



Original Article

## Diagnostic yield and complications of flexible bronchoscopy performed at Charlotte Maxeke Johannesburg academic hospital: A 5 year retrospective study

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Received: 05 November 2023

Accepted: 20 February 2024

Published: 27 March 2024

**DOI**

10.25259/JPATS\_26\_2023

**Quick Response Code:**



### ABSTRACT

**Objectives:** There is a high incidence of lung diseases but very little data in South Africa relating to bronchoscopy practice. The objectives of the study are to determine the diagnostic yield, indications, and complications as well as determine the effectiveness of biopsy and bronchoalveolar lavage (BAL) in making diagnoses of infectious and non-infectious diseases.

**Materials and Methods:** Six hundred and ninety-two patients were identified and 647 cases were analyzed due to 45 cases with inadequate data for analyses. A single-center retrospective cross-sectional review of patients 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 (64.14%), with a mean age of 55.9 years of age. The most common indication was suspected malignancy, followed by non-resolving pneumonia, 63.99%, and 14.53%, respectively. A total of 120 (18.55%) patients were diagnosed with a malignancy on biopsy and 83 (12.83%) on BAL. Of all bronchoscopies performed, 85.94% had no complications during or after bronchoscopy, whereas 10.97% were complicated with bleeding.

**Conclusion:** 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.

**Keywords:** Flexible bronchoscopy, Indications, Diagnostic yield, Human immunodeficiency virus (HIV), Lung cancer, Bronchoalveolar lavage, Outcomes

### 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.<sup>[1]</sup> The use of flexible bronchoscopy (FB) in pulmonary medicine has provided access to the tracheobronchial tree both by direct visualization and through radiographic visualization, allowing therapeutic and diagnostic interventions that were not previously possible.<sup>[2]</sup> Access is possible up to the fifth subsegmental bronchi, and when used appropriately, it is well tolerated by most patients with few complications.<sup>[3]</sup>

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The British Thoracic Society Guidelines (BTS) aimed to help those performing FB to better understand the procedure, its complications, and its role in the possible diagnosis and management of lung pathologies. FB 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 should be performed only in circumstances where the benefit outweighs the risk particularly when more invasive procedures are employed. The use of FB is limited by the paucity of skills and there is minimal literature in Africa, on the role, safety, and yield of FB. This study described the diagnostic yield, indications, and complications reported during flexible bronchoscopes at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and determined the effectiveness of biopsy and bronchoalveolar washings in making specific diagnoses.

## MATERIALS AND METHODS

This study was a retrospective cross-sectional review of all bronchoscopies performed on adult patients in the bronchoscopy suite at Charlotte Maxeke Academic Hospital during the period from 1 January 2015 and 31 December 2019. The population studied were all adults (above the age of 18 years) attending the respiratory clinic, referrals from respiratory, general wards, and peripheral hospitals with indications for bronchoscopy. Findings based on the clinical indications, medical background, chest X-ray features, computed tomography (CT) scan findings, and any complications were documented. Bronchoalveolar lavage (BAL) and endobronchial sampling were obtained based on the clinical situation, samples were sent off for histology and microbiology, and results were checked for the diagnosis obtained from the National Health Laboratory Services (NHLS) database. This data were tabulated using Excel spreadsheets and analyzed. Some records and results were not easy to trace, and so were not analyzed. There were 692 patients data entered and 647 cases analyzed due to 45 cases with inadequate data for analyses.

Age was categorized into four groups: 18–34, 35–44, 45–55, and 55+ years. Clinical data were comprised of comorbidities (such as human immunodeficiency virus (HIV) status, smoking, hypertension, malignancy, lung diseases), and in those that were HIV-positive, viral load and CD4 counts were included. CT scan findings, complications, and indications were also documented. 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*, *Mycobacterium tuberculosis* (MTB), *Pseudomonas*, and *Candida*. The diagnostic tests that were used were biopsy and BAL. Frequencies and percentages were reported for categorical data stratified by gender and HIV status. Not all patients had HIV tests done, so they were reported as HIV-positive

or HIV-unknown. To compare categorical variables for statistical significance by gender and HIV status, Chi-square analysis or Fisher's test was used. Descriptive statistics such as median, inter-quartile range (IQR), mean and standard deviation were presented for continuous measures. Student *t*-test and Kruskal–Wallis were used to compare continuous variables stratified by gender and HIV status. All statistical analysis was conducted in SAS Enterprise Guide 7.1 using the procedures FREQ, MEANS, NPAR1WAY, TTEST, and SGPLOT.

## Ethical considerations

This study was approved by the University of Witwatersrand Medical Human Research Ethics Committee (Ethics clearance number - M200561). The study was also approved by the National Health Laboratory Service (Project application number #PR20352).

## RESULTS

### Demographic and clinical characteristics of patients undergoing bronchoscopy

Of the 647 patients included in the analysis, the majority were 55 years or older (58.82%,  $n = 380$ ) with a median age of 58 (IQR: 48–66). Most patients were smokers (44.20%,  $n = 286$ ), HIV-unknown (79.90%,  $n = 517$ ), had CT scans showing a mass (40.49%,  $n = 262$ ), and had suspected malignancy (63.99%,  $n = 414$ ). Males were associated with smoking (53.0% vs. 28.5%,  $P < 0.0001$ ) compared to females [Table 1].

Of the 20% ( $n = 130$ ) who were HIV-positive there was a significantly low median CD4 count of 254.5 cells/ $\mu$ L (IQR: 94.0–521.5) [Table 1].

HIV-positive patients were significantly younger than those who were HIV-unknown (median: 47 [IQR: 39–56] vs. 60 [51–68];  $P < 0.0001$ ). HIV-positive patients were also more likely to have had previous pulmonary tuberculosis (PTB) and consequent bronchiectasis (24.6% vs. 8.9%,  $P < 0.001$ ), CT scan evidence of previous or active TB (8.5% vs. 1.9%,  $P = 0.0008$ ), as well as chronic cough as an indication (13.9% vs. 6.4%,  $P = 0.0048$ ) compared to those who were HIV-unknown. Although not statistically significant, HIV-positive patients had a slightly higher proportion of non-resolving pneumonia (19.2% vs. 13.4%,  $P = 0.0888$ ), possibly due to a lower immune system. Patients who were HIV-unknown were more likely to be smokers (47.8% vs. 30.0%,  $P = 0.0003$ ) and to have an indication of suspected malignancy (68.1% vs. 47.7%,  $P < 0.001$ ) [Table 1].

### Medical history and diagnostic yield

Overall, 5.26% ( $n = 34$ ) of patients had a previous bronchoscopy, and 2.01% ( $n = 13$ ) had tested positive for

**Table 1:** Demographic and clinical characteristics of patients undergoing bronchoscopy

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/ $\mu$ L)				
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
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

\*130 HIV-positive, only 127 had confirmed data entered for co-morbidity. IQR: Interquartile range, SD: Standard deviation, PTB: Pulmonary tuberculosis

GXP before bronchoscopy [Table 2]. Patients who were HIV-unknown were more likely to have normal tissue for biopsy (37.91% vs. 26.92%;  $P = 0.0194$ ) compared to HIV-positive [Table 2]. Although not statistically significant, HIV-unknown patients had a high proportion of carcinoma on biopsy (19.92% vs. 13.08%,  $P = 0.0726$ ).

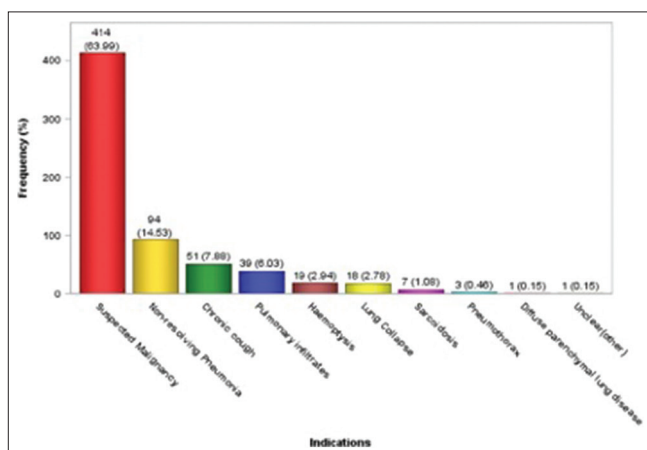
### Indications for bronchoscopy

The majority of patients had suspected malignancy (63.99%,  $n = 414$ ), followed by non-resolving pneumonia (14.53%,  $n = 94$ ), chronic cough (7.88%,  $n = 51$ ), and pulmonary infiltrates (6.03%,  $n = 39$ ) [Figure 1].

**Table 2:** Medical history and diagnostic yield.

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)	<0.00001
Inflammatory: ↑ Neutrophils±lymphocytes (%)	11 (1.70)	8 (1.55)	3 (2.31)	0.5489
<i>Mycobacterium tuberculosis</i> (%)	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)	
<i>Mycobacterium tuberculosis</i> (%)	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)	

HIV: Human immunodeficiency virus, GXP: GeneXpert

**Figure 1:** Indications of bronchoscopy.

### Diagnostic yield of the different sampling procedures

Biopsy diagnosed a higher number of patients with carcinoma (18.55%,  $n = 120$ ), whereas BAL diagnosed 12.83% ( $n = 83$ ) [Table 3]. One patient was diagnosed with sarcoidosis on biopsy. Conversely, BAL detected a higher number of patients with inflammatory results defined by non-diagnostic elevated white cells, including neutrophils and/or lymphocytes (13.60%,  $n = 88$ ), as well as MTB (2.9%,  $n = 19$ ) than biopsy.

### Diagnosis of lung cancer

In this audit, a total of 120 patients were diagnosed as having lung malignancy on biopsy and 83 on BAL. Of 203 patients confirmed to have a carcinoma, 102 had a definitive type identified. A higher proportion of patients had squamous cell carcinoma (33.33%,  $n = 33$ ) compared with adenocarcinoma (30.30%,  $n = 30$ ) [Table 4]. Smokers had a higher proportion of squamous cell carcinomas (35.38% vs. 29.41%,  $P = 0.5494$ ), non-small cell carcinomas (15.38% vs. 11.76%,  $P = 0.6235$ ), and small cell carcinomas (12.31% vs. 2.94%,  $P = 0.1587$ ) but this was not statistically significant. Non-smoking patients were more likely to have metastatic disease (29.41% vs. 1.54%,  $P < 0.001$ ) compared to smoking patients [Table 4].

### Bronchoscopy complications

The majority of patients had no complications (85.94%,  $n = 556$ ), whereas 10.97% ( $n = 71$ ) had hemorrhage, 1.55% ( $n = 10$ ) hypoxemia post-procedure, 1.24% ( $n = 8$ ) bronchospasm, and 0.77% ( $n = 5$ ) had an arrhythmia.

### Culture results

The majority of the BAL specimens showed no specific organisms grown on culture (79.4%,  $n = 514$ ). However,

**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)
<i>Mycobacterium tuberculosis</i> (%)	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:** Lung cancer type.

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)	<0.0001
Small cell carcinoma (%)	9 (9.09)	1 (2.94)	8 (12.31)	0.1587

10.8% of washings ( $n = 70$ ) grew *Pseudomonas* spp., 3.6% ( $n = 23$ ) *Candida* spp., 3.4% ( $n = 22$ ), and 2.9% ( $n = 19$ ) *Klebsiella* spp. Of the patients who had organisms identified, the majority had only one organism identified (81.3%,  $n = 91$ ), followed by two (17.9%,  $n = 20$ ) and three in one patient.

## DISCUSSION

FB 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 BTS guidelines for diagnostic FB in adults and the local institutional protocol dictate that bronchoscopy should be performed under conscious sedation by a specialist pulmonologist or by a pulmonology trainee/physician.<sup>[4]</sup>

During the five years of the study, we observed a male predominance of patients undergoing the procedure, but otherwise, the epidemiology was similar to other studies including the mean age years of 55.9.<sup>[5,6]</sup> The overall diagnostic yield revealed a 36.6% biopsy and 33.9% BAL yield.

The most common indication for bronchoscopy was a suspicion of malignancy in 63.99% of cases, and 44.20% were smokers with an obvious mass on chest radiology, with masses or lung nodules reported in 235 CT scans. A finding that was similar to other studies in Africa.<sup>[2,7]</sup> A survey reported in the United Kingdom also showed similar results, with malignancy being the most common indication for bronchoscopy.<sup>[8]</sup>

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.<sup>[9]</sup> A systematic review and meta-analysis showed clear evidence of the association between the amount smoked, the duration of smoking, and all lung cancer and not only histological type.<sup>[9]</sup> In this study, carcinoma was diagnosed in 203 cases, 120 on biopsy and 83 on BAL. Ninety-nine of the 203 were primary lung cancers, and of these, 33.33% were squamous, followed by adenocarcinomas at 30.30%. Of these, 35.38% were smokers and 29.41% were non-smokers, which was a finding similar to that of the meta-analysis in Great Britain. In contrast, a study conducted in Sao Paulo, Brazil, revealed that respiratory infections, such as MTB, were the most common indications for FB, with malignancy only third.<sup>[10]</sup>

Non-resolving pneumonia is an important indication for FB as the causes include serious but potentially treatable conditions such as i.e., *Staphylococcus* and *Klebsiella* species, as well as some fungal and parasitic infections.<sup>[11]</sup> Granulomatous diseases such as MTB infections and sarcoidosis, lung malignancies, vasculitides, and interstitial lung diseases are some of the treatable causes of non-resolving pneumonia that may be diagnosed using FB.<sup>[11]</sup> Non-resolving pneumonia and chronic cough were also common indications for FB in 14.53% and 7.88% of cases, respectively. Our study, similar to a study performed in New Delhi, India, by 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.<sup>[11]</sup> In the current

study in Johannesburg, South Africa, *Pseudomonas spp.* was the most common organism found in 70 cases, followed by MTB in 22 cases and *K. 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 HIV infection along with this MTB.<sup>[12]</sup> At CMJAH, not all patients who had bronchoscopy were tested for HIV, but of those that were tested, 20% were positive, with the remainder 79.90% being unknown. This was much lower in comparison to a study from the United States of America (USA) that recruited patients between 2012 and 2017, where 30.7% were found to be positive. Although the overall prevalence of HIV in the USA is lower than in SA, the low numbers reported might be due to the fact that many of our patients often decline testing due to fear or stigma.<sup>[13]</sup> Those who were HIV-positive were primarily between the ages of 45 and 55, followed by 34–44, the majority of whom were on anti-retroviral therapy (ART) and had a suppressed viral load.

The evolution of TB diagnostics has led to the GXP test, which uses single cartridge-based nucleic acid amplification which can identify MTB and detect rifampicin resistance within 2–3 h.<sup>[14]</sup> During the period of this audit, 21 cases were diagnosed with MTB by biopsy and BAL included. This is probably because the GXP assay performed on bronchial washings was more sensitive than induced sputum, as suggested by Lee *et al.*<sup>[15]</sup>

There was a 14.32% complication rate during the study period (94 of 656 cases), the most common of which was any hemorrhage which occurred in 71 cases. Arrhythmias, bronchospasm, hypoxemia, 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.<sup>[16]</sup> Another Egyptian study, performed over seven years with 3980 cases, reported bronchospasm as one of the major complications.<sup>[7]</sup> 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 hypoxemia.<sup>[2]</sup>

### Limitations

A limitation of the study was that it was retrospective, and data collected from the bronchoscopy information sheets frequently had missing data, particularly with regards to comorbidities 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 NHLS database for the microscopy, culture, cytology, and histology results, which were not always

available. This study was a single-center study and may not be generalizable to other centers. Not all patients who had bronchoscopy had HIV tests done as it was not a prerequisite, and some patients possibly declined.

### CONCLUSION

The availability of FB has significantly impacted the diagnosis and treatment of pulmonary diseases. FB 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 PTB, which, if identified early, increase the likelihood of cure.

### Author's contributions

Dr Mamokoma Becky Kgole for audit establishment and supervision, established the audit; Prof Guy Richards, for guidance and co-supervision; Prof Kennedy Otjombe, Associate Professor in the School of Public Health and Head of statistics, University of Witwatersrand, who advised and guided statistical analysis. All authors reviewed the manuscript before publication.

### Ethical approval

The author(s) declare that they have taken the ethical approval from Health Research Ethics Committee, number M200561, dated 23/04/2021.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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**How to cite this article:** Tsoka KV, Kgole MB, Richards G. Diagnostic yield and complications of flexible bronchoscopy performed at Charlotte Maxeke Johannesburg academic hospital: A 5 year retrospective study. *J Pan Afr Thorac Soc.* 2024;5:26-32. doi: 10.25259/JPATS\_26\_2023