The diagnostic yield and complications of flexible bronchoscopies performed at a tertiary academic Hospital: a 5-year retrospective study (2015-2019)

Dr Kurai Valerie Tsoka: MBChB HIV Diploma (SA)

Student Number / Staff number: 0602373N**/** A0065390

Supervisor: Dr Kgole MB

The University of Witwatersrand, Pulmonology MBChB BSc MMED FCP (SA)

Co-Supervisor: Prof Richards G.A.

The University of Witwatersrand, Critical Care MBBCh PhD FCP (SA) FRCP

DECLARATION

I, Kurai Valerie Tsoka, declare that research is based on my independent work done under supervision. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine. This research report is submitted in the submissible format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

……..

The ……. day of ……...2022

DEDICATION

To my family, thank you for the unwavering support and sacrifice, and for making it all possible. To my mother, Beauty for the many years of guidance, support, encouragement, and prayers.

PRESENTATION ARISING FROM THE RESEARCH PROJECT
NIL

PUBLICATION ARISING FROM THE RESEARCH PROJECT

NIL

ABSTRACT

Background: There is very little or no data in South African relating to bronchoscopy practice, with a high incidence of lung cancer and lung disease. We, therefore, analysed the performance, indications, and outcomes of bronchoscopies at a tertiary hospital in South Africa.

Objectives: To determine the diagnostic yield, indications and complications at a Tertiary Institution as well as determine the effectiveness of bronchoalveolar lavage (BAL) in making specific diagnoses such as cancer, sarcoidosis, asbestosis and infectious diseases like *Mycobacterium tuberculosis* (MTB) and *Pneumocystis jirovecii* pneumonia (PCP).

Methods: 692 patients were identified and 647 cases analysed due to 45 cases with inadequate data for analyses. A single-centre retrospective cohort study of 647 patients analysed who underwent bronchoscopy between January 2015 and December 2019 was conducted at the Charlotte Maxeke Johannesburg Academic Hospital.

Results: The epidemiology of the subjects showed a significant male predominance (63.65%), with a mean age of 55 years. The most common indication was suspected malignancy followed by non-resolving pneumonia, 41.19% and 40.87 % respectively. There were 116 of 401 (28.93%) malignancies confirmed on biopsy and 82 of 573 (14.41%) from bronchoalveolar lavage. Of all bronchoscopies performed, 85.92% had no complications during or after bronchoscopy but 10.8% were complicated with bleeding.

Conclusions: This audit revealed that flexible bronchoscopy is safe and effective and associated with minimal risk. This study revealed the use of bronchoscopy in diagnosing lung malignancies/carcinomas and highlights the necessity of the availability of bronchoscopy.

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NOMENCLATURE

AFB	Acid-Fast Bacilli
BAL	Bronchoalveolar lavage
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CXR	Chest radiography
DPLD	Diffuse parenchymal lung disease
EBUS	Endobronchial ultrasound
FB	Flexible Bronchoscopy
GXP	Gene X-pert
ILDs	Interstitial lung diseases
MTB	*Mycobacterium tuberculosis*
NHLS	National Health Laboratory services
PaO^2	Partial pressure of arterial oxygen
PCP	*Pneumocystis Jirovecii* pneumonia
PTB	Pulmonary Tuberculosis
SA	South Africa
SaO_2	Oxygen percentage saturation
SD	Standard Deviation
TB	Tuberculosis
TBNA	Transbronchial Needle aspiration
UK	United Kingdom

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Introduction

The lung is significantly exposed to airborne pollutants such as tobacco, biomass fuel and various pathogens. This impacts the five common respiratory conditions that contribute to the global burden of disease; acute respiratory infections, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis and lung cancer (1). Globally, lung cancer causes 1.5 million deaths per year and frequently this is related to cigarette smoking (1). The use of flexible bronchoscopy (FB) in pulmonary medicine has provided access to the tracheobronchial tree both by direct visualization and via radiographic visualisation allowing therapeutic and diagnostic interventions that were not previously possible (2). Access is possible up to the fifth sub segmental bronchi and when used appropriately it is well tolerated by most patients with few complications (3).

History and Epidemiology

The first visualisation of the bronchial tree occurred in 1897 by Gustav Killian using a rigid bronchoscope (3). Later the rigid bronchoscope was improved by Chevalier Jackson, who developed a lighting system to improve vision and added instrumentation (3). In 1967, Shigeto Ikeda developed the flexible bronchoscope which was better tolerated by patients and allowed greater visualisation of previously inaccessible areas of the bronchial tree (3). In the last 10 years, there have been many further advances in bronchoscopic techniques including the use of laser, use of stents for lung volume reduction, bronchial thermoplasty, vagal nerve ablation and endobronchial ultrasound (3). In patients with lung cancer, the diagnostic yield for bronchoscopy is considerable, especially in the presence of an endobronchial lesion; however, the yield is influenced by the technique and by the indication for the procedure (4). The British Thoracic Society (BTS) guidelines recommend that in the case of tumours, bronchial washings, biopsies and brushings for visible lesions should be performed together, as collectively they have been shown to have a diagnostic yield as high as 80% (5).

A study from the University Hospital in Switzerland revealed that most of the bronchoscopies were performed for suspected malignancy and infection, 45% and 27% respectively, compared to a Nigerian Tertiary Centre which showed that suspicion of bronchial cancer and pleural effusions were the main indications for flexible bronchoscopy (2, 4). Another study from Egypt revealed that the most common presenting complaints were dyspnoea and haemoptysis, 50% and 27% respectively (6). The Kuwait University in 2004 reported that suspicion of active pulmonary tuberculosis and non-resolving pneumonia were the top two indications for bronchoscopy (7). The detection rate for lung malignancy in the Egyptian study was 20% compared to 75,5% in the Swiss study (4, 6).

In a more recent study performed by the Nigerian Tertiary Centre, the overall diagnostic yield was 62% between 2009 and 2013, which was an improvement from the 44% found in the previous study from 1979 mentioned above (2, 4). This improvement was likely due to advances in flexible bronchoscopy techniques and testing (2). In the same Nigerian study, an interesting finding was that 6 of their patients were suspected to have pulmonary tuberculosis despite prior negative sputum smears for Acid-Fast Bacilli and of these 50% were confirmed to have pulmonary tuberculosis on flexible bronchoscopy (2). Of those with suspected interstitial lung disease, a third had the diagnosis confirmed by flexible bronchoscopy (2, 4).

Flexible bronchoscopy is an integral part of pulmonary diagnostics, and the constant evolution of new techniques allows safer and more effective ways to diagnose and treat patients. It is important, however, that they be performed only in circumstances where the benefit outweighs the risk particularly when more invasive procedures are employed.

Types of Bronchoscopy

There are many different types of bronchoscopes but the two main ones are flexible bronchoscopy and rigid bronchoscopy . Other advanced bronchoscopes include navigational bronchoscopy, robotic bronchoscopy and those that allow endobronchial ultrasound.

Flexible Bronchoscopy

Flexible Bronchoscopy, also known as standard, white-light bronchoscopy, may be performed either under conscious sedation or general anaesthesia, depending on the experience and expertise of the operator and the team, and it can reach the deep airways as it comes in different diameters and can flex and increase the extent of visualisation of the bronchial tree (8). Developed by Shigeto in 1967, it allowed for greater visualisation of previously inaccessible areas of the bronchial tree (3). Ikeda and others further demonstrated its value in the diagnosis of early-stage lung cancer, due to its ability to access segmental airways (3, 9, 10).

The main advantages of Flexible Bronchoscopy other than increased visualisation, are the broad spectrum of diagnostic and therapeutic uses, patient comfort during the procedure and the use of conscious sedation versus general anaesthesia (10, 11).

When using Flexible Bronchoscopy for diagnostic purposes, and in particular for pulmonary nodules or diffuse parenchymal lung diseases it is usually necessary to perform a minimum of three to five biopsy specimens, as this increases the diagnostic accuracy and yield to 85% (12, 13). The use of Flexible Bronchoscopy is critical to the management of adult patients presenting with a foreign body aspiration involving the lower airways and its success rate is between 61% to 97% (14). Concerning malignancy, the addition of bronchial washings, brushings, Endobronchial Needle Aspiration (EBNA), and/or Transbronchial Needle Aspiration (TBNA) adds to the yield increasing the sensitivity up to 88% (15, 16). Transbronchial Needle Aspiration allows sampling of mediastinal lesions by passing the needle through the bronchial wall and is used along with Endobronchial Needle Aspiration in the presence of endobronchial disease.

Rigid Bronchoscopy

Rigid Bronchoscopy originated from the discipline of otolaryngology, as this method allowed better visualisation of the larynx and central airways (9). The bronchial tree was first visualised in 1897 by Gustav Killian and Chevalier Jackson added a light source that facilitated the use of forceps and suction catheters (3, 8). The diagnosis of primary lung

carcinomas by needle biopsy of paratracheal nodal metastases while performing Rigid Bronchoscopy, was first achieved by Ko Pen Wang, among others (9, 17). Unlike other bronchoscopes, Rigid Bronchoscopy is performed under general anaesthesia and with this comes the potential for complications related to anaesthesia (11). Other common complications include trauma to the oropharynx, vocal cords and teeth, laryngospasm and pneumothorax and bleeding which are common with flexible bronchoscopy as well (11). The Rigid Bronchoscopy technique is usually used for tumour debulking, airway dilatation, removal of foreign bodies, placement or removal of stents and haemostasis in cases of massive haemoptysis (8).

Virtual Bronchoscopy

Virtual bronchoscopy is not readily available in South Africa (SA) but utilises a computer-generated image that allows for visualisation of the distal airways. It is a non-invasive procedure that provides information about surrounding structures as well as the bronchial tree, however, its limitations include availability, cost, a paucity of personnel skilled in its use, and most importantly access to tissue or washings (8).

Endobronchial ultrasound (EBUS)

Endobronchial Ultrasound is an advanced technique that uses ultrasound technology to visualise central airways and lung parenchyma which allows for easier image-guided Transbronchial Needle Aspiration (18). Endobronchial Ultrasound is commonly used to sample mediastinal or hilar lymph nodes and also to access peripheral pulmonary nodules although it is unable to stage the entire mediastinum in lung cancer, as access is limited to anterior and superior mediastinum (18, 19). New advances in equipment have facilitated the use of Endobronchial Ultrasound for the diagnosis and investigation of patients with sarcoidosis, tuberculosis and lymphoma (19).

Indications

Major indications for Flexible Bronchoscopy include the investigation of chronic cough, a suspicion of pulmonary malignancy and the diagnosis of some interstitial lung diseases (2).

Bronchial washings have been used for the identification of pathogens in infections of the lung and bronchial tree and for cytology where malignancy is suspected (4). Interventional indications for Flexible Bronchoscopy include foreign body retrieval, clearance of airway secretions, relief of airway obstruction, dilatation of tracheal stenosis and identification of a site of haemoptysis (4).

Cough

The presence of chronic (> 8 weeks) or less frequently subacute cough (3-8 weeks) can be an indication of underlying lung pathology, especially in patients that are immunocompromised and those that present with a normal chest x-ray (20). However, Flexible Bronchoscopy should only be used after careful evaluation for other causes like gastro-oesophageal reflux, asthma and a postnasal drip (21). In patients that have been diagnosed with bronchogenic carcinoma, the presenting problem was usually a cough, in 21-87% (20).

Malignancy

Besides cough as a presentation, chest x-ray findings may reveal a mass, or there could be unexplained atelectasis from an obstructive lesion (22). The use of Flexible Bronchoscopy allows one to determine the exact cause, whether a tumour or foreign body the additional possibility that the latter may be able to be retrieved using forceps (8, 22). Whereas Flexible Bronchoscopy aids in accessing peripheral nodules in the apical and superior basal segments, sampling in this area is more likely to cause pneumothoraces and possibly haemothoraces (20).

Haemoptysis

Haemoptysis is one of the most common presenting complaints associated with the diagnosis of malignancy, tuberculosis, fungal infections and bronchiectasis (20, 23). The presence of massive haemoptysis is a medical emergency and requires urgent attention (23). Massive haemoptysis is usually defined as more than 500mls over 24 hours (23, 24). The quantity of blood or the presence of ongoing haemoptysis can be a positive predictor of an underlying carcinoma (20). The use of Flexible Bronchoscopy can be therapeutic as it

allows for the injection of epinephrine, thrombin solutions, or balloon stenting and intubation if necessary, and it allows better evaluation of the location of bleeding (20, 24). The problem is that if bleeding is extensive the suction aperture of the Flexible Bronchoscopy may be too small to manage the condition.

Non-resolving Pneumonia

This has been defined in other studies as a persistent cough productive of sputum, with or without a fever, and failure of radiologic improvement by at least 50% by two weeks or complete resolution by four weeks, despite having received antibiotics for at least ten days (25). Although the resolution of pneumonia is dependent on age and prior structural lung disease, resolution can however take up to six weeks. If this does not occur, Flexible Bronchoscopy is indicated particularly if there is associated volume loss on chest X-ray (20). When the Flexible Bronchoscopy is performed, bronchoalveolar washings should be sent for microscopy, culture, sensitivity, and cytology to determine the diagnosis and to direct antimicrobial choice if infective in aetiology (20, 22). In immunocompromised patients the use of bronchoalveolar lavage with transbronchial biopsy, has a 100% sensitivity in patients with *Pneumocystis jirovecii* pneumonia, however, given the degree of hypoxaemia that these patients usually have, it is not always possible to do a bronchoscope *(20).* Flexible Bronchoscopy is useful to confirm a diagnosis of tuberculosis in sputum-negative patients, yielding a positivity rate of 65% with bronchoalveolar lavage sampling, compared to 45% with induced sputum alone in those with suspected tuberculosis (13). A study from the haematology and oncology department of the University of Mannheim, Germany, from July 1988 until March 2003, found that the main cause of infection-related pulmonary infiltrates was bacterial, followed by fungi and viruses (26).

Airway Disease

Diffuse parenchymal lung diseases (DPLDs) formerly known as Interstitial lung diseases (ILDs) are a spectrum of diseases affecting the interstitium, peripheral airways, alveoli and blood vessels. This group of diseases has multiple causes which may be idiopathic but also could be due to inter alia, environmental exposure, drug toxicities and autoimmune diseases

(27). Bronchoalveolar lavage has moderate utility in making a diagnosis or ruling out other causes by utilising cell counts, culture and cytology (27).

Tuberculosis

Tuberculosis is a communicable disease caused by *Mycobacterium tuberculosis (MTB)* and South Africa (SA) is among the top ten nations for tuberculosis burden of disease and it is also one of the leading causes of death (28, 29). Recently, the development of the sputum GeneXpert (GXP) test has revolutionised the early diagnosis of Tuberculosis, but despite this, results may still be negative in the Human Immunodeficiency Virus population due to ineffective contamination by *Mycobacterium tuberculosis* and lack of pulmonary cavity or granuloma formation (30, 31). A single GeneXpert can detect 98% of patients with smear-positive and culture-positive disease and 70% of patients with smear-negative and culture positive-disease. It can also identify whether resistance to rifampicin is present (32). There is also high sensitivity for the detection of smear-negative Tuberculosis, which is particularly relevant to Human Immunodeficiency Virus -infected individuals (32).

Abnormal Chest Radiography

Anomalies seen on chest radiography including masses, are the most common indications for performing Flexible Bronchoscopy. In the United Kingdom (UK) in the paediatric population, persistent pulmonary infiltrates are also one of the most common indications (33).

Contraindications

The success of Flexible Bronchoscopy depends highly on the pre-procedural assessment of the patient as well as continuous monitoring. Contraindications can be categorised as either cardiovascular or pulmonary.

Cardiovascular contraindications

Haemodynamic instability is possible in patients who are at high-risk for myocardial ischaemia due to the potential for an intraprocedural increase in mean systemic pressures, increased cardiac index and decreased oxygenation and as such, patient selection and risk

assessment before the procedure should include a thorough cardiovascular examination. Recent myocardial infarction, current cardiac arrhythmias and poorly controlled heart failure are considered to be relative contraindications (34).

Pulmonary contraindications

Severe hypoxaemia is a contraindication to performing a bronchoscope. This is defined as the partial pressure of arterial oxygen (PaO2) < 60 mmHg or an oxyhaemoglobin percentage saturation SaO_2 < 90% while receiving a the fraction of inspired oxygen (FiO2) of more than 0.6 (8). In patients that are not hypoxaemic, supplemental oxygen should be used if a desaturation of more than 4% occurs to reduce the risk of complications (12).

Pulmonary Hypertension is also considered to be a relative contraindication because of the rise in mean arterial pressure during the procedure but also because biopsy in these circumstances has the potential to cause significant bleeding. Patients that suffer from any unstable airway disease like asthma or Chronic Obstructive Pulmonary Disease (COPD) are at high risk for developing bronchospasm and therapy should be optimised before the procedure. Bullous lung disease increases the risk of pneumothorax, especially with transbronchial biopsy (34). Other considerations that may increase complications include the use of anticoagulants, renal insufficiency, pregnancy and age to name a few.

Procedure

Bronchoscopies require meticulous planning and consideration of any potential possible adverse events (35). In addition, investigations performed during the procedure should be aimed at obtaining the maximal amount of relevant information. Microscopy, culture and sensitivity, cytology, GeneXpert for *Mycobacterium tuberculosis*, histology and bronchoalveolar washings should be obtained where possible.

Biopsy

There have been multiple studies evaluating the bronchoscopic yield, however, this varies according to the site, size and accessibility of the lesion. Where possible, a biopsy of any directly or radiologically visualised lesion should be performed (33).

Bronchoalveolar lavage

Bronchoalveolar lavage is an integral part of the bronchoscopic procedure and is almost always performed unless there is a contraindication. Bronchoalveolar lavage is particularly important in the diagnosis of infections, especially in non-resolving pneumonia but can also increase the diagnostic yield in difficult-to-access tumours (33). Multiple aliquots of isotonic saline are instilled into the most distal airways and re-aspirated into Luki tubes to optimise yield (36).

Potential adverse events of flexible bronchoscopy

Potential adverse effects which include bleeding, bronchospasm and pneumothoraces have been reported in various studies. These should be anticipated and managed timeously. (see Appendix 1).

Bleeding

The risk of bleeding during bronchoscopy is less than 1% but that risk increases to 7.5% in patients who have an underlying coagulopathy or are on any anticoagulants (13). Those most likely to bleed include patients with haemophilia, a family history of bleeding, liver disease and renal failure (13). A study of the diagnostic yield of Flexible Bronchoscopy with Bronchoalveolar lavage in febrile patients with hematologic malignancies and pulmonary infiltrates, revealed that 15% bled after the scope, most likely due to low platelet count (26). Bleeding that occurs during Flexible Bronchoscopy is usually no more than 100ml and in the majority of cases can be stopped with the use of adrenaline or other vasoconstrictors or tamponade (12).

Bronchospasm

Patients that have an underlying chronic lung disease like Chronic Obstructive Pulmonary Disease and asthma, need to be evaluated carefully before performing Flexible

Bronchoscopy. Their symptoms may be worsened and cause a temporary decline in baseline function despite the use of a bronchodilator before the procedure (13). The use of supplemental oxygen in Chronic Obstructive Pulmonary Disease patients has however been found to decrease the incidence of acute bronchospasm (13). Concerning asthmatics, bronchospasm occurs in as many as 12.3% (37).

Arrhythmias

Myocardial stress occurs during Flexible Bronchoscopy as the procedure elevates blood pressure, and heart rate and worsens or causes hypoxaemia. This can manifest as ST-segment elevation or depression, bradycardia, or transient bundle branch block (12). This is more common in older patients and those with a significant smoking history (12). Arrhythmias are most likely to manifest as the bronchoscope passes through the vocal cords (12).

Hypoxaemia

Hypoxaemia is common during bronchoscopy although it is generally transient, and occurs especially after sedation and passing of the scope through the vocal cords (12). As mentioned above, the use of pre-oxygenation and the use of pulse oximetry for continuous monitoring during the procedure reduces the risk of developing hypoxaemia.

Pneumothorax

One in 1000 patients may develop a pneumothorax during or after a bronchoscopic procedure and the presentation may be delayed, so close monitoring is necessary (12). This is commonly associated with transbronchial biopsies and should be actively sought after the procedure.

Premedication

According to the British Thoracic Society guidelines, premedication should not be routinely used, as there is no evidence of benefit and it may cause harm such as impacting intra-procedural haemodynamics (38).

Sedation

Sedation during the procedure improves tolerance and co-operation and reduces adverse events. The most common agent used is a benzodiazepine, such as midazolam, which has both anxiolytic and sedative properties and induces antegrade amnesia. The preferred depth of sedation is in the realm of “conscious sedation” where airway patency and respiration are maintained without hypotension and verbal communication is possible. If deeper levels of sedation are required, adequate monitoring must be provided, and anaesthetic support must be available. Other agents that are effective such as propofol and ketamine could be used either singly or simultaneously (38). (see Appendix 2).

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CHAPTER 2: Article in Publication Ready Format

The diagnostic yield and complications of flexible bronchoscopies performed at a tertiary academic Hospital: a 5-year retrospective study (2015-2019)

K V Tsoka[1], MBChB, Diploma in HIV medicine, **M B Kgole,**[2] BSc, MBChB, MMED , FCP (SA) Cert Pulm (SA), **G A Richards,** [3] MBBCh, FCP (SA) ,FRCP, PhD, Cert Crit care

Affiliations:

[1]*Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand.*

[2]*Division of Pulmonology, Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand and Division of Pulmonology, Department of Medicine, Faculty of Health Sciences, Sefako Makgatho Health Science University.*

[3]*Division of Critical Care, Faculty of Health Sciences, University of the Witwatersrand.*

ABSTRACT

Background: There is very little or no data in South African relating to bronchoscopy practice, with a high incidence of lung cancer and lung disease. We, therefore, analysed the performance, indications, and outcomes of bronchoscopies at a tertiary hospital in South Africa.

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Conclusions: This audit revealed that flexible bronchoscopy is safe and effective and associated with minimal risk. This study revealed the use of bronchoscopy in diagnosing lung malignancies/carcinomas and highlights the necessity of the availability of bronchoscopy.

INTRODUCTION

The lung is significantly exposed to airborne pollutants such as tobacco, biomass fuel and various pathogens. This impacts the five common respiratory conditions that contribute to the global burden of disease; acute respiratory infections, Chronic Obstructive Pulmonary Disease (COPD), asthma, tuberculosis and lung cancer (1). The use of Flexible Bronchoscopy (FB) in pulmonary medicine has provided access to the tracheobronchial tree both by direct visualization and via radiographic visualisation, allowing therapeutic and diagnostic interventions that were not previously possible (2). Access is possible up to the fifth subsegmental bronchi and when used appropriately it is well tolerated by most patients with few complications (3).

The British Thoracic Society guidelines aimed to help those performing Flexible Bronchoscopy to better understand the procedure, its complications and its role in the possible diagnosis and management of lung pathologies. Flexible Bronchoscopy is an integral part of pulmonary diagnostics, and the constant evolution of new techniques allows safer and more effective ways to diagnose and treat patients. It is important ,however, that they be performed only in circumstances where the benefit outweighs the risk particularly when more invasive procedures are employed. The use of Flexible Bronchoscopy in developing countries is however limited and studies in South Africa have not been done at a tertiary level hospital or audits published on the role, safety, and yield of flexible bronchoscopy.

OBJECTIVES

- Data will be collected on all bronchoscopies performed at Charlotte Maxeke Johannesburg Academic Hospital from January 2015 to December 2019 and it will be analysed to determine the diagnostic yield, indications and complications reported in that time frame.

- To determine the effectiveness of bronchoalveolar lavage (BAL) in making specific diagnoses such as cancer, sarcoidosis, asbestosis and infectious diseases like *Mycobacterium tuberculosis* (MTB) and *Pneumocystis jirovecii* pneumonia (PCP)

Research design

This is a retrospective review of bronchoscopies performed on adult patients in Charlotte Maxeke Johannesburg Academic Hospital from 2015 to 2019. The study design is a cross-sectional study of patients undergoing bronchoscopy at CMJAH.

METHODS

Data collection

This study was a retrospective cross-sectional review of all bronchoscopies performed on adult patients in the Bronchoscopy suite at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa. The data was collected during the period from January 2015 to December 2019. The population studied were all adults (above the age of 18 years) attending the respiratory clinic and referred from peripheral hospitals or the general wards with indications for bronchoscopy. Findings based on the clinical indications, background medical illness, chest X-ray features, Computed Tomography scan findings, and any complications were documented. Bronchoalveolar lavage and endobronchial sampling were obtained as per clinical indication. The samples obtained were then sent for histology and microbiology and the results accessed from the National Health Laboratory Services database. These data were tabulated using excel spreadsheets and analysed. Some records and results were not found and so were not included in the study.

Study Participants

All patients above the age of 18 years that had a bronchoscopy performed at the Charlotte Maxeke Johannesburg Academic Hospital Pulmonology department in the study period.

There were 692 patient's data entered and 647 cases analysed due to 45 cases with inadequate data for analyses. Therefore study of 647 bronchoscopies analysed (see Figure 1).

A data sheet (Appendix 4) was used to collect and record the bronchoscopies done and enter the results i.e. cytology, culture and histology with the use of the National health laboratory services (NHLS) or National Institute of Occupational Health (NIOH) website.

Measurements

Demographic characteristics

Age and gender were collected. Age was categorized into four groups: 18-34, 35-44, 45-55 and 55+ years.

Clinical information

Clinical data comprised of comorbidities (such as Human Immunodeficiency Virus, smoking history, hypertension, malignancy, lung diseases, etc.), and in those that were Human Immunodeficiency Virus positive, viral load and CD4 counts (cell/μL), CT (Computed Tomography) scan findings, complications, and indications. It was not clear those who were not documented HIV-positive were if they were negative or not tested at all, so were labeled unknown.

Medical history and diagnostic tests

Patients were asked about previous bronchoscopy (Yes or No) and sputum Cepheid® GeneXpert (GXP) results (Negative or Positive) before bronchoscopy. Bacteriological analysis of specimens was conducted to identify organisms such as *Klebsiella spp., Mycobacterium tuberculosis*., *Pseudomonas spp., Candida spp.,* etc. The diagnostic tests that were used were biopsies and Bronchoalveolar lavage.

Ethical consideration

Permissions for the study were granted by the Chief Executive Officer (CEO) of Charlotte Maxeke Johannesburg Academic Hospital and the Head of the Pulmonology Department.

Ethical clearance was acquired, number M200561, in accordance with the requirements for the Masters in Medicine degree, from the University of the Witwatersrand Human Research Ethics Committee. (see Appendix 3). Ethical clearance had to be amended to include permission from the National Health Laboratory Services (NHLS) and the Department of Anatomical Pathology to obtain data from their systems access (Project application number #PR20352).

Statistical analysis

Frequencies and percentages were reported for categorical data, stratified by gender and Human Immunodeficiency Virus status. To compare categorical variables for statistical significance by gender and Human Immunodeficiency Virus status, Chi-squared test analysis or Fisher's test was used. Descriptive statistics such as mean, median, inter-quartile range (IQR), standard deviation, range, standard error, and frequencies were be performed to describe the variables in the study. Kruskal-Wallis and student t-tests were used to compare continuous variables stratified by gender and Human Immunodeficiency Virus status. Complications and indications for bronchoscopy were presented graphically.

Additionally, biopsy and Bronchoalveolar lavage results were presented according to previous GeneXpert sputum results, if available. Data of patients with various lung cancers (such as squamous cell carcinoma, adenocarcinoma, non-small cell carcinoma, metastatic and small cell carcinoma) were stratified by smoking status “non-smokers” vs. “smokers”. All statistical analysis was conducted in SAS Enterprise Guide 7.1 using the procedures FREQ, MEANS, NPAR1WAY, TTEST and SGPLOT.

Implications

Many lung pathologies contribute to the global burden of diseases. The use of routine Flexible Bronchoscopy aids in the diagnosis of many of these conditions which include Tuberculosis and other infectious diseases, sarcoidosis, and asbestosis and the yield thereof is high. This research is important as it evaluates the yield of bronchoscopies at a

South African hospital, which has not previously been done. It will help us to identify if this facility meets international standards and if more can be done to hasten diagnoses. The study could also help to identify any challenges prevalent in our setting and may help identify the most frequent respiratory illnesses in our setting.

RESULTS

Demographic characteristics, comorbidities, and CT scan findings by HIV status

Of the 647 patients included in the analysis, the majority were 55 years or older (58.8%, n=380) with a median age of 58 years (IQR: 48-66) (Table 1). A high proportion of patients were smokers (44.2%, n=286), HIV-negative (79.9%, n=517), had Computed Tomography scan showing a mass (36.3%, n=235) and had suspected malignancy (64.0%, n=414). Males were more likely to smoke (53.0% vs. 28.5%, p<.0001) compared to females.

Of the 20% (n=130) who were HIV-positive and had an overall median CD4 count, the count was 254.5 cells/μL (IQR: 94.0-521.5).

HIV-positive patients were significantly younger than those who were negative (median: 47 [IQR: 39-56] vs 60 [51-68]; p<.0001) respectively (Table 1). HIV-positive patients were also more likely to have had previous pulmonary tuberculosis and consequent bronchiectasis (24.6% vs. 8.9%, p<.0001), evidence of previous and in some, active Tuberculosis from Computed Tomography scan findings (8.5% vs. 1.9%, p=0.0008), and chronic cough (13.9% vs. 6.4%, p=0.0048) relative to those who were HIV-unknown. Though not significant, patients who were HIV-positive had a slightly higher proportion of non-resolving pneumonia (19.2% vs. 13.4%, p=0.0888) than those that were unknown (Table 1).

Conversely, patients who were HIV-unknown were more likely to be smokers (47.8% vs. 30.0%, p=0.0003) and to be suspected of underlying malignancy (68.1% vs. 47.7%, p<.0001) (Table 1).

Medical history and diagnostic yield by HIV status

An overall 5.2% (n=34) of patients had had a previous bronchoscopy, and 2% (n=13) had tested positive for GeneXpert before bronchoscopy (Table 2). Patients who were HIV-unknown were more likely to have normal tissue on biopsy (37.9% vs. 26.9%; p=0.0194) compared to HIV-positives (Table 2). Though not significant, HIV-unknown patients had a higher proportion of carcinoma diagnosed (19.9% vs. 13.1%, p=0.0726) relative to HIV-positive patients.

Indications in patients undergoing bronchoscopy

A majority of patients had suspected malignancy (63.3%, n=414) followed by non-resolving pneumonia (14.5%, n=94), chronic cough (7.9%, n=51) and pulmonary infiltrates (6.0%, n=39) (Figure 2).

Diagnostic yield of the different sampling procedures

Biopsy diagnosed a higher number of patients with carcinoma (18.6%, n=120) whereas Bronchoalveolar lavage diagnosed 12.8% (n=83) (Table 3). A biopsy is the only test that detected sarcoidosis in one patient. Conversely, bronchoalveolar lavage detected a higher number of patients with inflammatory results defined by non-diagnostic elevated white cells, including neutrophils and/or lymphocytes (13.6%, n=88) as well as *Mycobacterium tuberculosis* (2.9%, n=19) compared to biopsy.

Diagnostic yield of the different sampling procedures by previous GXP sputum results

Those who had a positive GeneXpert previously also had a higher proportion of normal tissue from biopsy (72.7% vs. 65.0%, p=0.0774) compared to negative GeneXpert, though not significant and were more likely to be diagnosed with *Mycobacterium tuberculosis* from Bronchoalveolar lavage (16.7% vs. 3.3%, p=0.0148) (Table 4).

Lung cancer by smoking status

In this audit, a total of 120 patients were diagnosed as having a carcinoma on biopsy, and 83 on Bronchoalveolar lavage. Of 203 patients confirmed to have a carcinoma, 102 had a definitive type identified. A higher proportion of patients had squamous cell carcinoma

(33.3%, n=33) compared to adenocarcinoma (30.3%, n=30) (Table 5). Though not statistically significant, smokers had higher proportion of squamous cell carcinomas (35.4% vs. 29.4%, p=0.5494), non-small cell carcinomas (15.4% vs. 11.8%, p=0.6235) and small cell carcinomas (12.3% vs. 2.9%, p=0.1587). Non-smoking patients were more likely to have metastatic disease (29.4% vs. 1.5%, p<.0001) compared to smoking patients (Table 5).

Complications in patients undergoing bronchoscopy

The majority of patients had no complications (85.9%, n=556), whereas 11.0% (n=71) had haemorrhage, 1.6% (n=10) hypoxaemia post procedure, 1.2% (n=8) bronchospasm and 0.8% (n=5) an arrhythmia (Figure 3).

Organisms identified in patients undergoing bronchoscopy

The majority of the bronchoalveolar lavage specimens showed no specific organisms grown on culture (79.4%, n=514), however 10.8% of washings (n=70) grew *Pseudomonas* spp., 3.6% (n=23) *Candida spp.,* 3.4% (n=22) *Mycobacterium tuberculosis* and 2.9% (n=19) *Klebsiella spp*. Of the patients who had organisms identified, the majority grew only one (81.3%, n=91) followed by two in (17.9%, n=20) and three in one patient.

DISCUSSION

Flexible Bronchoscopy is a crucial part of pulmonary medicine. Access to the procedure is unfortunately limited and is available only in tertiary/quaternary hospitals in Africa. Bronchoscopies need to be performed in a safe environment and are usually dependent on the expertise of the individual performing them. The British Thoracic Society guidelines for diagnostic Flexible Bronchoscopy in adults and the local institutional protocol dictates that bronchoscopy be performed under conscious sedation, by a specialist pulmonologist or by a pulmonology trainee/physician (12).

During the 5 years of the study, we observed a male predominance of patients undergoing the procedure but otherwise, the epidemiology was similar including the mean age years of 55 (39, 40). The overall diagnostic yield, excluding those patients in whom results were not found and those in whom the biopsy or bronchoalveolar lavage was not indicated, was 36.6% for biopsy and 33.9% for bronchoalveolar lavage.

The most common indication for Flexible Bronchoscopy was a suspicion of malignancy in 63% of cases with 44.2% of the patients being smokers, with an obvious mass on chest radiology and 235 Computed Tomography scans reporting masses or lung nodules suspicious for metastases, a finding that was similar to other studies in Africa (2, 41). A survey reported from the United Kingdom also showed similar results, with malignancy being the most common indication for Flexible Bronchoscopy (42).

The association between smoking and lung cancer has been well established and documented since the 1930s in Germany and later in Great Britain and America in the 1960s (43). A systematic review and meta-analysis showed clear evidence of the association between the amount smoked and the duration of smoking and all lung cancers, not only

histological type (43). In this study carcinoma was diagnosed in 203 cases, 120 on biopsy and 83 on bronchoalveolar lavage. Ninety-nine of the 203 were primary lung cancers and of these, 33.33% were squamous, followed by adenocarcinomas at 30.3% (43). Of these 35.38% and 26.15% were smokers respectively, which is a finding similar to that of the meta-analysis mentioned above (43). In contrast, a study conducted in Sao Paulo, Brazil, revealed that respiratory infections like *Mycobacterium tuberculosis* were the most common indications for flexible bronchoscopy with malignancy only third (44).

Non-resolving pneumonia is an important indication for flexible bronchoscopy as the causes include serious but potentially treatable conditions such as single or multi-drug resistant organisms i.e. *Staphylococcus* and *Klebsiella species* as well as some fungal and parasitic infections (25). Granulomatous diseases such as *Mycobacterium tuberculosis* infections and Sarcoidosis, lung malignancies, vasculitides and interstitial lung disease are some of the treatable causes of non-resolving pneumonias that may be diagnosed using Flexible Bronchoscopy (25). Non-resolving pneumonia and chronic cough were also common indications for Flexible Bronchoscopy in 14.54%, and 7.88% of cases respectively in our study similar to a study performed in New Delhi, India, by Chaudhuri et al. Chaudhuri et al, also revealed that bacterial pneumonia, due to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa,* were the most common organisms cultured causing non-resolving pneumonia, followed by bronchogenic carcinoma (25). In the current study in Johannesburg, South Africa, *Pseudomonas spp*. was the most common organism found in 70 cases, followed by *Mycobacterium tuberculosis* in 22 cases, and *Klebsiella pneumoniae* in 19 cases. Twenty-three cultured *Candida albicans* which was unlikely to be pathogenic in the lower respiratory tract.

Africa, and in particular sub-Saharan Africa, has a very high burden of Human Immunodeficiency Virus infection and along with this, *Mycobacterium tuberculosis* infection (31). At Charlotte Maxeke Johannesburg Academic Hospital, not all patients that had bronchoscopy were tested for Human Immunodeficiency Virus, but of those that were, 19.63% were positive with the remainder 80,37%, unknown. This was much lower in comparison to a study from the United States of America (USA) that recruited patients

between 2012-2017 where 30.7% were found to be positive (45). Those that were Human Immunodeficiency Virus positive were primarily between the ages of 45-55, followed by 34-44 and the majority were on antiretroviral therapy and had a suppressed viral load.

The evolution of Tuberculosis diagnostics has led to the GeneXpert test, which uses single cartridge-based nucleic acid amplification which can identify *Mycobacterium tuberculosis* and detect rifampicin resistance within 2-3 hours (46). During the period of this audit, 2.01% of the cases had Pulmonary Tuberculosis at the time of Flexible Bronchoscopy and a further 21 cases were diagnosed by the procedure. This is probably because the GeneXpert assay performed on bronchial washings was more sensitive than induced sputum, as suggested by Lee et al (47).

There was a 14.32% complication rate during the study period (94 of 656 cases), the most common of, which was any haemorrhage which occurred in 71 cases. Arrhythmias, bronchospasm, hypoxaemia, pneumothorax, severe cough, and a single respiratory arrest, with survival, also occurred, but were less common and importantly there was a zero-mortality rate. A study in Egypt in 2013, reported that desaturation and bleeding were the most common complications, although this was on a sample size of only 100 (6). Another Egyptian study, performed over 7 years with 3980 cases, reported bronchospasm as one of the major complications (41). In the Nigerian Tertiary Centre, 163 diagnostic bronchoscopies were studied with an overall complication rate of 5% with the majority of these being minor such as spontaneously resolving epistaxis, vasovagal reaction and hypoxaemia (2).

Study Limitations

A limitation of the study was that it was retrospective, and data collected from the Flexible Bronchoscopy information sheets frequently had missing data, particularly concerning co-morbidities and the indication for bronchoscopy. Despite this, the available information was extensive and enabled the data collection process to take place. It was also necessary to access the National Health Laboratory Services (NHLS) for the microscopy, culture, cytology, and histology results which were not always available. This study was a single

centre study and may not be generalizable to other centres. Not all patients who had bronchoscopy had HIV tests as it was not a prerequisite.

CONCLUSIONS

The availability of Flexible Bronchoscopy has significantly impacted the diagnosis and treatment of pulmonary diseases. Flexible Bronchoscopy should be accessible to a wider range of public sector patients, especially those in whom there is a diagnostic dilemma. This study has shown that there is significant diagnostic utility in terms of lung malignancy and other pulmonary diseases such as Pulmonary Tuberculosis which if identified early increase the likelihood of cure.

DECLARATION
None

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AUTHOR CONTRIBUTIONS
BK established the audit, KO analysed the data, All authors reviewed the manuscript prior to publication.

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None

CONFLICTIONS OF INTEREST
None

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Figure 1: Disposition flow chart

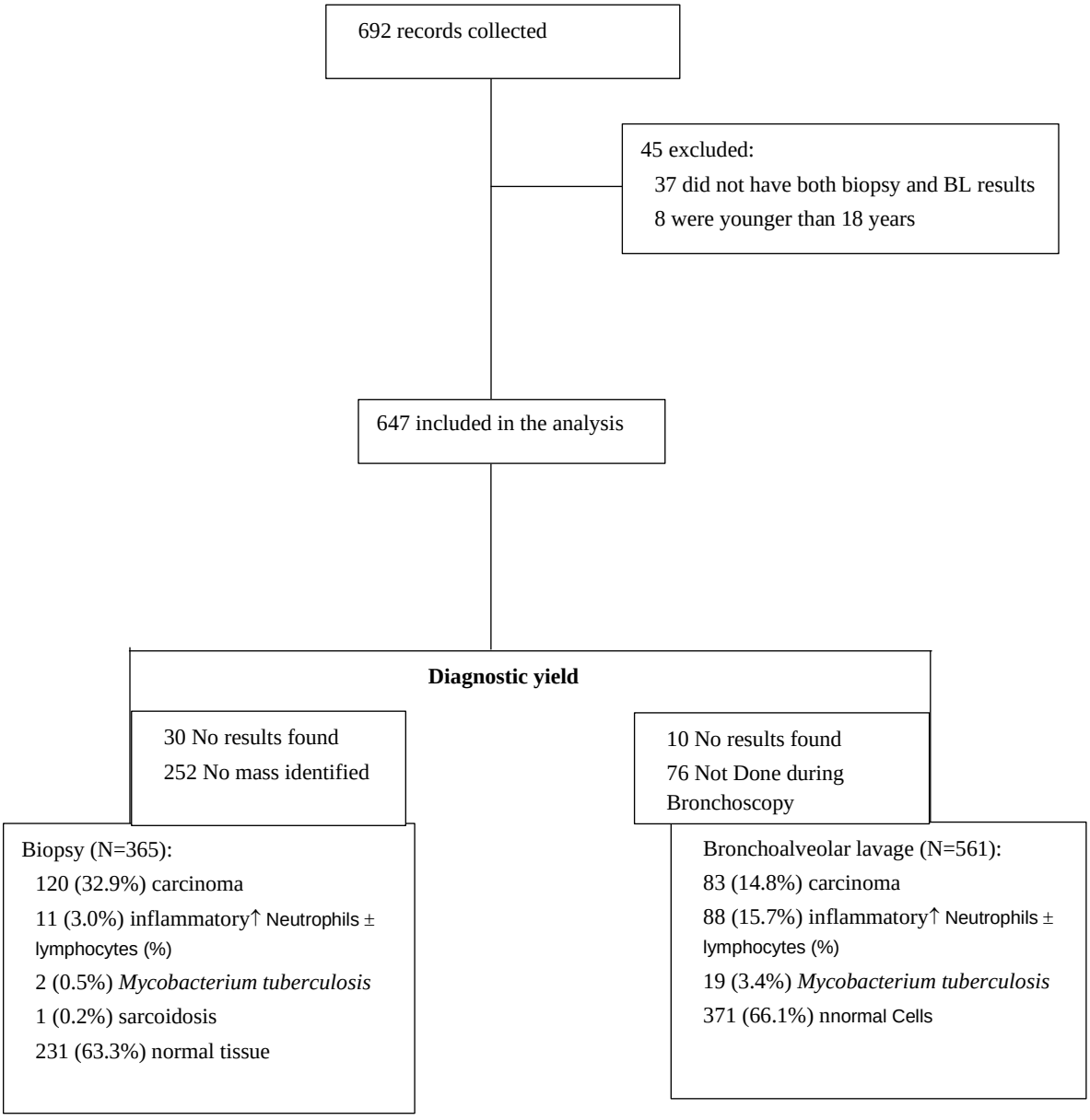

Figure 2: Indications for flexible bronchoscopy

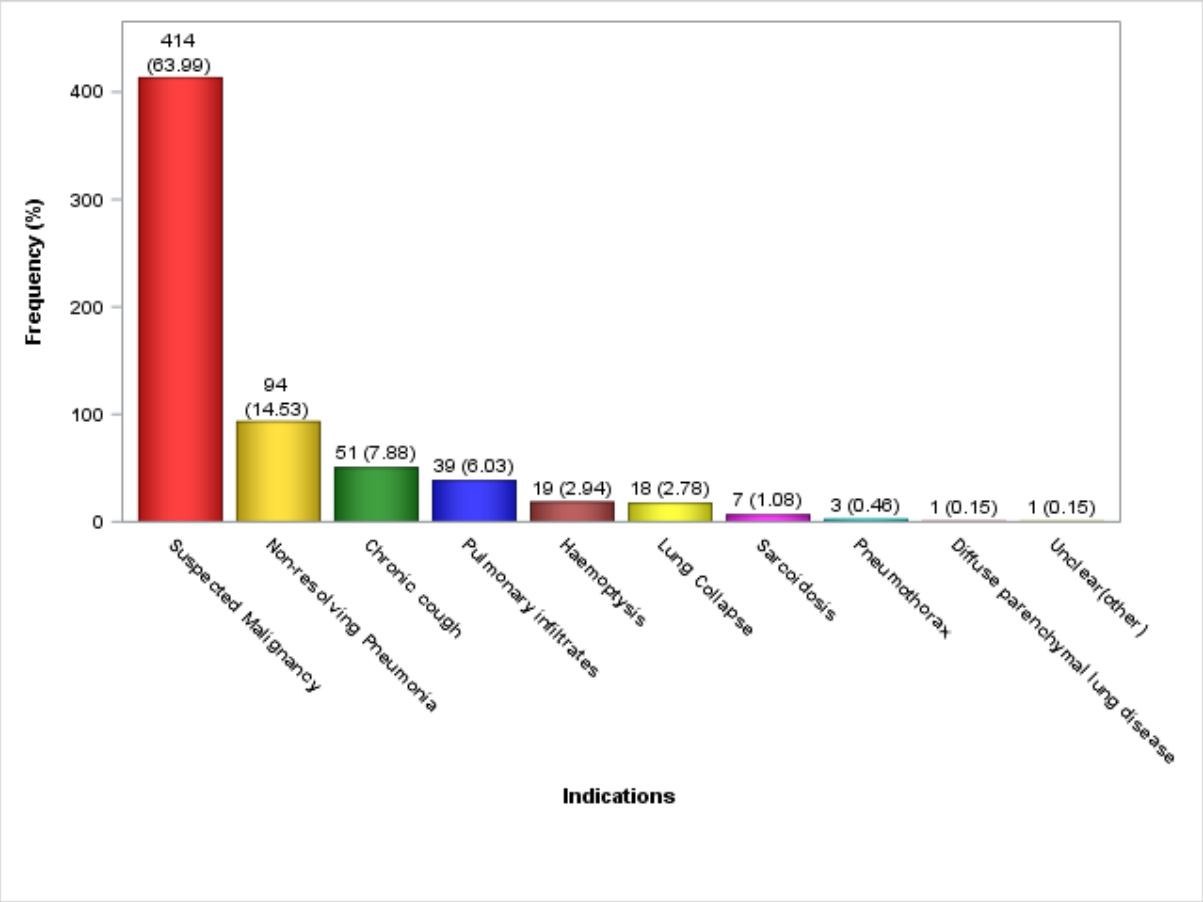

Figure 3: Complications in patients undergoing bronchoscopy

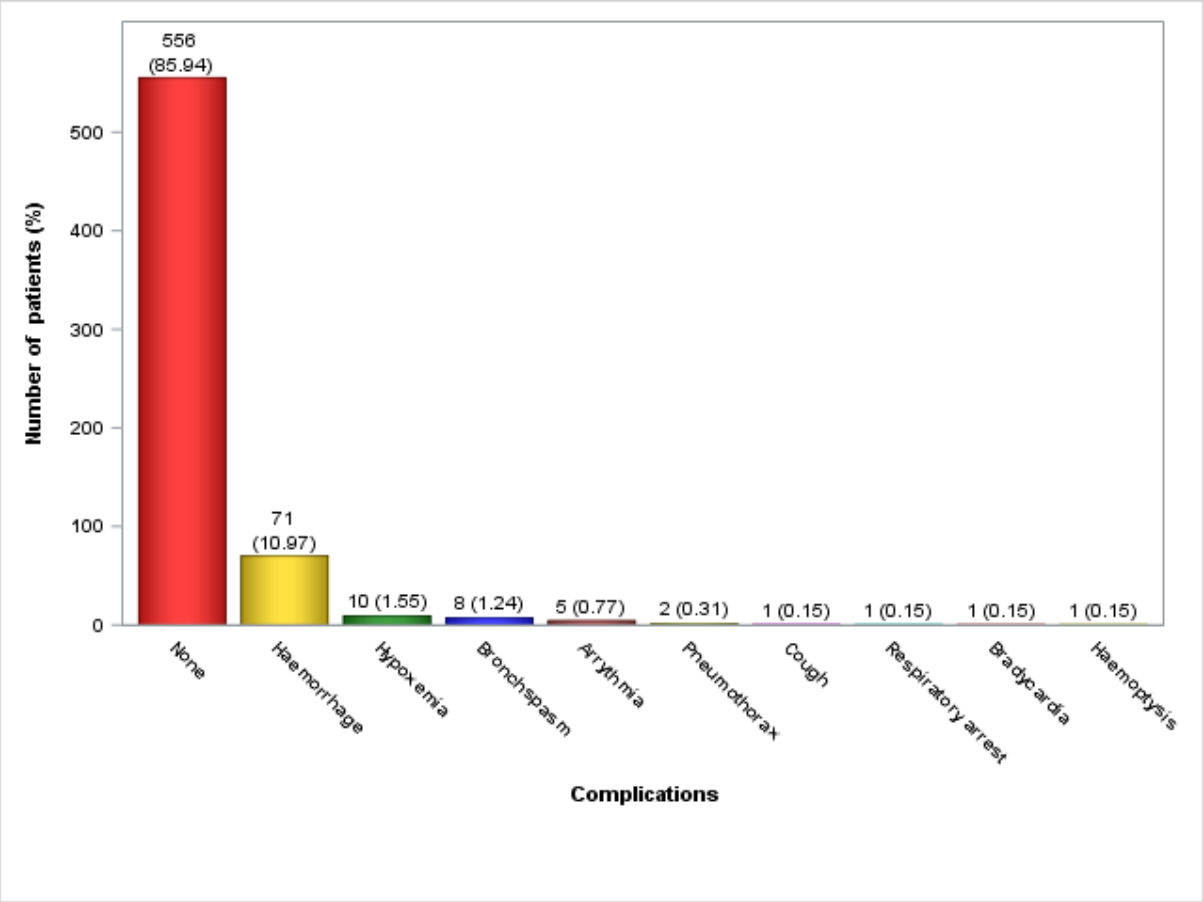

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Table 1: Demographic and clinical characteristics of patients undergoing bronchoscopy by HIV status

Variable	Overall (n=647)	HIV Unknown (n=517)	HIV Positive (n=130)	P-Value
Age (in years)				
18-34 years (%)	60 (9.29)	38 (7.36)	22 (16.92)	0.0008
35-44 years (%)	76 (11.76)	41 (7.95)	35 (26.92)	<.0001
45-55 years (%)	130 (20.12)	92 (17.83)	38 (29.23)	0.0038
55+ years (%)	380 (58.82)	345 (66.86)	35 (26.92)	<.0001
n, Median (IQR)	646, 58.00 (48.00-66)	516, 60.00 (51.00-68)	130, 47.00 (39.00-56)	<.0001
n, Mean (SD)	646, 55.9 (14.2)	516, 58.4 (13.7)	130, 46.3 (11.9)	<.0001
n, Min, Max	646, (18, 91)	516, (19, 91)	130, (18, 75)	
Gender				
Female (%)	232 (35.86)	178 (34.43)	54 (41.54)	0.1308
Male (%)	415 (64.14)	339 (65.57)	76 (58.46)	
Comorbidities				
None (%)	135 (20.87)	134 (25.92)	1 (0.77)	<.0001
HIV positive (%)	127 (19.63)	0 (0.00)	127 (97.69)	-
Smoking (%)	286 (44.20)	247 (47.78)	39 (30.00)	0.0003
Hypertension (%)	40 (6.18)	40 (7.74)	0 (0.00)	-
Previous PTB with Bronchiectasis (%)	78 (12.06)	46 (8.90)	32 (24.62)	<.0001
Chronic Kidney Disease (%)	14 (2.16)	13 (2.51)	1 (0.77)	0.3220
Neurological illness (%) (%)	9 (1.39)	7 (1.35)	2 (1.54)	0.9999
Occupation exposure (%)	16 (2.47)	15 (2.90)	1 (0.77)	0.2162
Lung Disease (%)	52 (8.04)	46 (8.90)	6 (4.62)	0.1084
Heart Disease (%)	8 (1.24)	8 (1.55)	0 (0.00)	-
Deep vein thrombosis (%)	7 (1.08)	7 (1.35)	0 (0.00)	-
Cancer (Breast, cervical, ovarian, prostate, etc.) (%)	55 (8.51)	45 (8.72)	10 (7.69)	0.7072
Endocrine Disease (%)	29 (4.48)	29 (5.61)	0 (0.00)	-
Other (%)	10 (1.55)	10 (1.93)	0 (0.00)	-
Viral suppression				
Suppressed (%)	42 (64.62)	-	42 (64.62)	-
Unsuppressed (%)	23 (35.38)	-	23 (35.38)	
n, Median (IQR)	65, 1.32 (-2.00-3.97)	-	65, 1.32 (-2.00-3.97)	-
n, Mean (SD)	65,1.33 (3.17)	-	65,1.33 (3.17)	-
n, Min, Max	65,(-2-6)	-	65,(-2-6)	
CD4 count (cells/μL)				
n, Median (IQR)	80,254.5 (94.00-521.5)	-	80,254.5 (94.00-521.5)	-
n, Mean (SD)	80, 321 (283)	-	80, 321 (283)	-
n, Min, Max	80,(3-1565)	-	80,(3-1565)	
CT Scan findings				
Lymphadenopathy (including mediastinal) (%)	17 (2.63)	12 (2.32)	5 (3.85)	0.3312

Variable	Overall (n=647)	HIV Unknown (n=517)	HIV Positive (n=130)	P-Value
Mass (%)	262 (40.49)	217 (41.97)	45 (34.62)	0.1266
Cavity (including bronchiectasis) (%)	35 (5.41)	26 (5.03)	9 (6.92)	0.3934
Nodules (%)	26 (4.02)	21 (4.06)	5 (3.85)	0.9109
Collapse/atelectasis (%)	17 (2.63)	14 (2.71)	3 (2.31)	0.9999
Pleural effusions (%)	23 (3.55)	20 (3.87)	3 (2.31)	0.5956
Consolidation (%)	27 (4.17)	20 (3.87)	7 (5.38)	0.4397
Suggestive of TB	21 (3.25)	10 (1.93)	11 (8.46)	0.0008
Other (%)	29 (4.48)	23 (4.45)	6 (4.62)	0.9346

Table 2: Medical history and diagnostic yield by HIV status

Variable	Overall (n=647)	HIV Unknown (n=517)	HIV Positive (n=130)	P-Value
Previous Bronchoscopy				
No (%)	613 (94.74)	490 (94.78)	123 (94.62)	0.9409
Yes (%)	34 (5.26)	27 (5.22)	7 (5.38)	
Previous Sputum GXP results				
Negative (%)	513 (79.29)	403 (77.95)	110 (84.62)	0.2451
Not done (%)	121 (18.70)	103 (19.92)	18 (13.85)	
Positive (%)	13 (2.01)	11 (2.13)	2 (1.54)	
Diagnostic yield: Biopsy				
Carcinoma (%)	120 (18.55)	103 (19.92)	17 (13.08)	<.00001
Inflammatory : ↑ Neutrophils ± lymphocytes (%)	11 (1.70)	8 (1.55)	3 (2.31)	0.5489
Mycobacterium tuberculosis (%)	2 (0.31)	2 (0.39)	0 (0.00)	-
Sarcoidosis (%)	1 (0.15)	1 (0.19)	0 (0.00)	-
Normal Tissue (%)	231 (35.70)	196 (37.91)	35 (26.92)	0.0194
No results found (%)	30 (4.64)	21 (4.06)	9 (6.92)	0.1655
Not indicated (%)	252 (38.95)	186 (35.98)	66 (50.77)	0.0020
Diagnostic yield: Bronchoalveolar lavage				
Carcinoma (%)	83 (12.83)	71 (13.73)	12 (9.23)	0.6547
Inflammatory: ↑ Neutrophils ± lymphocytes (%)	88 (13.60)	68 (13.15)	20 (15.38)	
Mycobacterium tuberculosis (%)	19 (2.94)	15 (2.90)	4 (3.08)	
Normal cells (%)	371 (57.34)	298 (57.64)	73 (56.15)	
No Results Found (%)	10 (1.55)	7 (1.35)	3 (2.31)	
Not indicated (%)	76 (11.75)	58 (11.22)	18 (13.85)	

Table 3: Diagnostic yield of the different sampling procedures

Variable	Biopsy (n=647)	Bronchoalveolar lavage (n=647)
Results		
Carcinoma (%)	120 (18.55)	83 (12.83)
Inflammatory: ↑ Neutrophils ± lymphocytes (%)	11 (1.70)	88 (13.60)
Mycobacterium Tuberculosis (%)	2 (0.31)	19 (2.94)
Sarcoidosis (%)	1 (0.15)	-
Normal Tissue (%)	231 (35.70)	371 (57.34)
No results found (%)	30 (4.64)	10 (1.55)
Not indicated (%)	252 (38.95)	76 (11.75)

Table 4: Diagnostic yield of the different sampling procedures by previous GXP sputum results

Variable	Overall (n=466)	Negative (n=454)	Positive (n=12)	P-Value
Diagnostic yield: Biopsy				
Carcinoma (%)	90 (30.20)	87 (30.31)	3 (27.27)	0.6132
Inflammatory: ↑ Neutrophils ± lymphocytes (%)	10 (3.36)	10 (3.48)	0 (0.00)	-
Mycobacterium tuberculosis (%)	2 (0.67)	2 (0.70)	0 (0.00)	-
Normal Tissue (%)	195 (65.44)	187 (65.16)	8 (72.73)	0.0774
Sarcoidosis (%)	1 (0.34)	1 (0.35)	0 (0.00)	-
Diagnostic yield: Bronchoalveolar lavage				
Carcinoma (%)	66 (14.16)	65 (14.32)	1 (8.33)	0.5573
Inflammatory (%)(↑ Neutrophils ± lymphocytes)	79 (16.95)	79 (17.40)	0 (0.00)	-
Mycobacterium tuberculosis (%)	17 (3.65)	15 (3.30)	2 (16.67)	0.0148
Normal cells (%)	304 (65.24)	295 (64.98)	9 (75.00)	0.4718

Table 5: Lung cancer type by smoking status

Variable	Overall (n=99)	Non-smokers (n=34)	Smokers (n=65)	P-Value
Lung cancer				
Squamous cell carcinoma (%)	33 (33.33)	10 (29.41)	23 (35.38)	0.5494
Adenocarcinoma (%)	30 (30.30)	13 (38.24)	17 (26.15)	0.2142
Non-small cell carcinoma (%)	14 (14.14)	4 (11.76)	10 (15.38)	0.6235
Metastatic (%)	11 (11.11)	10 (29.41)	1 (1.54)	<.0001
Small cell carcinoma (%)	9 (9.09)	1 (2.94)	8 (12.31)	0.1587

CHAPTER 3: APPENDICES

Appendix 1: *Adverse events of flexible bronchoscopy* (12)

Adverse events of flexible bronchoscopy that might require hospitalisation admission to ICU or even death
• Bronchospasm • Hypoxaemia • Haemoptysis • Arrhythmias • Seizures • Myocardial infarction/ pulmonary oedema • Pneumothorax requiring aspiration/intercostal drain • Over sedation requiring ventilatory support or reversal

Appendix 2: Types of sedation (48)

	Minimal sedation/ anxiolysis	Moderate sedation/ analgesia ('Conscious sedation')	Deep sedation/ analgesia
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation	Purposeful* response after repeated or painful stimulation
Airway	Unaffected	No intervention required	Intervention may be required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained

Appendix 3: Ethical Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

23 April 2021

Dr Kurai Tsoka
School of Clinical Medicine
Department of Internal Medicine
University of the Witwatersrand
Parktown

Sent by email to: kuraitsoka@gmail.com

Dear Dr Tsoka

Re: **Protocol Ref No:** M200561
Protocol Title: The diagnostic yield and complications of flexible bronchoscopies performed at a tertiary academic hospital: a 5 year retrospective study (2015 – 2019)
Principal Investigator: Dr Kurai Tsoka
Protocol Amendment/s: Addition of collaborators

This letter serves to confirm that the Chairperson of the Human Research Ethics Committee (Medical) has approved the amendments for the abovementioned protocol, as detailed in your letter, dated 20 March 2021.

Thank you for keeping us informed.

Yours Sincerely,

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
23 APR 2021
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Miss Mapula Ramaila
Administrative Officer
Human Research Ethics Committee (Medical)

Research Office: Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 302, Corner York Road and 29 Princess of Wales Terrace, Parktown, 2193 Private Bag 3, Wits 2050 I **T**+27 (0)11-717-1234/2656/2700/1252I **Office E** HREC-Medical.ResearchOffice@wits.ac.za
IWebsite: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Appendix 4: Data collection sheet

MMED-The diagnostic yield and complications of Flexible bronchoscopies performed at a tertiary academic Hospital: a 5 year retrospective study (2015-2019)- Dr K Tsoka

Data Collection Sheet

*Required

1. GT

_____

2. Age *

_____

3. Gender *

Mark only one oval.

Female
Male

4. Co- Morbidities *

Tick all that apply.

- [ ] HIV
- [ ] Smoking
- [ ] Hypertension
- [ ] Diabetes
- [ ] Dyslipidemia
- [ ] Asthma
- [ ] COPD
- [ ] Heart disease
- [ ] Previous Malignancy
- [ ] Chronic Kidney Disease
- [ ] Previous PTB with Bronchectasis
- [ ] None

Other: [ ] _____

5. Absolute CD4 Count

_____

6. HIV viral load (copies/mL)

_____

7. Which ARV regimen

Mark only one oval.

- ◯ TDF/FTC/EFV
- ◯ ABC/3TC/EFV
- ◯ AZT/3TC/EFV
- ◯ TDF/3TC/Aluvia
- ◯ ABC/3TC/Aluvia
- ◯ Unknown
- ◯ Not on Treatment

8. Previous Bronchoscopy *

Mark only one oval.

- ◯ Yes
- ◯ No

9. Previous Bronchoscopy Date

_____

Example: 7 January 2019

10. Previous Bronchoscopy Indication

_____

11. Who performed current Bronchoscopy * *Mark only one oval.*

- ◯ MO
- ◯ Reg 1
- ◯ Reg 2
- ◯ Reg 3
- ◯ Reg 4
- ◯ Fellow
- ◯ Pulmonologist

12. Indications *

Tick all that apply.

- [ ] Haemoptysis
- [ ] Shortness of breath
- [ ] Cough
- [ ] Mass on Xray
- [ ] Chest pain
- [ ] Weight loss
- [ ] Pulmonary infiltration
- [ ] Atelectasis
- [ ] Pneumonia
- [ ] Lung Abscess
- [ ] Voice change
- [ ] Collapse

Other: ☐ _____

13. Chest Xray findings *

Tick all that apply.

- [ ] Infiltrates
- [ ] Mass
- [ ] Consolidation
- [ ] Pleural effusion
- [ ] Reticular nodular pattern
- [ ] Lung Collapse
- [ ] Atelectasis
- [ ] Normal
- [ ] Cavity

Other: ☐ _____

14. CT Scan Findings *

Tick all that apply.

- [ ] Emphysema
- [ ] Lymphadenopathy
- [ ] Collapse
- [ ] Cavitatory lesion
- [ ] Honeycombing
- [ ] Nodular pattern
- [ ] Normal
- [ ] Mass
- [ ] Not Done
- [ ] consolidation

Other: ☐ _____

15. Complications *

Tick all that apply.

- [ ] Bleeding
- [ ] Hypoxemia (during procedure)
- [ ] Pneumothorax (post procedure)
- [ ] Haemopytis
- [ ] Bronchspasm
- [ ] Seizures
- [ ] Arrythmia
- [ ] Apneoa
- [ ] None

Other: ☐ _____

16. Previous Sputum GXP results * *Mark only one oval.*

- ◯ Positive
- ◯ Negative
- ◯ Not Done

17. Diagnostic yield of different sampling procedures *

Mark only one oval per row.

	Carcinoma	Inflammatory	Mycobacterium tuberculosis	NAD	Not Done	NO results found
Biopsy	◯	◯	◯	◯	◯	◯
Bronchoalveolar lavage	◯	◯	◯	◯	◯	◯

18. Bacteriological analysis of specimens *

Tick all that apply.

	No Growth	MTB	Klebsiella	Pseudomonas	Candida	other	No Results found
Organism	☐	☐	☐	☐	☐	☐	☐

19. Mortality

Mark only one oval.

◯ Yes
◯ No

20. Extra Findings

Appendix 5: Timeline to completion

	Jan-Mar 2020	April-May 2020	June 2020	Aug 2020	Dec 2020	April 2021	May 2021	Jun 2021	July 2021	Dec-21	Jan-July-22
Literature review											
Preparing Protocol											
Protocol assessment											
Ethics Application											
Data Collection											
Data Analysis											
Write Up											
Submission											

Appendix 6: Protocol

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

The diagnostic yield and complications of flexible bronchoscopies performed at a tertiary academic Hospital: a 5 year retrospective study (2015-2019)

Dr Kurai Valerie Tsoka: MBChB HIV Diploma (SA)

Student Number / Staff number: 0602373N**/** A0065390

Supervisor: Dr MB Kgole
University of Witwatersrand, Pulmonology MBChB BSc MMED FCP (SA)
Co-Supervisor: Prof G.A. Richards
University of Witwatersrand, Critical Care MBBCh PhD FCP (SA) FRCP

Table of Contents

Nomenclature

BAL Bronchoalveolar lavage

BTS British Thoracic Society

COPD Chronic obstructive pulmonary disease

CMJAH Charlotte Maxeke Johannesburg Academic Hospital

FB Flexible Bronchoscopy

PaO^2 Partial pressure of arterial oxygen

PCP Pneumocystis carinii pneumonia

SaO^2 Oxygen percentage saturation

SD Standard Deviation

TB Tuberculosis

UK United Kingdom

NHLS National Health Laboratory services

1. INTRODUCTION

The lung is significantly exposed to airborne pollutants such as tobacco, biofuels and various pathogens. This impacts on the five common respiratory conditions that contribute to the global burden of disease; acute respiratory infections, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis and lung cancer (1). Globally lung cancer causes 1.5 million deaths per year and frequently this is related to cigarette smoking (1). The use of Flexible bronchoscopy in pulmonary medicine has provided access to the tracheobronchial tree both by direct visualization and via radiographic visualisation allowing therapeutic and diagnostic interventions that were not possible previously (2). Access is possible up to the fifth subsegmental bronchi and when used appropriately it is well tolerated by most patients with few complications (3).

1.1 History and Epidemiology

The first visualisation of the bronchial tree occurred in 1897 by Gustav Killian using a rigid bronchoscope (3). Later the rigid bronchoscope was improved by Chevalier Jackson, who developed a lighting system to improve vison and furthermore added instrumentation (3). In 1967, Shigeto Ikeda developed the flexible bronchoscope which was better tolerated by patients and allowed greater visualisation of previously inaccessible areas of the bronchial tree (3). In the last 10 years there have been many further advances in bronchoscopic techniques including the use of laser, lung volume reduction using stents, bronchial thermoplasty, vagal nerve ablation and endobronchial ultrasound (3).

In patients with lung cancer the diagnostic yield for bronchoscopy is considerable but is determined by the technique and by the indication for the procedure (4). The British Thoracic Society (BTS) guidelines recommended that in the case of tumours, bronchial washings, biopsies and brushings for visible lesions should be performed together as collectively they have been shown to have a diagnostic yield as high as 80% (5).

In the University Hospital in Switzerland, results revealed that most of the bronchoscopies were performed for suspected malignancy and infection, 45% and 27% respectively compared to a Nigerian Tertiary Centre showed that suspicion of bronchial cancer and pleural effusions were the main indications for bronchoscopy with 51.5 % confirmed cancers (2, 4). Egypt, revealed the most common presenting complaints as dyspnoea and haemoptysis compared to 75.4 % of the cases in The Kuwait University in 2004 (4, 6). 20% of the cases included in the study confirmed a malignancy in Egypt compared to Switzerland detection rate of 75,5% (4, 6).

The Nigerian Centre's overall diagnostic yield was 62% which was an improvement from 44% in a previous study compared to Switzerland's overall diagnostic yield of 57% (2, 4).

An interesting finding is that 6 .1% of patients were found to have PTB, despite sputum being negative for PTB and identified in 27% of the suspected cases and those with suspected interstitial lung disease, a third of the cases had a confirmed diagnosis post bronchoscopy (2, 4).

Flexible bronchoscopy is an integral part of pulmonary diagnostics and the constant evolution of new techniques allows safer and more effective ways to diagnose and treat patients. It is important to that they be performed only in circumstances where the benefit outweighs the risk particularly when more invasive procedures are employed.

This study seeks to evaluate the experience with flexible bronchoscopies at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 2015 to 2019 and to document the indications, yield and complications in this period of time.

1.2 Types of Bronchoscopy

There are 3 types of bronchoscopes; flexible, rigid and virtual. Flexible bronchoscopy, also known as standard white light bronchoscopy may be performed either under conscious sedation or general anaesthesia depending on the experience and expertise of the operator and team and it has the ability to reach the deep airways as it can flex and extend (49).

Rigid Bronchoscopy allows for simultaneous ventilation, has a light source, and allows the use of forceps and suction catheters (49). This technique requires general anaesthesia and is usually used for tumour debulking, airway dilatation, removal of foreign bodies, placement and or removal of stents and haemostasis in cases of massive haemoptysis (49).

Virtual bronchoscopy is not readily available, but utilises a computer-generated image that allows for visualisation of the distal airways. It is a non-invasive procedure that provides information about surrounding structures as well as the bronchial tree however its limitations include availability, cost and a paucity of personnel skilled in its use (49).

1.3 Indications

Major indications for bronchoscopy include the investigation of chronic cough, a suspicion of pulmonary malignancy and the diagnosis of some interstitial lung diseases (2). Bronchial washings were used for identification of pathogens in the case of lung infections and for cytology where malignancies are suspected(4). Procedures that are performed under bronchoscopic visualization include bronchial brushings and transbronchial needle aspiration and biopsies (4).
Interventional indications for bronchoscopy include: foreign body retrieval, clearance of airway secretions, relief of airway obstruction, dilatation of tracheal stenosis and haemoptysis (4).

1.4 Contraindications

The success of flexible bronchoscopy depends highly on the pre-procedural assessment of the patient as well as continuous monitoring. Contraindications can be categorised as either cardiovascular or pulmonary.

1.4.1 Cardiovascular contraindications:

Haemodynamic instability is possible in patients who are at high risk for myocardial ischaemia due to the potential for an intraprocedural increase in mean systemic pressures, increased cardiac index and decreased oxygenation and as such patient selection and risk assessment prior to the procedure should include a thorough cardiovascular examination. Recent myocardial infarction, current cardiac arrhythmias and poorly controlled heart failure are considered to be relative contraindications (50).

1.4.2 Pulmonary contraindications:

Precautions should be taken in patients with severe hypoxaemia. This is defined as a Partial pressure of arterial oxygen (PaO^2) <60 mmHg or an oxyhaemoglobin percentage saturation SaO_2 <90% while receiving an FiO2 of more than 100% (50). Supplementation of oxygen should be used if a desaturation of more than 4% occurs to reduce the risk of any harm related to hypoxaemia (12).

Pulmonary hypertension is also considered to be a relative contraindication because of the rise in mean arterial pressures during the procedure but also because biopsy in these circumstances has the potential for significant bleeding. Patients that suffer from any unstable airway disease like asthma or COPD are at high risk for developing bronchospasm and should be stabilized prior to the procedure. Bullous lung disease increases the risk of pneumothorax especially with transbronchial biopsy (50).

Other considerations that may increase complications include the use of anticoagulants, renal insufficiency, pregnancy and age.

1.5 Procedure

Bronchoscopies require meticulous planning and consideration of possible adverse events (35). In addition, investigations should be aimed at obtaining the maximal amount of relevant information. Microscopy, culture, sensitivity, cytology, GeneXpert for M tuberculosis, histology and bronchoalveolar washings should be obtained where possible.

1.5.1 Potential adverse events of flexible bronchoscopy

Potential adverse effects (Table 1) have been reported in various studies. These should be anticipated and managed timeously.

1.5.2 Premedication

According to the British Thoracic Society guidelines, premedication should not be routinely used, as there is no evidence of benefit and may pose possible harm such as haemodynamic changes (38).

1.5.3 Sedation

Sedation improves tolerance and co-operation and reduces adverse events. The most common agent used is a benzodiazepine, such as midazolam, which is an anxiolytic with sedative properties and induces antegrade amnesia. The preferred depth of sedation is in the realm of “conscious sedation” where airway patency and respiration is maintained without hypotension and verbal communication is possible. If deeper levels of sedation are required, adequate monitoring must be provided and anaesthetic support must be available. Other agents that are effective such propofol and ketamine used either singly or together (Table 2) (38).

2. HYPOTHESIS WITH AIMS AND OBJECTIVES

2.1 Hypothesis

Bronchoscopies at CMJAH are par with international standards and yield similar results when compared to other studies.

2.2 Aims and Objectives

- The aim of this study is to describe the diagnostic yield, indications and complications reported during flexible Bronchoscopies at CMJAH from 2015 to 2019.
- The determine the effectiveness of bronchoalveolar washings in making specific diagnoses such as cancer, sarcoidosis, asbestosis and infectious diseases like TB and PCP

3. METHODOLOGY

3.1 Study design

This is a retrospective review of bronchoscopies performed on adult patients in CMJAH from 2015 to 2019. The study design is a cross-sectional study of patients undergoing bronchoscopy at CMJAH.

3.2. Study Participants

All patients above the age of 18 who had a bronchoscopy performed at CMJAH Pulmonology department in the study period. Possibly 500 bronchoscopies to be analysed.
A data Sheet (Appendix A) will be used to collect and record the bronchoscopies done and enter the results of i.e cytology, culture and histology with the use of the National health laboratory services (NHLS) or National Institute of Occupational health (NIOH) website.

4. DATA ANALYSIS

The researcher will be assisted by the staff in the bronchoscopy suite and the Pulmonology Fellows who perform the bronchoscopies, to retrieve relevant records.

The records will be analysed by the researcher and the data collected with the aid of the data collection sheet attached in appendix A.

Descriptive statistics such as mean, median, standard deviation, range, standard error, and frequencies will be performed to describe the variables in the study. Continuous variables will be reported using mean, and standard deviation from the mean if the data is normally distributed. When the data is not normally distributed the median and interquartile range will be applied. The categorical variables will be reported using frequencies and percentages. Categorical data will be expressed as proportions and numerical data as mean and standard deviation. Differences in proportion will be tested with Chi-square (χ^2) test or Fisher's exact test. Statistical significance will be set at P-value ≤ 0.05. The diagnostic yield will be assessed using univariate and multivariate logistic regression analyses.

5. ETHICS

Permissions will be requested from the Chief Executive Officer (CEO) of CMJAH, and the Head of the Pulmonology Department. Ethical clearance will be obtained as per requirements for the Masters in Medicine degree, from the University of the Witwatersrand Human Research Ethics Committee.

Permissions will be requested from the National Health Laboratory services (NHLS) and the department of Anatomical Pathology with collaborators.

Personal identifiers will be removed from the data collection sheets and unique codes used for each patient. No Compensation will be received by the investigators or any hospital staff. The study findings will be published in an academic journal and potentially used to modify the indications for bronchoscopies and reduce adverse events as far as possible.

6. IMPLICATIONS

There are many lung pathologies that contribute to the global burden of diseases. The use of routine bronchoscopy aids in the diagnosis of many of these conditions like, TB, sarcoidosis, asbestosis and other infectious diseases and the yield thereof is high. This research is important as it evaluates the yield of bronchoscopies at a South African Hospital, which has not been done before. It will help us to identify if we meet international standards and if more can be done to hasten diagnosis i.e. Pulmonary tuberculosis. The study can also help to identify any challenges in our setting and help identify the most common respiratory illness in our African setting.

7. TIMELINE TO COMPLETION

Gant Chart showing the timeline of the study:

2019-2020	Dec 2019	Jan	Feb	Mar	April	May	Jun
Literature review							
Preparing Protocol							
Protocol assessment							
Ethics Application							

2020-2021	July	Aug	Sept	Oct	Nov	Dec	Jan
Data Collection							
Data Analysis							
Write Up							
Submission							

8. FUNDING

Self-funded; basic costs include stationary, printing and transport.

8.1 Proposed budget

- Internet R700
- Photocopies R300
- Petrol R2000
- Airtime R200

9. LIMITATIONS

Data collection will be dependent on the quality of records kept on bronchoscopies performed and data might be missing for some variables..

10. PUBLISHING INTENTION

We intend to publish the study in an appropriate peer reviewed journal.

11. REFERENCES

1.

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12. APPENDICES

Table 1: *Adverse events of flexible bronchoscopy* (12)

Adverse events of flexible bronchoscopy that might require hospitalisation admission to ICU or even death
• Bronchospasm • Hypoxaemia • Haemoptysis • Arrhythmias • Seizures • Myocardial infarction/ pulmonary oedema • Pneumothorax requiring aspiration/intercostal drain • Over sedation requiring ventilatory support or reversal

Table 2: Types of sedation (48)

	Minimal sedation/ anxiolysis	Moderate sedation/ analgesia ('Conscious sedation')	Deep sedation/ analgesia
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation	Purposeful* response after repeated or painful stimulation
Airway	Unaffected	No intervention required	Intervention may be required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained