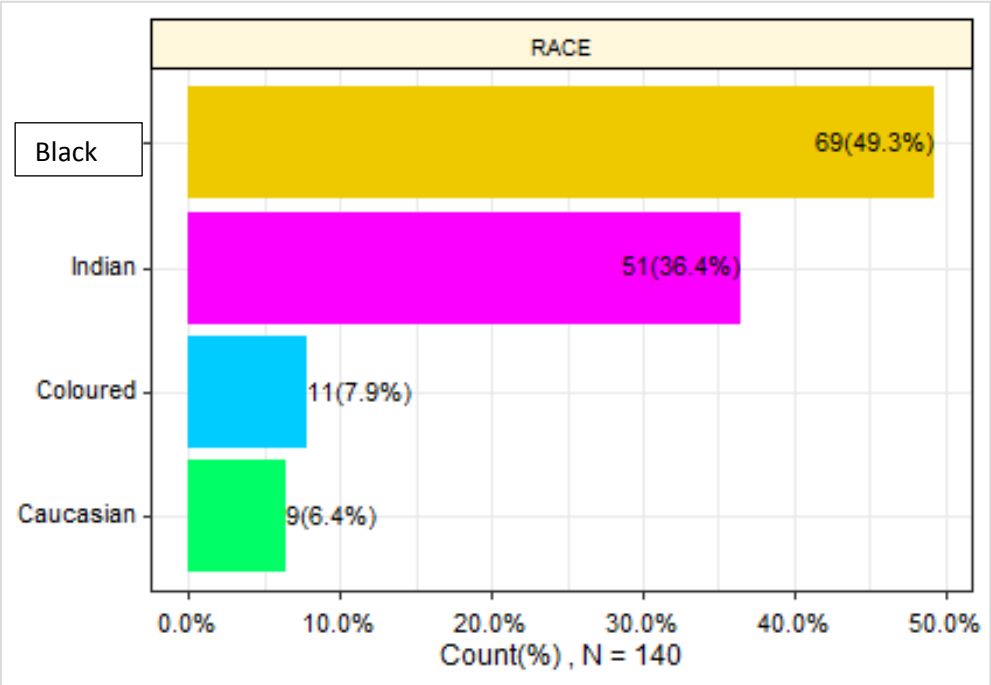


Figure 5 Race

In Figure 5.1, the Coloured group had the highest measurements and also among the younger patients. Another notable pattern was among the Caucasians, who constituted the oldest group and their FVC and FEV_1 measurements were high but slightly lower than those of the Coloured group. The Indians were among the youngest in the study with the lowest FEV_1 and FVC but their ratios were generally high. The results further revealed that the FEV_1 and FVC measurements from the African ethnic group (also younger patients), were in between the other ethnic groups and the ratios generally high too.

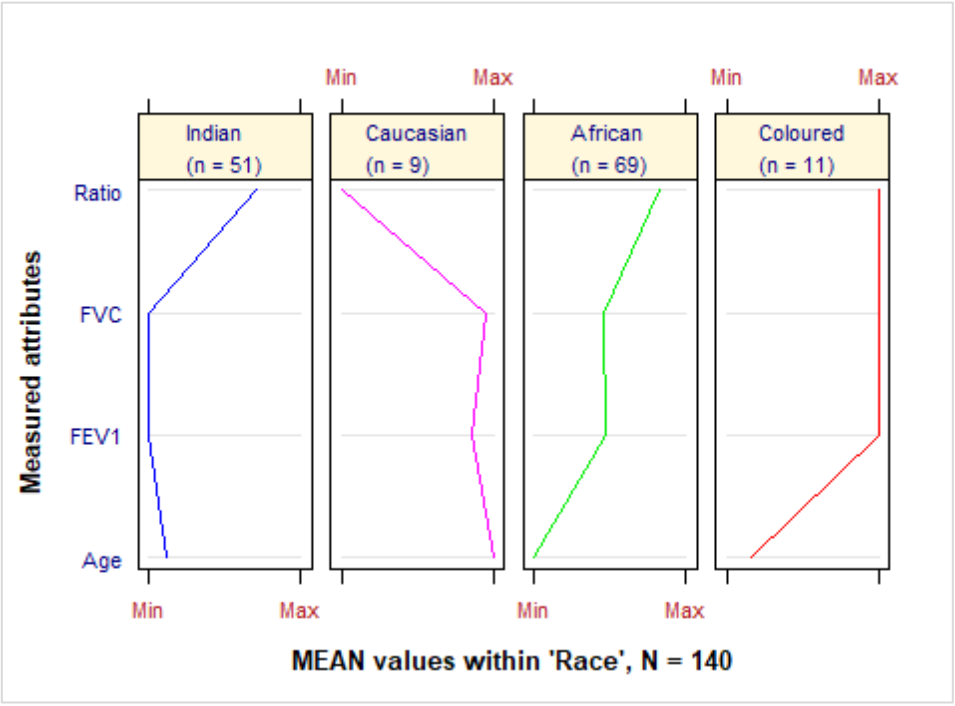


Figure 5.1 Parallel plot of Age, FEV1, FVC and Ratio by race

Figure 6 shows the age distribution of the patients. The ages were normally distributed and overage the patients were 60.9 years old. The youngest patient was aged 23 and the oldest was 87 but most of the patients were between the ages of 50-65 years old with a median age of 60.0.

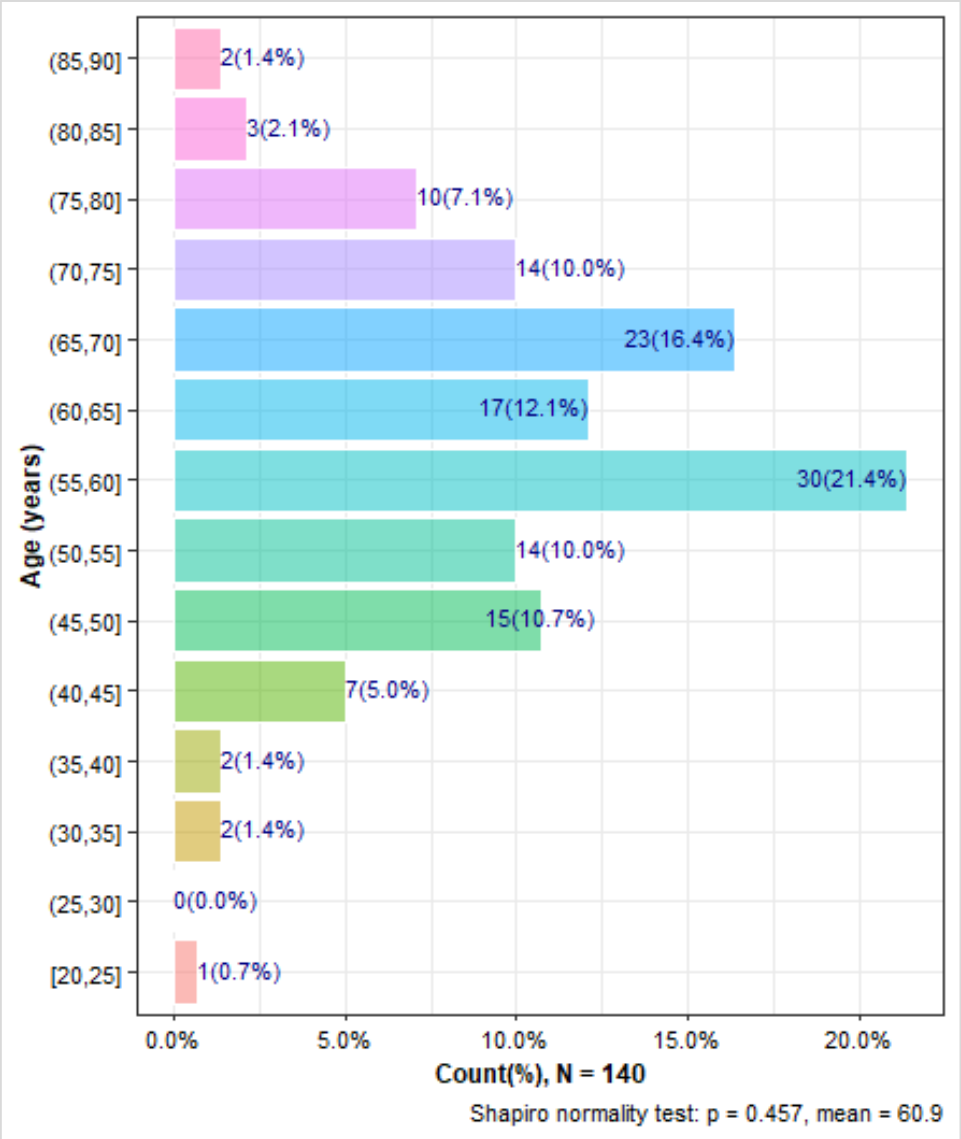


Figure 6 Age Distribution

Table 6 Age by Gender

Sex	Female (N=117)	Male (N=23)	p-value	Overall (N=140)
Age			p = 0.213	
Mean±SD(CV%)	60.4±11.7(19.5)	63.7±11.3(17.8)	t-test	60.9±11.7(19.2)
Median(Q1-Q3)	59.0(53.0-69.0)	68.0(56.5-72.5)		60.0(53.0-69.0)
Min-Max	23.0-87.0	41.0-79.0		23.0-87.0

Of the n=140 patients under investigation, 42.1% (n=59) did not show respiratory symptoms (Figure 7). A considerable proportion had more than one symptom. Of the 81 patients that complained of some respiratory symptoms, the most prevalent was shortness of breath (n= 57, 70.4%), followed by cough (n= 51, 63.0%). Fatigue (n= 17, 21.0%) and chest pain (n= 1, 0.7%) were among the least reported symptoms.

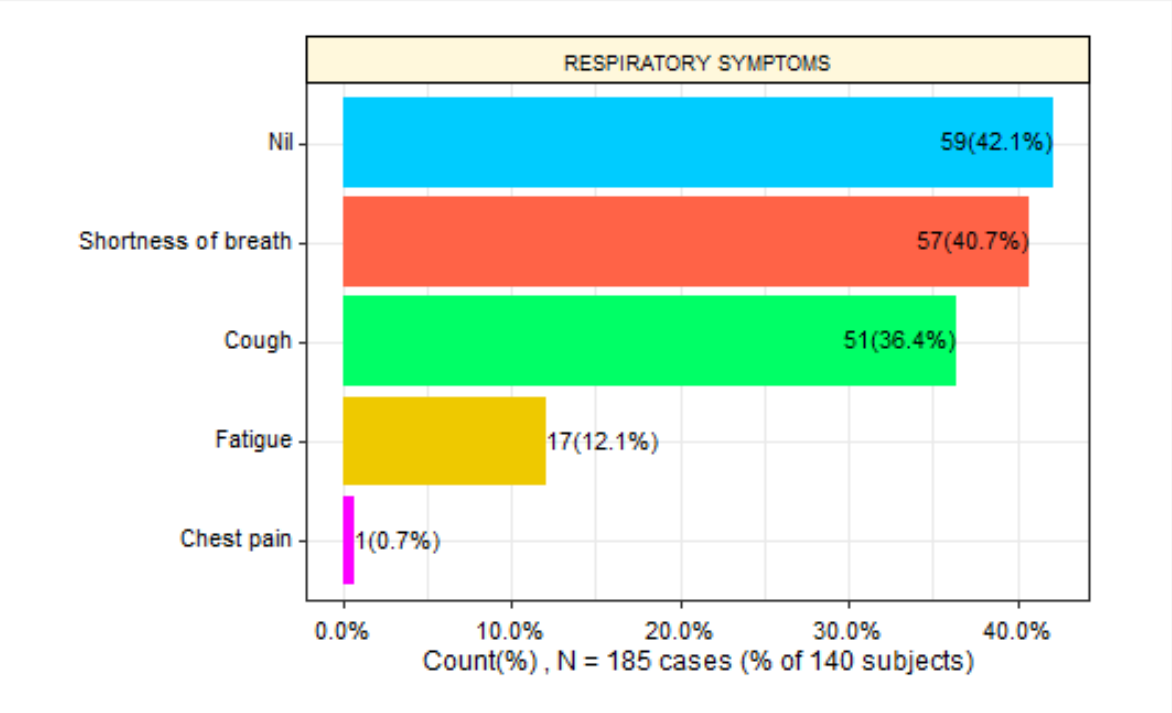


Figure 7 Respiratory Symptoms

There was no statistically significant association between gender and respiratory symptom (p=453, Figure 8). However, 84.6% (n=11) males experienced coughing whilst 58.8% (n=40) were among the females. On the other hand, of the n=17 patients reported to have fatigue, only one was a male. The single report of chest pain was noted in a female patient.

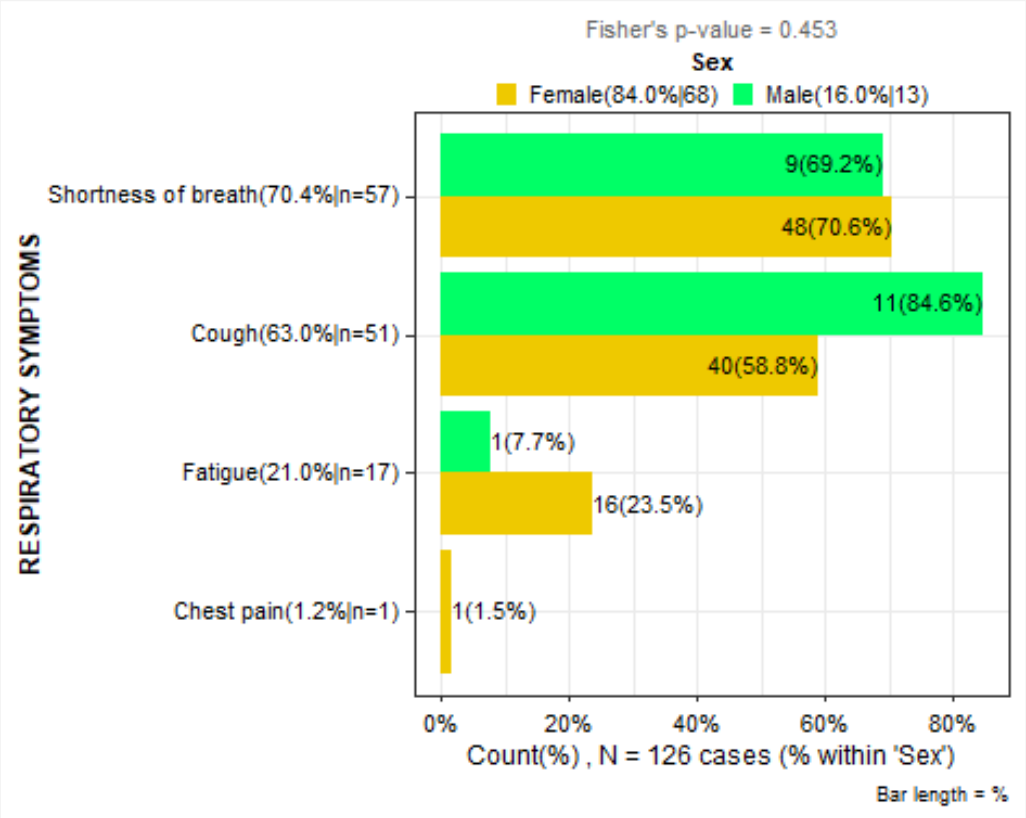


Figure 8 Respiratory Symptoms by Gender

Of all the investigated patients (n=140), 47.1% (n=66) of them had a normal spirometry pattern, characterised by an FEV_1 of 80%, FVC of 80% and FEV_1/FVC ratio of 70%. An obstructive defect was seen in 32.9% (Figure 9). Statistically, the normal and obstructive groups had similar number of patients (p=0.059). The proportions of restrictive 17.9% (n=25) and mixed 2.1% (n=3) spirometry patterns were significantly smaller than the other patterns (p<0.001).

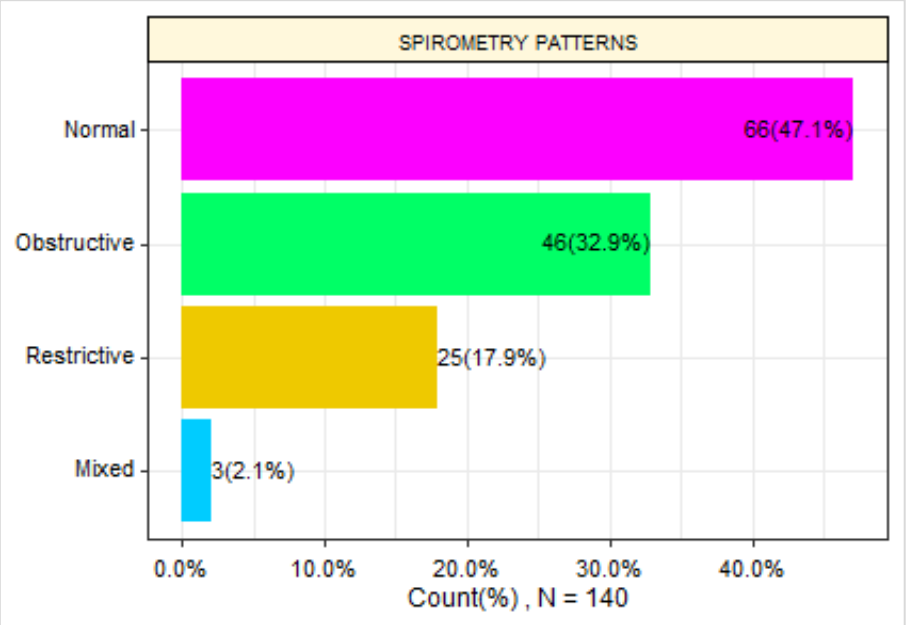


Figure 9 Spirometry Patterns

Figure 10 shows that there were some patients with more than one abnormality on HRCT. In most of these combinations interstitial lung disease (ILD) was the most common. This ILD was also found to be the most prevalent, that is, accounting to 66.7% of the 72 patients whose records were available. The second most prevalent HRCT pattern was bronchiectasis constituting 23.6% (17/72) of the 72 patients.

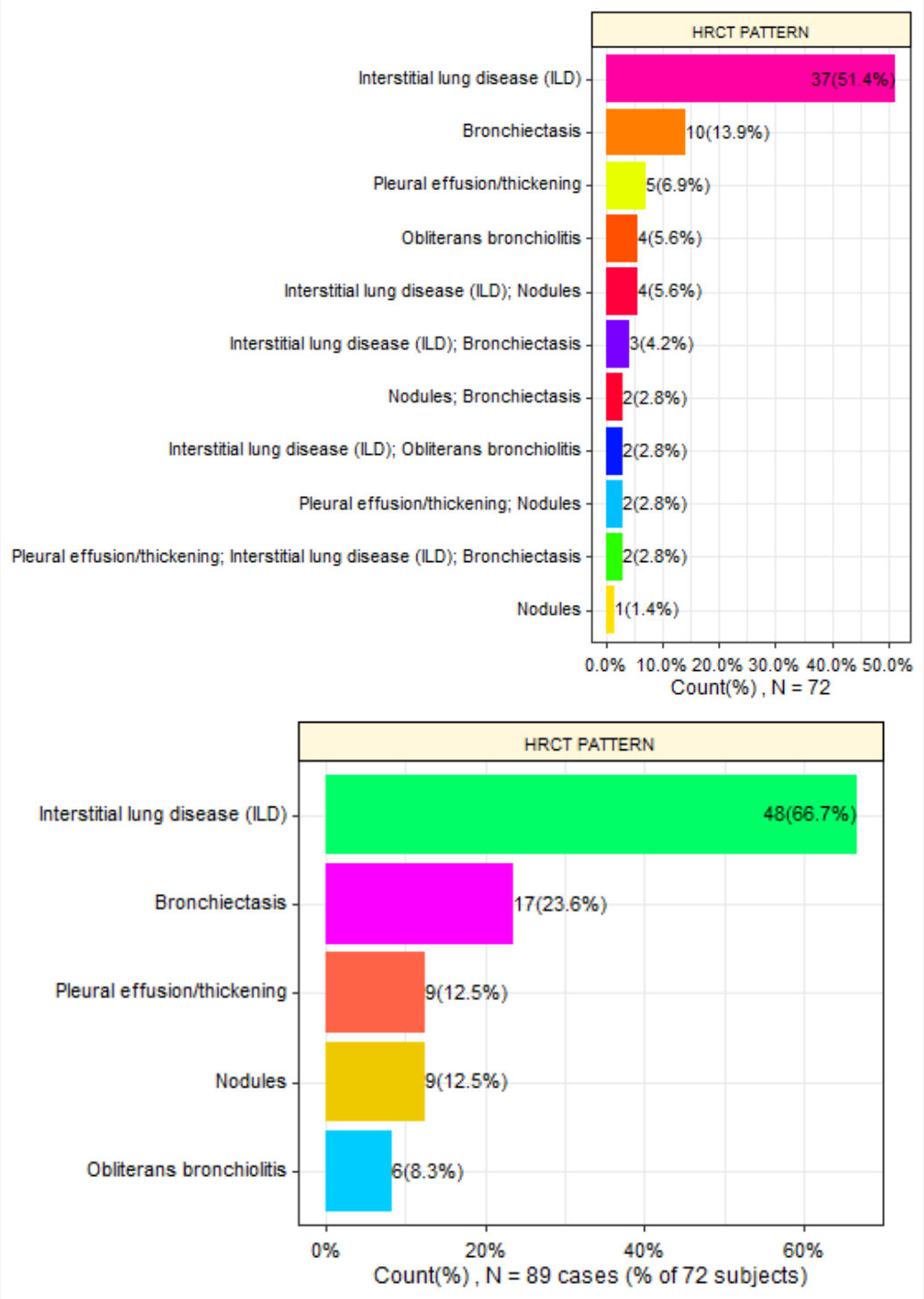


Figure 10 HRCT patterns

Interestingly, the investigated data did not show a significant association between the spirometry patterns and the HRCT patterns (p=0.921, Figure 11). That is, the proportions of the spirometry patterns within the HRCT patterns were similar. The outstanding finding was that the two patients with mixed spirometry patterns presented with ILD.

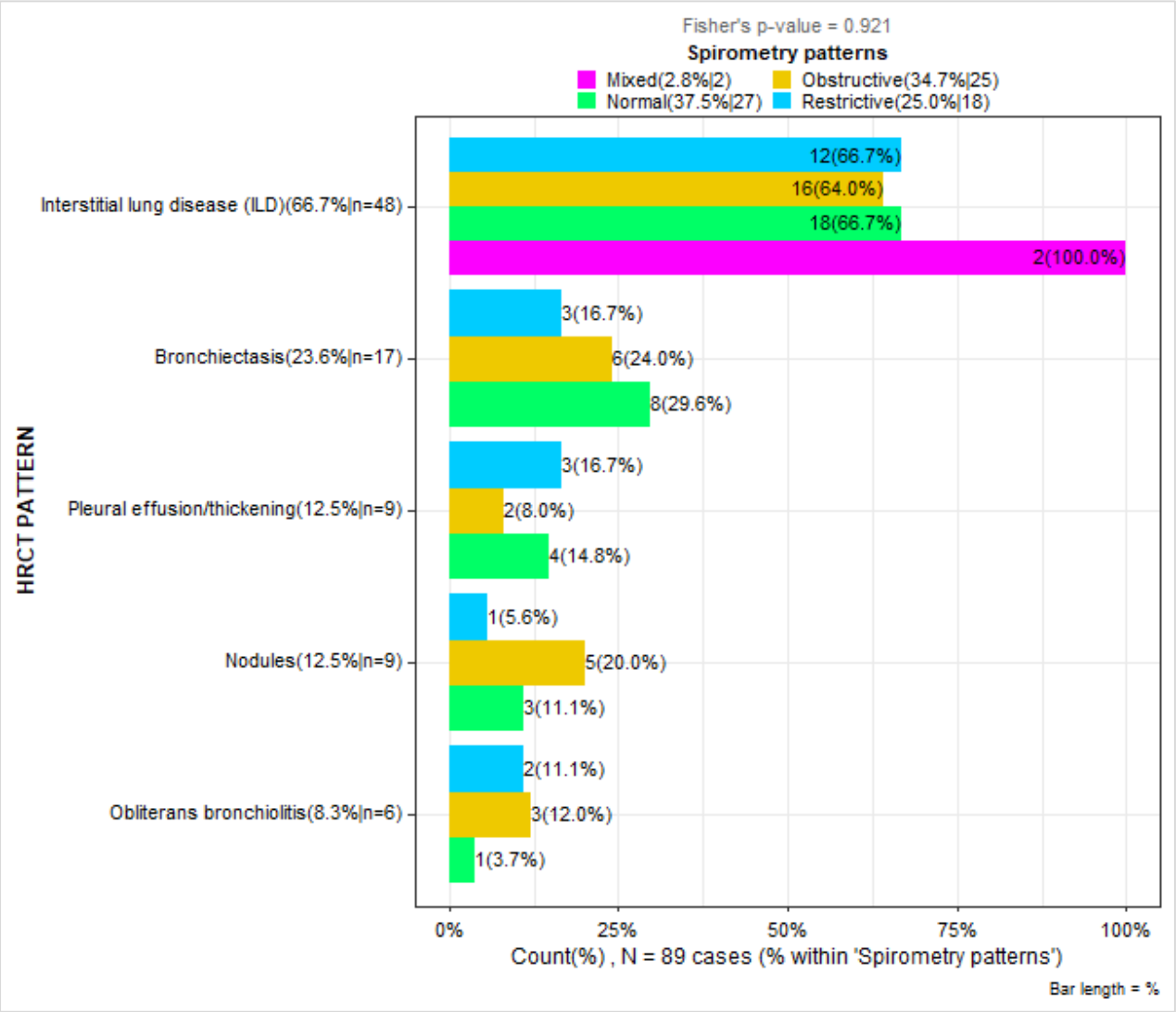


Figure 11 The association between the HRCT patterns and the spirometry patterns

Figure 12 describes the HRCT patterns within the sex distribution. Each HRCT finding predominantly affected more females than males, with an outstanding finding that showed a larger number of females (43) as opposed to males (5) that were affected by ILD. Pleural effusion/thickening and nodules showed similar proportions within gender but once again with females being predominant. Obliterans bronchiolitis was shown only to affect women.

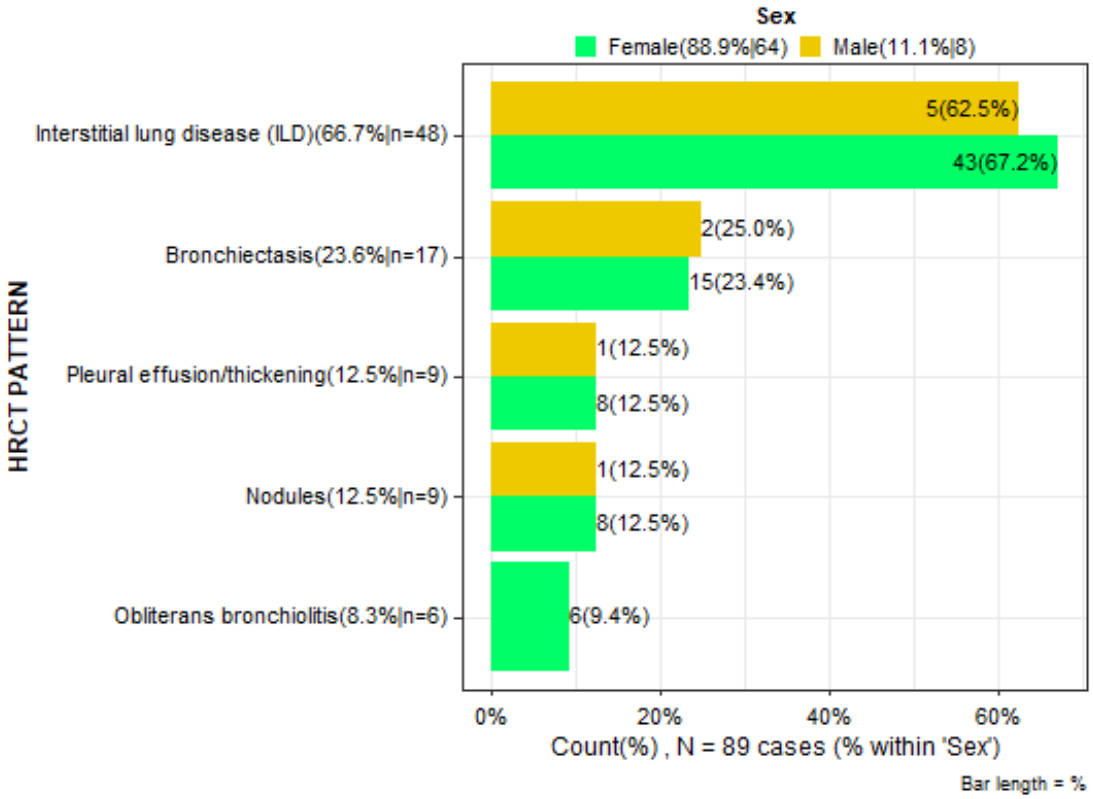


Figure 12 HRCT findings by Sex

5. Chapter Five: Discussion

5.1. Introduction

This study sought to determine which of the abnormal spirometry patterns (obstructive, restrictive or mixed) were prevalent among rheumatoid arthritis (RA) patients since RA affects multiple bodily systems, most commonly the respiratory system (Yunt and Solomon 2015: 1) in the form of extra-articular manifestations.

Research on this topic in South Africa is scarce mainly due to the fact that relevant articles for the present study resourced were not from South Africa but rather from international studies. It was also mentioned that certain characteristics of the study population will play a role in the results obtained; as we know South Africa encompasses many different race groups. Hence, this study would aid in providing useful information on the KZN province.

Demographics of the population and respiratory symptoms experienced were noted during data collection then statistically analysed. Another objective of the study aimed to determine if spirometry patterns obtained from PFTs correlated with what may be observed on HRCT scans, since it has been reported that a small number of studies have assessed both the use of PFTs and HRCT scans in patients with RA (Cortet et al. 2004: 596).

5.1.2. Summary of key findings

The findings of this study disproved the hypothesis, of which predicted a restrictive pattern would be prevalent. The statistical analysis revealed an obstructive pattern on spirometry to be the most common in this study. In the present study it was also suggested that there was no significant association between the spirometry patterns and HRCT patterns. A possible reason for this may be because many of the patients did not have an HRCT scan performed. In addition, ILD was the most common extra-articular manifestation of RA detected on HRCT, majority of which were found in females. The most common respiratory symptom experienced was shortness of breath.

5.2. Discussion of findings

There were a total of 387 patients who visited the PFL between the years of 2017 to 2019. However, only a total of 140 patients met the inclusion criteria and thus were recruited in the study; this was larger than most numbers recruited from previous studies reviewed. This is most likely due to the adoption of a 3 year selection period which increased the possibility of more patients being enlisted.

5.2.1. Demographic characteristics

From the 140 patients, 83.6% (117) were females whereas only 16.4% (23) of males made up the remainder of the population ($p<0.001$). Statistically in South Africa 51.2% of the population is made up of the females (Statistics South Africa 2019). However, this finding also suggests that RA tends to affect females more than males. This statement is supported by a study conducted by Kadhum *et al.* (2017:113) where more females than males were present. It was mentioned that the results were consistent with the worldwide reports which demonstrates a tendency for RA to affect the female gender. Vollenhoven (2009: 1) explained that the possible reason for this “overrepresentation” is not completely clear, however, it is suggested that the differing exposures experienced between men and women, as well as genetic and hormonal factors may play a role in causing this phenomenon.

A study conducted in South Africa by Morrison *et al.* (1996: 829) on 104 RA patients did not stipulate race distribution. Other studies reviewed were conducted in India where the population is largely of the Indian ethnicity which limits comparisons among race groups. Nevertheless, the race distribution observed in the present research largely consisted of the Black African race (69) followed by Indians (51) then similar proportions of Coloured and Caucasian were observed, 11 and 9 respectively. Statistically South Africa bodies more, approximately 81%, Blacks than any other race group (Statistics SA 2019).

The ages were normally distributed and the mean age was 60.9 years with most patients between the ages of 50 to 65 years old. This finding is in keeping with literature reported by Essam *et al.* (2013: 286), which states that RA usually occurs during the 3rd to 5th decades of life and its incidence increases with age. There was also no statistically and significant difference between males and females on age.

5.2.2. Clinical characteristics – respiratory symptoms

Of the 140 participants, 42.1% (59) did not show respiratory symptoms. This was a similar case in a study conducted by Bilgici *et al*. (2004: 431), which included a total of 52 RA patients and majority (31) of them revealed no symptoms. However, just like in the present study, shortness of breath (dyspnoea), followed by cough were the most common symptoms experienced. In this study, a total of 57 of the 81 patients who showed respiratory symptoms experienced shortness of breath and 51 (of the 81) had a cough; least reported symptoms included fatigue (17/81) and chest pain (1/81). This result was contrasted in a cross-sectional, case control study by Madhavan *et al*. (2017: 2001), where the prevalent respiratory symptom was cough whilst none experienced dyspnoea. The commonness of experiencing respiratory symptoms is due to various conditions that affect the parenchyma, pleura, airways or vasculature of the lungs, as reported by Shaw *et al.* (2014:1).

A few studies have reported on the frequency of respiratory symptoms experienced in RA patients, however, none has established if there is an association between respiratory symptoms and gender. This study found that there is no statistically significant association between the two. There was also no statistically significant association between spirometry patterns and respiratory symptoms. However, it is evident that respiratory symptoms are more commonly present in patients with abnormal spirometry than with normal spirometry results. A study by Pappas *et al.* (2010: 7) reported that respiratory symptoms were statistically more common in patients who presented with an abnormal spirometry.

5.2.3. Prevalence of pulmonary function abnormalities

Several studies have reported that patients with RA tend to have an increased incidence of showing abnormal findings on PFT (Chattopadhyay *et al.* 2015: 29). The present study also demonstrated similar findings; lung function abnormalities was detected in 52.9% of the patients, with the obstructive defect being the most common (32.9%), followed by restrictive (17.9%) then mixed (2.1%); therefore disproving the study's hypothesis. In addition, a fair amount, 47.1% of the patients still revealed a normal PFT. Patients may reveal a normal PFT due to early disease activity or lung involvement.

Kawassaki *et al.* (2015: 337) conducted a study on 246 RA patients using 3 diagnostic testing tools (spirometry, chest x-ray and pulse oximetry). Lung

abnormalities using spirometry was detected in 30% of their sample (11.4% obstructive, 11% restrictive and 4.9% mixed), however, more RA patients still revealed a normal PFT (69.9%) which is not in keeping with this study's results. Another study done by Kadhum *et al.* (2017: 112) also contrasted the present study's results. An abnormal PFT was detected in 25% of their sample, observing more restrictive defects (22.5%) than obstructive (2.5%) patterns. The aforementioned study may provide more accurate results even though a smaller sample size (40 RA patients) was observed since it was prospective study unlike the present one.

Praba *et al.* (2017: 695) explained that a restrictive ventilatory defect may be due to activation of immune complexes in the alveolar walls, resulting in the release of myeloperoxidase, elastase and collagenase. This leads to the destruction of lung tissue by phagocytosis and protease, which prevents lung expansion. The same author explained that an obstructive ventilatory defect in RA patients may be due to airway inflammation. When plasma immunoglobulin E level increases, neuropeptides and chemokines are released from eosinophils, and mast cell damages the airway epithelium and hyperresponsiveness. This results in partially reversible airway obstruction due to bronchial narrowing.

Results of this study reported that age was not associated with spirometry patterns. There was no statistically and significant difference between males and females on FEV_1. However, FVC measurements were found to be higher among males than females, who were fairly younger than their counterparts, and the opposite was observed in terms of the FEV_1/FVC ratio. In saying this, males in general have larger lung volumes than females due to body size and thus larger lungs; height differences also play a role (LoMauro and Aliverti 2018: 138) in lung volume differences.

This study also found that race did not show a significant influence on the FEV_1, FVC and the ratio. However, across all ethnic groups the Coloureds and Caucasians had the highest lung function measurements but still lower than normal values. The Indians were among the youngest in the study with the lowest lung function parameters (FEV1, FVC and a generally high ratio but not as significantly high as compared to other races). A study conducted by Chattophadyay *et al.* (2015: 29) in a semi-urban population of Eastern India reported that lung parameters among the RA patients were also decreased. The difference in lung function is because race

influences body proportions and stature, resulting in lung volumes that differ significantly among races (Mottram 2018: 1055).

5.2.4. HRCT findings

Pulmonary function tests failed to predict HRCT scan findings in majority of the patients in this study, similar to the result reported by Bilgici (2004: 434). It appears that PFTs only are not sufficient enough for guiding diagnosis. A possible reason for the data not showing a significant association between spirometry patterns and HRCT patterns in this study may be due to the small number of participants who had an HRCT scan performed, which constituted of 72 out of a total of 140 patients. Of the 72 patients, 14 (21%) of them revealed to have overlapping features detected by HRCT, in most of these combinations ILD was common. This ILD was also found to be the most prevalent, that is, accounting for 66.7% of the 72 patients. This suggests that the prevalence of ILD within the RA population is common. The same conclusion was also reported by Salaffi *et al.* (2019: 4). However, one study conducted by Cortet *et al.* (1997: 598) on 68 RA patients revealed that bronchiectasis was the most frequent abnormality detected on HRCT, accounting for 30.5% of the sample population.

A similar result was seen in a study by Perez *et al.* (2016: 79). Bronchiectasis was the second most prevalent HRCT finding in this study. This study concluded that the proportions of spirometry patterns within the HRCT patterns were similar. This means that under each HRCT pattern observed there were similar numbers of patients who showed obstructive, restrictive, mixed or normal. There was no one dominant pattern. Of the restrictive diseases observed on HRCT (ILD, pleural effusion/thickening and nodules) 16 of the 72 participants revealed a restrictive pattern on PFT and this can be expected as these diseases are considered diseases of the parenchyma/pleura rather than of the airway. Connective tissue diseases such as RA can cause pulmonary fibrosis which leads to scarring of the lung tissue. This in turn causes the lung to become stiff resulting in a restrictive ventilatory defect. Pleural effusion causes restriction by an abnormal accumulation of fluid in the plural space (Mottram 2018: 20-23).

Furthermore, 23 participants who revealed an obstructive pattern on PFT was found to have a restrictive process on HRCT. The possible reason for the obstruction may

be due to other respiratory diseases that the patient may have such as asthma or COPD. A smoking history or biomass fuel exposure may also contribute to this pattern seen as these are known to cause deterioration in the physiological lung function as reported by Biomdo et al. (2013: 43). There were 9 patients that revealed some sort of obstructive process on HRCT (bronchiectasis and obliterans bronchiolitis) who had an obstructive pattern on PFT. This is expected as these diseases affect the airways as opposed to restrictive diseases. Biomdo et al. (2013: 43) also explained that the high prevalence of PFT abnormality in their study may have been due to ongoing RA disease activity, hence, a reason for a fair amount of participants revealing a normal PFT in this study may in fact be due to early disease activity and lung involvement.

This no association between HRCT findings and spirometry patterns may be largely due to the inclusion criteria which did not exclude patients who may have other respiratory diseases such as asthma or COPD which is a limitation in this study. A study by Spagnolo *et al.* (2018: 1545) mentioned that on HRCT, ILD abnormalities are more extensive in males. However, in this study more females than males revealed abnormal findings with a large proportion of them being affected by ILD more than any other HRCT finding. One of the reasons for this may be due to the large proportion of females in the study.

5.3. Contribution to the body of knowledge

This study has provided a small scale insight on how rheumatoid arthritis has affected the lung function of the South African population, which largely consists of various races. It has shown that abnormal findings on both the HRCT scan and PFTs are common but a large proportion of patients can still reveal a normal lung function. Even though the prevalent pattern on spirometry revealed to be obstructive, disproving the study's hypothesis, there was still evidence on HRCT that ILD is a common extra-articular manifestation of RA which is in keeping with other studies, in a sense it is providing more evidence to the body of knowledge in regards to RA and respiratory function.

5.4. Strengths and limitations

- This study had a small sample size as it did not meet the required 224 participants; however, it was still significantly larger than previous studies (Kadhum *et al.* 2017: 112; Chattopadhyay *et al.* 2015: 29).
- Lack of potential depth. Other lung parameters could have been investigated using other tests such as the diffusing capacity (Cortet *et al.* 1997: 599) and body plethysmography (lung volumes). A possible subgroup which consists of patients with a smoking history could have been noted and analysed since cigarette smoking has a significant effect on lung function. It would have provided insight on whether the large proportion of patients with an obstructive pattern in this study was possibly due to this factor.
- Another limiting factor was that most patients at the time were on treatment with methotrexate or prednisone which are drugs that may affect with PFT results.

5.5. Conclusion and recommendations

From the present study it was found that spirometry and HRCT scans frequently identified lung abnormalities in patients with RA. Although there was no statistically significant association between spirometry and HRCT in this study, these screening tools should still be incorporated into practice as routine tests for RA patients from the time of diagnosis and this is especially important because a large proportion of patients can reveal normal lung functions and nil symptoms. In addition, HRCT scans are sensitive enough to detect lung alterations. This will also aid in early detection of abnormal lung parameters which may help in altering treatment regimens which could possibly reduce morbidity and mortality in this population. Additional prospective studies need to be conducted on RA patients using PFTs as well as HRCT scans as screening tools to provide more reliable results on this topic.

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7. Appendices

APPENDIX A

Provincial Health Research Committee
Health Research and Knowledge Management Unit
KwaZulu-Natal Department of Health
Natalia Building
330 Langalibalele Street
Pietermaritzburg
3201

APPROVAL TO CONDUCT RESEARCH PROJECT

Attention: Chairperson Provincial Health Research Ethic Committee
I hereby request approval to conduct a retrospective research project in order to obtain a Bachelor's of Science in Pulmonology Clinical Technology through the Department of Biomedical and Clinical technology at the Durban University of Technology (DUT).

The area of research includes patients diagnosed with Rheumatoid Arthritis seen at Inkosi Albert Luthuli Central Hospital. The provisional title is as follows: *Abnormal spirometry in patients with Rheumatoid Arthritis attending a quaternary clinic in Durban, South Africa.*

The following attachments include all supporting documents:
1. Research proposal
2. Ethical clearance approval certificate from the Durban University of technology (DUT).

My supervisor's details are as follows:

- Mr DC Mdluli (dalincebom@dut.ac.za) 078 787 9214
- Dr. D. Fakey Khan (dilshaadf@gmail.com) 031 240 1346 (work)/ 083 794 3221 (cell)
- Mrs. K. Naidoo (veena.n@live.co.za) 031 240 1340 (work)/ 073 235 5897 (cell)

Biostatistician:

- P. Tinarwo, PhD, (statistician@analytics-consultina.com and UKZN Medical school) 061 006 9432

Please feel free to contact me or my supervisor should you have any queries.
Thank you for your consideration.

Kind regards.

Anisa Parasram (066 227 1766)

APPENDIX B

12 February 2021

IALCH Management Committee
Inkosi Albert Luthuli Central Hospital
800 Vusi Mzimela Road
Mayville
4091

Request for Permission to Conduct Research

Dear Sir/Madam

My name is Anisa Parasram, a Bachelor in Clinical Technology student at the Durban University of Technology. The research I wish to conduct for my Degree involves the prevalence of abnormal spirometry in patients with Rheumatoid Arthritis attending a quaternary clinic in Durban, South Africa.
I am hereby seeking your consent to conduct this proposed research at Inkosi Albert Luthuli Central Hospital.

I have provided you with a copy of my proposal which includes copies of the data collection tools and consent and/ or assent forms to be used in the research process, as well as a copy of the approval letter which I received from the Institutional Research Ethics Committee (IREC).

If you require any further information, please do not hesitate to contact me on:
Cell number: 066 227 1766
E-mail address: anisaparasram@gmail.com

Thank you for your time and consideration in this matter.
Yours sincerely,
Anisa Parasram
Durban University of Technology

APPENDIX C

ANALYTICS CONSULTINA
Data-driven solutions

27 May 2021

The Chairperson,
Department of Biomedical and Clinical Technology
DURBAN UNIVERSITY OF TECHNOLOGY

Dear Sir/Madam

RE: STATISTICAL DATA ANALYSES

I have studied the research protocol of PARASRAM ANISA (21800764) project title

"Abnormal spirometry in patients with Rheumatoid Arthritis attending a quaternary clinic in Durban, South Africa"

and the student attended a Zoom meeting to discuss the statistical aspects of the protocol related to sample size and statistical data analysis methods. The Biostatistician will also be assisting in the statistical data analyses.

Should you require any further details, please feel free to contact us.

Sincerely,

The Analytics Team - (Bio)Statistician
PARTSON TINARWO, PhD
Cell : +27(0)61 006 9432 (Tina)
E-mail : statistician@analytics-consultina.com
Analytics Consultina is a DUT approved service provider.
The Biostatistician is also affiliated to the University of KwaZulu Natal medical school.

APPENDIX D

Flow-Volume Loop

1. Rapid rise from maximal inspiration to PEF (some suggest a rise time of < 120 ms).
2. Maximal effort until flow returns to zero baseline; no glottic closure or abrupt end of flow.
3. Maximal inspiratory effort with return of volume to point of maximal inspiration. (Failure to close loop indicates that effort was not started from maximal inspiration, inspiratory effort was submaximal, or spirometer error.)
4. At least three acceptable loops recorded; superimposed or side-by-side loops should be repeatable unless bronchospasm occurs.
5. Report the F-V loop from the single best test maneuver (highest sum of FEV_1 and FVC).

(Mottram 2018: 1)

APPENDIX E

APPENDIX E

10 August 2021
18 Tyne Park Close
Shastri Park
Phoenix
4068

Dear Ms. Anisa

Your request to conduct the study: **Abnormal spirometry in patients with Rheumatoid Arthritis attending a quaternary clinic in Durban, South Africa** at the Pulmonology Department in Inkosi Albert Luthuli Central Hospital (IALCH) has been approved.

Yours Sincerely,

31/08/2021

Prof. K. Nyamande (nyamande@ukzn.ac.za)
Head of Pulmonology Department at IALCH

APPENDIX F

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_202109_008

Dear Ms A. Parasram
(UKZN)

Approval of research

1. The research proposal titled **'Abnormal spirometry in patients with Rheumatoid Arthritis attending a quaternary clinic in Durban, South Africa'** 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. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 15/09/2021.

APPENDIX G

Institutional Research Ethics Committee
Research and Postgraduate Support Directorate
2nd Floor, Berwyn Court
Gate 1, Steve Biko Campus
Durban University of Technology

P O Box 1334, Durban, South Africa, 4001
Tel: 031 373 2375 Email: lavishad@dut.ac.za
http://www.dut.ac.za/research/institutional_research_ethics
www.dut.ac.za

22 September 2021

Ms A Parasram
18 Tyne Park Close
Shastri Park
Phoenix
4068

Dear Ms Parasram

Abnormal spirometry in patients with Rheumatoid Arthritis attending a quaternary clinic in Durban, South Africa
Ethical Clearance number **BIREC 103/21**

The Institutional Research Ethics Committee acknowledges receipt of your gatekeeper permission letters.

Please note that FULL APPROVAL is granted to your research proposal. You may proceed with data collection.

Any adverse events [serious or minor] which occur in connection with this study and/or which may alter its ethical consideration must be reported to the IREC according to the IREC Standard Operating Procedures (SOP's).

Please note that any deviations from the approved proposal require the approval of the IREC as outlined in the IREC SOP's.

Yours Sincerely

Dr K Padayachy
Deputy Chairperson: IREC

APPENDIX H

ANALYTICS CONSULTINA
Data-driven solutions

Thursday, 14 October 2021

The Chairperson,
Department of Biomedical and Clinical Technology
DURBAN UNIVERSITY OF TECHNOLOGY

To whom it may concern

STATISTICAL DATA ANALYSIS

I, the professional (Bio)Statistician, hereby declare that I have carefully studied the research protocol/Data collection instrument of **PARASRAM ANISA (21800764)**, project title:

"Abnormal spirometry in patients with Rheumatoid Arthritis attending a quaternary clinic in Durban, South Africa"

and performed all the appropriate statistical data analysis. The student also attended at least one Zoom meeting to discuss the statistical aspects of the protocol related to data cleaning and other necessary data preparations.

Should you require any further details, please feel free to contact us.

Yours Sincerely,

The Analytics Team
| Biomedical | Surveys | Business Analytics | up to PhD |
(Bio)Statistician: Tina, PhD
Member of the Royal Statistical Society, UK | Engineering Technologist
+27(0)61 006 9432
statistician@analytics-consultina.com
www.analytics-consultina.com

ANALYTICS CONSULTINA