Factors influencing pneumothorax rates of transthoracic CT-guided lung biopsies in a Tertiary Centre in Cape Town, South Africa.

by

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Declaration Page

I, Dr. William H Richards-Edwards hereby declare that the work on which this dissertation is based on my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree at this or any other university.

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I. Literature Review

1. Introduction

Pulmonary lesions are common findings on computed tomography (CT) studies of the chest, whether they are symptomatic, incidental or part of a metastatic workup. With more patients receiving medical imaging than before and the subsequent increase in pulmonary nodule detection rates, (1) the need for CT-guided lung biopsies has followed this upward trend. Transthoracic lung biopsies were historically performed under fluoroscopic guidance, with the first documented CT-guided procedure performed by Haaga in 1976.(2) Advances in CT technology and the implementation of lung cancer screening programmes in some countries has seen both a reduction in lung cancer related mortality (3) and the increase in detection of smaller pulmonary lesions. (3,4) The need to differentiate between benign and malignant disease is imperative, compounded by the need to determine the cytology and histology of a pulmonary lesion to facilitate earlier specific treatment (5) and improved prognosis. (6) Benign and malignant pulmonary pathology share many imaging characteristics (7) making it difficult to diagnose more sinister pathology on imaging alone. Pulmonary lesions often require imaging follow-up or biopsy, the latter being best decided by multidisciplinary teams and using the least invasive, most convenient technique to obtain a pathology sample. (6) Transthoracic CT-guided lung biopsies have been shown to have better diagnostic yields for small peripheral lung lesions compared to those obtained by endobronchial approaches, despite an increased risk of complications. (5) The literature does show that transthoracic CT-guided lung biopsy has high technical success rates, especially when a core needle is used. (3,8–11) The incidence of procedure related complications is highly variable, with the range between 6-61%. (12,13)

2. Lung Carcinoma

Lung cancer is one of the most common forms of cancer in South Africa (SA), accounting for 7.7% of the total cancer incidence in 2018 with an associated high mortality rate of 13.5%. According to the WHO the estimated past and future trends in total cases of lung cancers will continue to rise in SA. (14) In 2012 the number of new lung cancer cases worldwide accounted for 13 % of all cancer diagnosed and it was the leading cause of cancer related deaths in men, and the leading cause of female deaths in developed countries. Lung cancer mortality in many developed countries has either plateaued or is in decline in recent times. However, the mortality associated with lung cancer has conversely been increasing in developing countries due to a delay in the establishment of the tobacco epidemic, combined with greater exposures to indoor air pollution. (15,16) The disease burden associated with lung cancer will continually shift to developing countries due to the growth of larger, aging populations with increased risk factors and an immature tobacco epidemic. (15)

Primary lung carcinomas are a heterogenous group of tumours which can be broadly divided into two histological categories; namely Small Cell Lung Carcinoma (SCLC) and Non-Small Cell Lung Carcinomas (NSCLC). The latter includes squamous cell carcinoma, adenocarcinoma and large cell carcinoma. (6) SCLC and NSCLC account for approximately 13-15% and 85% of lung carcinomas respectively. (17) The histological differentiation of these two main groups remains significant for the treatment and further prognosis of the patient. (6) SCLC and squamous carcinoma are both typically centrally-located neoplasms which may involve the mediastinum or arise from an endobronchial location. SCLC is an aggressive tumour which is associated with early extra-thoracic metastatic spread and paraneoplastic syndromes such as Eaton-Lambert syndrome. (5) Even though SCLC responds well to chemotherapy, the prognosis is generally poor. Adenocarcinoma and large cell carcinoma are more peripherally located lesions and often metastasise early. (6)

3. Confirming a Diagnosis

There are many non-specific findings of lung carcinoma on CT imaging with significant imaging cross-over with benign lesions. Image findings include pulmonary nodules, masses and focal ground glass opacification. (7) These radiological findings are seen in inflammatory, infective, benign and malignant disease processes. (7)

A range of different techniques are available to make the diagnosis of lung cancer and the decision on which technique to utilise should be made by a multidisciplinary team that includes a chest radiologist, pulmonologist, cardiothoracic surgeon and pathologist. (5) These techniques include sputum cytology, thoracocentesis of pleural fluid, excisional nodal biopsy, conventional bronchoscopy with or without transbronchial needle aspiration, endobronchial adjuncts like endobronchial ultrasound (EBUS) and electromagnetic navigation (EMN), transthoracic needle aspiration, video-assisted thoracoscopy and thoracotomy. (5,6)

Cytology and/or adequate tissue histology are also of paramount importance in deciding appropriate management of patients with NSCLC, as molecular analysis and determination of histological subtype are required for specific managing agents. (5) Defining the histological subtype also allows for better prognostication. (6) The technique used to make the diagnosis should take into consideration the likely type of lung cancer based on radiological characteristics, size, location and the stage of the tumour. (5) When only a diagnosis needs to be made, the least invasive and most convenient method should be used. A practical initial approach for more central and endobronchial lesions is to obtain sputum cytology or make the diagnosis on conventional bronchoscopy. Sputum cytology is a non-invasive technique but has limited efficacy for more peripheral tumours and a negative result will require further investigation. (6) The sensitivity of conventional bronchoscopy is reduced for more peripheral and smaller lesions that are < 20 mm in diameter. For more peripheral lesions, emerging adjuncts such as radial EBUS and EMN can be utilised in addition to conventional bronchoscopy. These endobronchial techniques have shown diagnostic yields of 73% and 71% respectively. (5) Radial EBUS utilises a small ultrasound transducer that is placed within the working channel of flexible bronchoscope. It provides a 360° ultrasound image of the surrounding tissue and enables better visualisation of the lung lesion and target biopsy. (5) EMN allows for the sampling of endobronchially occult lesions using virtual bronchoscopy derived from reconstructions of multiplanar CT images. This adjunct uses a locatable sensor probe and real-time guidance within the bronchial-tree to achieve lesion sampling. (18)

Patients with small peripheral lesions are recommended for transthoracic needle aspiration (TTNA), with a core needle, if possible. TTNA has a superior diagnostic yield but increased complication rates (5) when compared to bronchoscopy. Open surgical biopsy and video assisted thoracoscopic surgery (VATS) have the best tissue yield and highest specificity of all the available diagnostic techniques, but are associated with increased morbidity and longer hospital admissions. (19) Ultrasound plays a limited role when it comes to image-guided biopsies of the chest. Ultrasound-guidance can be utilised for pleural-based, very peripheral and superficial lesions that are accessible using a pleural effusion as a sonographic window. (20) The overwhelming majority of image-guided chest biopsies are performed with CT-guidance due to its improved spatial resolution, multiplanar reconstruction and better diagnostic performance over ultrasound for pulmonary lesions. (20)

4. Trans-thoracic CT guided lung biopsy

Traditionally fluoroscopy was the workhorse of transthoracic needle biopsies, but this has largely been replaced by the use of CT.

CT-guided transthoracic biopsy can be performed by two different techniques.

Firstly, conventional spiral/sequential CT-guidance ("step-and-shoot" technique) with intermittent image acquisition and biopsy needle adjustment. (21) This technique is performed with the assistance of a CT radiographer.

The second technique of CT-fluoroscopy has the image acquisition controlled by the radiologist performing the procedure and the images viewed in near real-time. Fine adjustments to needle position and trajectory can be made with the aid of a monitor near the CT gantry. (21)

Both conventional and fluoroscopic CT techniques have similar diagnostic accuracies, although Kim et al found a reduction in the number of complications when fluoroscopic CT guidance was utilized. (22) The disadvantage of fluoroscopic CT-guidance technique is the higher radiation dose to both patient and radiologist. (21,22)

A wide variety of sampling needles are available, with variations in needle tip, length, gauge and sampling mechanism. (21) Biopsy needles are classified into two main categories; aspiration needles for cytological analysis and core needles for histological specimen acquisition. The choice of biopsy needle is dependent on the required sample, the predicted procedural difficulty, pulmonary lesion characteristics and clinician preference. (21) In addition to the diagnostic cell type of the lesion, there is an increased requirement for histological tissue samples for evaluation of tumour mutation and markers. (20,21)

These needles can be used with or without a co-axial system. The co-axial technique uses a larger gauge, shorter outer needle as a guidance cannula through which a smaller biopsy needle can pass. (21) The technique allows the shorter, larger gauge outer needle to remain fixed in the soft tissues and/or lesion and permits multiple passes to be performed without having to repeatedly puncture the pleura or adjust the needle trajectory. (21) The co-axial technique reduces procedural time and number of passes but was found to have similar diagnostic accuracy and complications rates to biopsies without its use. (21,23) Reduced number of pleural passes is also achievable by having a cyto-pathologist or technician present during the procedure to examine specimens. (19)

I.4.1 Indications

The spectrum of clinical indications for image-guided lung biopsy has changed significantly and increased since the first CT-guided lung biopsy procedure was performed over 40 years ago. This is due to advances in diagnostic image quality, needle technology, wide availability of CT scanners and the requirement for pathological assessment. With increasing annual rates of CT chest studies and incidental pulmonary nodule detection, (1) the demand for CT guided lung biopsies has followed this trend. The most common indication for biopsy is the presence of a new or enlarging solitary pulmonary nodule, taking into consideration the prevalence of incidental pulmonary nodules being as high as 8.5-13% on CT chest studies performed for different indications. (20,24)

Hall et al found that a new incidental nodule was discovered in 13% of patients undergoing emergency computed tomography pulmonary angiogram (CTPA) for suspected pulmonary embolus. (24) Of the incidentally discovered nodules, 96% required further follow-up imaging or an investigative procedure. (24)

Common indications for patients to undergo image-guided chest biopsy as stated by Anzidei et al. include:

i. A new or enlarging solitary nodule or mass.
ii. Multiple nodules in a patient without known neoplastic disease or in prolonged remission.
iii. Focal parenchymal infiltrates in which an infectious organism cannot be isolated.
iv. Diagnosis of hilar mass following negative bronchoscopy.
v. Undiagnosed mediastinal mass.
vi. Biopsy or re-biopsy of malignancy for targeted therapy. (20)

I.4.2 Contraindications

Pulmonary haemorrhage is well known to complicate transthoracic needle biopsies at rates between 4-27%, second only to pneumothorax. (25) Therefore bleeding diatheses should be excluded prior to undergoing the procedure. Pulmonary haemorrhage ranges from minimal perilesional haemorrhage to exceedingly rare haemothorax (0.092%). (25) The patient’s recent platelet count, International Normalised Ratio (INR) (<1.5) and activated partial thromboplastin time (PTT) (less than 1.5 time control value) should be scrutinised. (20,21)

Thrombocytopaenia should be corrected with platelet transfusion if below 50 x 10^9/l and there should be temporary reduction or cessation of anticoagulant medication such as heparin, warfarin or aspirin.

Specific pulmonary lesions such as pulmonary arterio-venous malformations, aneurysms and hydatid cysts should not be biopsied due to severe sequelae. However, these should be excluded at time of diagnostic contrasted CT chest and with multidisciplinary input. (19,20)

Relative contraindications include patient-related factors that may increase complications such as pulmonary hypertension (bleeding), severe emphysematous disease, mechanical ventilation, large lung bulla, intractable cough and poor patient cooperation (pneumothorax). (20,21)

5. Factors affecting complication and pneumothorax rate

CT-guided lung biopsies are considered relatively safe procedures with a wide variation of procedure related complications. Transthoracic CT-guided lung biopsy complication rates overall are low at approximately 20% (9,26) but there is large variability between different institutions with complication rates ranging between 6-61%. (12,13)

The most commonly encountered procedural complication is a small and stable pneumothorax that requires no further management or intervention. (9,11,12,19–21,25)

Other reported complications include pulmonary haemorrhage, tension pneumothorax, air embolism, systemic hypertension, bradycardia, subcutaneous emphysema/ haematoma, spinal cord ischaemia and with one case of posterior reversible encephalopathy syndrome (PRES). (27)

In one study performed by interventional radiologists found a complication rate of 61%, mostly pneumothoraces (74.7%). (13) In the same study intercostal drain thoracostomy was required in 21% of all patients undergoing transthoracic CT-guided lung biopsy. (13) Relatively few studies have high complication rates, with most complications being mild and managed conservatively, while severe complications are rare. Procedure-related mortality is very low, with smaller studies reporting no mortality, (27) whilst larger cohorts had rates of between 0.12 and 0.16%. (9)

Multiple previous studies have shown a variety of risk factors associated with increased biopsy-related complications. There were independent lesion-, patient- and procedural-related factors.

Lesion-related factors include the size of the lesion determined by dimensions in the axial plane, the distance of the lesion from the pleura along the needle trajectory and the lobar position of the lesion. Hiraki et al. reviewed 1,098 CT-guided lung biopsies and found that parenchymal lesions in the anatomical lower lobes had more procedure-related pneumothorax ($p<0.0001$). The authors hypothesised that due to the increase in respiratory-associated motion in lung closer to the diaphragm, the needle position underwent increased redirections. This was compounded by the time spent trying to obtain a specimen. (28) Another study which looked at a smaller cohort, specifically investigated the relationship between pneumothorax rate and lesion proximity to the diaphragm and could not confirm this relationship. (29) Lesion size was observed as having an inverse determining factor for post-procedural pneumothorax rate. (4,8,12,13,28,30) One study found that for every 1 cm increase in lesion diameter, there was a corresponding 25% reduction in odds-ratio. (13) The increase in pneumothorax rate for smaller lesions was thought to be related to increase in technical difficulty and longer procedure times. (8) Ng et al. looked specifically at a subgroup of biopsied lesions < 10mm in size, which constituted 5 % of all biopsies performed at their institution. They found a significantly higher pneumothorax rate of 52.7% compared to their average of 35%. (4) One study encountered a very low pneumothorax rate of 4% which they attributed to having very few lesions under 10 mm in size. (12)

Another lesion-related factor that multiple authors have found correlated with an increased rate of pneumothorax was the distance of the lesion from the pleural surface (or skin surface), along the path of the biopsy needle. (8,13,27,28,30,31) Aktas et al. found a statistically significant relationship between pneumothorax rates and the distance from the pleural surface. They found that mean lesion distances where pneumothorax did occur was 1.00 ± 1.24 cm, versus 0.46 ± 0.95 cm in patients without pneumothoraces. In the same study, pleural-based lesions where lung parenchyma was not traversed showed a pneumothorax rate of 17.5% compared to deeper parenchymal lesions with a rate of 51.6%. (30) A similar relationship was also demonstrated by Anderson et al. with the average depths of lesions between the pneumothorax and non-pneumothorax outcomes being 24 mm and 6 mm respectively. (8) Multivariate analysis has shown that increased lesion depth is associated with higher occurrence of pneumothorax and need for intercostal drain thoracostomy. This was thought to be related to increased difficulty of needle-lesion placement, increased needle re-directions and therefore more tearing of the pleura and lung parenchyma. (28)

Patient-related factors are more controversial and have had varying results; these include emphysema, age and previous ipsilateral chest surgery. One study evaluating nontechnical factors that may influence complication rates of transthoracic CT-guided lung biopsies found no statistically significant relationship between pneumothorax and the presence of emphysema, or the patient's age. (25) Others found no significant relationship between emphysema and pneumothorax rate (13,30) whilst another study found a relationship only when core-needle was used instead of FNA. (3) Chami et al contradicted these findings after evaluating quantitative percentage of emphysema versus post procedural pneumothoraces. The percentage of emphysema was defined as the percentage of voxels with density below -950 HU. A linear correlation of 7.4% increase in pneumothorax rate for every unit percent increase in the quantity of emphysema was elicited. (32)

Patient age had no effect on pneumothorax rate in some studies (11,30,32) whilst Otto et al. found patients who complicated were on average 4 years older and with an increase of complication rate at 4% per year. (13)

Procedure-related factors include patient positioning during the procedure, biopsy needle size and level of experience of the radiologist performing the procedure. Takeshita et al. found that supine positioning of patients undergoing CT-guided lung biopsy was an independent risk factor for developing a post-procedural pneumothorax requiring drainage ($p=0.0001$). (27) Whilst several authors found with multivariate analysis that prone positioning was a determining risk factor for developing pneumothorax. (9,32) There was agreement between several authors that the needle gauge had no significant influence on pneumothorax rate. (11,32–34)

The experience of the radiologist performing the biopsy has been identified as a contradictory risk factor for pneumothorax. Topal et al. found that the pneumothorax rate increased with increasing experience when compared between first year (20/141; 14.2%), final year registrars (41/225; 18.2%) and chest radiologists (24/87; 27.6%). This difference was deemed to be significant ($p<0.01$) with univariate analysis but no significance was found with multivariate analysis ($p>0.05$). (34) Contrary to this, Yeow et al. demonstrated a lower pneumothorax rate with a more experienced radiologist (17 vs 29%), however, this was only significant in lesions larger than 2cm. (33)

6. Factors affecting technical success rate

Biopsy technical success is equivocally defined as a biopsy providing adequate pathology material to make a diagnosis. Rates are largely reported to be over 80% and are higher when a core-needle technique is used. Numerous studies have shown that transthoracic CT guided lung biopsy is associated with high technical success rates (9-11,13,26) and accuracy (>90%) (11,26,27,35) whether fine- or core-needle technique is used. (3,8) Core needle and larger gauge (22G) FNA needles have been found to be independent factors associated with an improved technical success. (9) Even though the technical success rates associated with CT-guided lung biopsies are high, there remains uncertainty about which factors affect these rates. Loh et al. had an overall technical success rate of 89.5%, with a marginally higher success with core and/or FNA, than just FNA alone (92% and 88.8%). (11) Anderson et al. found significantly increased sample acquisition and diagnostic accuracy when using a core needle (93%) over fine needle biopsies (78%). (8) Other studies reported lower than expected technical success rates when a FNA technique was used in smaller pulmonary lesions. (4,26) Li et al. found differing results when FNA's were performed in different sized lesions with technical success rates of 74% and 97% in lesions smaller and larger than 15 mm respectively. (26) One study that focused on transthoracic CT-guided lung FNA biopsies performed only on pulmonary lesions smaller than 10 mm was associated with a lower technical success rates of 45.5%. (4) Larger lesions were associated with higher technical success rates (10,35) with some authors finding a bimodal distribution of technical success when looking at success rates based on size. Technical success rates decreased with lesions greater than 5cm and this was thought to be attributed to increased central necrosis within the biopsied lesions (8,29) and increased surrounding parenchymal atelectasis and consolidation. (8)

Other lesional factors that were found to reduce success rates were increased distances from the skin or pleura. (29,35) Zhoa et al. found that lesions which abutted the pleura were associated with higher diagnostic yields. Patel et al. was able to demonstrate a 67% increase in the likelihood of positive biopsy for every 5 cm the lesion was further away from the diaphragm. (29)

Contrary to these findings, some studies demonstrated that patient factors such as age, emphysema as well as lesion descriptors such as diameter, distance from skin (3) and number of biopsy passes had no statistically significant influence on technical success. (13) The same author found that the only factor which influenced technical success, was the experience of the individual radiologist performing the procedure, with ranges as wide as 25%-100%. (13) Haas et al. looked at the pre-procedural suspicion of a pulmonary lesion being related to infection and found a 73% non-diagnostic rate in lesions that were suspicious for infection, compared with 13% in those lesions suspected to be carcinoma. (36)

7. This study in context of the literature

While the literature suggests that transthoracic CT-guided lung biopsies have a high diagnostic yield and are considered relatively safe procedures, there remains a wide variation in results between different institutions. Reports on the subject are especially limited in our local population, and the outcomes and factors influencing the results of these common diagnostic procedures are unknown in our setting.

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II. Full Text Journal Article For Submission

1. Title Page

Factors influencing pneumothorax rates of transthoracic CT-guided lung biopsies in a Tertiary Centre in Cape Town, South Africa.

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Author's contributions:

All authors contributed to the study concept and design. Data collection, data analysis and the first draft of the manuscript was written by William Richards-Edwards. Qonita Said-Hartley commented on previous versions of the manuscripts and approved the final manuscript.

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2. Abstract

Background:

Histological sampling of pulmonary lesions is important in diagnosis of lung carcinoma and affects subsequent decisions on specific management. Transthoracic CT-guided lung biopsy is considered an effective option to obtain tissue with low rates of complications, with pneumothorax being the most common.

Objectives:

To determine the pneumothorax rate of transthoracic CT-guided lung biopsies of focal lung lesions at Groote Schuur Hospital, and assess how procedural, patient and lesion factors influence these results.

Methods:

A retrospective review of 237 CT-guided lung biopsies performed over a 24-month period. Patient's CT, biopsy reports and post-procedure x-rays were reviewed. The relationship between pneumothorax rates and categorical demographic and clinical variables was analysed with Cochran's trend test. Mann-Whitney U tests were used to assess differences in continuous variables.

Results:

Pneumothorax occurred in 43 (18.1%) of the 237 biopsies. A chest drain was required in 7 of 43 pneumothoraces (16%; 3% overall). Risk factors that were significantly associated with pneumothorax rate include pleural-lesion distance ($p<0.001$), smaller lesion size ($p=0.002$), smaller needle gauge ($p=0.012$) and perilesional emphysema ($p=0.011$). Patient age, sex,

position, lesion location and level of experience of the performing radiologist had no significant influence on the pneumothorax rate.

Conclusion:

Our post-procedure pneumothorax rate is within the acceptable range when compared to other institutions. Pleural-lesion distance, lesion size, smaller needle gauge and presence of perilesional emphysema were the most significant risk factors influencing pneumothorax rate. Knowledge of these findings may be applicable in pre-procedure planning to reduce complications and useful to local referring clinicians and patients.

3. Introduction

Owing to its high spatial resolution, multiplanar reconstruction and high diagnostic performance, transthoracic computed tomography (CT)-guided lung biopsy has become a well-established method of obtaining a histological diagnosis for pulmonary lesions. (1–4) This method has also been preferred over bronchoscopic techniques especially in smaller more peripheral pulmonary lesions. (1,2) Histological confirmation of a pulmonary lesion is of major importance in determining the aetiology, directing specific management and allowing for better prognostication of lung carcinomas. (1,2)

Transthoracic CT-guided lung biopsies provide high diagnostic yield and accuracy with varied, but acceptable rates of complications. Pneumothorax is recognised as the most common complication, occurring between 8 % and 64 % in patients undergoing CT-guided lung biopsy. (5) Most pneumothoraces are managed conservatively, while a lower percentage require further intervention by placement of an intercostal chest drain. It is well recognised that multiple variables influence safety when performing transthoracic CT-guided biopsies of pulmonary lesions. Many institutions however have results that either confirm or contradict one another.

This study intends to examine procedure, patient and lesion factors that influence pneumothorax rates in our local setting and hence provide more predictable outcomes and modifiable procedural practices.

4. Research Methods and Study Design

II.4.1 Study design and setting

This retrospective study was performed at Groote Schuur Hospital, Cape Town, South Africa, in patients who underwent transthoracic CT-guided lung biopsies for pulmonary lesions for the period between January 2017 to December 2018. Using a consecutive sampling strategy, we reviewed 314 CT-guided lung biopsies performed during this period, of which 237 adult (> 18 years old) patients were included in the study. Patients were excluded if significant and relevant data was absent such as missing biopsy reports or CT images. Repeat biopsies performed on a patient who were already in the data set and lesions that demonstrated extensive mediastinal and/ or pleural invasion negating the need for pleural transgression were also excluded.

The frequency of pneumothoraces were determined and factors related to the patient, procedural and the pulmonary lesions were recorded. Factors that were reviewed included patient's age, sex, patient position during the procedure, experience of radiologist performing the biopsy (registrar or consultant), biopsy needle gauge, lesion lobe location, average axial diameter of the lesion, pleural-lesion distance and the presence of perilesional emphysema. The lesion size was averaged between the measurements of the longest axis of the lesion and a measurement perpendicular to this in the axial plane. The pleural-lesion distance was measured from the site of pleural puncture to the nearest margin of the lesion along the trajectory of the needle path.

These measurements are demonstrated on Figure 3.

II.4.2 Procedure and data collection

Biopsies were performed on two departmental CT scanners using a conventional CT-guided biopsy technique:

1. Toshiba Aquilion PRIME (Tochigi, Japan) 160 slice MDCT
2. Siemens Somatom Emotion 16 (Erlangen, Germany) 16 slice MDCT

Patients undergoing transthoracic CT guided lung biopsies were consented and their blood profiles reviewed prior to undergoing the procedure to exclude any bleeding risks manifested by an elevated INR >1.5 or low platelet count < 50 x 10^9/l. At the time of biopsy, a limited scan of the predetermined region of interest was performed to minimise radiation exposure. Scans were reviewed in the lung window setting and the routine biopsy approach was to traverse the shortest distance of lung parenchyma as possible, with the patient being appropriately positioned in a prone, supine or lateral decubitus position. The biopsy needle trajectory was planned to avoid structures such as lobar fissures, lung bullae and blood vessels in order to diminish any inadvertent complications. All our biopsies were performed using either an 18 or 20G co-axial biopsy needle system (Angiotech ®) to allow for a single pleural puncture. Biopsies were performed using a conventional spiral/sequential CT-guidance ("step-and-shoot" technique) with intermittent image acquisition. The needle size and number of core samples taken was determined by, and at the preference of the radiologist performing the procedure at the time of biopsy. The gauge of the inner cutting needle was recorded on the CT report. CT images were obtained with the tip of the co-axial needle within the targeted lesion prior to samples being taken.

Post procedure, patients were sent for an immediate erect chest x-ray performed in expiration with subsequent clinical surveillance in the radiology department for 2 hours. Patients who sustained small (<2cm at the level of the hilum) asymptomatic pneumothoraces that remained stable on a repeat chest x-ray (after 2 hours) were treated conservatively and counselled prior to discharge. Patients with large (>2cm at the hilum), symptomatic and/ or enlarging pneumothoraces were transferred to the Emergency Unit (EU) for further assessment and possible intercostal chest drain placement.

Figure 1 demonstrates a right apical lung mass with a large post procedure pneumothorax.

Figure 2 demonstrates re-expansion of the right lung after the placement of a right intercostal chest drain.

A database of all CT-guided lung biopsies performed was together with their corresponding reports was obtained from the department's Picture Archiving and Communication System (PACS) and entered onto an Excel spreadsheet. A study number cypher system was used to protect patient confidentiality. CT measurement data was collected by the primary investigator using 0.5 mm lung window (width 1500 HU, level -70HU) reconstructions on the Phillips iSite Enterprise Volume Vision (Eindhoven, Netherlands) CT viewer.

II.4.3 Data analysis

Statistical analyses were performed using SPSS Statistics Version 26 (Armonk, New York, USA). The prevalence of pneumothorax rates was reported as a percentage. Cochran's Trend Test was used to analyse the relationship between pneumothorax rates and categorical demographic and clinical variables. Mann-Whitney U tests were used to assess differences in continuous variables of patients with and without pneumothorax. Mann-Whitney U tests were used to assess differences in continuous variables and (a) level of experience of the clinician who performed the biopsy (consultant or registrar), and (b) gauge of needle (18 or 20G). A Pearson's Correlation was used to assess the relationship between the size and depth of lesions. Differences were considered significant when the P value was below 0.05.

II.4.4 Ethical considerations

Institutional permission was obtained from Groote Schuur Hospital and ethical approval was granted by the Human Research Ethics Committee of the University of Cape Town. HREC Ref (164/2020).

5. Results

Post-procedural pneumothorax occurred in 43 of 237 biopsies (18.1%) with intercostal chest drain placement required in 7 patients (3%, n=7/43). The number of biopsies were relatively evenly distributed between female (49%, n=115/237) and male (51%, n=122/237) patients with pneumothorax rates of 16.5 % and 19.7% respectively. The median age for patients undergoing biopsy was 62, with an age range between 23-86 years. No statistical correlation was found between patient gender ($p=0.270$) or age ($p=0.530$) and pneumothorax rate. The demographic data of the 237 biopsies performed are summarised in Table 1.

The pleural-lesion distance or the depth of the lesion within the lung parenchyma was found to be the most significant variable influencing pneumothorax rates ($p<0.001$) and is summarised in Table 2. Pneumothoraces occurred at a median lesion depth of 19 mm with the pneumothorax rate increasing with lesion depth. The overall mean lesion depth for biopsied lesions was 10.7 mm with the deepest lesion biopsied at 60 mm from the visceral pleura. One hundred and six lesions contacted the pleural surface, of which 6 (5.6%, n=6/106) developed post-procedural pneumothoraces, none of which required intercostal chest drain placement.

Pulmonary lesions were separated into two size categories, namely a nodule (< 30 mm) and a mass (≥30 mm). The rate of pneumothorax was significantly higher ($p=0.006$) in smaller pulmonary lesions (nodules) <30 mm (26.3%, n=99/237) when compared to larger lesions (masses) ≥30 mm (12.3 %, n=138/237).

Seventy-two patients demonstrated the presence of perilesional emphysema (30.3%, n=72/237). An increased pneumothorax rate was demonstrated in patients with emphysema (27.8%) with a significant correlation ($P=0.011$).

No significant relationship between the lesion lobe location and pneumothorax rates ($P=0.781$) was identified.

We evaluated the relationship between clinician experience and pneumothorax rates with an even distribution of biopsies performed by the two groups. Training registrars performed

119 (50.2%) and consultants performing 118 (48.8%) biopsies of the total. The pneumothorax rate was marginally lower with consultants than with training registrars with a rate of 19.3% and 16.9% respectively, with no statistical significance between the two groups ($p=0.635$). Since the pneumothorax rates were similar between the two levels of differing experience we determined if lesion characteristics had an influence on case selection between the two groups. Mann Whitney U tests revealed that neither lesion size ($p = 0.181$) nor depth ($p = 0.298$) differed significantly depending on whether the radiologist was a consultant or registrar.

Biopsies were performed with either an 18 or 20 G core needle, with most lesions biopsied with a 20G needle (72.9%, 173/237). Pneumothorax rates were significantly ($P=0.012$) higher in patients when a 20G needle (21.9%, n=38/173) was utilised when compared with an 18G needle (7.8%, n=5/64). Both lesion size ($p <.001$) and depth ($p <.001$) differed significantly depending on whether an 18- or 20-gauge needle was used. Lesions were significantly larger when an 18-gauge needle was used (median 59mm vs 27mm), but significantly deeper when a 20-gauge needle was used (median 11mm vs 0mm).

The positioning of the patient during the procedure had no significant correlation with pneumothorax rate ($p=0.506$). The relationship between pneumothorax rates and categorical demographic and clinical variables are summarised in Table 3, whilst continuous variables are summarised in Table 4.

6. Discussion

A high prevalence of both lung carcinoma and overall prevalence of pulmonary disease, specifically pulmonary TB in our local population, (6) compounded by increasing pulmonary lesion detection rates on CT has necessitated the need to perform regular, safe and effective transthoracic CT-guided lung biopsies. On imaging, pulmonary lesions manifest as a non-specific spectrum of findings ranging from an incidental solitary pulmonary nodule (SPN) to multifocal consolidation making interpretation challenging (7) and histological confirmation mandatory. The preferred outcome is the timeous establishment of a diagnosis to prevent mortality, lower morbidity and implementation of lesion-specific directed management whether it be antimicrobial, chemotherapeutic or surgical. (1) CT-guided lung biopsies provide high diagnostic yields with acceptable but variable complications rates, pneumothorax being the most common. (3–5,8–11) The overall pneumothorax rate in our study was 18.1% with 16% (n=7/43) of these requiring intercostal chest drain placement. This correlated well with the reviewed literature which reported a post procedure pneumothorax range of 12-45%. (12) The percentage of pneumothoraces requiring chest drain placement has been reported as high as 53%. (12) The overall pneumothorax rate and chest drain requirement in our study was similar to that reported by Khan et al who had a smaller sample size but demonstrated a pneumothorax rate of 17% of which 13% (n=3/23) required intercostal drain placement.(13) Our study showed the most single significant variable influencing pneumothorax rates was the distance between the pleura and lesion (p<0.001) with this finding being corroborated by multiple studies. (8,12,14–17)

In our study 106 of the total 237 biopsied lesions contacted the pleura with a pneumothorax rate of 5.7 %, none of which required chest drain placement. The pneumothorax rate increased to 20% in subpleural lesions (depth 0.1-10mm) and 50% in lesions deeper than 30.1 mm. This finding differed to the findings of Yeow et al. who reported a sevenfold higher risk of pneumothorax in subpleural lesions and lesions not deeper than 2cm in depth, compared to only 4.4 times higher risk in lesions deeper than 2cm. This was hypothesized to be due to less stability and increased movement at the needle tip in subpleural lesions due to the reduced amount of transgressed tissue to facilitate the anchoring of the biopsy needle. (18) We demonstrated a directly proportional relationship between pneumothorax rate and lesion depth with the lowest rates of pneumothorax in lesions that contacted the pleura. Lesions peripheral in location, viz. those being within 10 mm of the pleura had a pneumothorax rate of 20%. Lesions greater than 30 mm from the pleura demonstrated a 50% pneumothorax rate. These findings are demonstrated in Table 2. Reasonable agreement exists with previous studies that suggested that an increasingly longer needle path would cause an increased likelihood of tearing the lung parenchyma and pleura with resultant pneumothorax.

Other factors that may need to be considered when performing a biopsy on deeper lesions include both the number of needle angle corrections and the length of time required to perform the biopsy (dwell time). The procedure time was not considered in our study as it was not routinely recorded.

A significant relationship between lesion size and pneumothorax rate was established in our study ($p=0.006$) with consensus found in numerous other studies. (9,16,19–22) This finding was supported by Ng et al. who looked at pneumothorax rates in biopsied lesions <10 mm in size and found a pneumothorax rate of 52.7% compared to their institutional average of 35% when lesions of all sizes were taken into consideration. (19) The increase in pneumothorax rate of smaller lesions is thought to be related to increase in technical difficulty and longer procedure times. (20) A minority of studies reviewed revealed no relationship between lesion size and pneumothorax rate. (13) We also established that smaller lesions had an increased pleural-lesion distance when compared with larger lesions ($r = -0.399$, $p < .001$).

The presence of perilesional emphysema was identified as a significant patient-related variable for the development of a post-procedural pneumothorax, as 27.8 % of patients with perilesional emphysema developed pneumothoraces, compared with 13.9% without emphysema. In our study perilesional emphysema was determined by subjective visual assessment by the primary investigator alone, without the use visual scoring or quantitative CT techniques utilised by some authors who also supported the relationship between emphysema and the development of pneumothorax. (12,17)

There was no significant relationship between the lesion lobar location and pneumothorax rates (p=0.781). This was supported by Patel et al. who could not establish a relationship between lesion distance from the diaphragm and pneumothorax rate. (23) This is contrary to findings of Hiraki et al. who discovered a significant relationship between parenchymal lesions in the anatomical lower lobes and an increased pneumothorax rate. They thought this was related to relatively increased respiratory motion in the lung bases and resultant increase in the number of needle tip redirections. (22)

We found no statistical significance between the two groups with differing levels of experience performing biopsies which is corroborated in the literature. (17) The number of biopsies performed were evenly distributed between the two groups with registrar and consultants incurring a pneumothorax rate of 19.3% and 16.9% respectively (p=0.635). We assumed the consultant group would demonstrate a comparatively reduced pneumothorax rate, but this number may be influenced by consultants preferentially selecting deeper and smaller lesions. We however established that the lesion size or depth did not significantly differ between the groups. Yeow et al. found that the level of expertise only influenced pneumothorax rates when lesions ≥ 2cm were biopsied. (18)

All our biopsies were performed with either an 18 or 20G co-axial core needle biopsy allowing for a single pleural transgression as compared with multiple passes when a non-coaxial technique was utilised. A 20G needle was more commonly used (72.9%, n=173/237) and was also associated with a higher pneumothorax rate ($p=0.012$). There was a significant difference in the characteristics of the lesions biopsied by 18 and 20 G needles ($p<0.001$). 20G needles were preferentially used in smaller lesions (median 27 mm vs 59 mm) and lesions with an increased pleural-lesion distance (median 11 mm vs 0 mm). We found no statistical relationship between pneumothorax rate and patient age, sex and procedural positioning.

II.6.1 Strengths and limitations:

The strength of this study is that it represents a single institution experience with unique patient demographics, experienced radiologists and modern radiology equipment that produced results consistent with the literature. The results of this study can possibly be extrapolated to other institutions in the region. In addition, strengths include the uniform use of co-axial core biopsy needles and conventional CT-guided technique with minimal variation in needle size.

Limitations include the retrospective study design and the risk of any associated unknown bias. The retrospective study design limited the number of variables that could be assessed with the available data. The number of core samples taken, needle dwell time, level of attending consultant's supervision and patients' clinical condition at time of biopsy was not recorded due to lack of documentation. These variables could therefore not be considered when assessing pneumothorax rates. Individual radiologist's procedural preferences in needle size, needle approach and patient positioning were also not evaluated.

Our reported pneumothorax rate may have been influenced had we performed post procedure CT scans due to increased detection rates instead of plain film. Additionally, delayed post procedure chest x-ray (after 3 hours) may have increased sensitivity. Pneumothoraces occurring after 3-4 hours have been reported to occur in the range of 3.3-18%. (20,24)

Due to the study population size and lower than expected pneumothorax rate, a more robust multivariate analysis and logistical regression could not be performed for subgroup variables.

II.6.2 Implications or recommendations

Given the increasing frequency of pulmonary pathology detection rates and challenges in establishing a diagnosis in chest radiology, CT-guided lung biopsies have become common practice. CT-guided lung biopsies need to be performed and documented in a systematic manner so that more variables may be evaluated and risks further mitigated. Patient selection will require input from a multi-disciplinary team. Hospital based and external referring clinicians will be better informed as to which patients and which specific lesion characteristics are at higher risk of developing post procedure pneumothoraces, determining which biopsy technique will best suit their patient's profile and whether the patient would better tolerate an alternative technique. Consenting patients undergoing CT-guided lung biopsy can be provided with institution specific information of expected outcomes so that well informed decisions can be made, and adverse outcomes better understood. Going forward in terms of a more comprehensive review of practice and outcomes, a data collection sheet addressing these shortfalls and variables will be recommended.

7. Conclusion

The diagnosis of lung cancer remains a challenge with CT-guided lung biopsies demonstrating acceptable levels of risk and largely mild complications. Our post-procedure pneumothorax rates are comparable to that of other institutions. The risk of pneumothorax at CT-guided lung biopsy is increased by the pleural-lesion distance or lesion depth, presence of perilesional emphysema and decreased by lesion size. Knowledge of these findings may be useful to referring clinicians, patients and regional hospitals in pre-procedure planning to minimise complications.

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9. Tables

Table 1: Pneumothorax rates distributed by age and sex (n=237)

	n	No Pneumothorax	Pneumothorax	Pneumothorax rate	*p*
Sex					.530
Female	115	96	19	16.5%	
Male	122	98	24	19.7%	
Age					.270
*Age	237	62 (53-68)	62 (56-69)		

*Medians presented with IQR in parentheses

Table 2: Pneumothorax rates based on pleural-lesion distance (n=237)

Pleural-lesion distance (mm)	Total number *n=237*	No Pneumothorax *n = 194*	Pneumothorax *n*= 43	Pneumothorax %
Pleural contact	106	100	6	5.7%
0.1-10	30	24	6	20%
10.1-30	77	58	19	24.7%
>30.1	24	12	12	50%

Table 3: Relationship between pneumothorax rates and categorical demographic and clinical variables. Differences were considered significant when the P value was below 0.05*

	n	No Pneumothorax	Pneumothorax	Pneumothorax rate	*p*
Sex					.530
Female	115	96	19	16.5%	
Male	122	98	24	19.7%	
Patient position					.506
Supine	87	72	15	17.2%	
Prone	141	116	25	17.7%	
Lateral decubitus	9	6	3	33.3%	
Lesion site					.781
Lower	84	70	14	16.7%	
Middle	6	4	2	33.3%	
Upper	147	120	27	18.4%	
Lesion size					.006*
< 30mm	99	73	26	26.3%	
> 30mm	138	121	17	12.3%	
Emphysema					.011*
Yes	72	52	20	27.8%	
No	165	142	23	13.9%	
Operator experience					.635
Consultant	118	98	20	16.9%	
Registrar	119	96	23	19.3%	
Gauge of biopsy needle					.012*
18	64	59	5	7.8%	
20	173	135	38	21.9%	

Table 4: Relationship between pneumothorax rates and continuous variables.

	No Pneumothorax *n* = 194	Pneumothorax *n*= 43	*p*
Age	62 (53-68)	62 (56-69)	.270
Lesion size (mm)	41.5 (21-60.25)	26 (17-39)	.002*
Pleura-lesion distance (mm)	0 (0-16)	19 (9-31)	<.001*

Note. Medians presented with IQR in parentheses

10. Figures

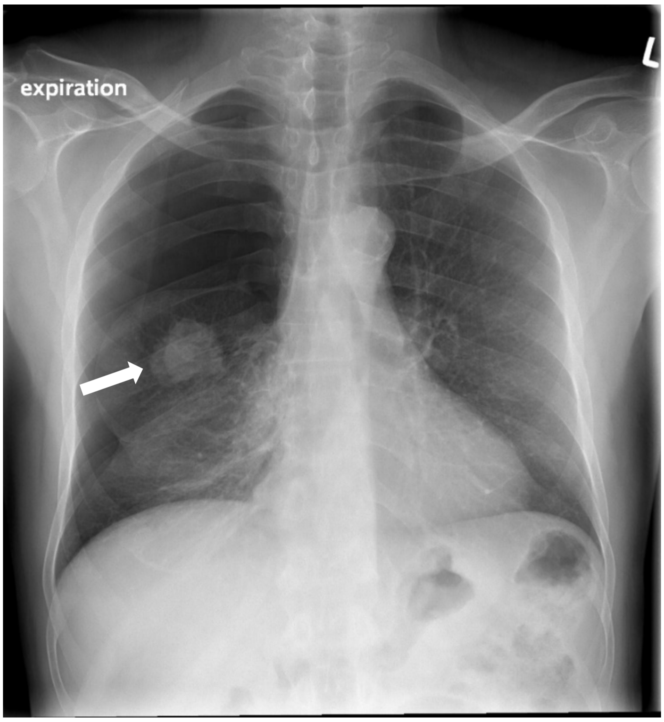

Fig. 1 Immediate post-biopsy chest x-ray demonstrates a large right sided pneumothorax. The right apical lung mass is displaced inferiorly (arrow).

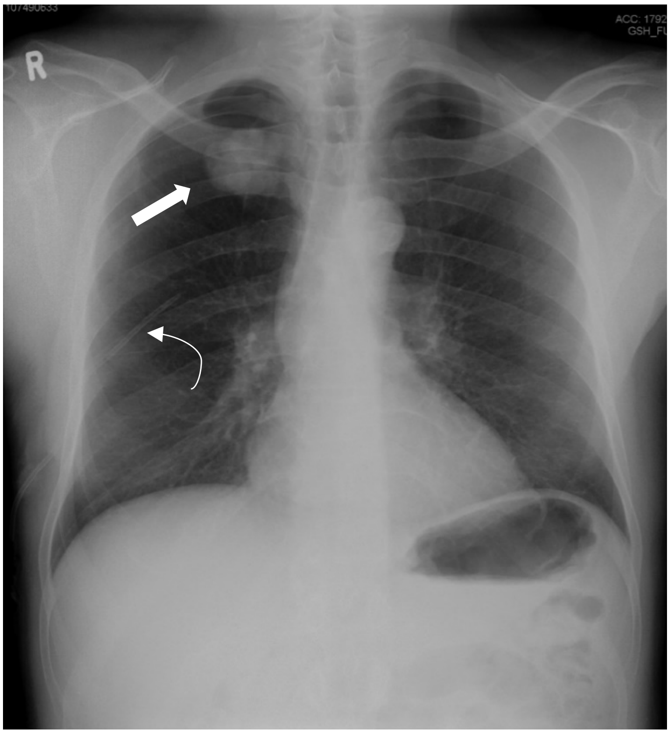

Fig 2. Placement of a right sided intercostal drain (curved arrow) with re-expansion of the right lung. Subsequent elevation of the right apical lung mass which projects over the right first rib (arrow).

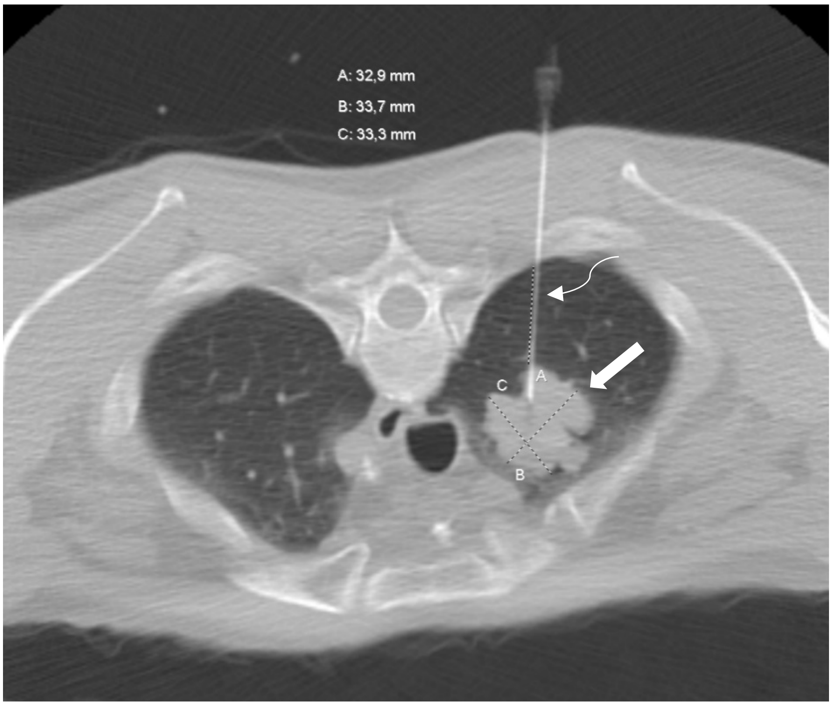

Fig.3 CT image of a patient undergoing a CT-guided lung biopsy in the prone position. Right upper lobe pulmonary mass (arrow) with biopsy needle (curved arrow) in situ.
A = Pleural-lesion distance from the visceral pleura to the closest margin of the lesion along the trajectory of the biopsy needle measuring 32.9 mm.
B and C = Axial diameters of the lesion averaged to 33.5 mm

III. Addenda

1. Addendum 1: Ethics approval letter

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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 March 2020

HREC REF:164/2020

Dr Q Said-Hartley
Division of Radiology
C-Floor, C7
Radiology Department- GSH

Dear Dr Said-Hartley

PROJECT TITLE: FACTORS INFLUENCING PNEUMOTHORAX RATES OF TRANSTHORACIC CT-GUIDED LUNG BIOPSIES IN A TERTIARY CENTRE IN CAPE TOWN, SOUTH AFRICA. MMED CANDIDATE DR WH RICHARDS-EDWARDS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr W Richard-Edwards will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 164/2020sa

2. Addendum 2: Author instructions for South African Journal of Radiology

Original Research Articles

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Word limit	3000 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Background, Objectives, Method, Results and Conclusion
References	60 or less
Tables/Figures	no more than 10 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative change or differences on answers to questions.

- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)
  Do not cite references and do not use abbreviations excessively in the abstract.

  Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.
  Research methods and design: This must address the following:
- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution’s name and permit numbers should be stated here.
  Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use

quotations as required to establish your interpretation of qualitative data. All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.
  Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our policy on competing interests.
- Author contributions: All authors must meet the criteria for authorship as outlined in the authorship policy and author contribution statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.
  References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.