

Etiology and Clinical Patterns of Chronic Cough in the Chest Clinic of a Tertiary Hospital in Nigeria

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Purpose: The burdens of chronic cough are mostly reported from Western and Asian countries. We aimed to determine the etiology and clinical patterns of chronic cough (CC) in the chest clinic of a tertiary hospital in Nigeria.

Patients and Methods: This survey was a cross-sectional study of 218 patients. Chronic cough was defined as cough >8 weeks duration. The evaluation and diagnosis of patients was based on a diagnostic protocol developed from the international respiratory societies cough guidelines and a previous study.

Results: The median age of patients was 50 years (interquartile range 30–68). One etiology was identified in 96.3% of cases; dual etiologies in 2.3%, and 1.4% had an unexplained cough. The most frequent causes of cough were COPD (33.5%), PTB (27.1%), and asthma (21.1%) which included 3 cases of cough variants of asthma (CVA). Other causes were post-tuberculosis lung disease (bronchiectasis and fibrosis) in 6.9%, lung cancer in 4.7%, and interstitial lung disease (ILD) in 3.2%. Gastroesophageal-related cough (GERC) accounted for <1.0%. Before the age of 45, the chronic cough was more frequent in the females than in the males, and the commonest cause was asthma, whereas, beyond age ≥ 45 , the occurrence in males surpasses that of the females, and the commonest cause was COPD. Eighty-six percent reported shortness of breath as the most associated symptom. Systemic hypertension (15.6%) was the most frequent comorbidity, followed by HIV infection (3.7%). Chest radiograph, sputum GeneXpert MTB/RIF for TB, spirometry, and detailed history and trial of treatment, were enough to identify the cause in 72% of cases.

Conclusion: The etiology and clinical patterns of chronic cough in this study are different from the western countries. When evaluating and managing chronic cough, clinicians in sub-Saharan Africa and TB endemic countries should consider these geographical variations in etiologies and clinical presentation.

Keywords: chronic cough, asthma, COPD, pulmonary tuberculosis, etiology, pattern, Nigeria

Introduction

Cough is an important defense mechanism in the respiratory system responsible for clearing excessive secretions, foreign material, and infectious organisms from the airway.^{1–3} Despite its protective function, paradoxically, it also assists in the spreading of infections.³ Cough may be benign, self-limiting, or a warning sign of an impending disease.^{1,2} The global prevalence of chronic cough from a recent meta-analytic study was 10%.³ In North America, cough is the commonest symptom for which most patients seek medical attention, and it affects a large proportion of the general population.^{1,2} In a sampled population of urban North Central Nigeria, 20.6% had a cough in the previous 12 months, 3.8% had acute, and 1.1% had chronic cough.⁴ Chronic cough was defined by the American College of Chest Physicians (ACCP) and the European Respiratory Society (ERS) as cough in patients 15 years of age lasting more than 8 weeks.⁵ However, some respiratory infections (eg, atypical pneumonia and viruses) can elicit cough lasting ≤ 8 weeks.^{5,6} History and thorough physical examination are sufficient for diagnostic workup in patients with acute cough in clinical practice. Patients with chronic cough will need additional diagnostic measures like imaging, pulmonary function studies, and bronchoscopy. If these tests

prove inconclusive, the physician will need to evaluate for upper airway disease, cough variant asthma, or gastroesophageal reflux disease.^{5,6} Chronic cough may originate from single or dual conditions in the same patients.⁶ The common causes of chronic cough in the western world are upper airway cough syndrome (UAWCS), asthma, and GERD.

In contrast, tuberculosis is a common cause in HIV-positive and negative patients in Southern Africa.⁷ It might be unrealistic to extrapolate the pattern of chronic cough in other regions of the world to Sub-Saharan Africa because of the geographical variation in the epidemiology of risk factors like tobacco smoking, HIV /AIDS, malnutrition, environmental pollution, and poverty. Most patients with chronic cough experienced considerable physical and psychological morbidity.⁸ There is a lack of information on the presentations of chronic cough in Africa. It is important to understand chronic cough's etiology and clinical pattern from our perspectives for efficient and cost-effective diagnosis and treatment. Therefore, our objective was to determine chronic cough etiology and clinical patterns among patients attending the chest clinic of a tertiary hospital in Nigeria.

Materials and Methods

Study Design and Setting

This survey was a cross-sectional study of patients reporting chronic cough at a tertiary center chest clinic in Nigeria from July 2018 to June 2019. The clinic is a general chest (respiratory) clinic run by three chest physicians and three senior residents on Friday afternoon. The center has 500 beds with an average of 10,000 annual admissions and 12,000 outpatient visits in the last five years and is a referral center for primary and secondary care services in the six neighboring states. In Nigeria's public primary and secondary care, the patients have access to basic radiography (x-rays) and laboratory facilities (sputum for bacteriology/ GeneXpert for TB). In contrast, in private primary and secondary care, patients can access any state of art facilities depending first on the availability and affordability.

Ethical Consideration

The University of Ilorin Teaching Hospital Ethics Committee granted the study approval (reference number: UITH/CAT/189/19/388), and informed written consent was obtained to participate in the research before enrollment. Permission was obtained from their legal guardians in the study participants who are not adults. The participant data were anonymized, and this alteration has not distorted the scholarly integrity. This study protocol complies with the Declaration of Helsinki on bioresearch.

Sample Size Determination

The required sample size was obtained using the Raosoft sample formula for estimating the minimum sample size in descriptive health studies when the population size is >10,000.⁹ The normal standard deviation was set at 1.96, corresponding to a 95% confidence level, the prevalence of chronic cough in a previous study was 1.1%.⁴ The degree of accuracy desired was set at 0.02. Given attrition of 20%, the final sample size calculated was 127.

Data Collection

A cohort of ambulatory patients (aged ≥ 15 years) was recruited from the outpatient chest clinic of the tertiary hospital. Inclusion criteria were patients with cough for >8 weeks (regardless of other symptoms). A potential participant was excluded if he required immediate hospital admission and was unwilling to undergo a chest radiograph and sputum GeneXpert for TB, which is cost-free. Consecutive patients with chronic cough were recruited from the outpatient chest clinic. Trained senior registrars administered the questionnaire in the clinic and performed a physical examination for all patients that included respiratory and cardiac assessment. The results of patient investigations were extracted a month after completing the study using their hospital identification number.

Diagnostic Protocol

A diagnostic protocol was prepared from available cough guidelines and modified based on a previous study in the southern African region was used to evaluate the patients.^{5,7,10,11} Furthermore, the patient demographic profile, onset and

duration of cough, associated symptoms, smoking status, domestic use of solid fuel, and past medical history were also obtained. The initial evaluation included a detailed history and a physical examination for all patients, followed by investigations. These included sputum examination for bacterial culture if the cough is productive, GeneXpert MTB/RIF, chest radiograph, and voluntary testing for HIV. If the cough is suggestive of infectious origin, sputum for fungal studies was ordered. If the initial evaluation did not reveal an etiology, we evaluated for obstructive and allergic airway disease by spirometry and serum Immunoglobulin E level. The chest computed tomography scan and echocardiography were ordered in those who continued to have a protracted cough to identify other causes. After that, if these tests were not helpful, a bronchoscopy was done. If the bronchoscopy was non-diagnostic and the patient continued to have a cough, and the symptoms were suggestive of GERD or upper airway cough syndrome, an ear, nose, and throat (ENT) specialist or gastroenterologist was consulted in suspected cases of cough variants of asthma (CVA), upper airway cough syndrome (UACS), or gastroesophageal reflux disease cough (GERC). GERC diagnosis was based on the patients presenting with typical and frequent esophageal complaints such as daily heartburn and regurgitation and extraesophageal symptoms like throat clearing, voice changes, globus, and dysphagia. With/without findings of imaging studies and clinical syndrome consistent with an aspiration syndrome, and response to antireflux therapy (proton pump inhibitor, prokinetic agents, and dietary and lifestyle modifications).^{5-7,10,11} It is worthy of note that some subjects with GERC lack classic GERD symptoms. This is why we used a multidisciplinary approach in the workup of patients with suspected GERC. After that, if these specialist referrals were not helpful, a psychogenic cough was considered, a diagnosis of exclusion. Patients were given a trial of therapy if the history and examination were highly suggested, but the radiological and laboratory test were negative. The final diagnosis of the cause of cough for each patient required meeting the diagnostic pretreatment criteria and resolution of symptoms with specific treatment.^{5,7,10,11}

Operational Definitions

Pulmonary tuberculosis (PTB): a clinical diagnosis of pulmonary tuberculosis was made in patients with cough and positive bacteriology, GeneXpert MTB/RIF, or histology for TB.¹² Asthma: clinical diagnosis of asthma was considered when there are symptoms such as episodic breathlessness, wheezing, cough, and chest tightness with reversible airflow limitation on spirometry or peak expiratory flow.¹³ COPD: a clinical diagnosis of COPD was considered in any patient with dyspnoea, chronic cough or sputum production, and a history of exposure to risk factors for the disease. The diagnosis was confirmed by the presence of an airflow limitation that is not fully reversible (ie, post-bronchodilator FEV1/FVC < 0.70 and FEV1 < 80% predicted).¹⁴ Lung cancer: a diagnosis was made based on clinico-radiologic findings and confirmed by tissue histology. Upper airway cough syndrome (UACS) diagnosis was established in patients with a feeling of drainage in the posterior pharynx, frequent throat clearing, nasal discharge, and response to empirical treatment of oral antihistamines and decongestants, intranasal corticosteroids for two to eight weeks.⁵ As previously mentioned above, GERC diagnosis was based on esophageal or extra-esophageal symptoms, imaging studies, and response to anti-reflux therapy and lifestyle modifications.^{5-7,10,11} Other medical conditions were based on the current standardized diagnostic criteria.¹⁵

Data Analysis

All analyses were performed using Statistical Package for Social Sciences (SPSS)/IBM version 23. Descriptive and frequency statistics were generated to examine demographic and other clinical variables. Charts were used to illustrate relationships in the data visually.

Results

General Characteristics of the Patients

Of the 353 who attended the specialist chest clinic during the study period, 315 (89.2%) presented with a cough. Twenty-four (6.8%) were classified as acute cough, 73(20.7%) as sub-acute cough, and 218(61.8%) as chronic cough. All the patients with CC were enrolled in this study (Figure 1). Out of 218 recruited, 126(57.8%) were males. The median age of patients was 50 years (interquartile range 30–68). The majority were married and belonged to a lower socioeconomic group. Before their

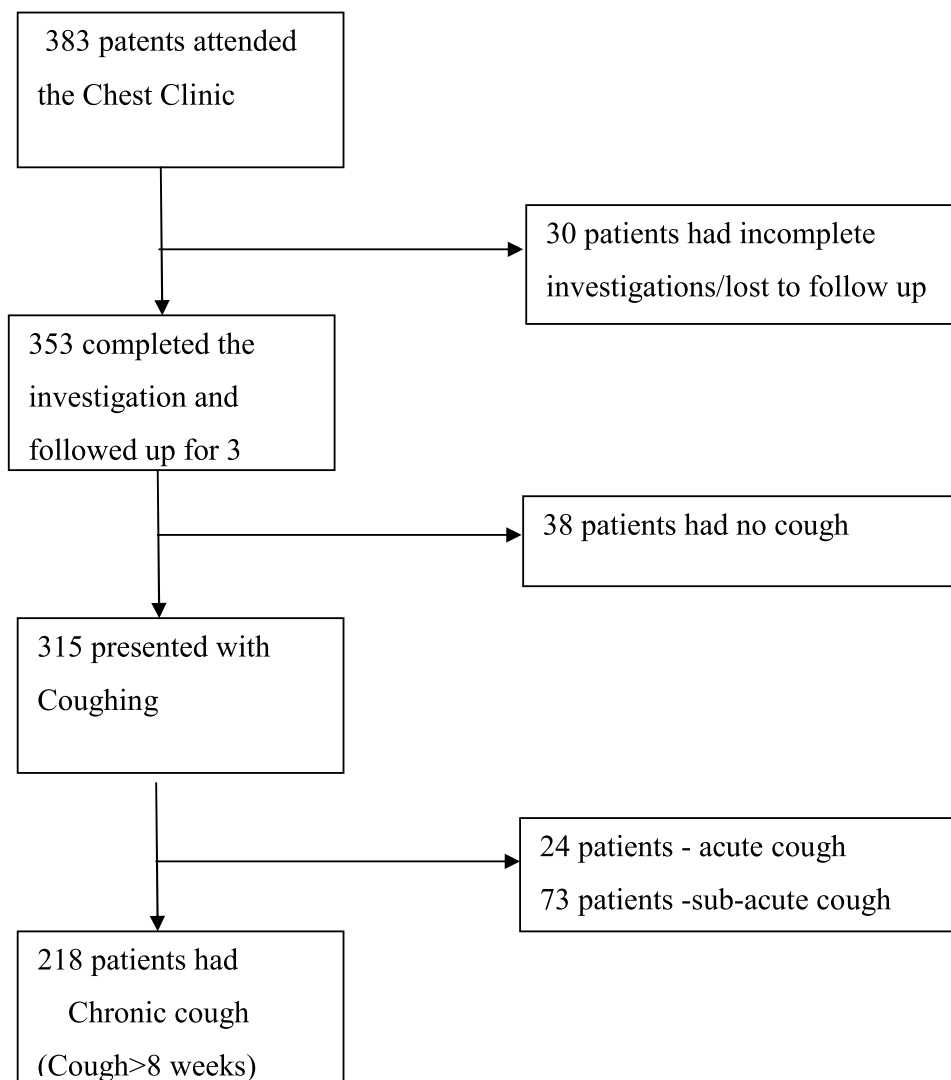


Figure 1 Flow chart showing patients selection.

visitation, the median duration of cough was 24 weeks, with an interquartile range (16–40 weeks). Six (2.8%) were current smokers, 29(13.3%) were former smokers, and 110 (50.5%) reported the use of biomass fuel for cooking (Table 1). Sub analysis shows that women significantly reported more use of biomass fuels than men (39.7% vs 65.2%, $p < 0.001$).

Age and Sex Distribution of Chronic Cough Patients

Figure 2 shows that the frequency of CC decreased with age in both sexes. Before the age of 45, the frequency of CC was higher among the females than in the males, whereas above age 45, the occurrence in males surpasses that of the females. Almost half of the females with CC were young adults below 45 years, while approximately two-thirds of male cases were above 45.

Causes of Chronic Cough

We identified a single etiology of CC in 210 (96.3%) patients and dual etiology in 5(2.3%) patients. Only 3 (1.4%) had an unexplained chronic cough. COPD was the leading cause of CC in 72(33.5%), followed by pulmonary tuberculosis in 59 (27.1%), asthma in 46(21.1%), and 15(6.9%) had post TB lung disease (6 had bronchiectasis and 9 fibrosis). Ten (4.7%) had lung cancer, and 7(3.2%) had interstitial lung disease (ILD). Two patients (0.9%) had GERD and asthma-COPD overlap, respectively (Figure 3).

Table 1 General Characteristics of the Patients

Characteristics	n(%)
Median age	50(IQR 38–68)
Median duration of cough (wk)	24(16–40 weeks)
Gender	
Males	126(57.8)
Females	92(42.2)
Tribes	
Yoruba	203(93.1)
Others	15(6.9)
Marital status	
Married	169(77.5)
Single	42(19.3)
Others	7(3.2)
Occupation	
Trading	70(32.1)
Farming	16(7.3)
Driving	13(6.0)
Student	28(12.8)
Teaching	13(6.0)
Professionals	14(6.4)
Others	64(29.4)
SES	
I	1(0.5)
II	11(5.0)
III	18(8.3)
IV	17(7.8)
V	171(78)
Smoking history	
Current smokers	6(2.8)
Ex-smokers	29(13.3)
Never smokers	183(83.9)
Exposure to biomass	110(50.5)

Abbreviation: SES, socioeconomic status.

Age Group Distribution by Causes

The most frequent cause of chronic cough among young adults (18–44 years) was asthma, followed by PTB. COPD is an uncommon cause below age 45. Above the age of 45, COPD was the leading cause of CC, followed by PTB (Figure 4).

Sex Distribution by Causes

Figure 5 shows the sex distribution by causes of chronic cough. Approximately one-third of female patients (31.1%) with chronic cough have asthma. The second common cause in females was COPD (29.3%), followed by PTB (17.4%). In the male patients, COPD (36.5%) was the leading cause of the chronic cause, followed by PTB (34.1%).

Clinical Presentation of Chronic Cough

Table 2 shows the symptoms associated with chronic cough. Shortness of breath (86.2%) was the second most commonest respiratory symptom, 31.7% reported wheezing, and 6% had chest pain and hemoptysis, respectively. On

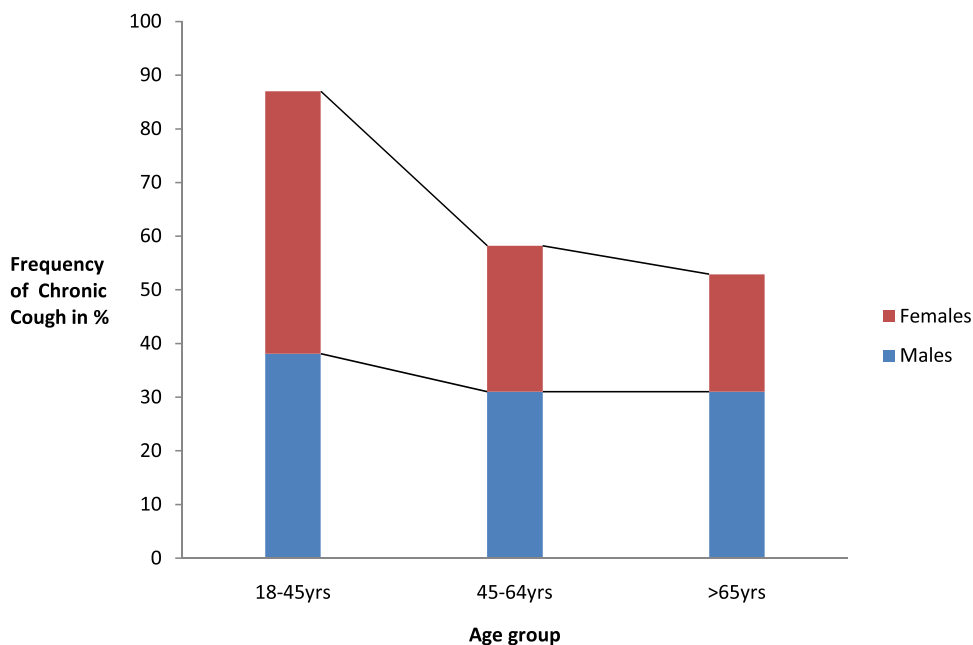


Figure 2 Age and sex distribution of chronic cough patients.

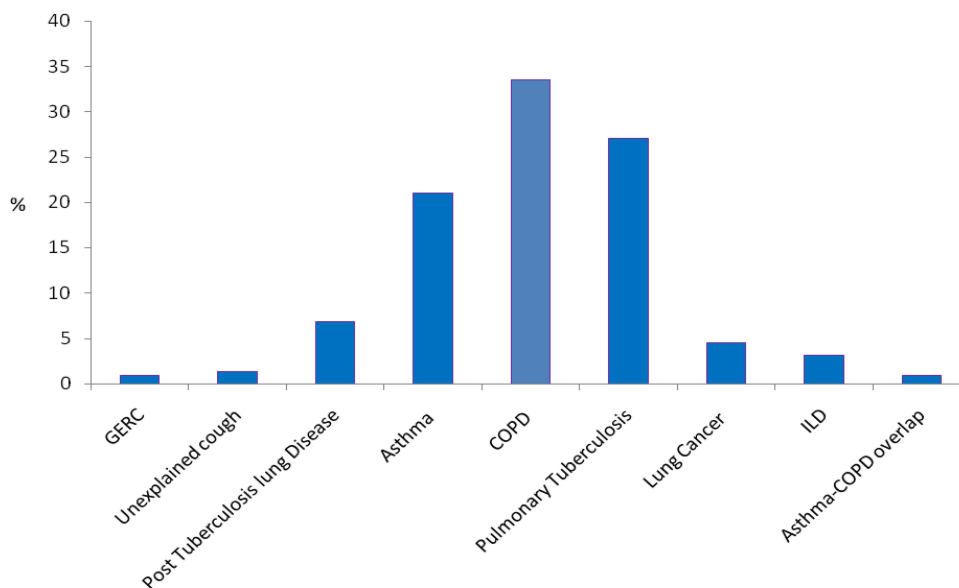


Figure 3 Causes of chronic cough.

further analysis of those with an SOB, 70% were due to COPD, asthma, and PTB. Only 47(21.6%) had identified comorbidity, and the most common comorbidity in these patients was systemic hypertension.

Diagnostic Approach to Chronic Cough

In this study, chest radiograph (100%), sputum geneXpert for TB (80.0%), and lung function test (60.1%) were the leading tests used in the diagnosis of chronic cough. Chest CT was ordered in only 29(13.3%) and bronchoscopy in 7 (3.2%) of them (Table 3). The causes of CC were determined in 174(79.8%) of the patient with a chest radiograph,

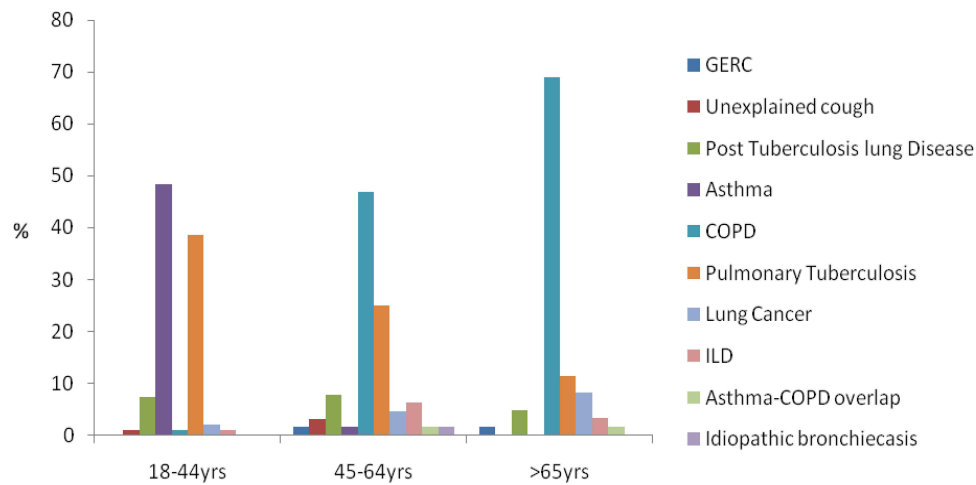


Figure 4 Age group distribution by causes.

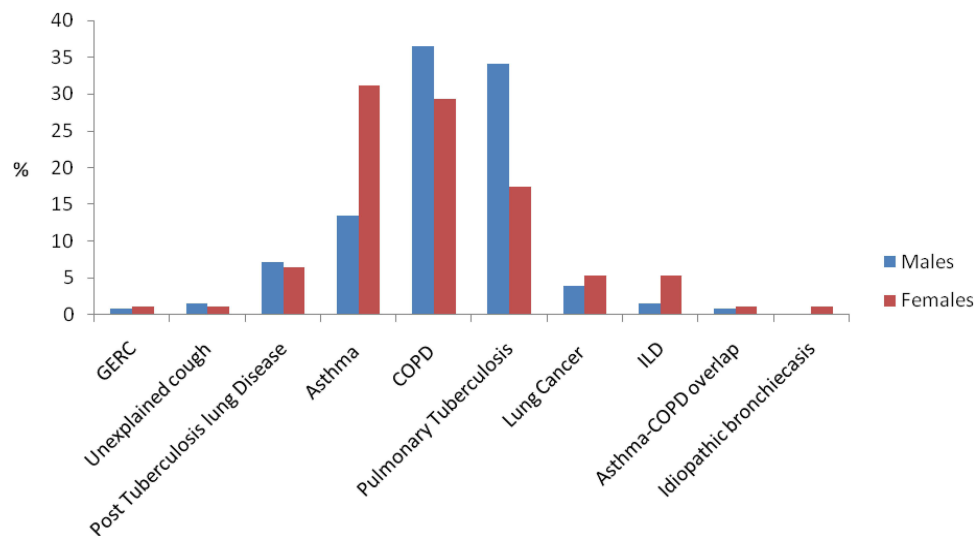


Figure 5 Sex distribution by causes of chronic cough.

sputum gene pert for TB, lung function test, and Chest CT. Chest radiograph, sputum GeneXpert for TB, lung function test and detailed history and trial of treatment were enough to identify the cause of CC in 157(72%) of patients (Table 3).

Discussion

This study has shown that many of those with CC were in the lower socioeconomic class and were never smokers. A single etiology was identified in 96.3% of cases, and 1.4% had an unexplained etiology. Overall, the most frequent causes were COPD (33.5%), pulmonary tuberculosis (27.1%), and bronchial asthma (21.1%). Approximately one-third of male and female patients with chronic cough have asthma (35.5%) and COPD (35.1%). Systemic hypertension (15.6%) was the most frequent comorbidity. In 72% of cases, chest radiograph, sputum GeneXpert for TB, spirometry, and detailed history and trial of treatment were enough to establish a cause.

Table 2 Clinical Characteristics of Patients

Symptoms	n(%)
SOB	188(86.2)
Sputum	175(80.3)
Wheezing	69(31.7)
Chest pain	13(6.0)
Hemoptysis	13(6.0)
Hypertension	34(15.6)
HIV positive	8(3.7)
Smoker	34(15.6)
Biomass use	110(50.5)

Note: Results are expressed in percentages.

Abbreviations: HIV, human immunodeficiency virus; SOB, shortness of breath.

Table 3 Summary of Diagnostic Tests

Diagnostic Tests	n (%)
Chest radiograph	218(100)
Sputum GeneXpert	170(80.0)
Lung function test	131(60.1)
HIV screening	122(56.0)
Sputum culture	55(25.2)
Chest CT	29(13.3)
Sputum for fungal studies	10(4.6)
Therapeutic trial	10(4.6)
Serum IgE	16(7.3)
Bronchoscopy/histology	7(3.2)
Serum ACE	5(2.3)
Psychiatric evaluation	–

Abbreviation: ACE, angiotensin converting enzymes.

Previous studies in western countries have reported that chronic cough was commonly caused by cough variant asthma (CVA), upper airway cough syndrome (UACS), non-asthmatic eosinophilic bronchitis (NAEB) and gastroesophageal reflux cough (GERC).^{16,17} This observation contrasts with this study, where the most frequent causes of CC were COPD, pulmonary tuberculosis, and bronchial asthma. Our results are similar to what was obtained from a previous study by McGarvey et al in a retrospective survey of all new patient referrals with chronic cough to a general respiratory clinic over 12 months.¹⁸ A diagnosis of asthma or chronic airflow obstruction was made in 43% of patients; GERD and UACS were infrequently identified in that study (4% and 2%, respectively), which contrasts with 60% in specialist cough

clinics. A variety of factors could explain why our findings are different from those obtained from specialist cough clinics in western countries. Firstly, the differences in diagnosis and outcome may be due to different patient populations, which is a function of the study setting. The present study setting is a general respiratory clinic in contrast to specialist cough clinics. Similarly, it may also be due to the organization of the health care system in Nigeria, which determines patients' selection process and characteristics of those attending the tertiary center in this cohort, which is at variance with the western countries. In our setting, primary care mostly has basic radiography and laboratory services, while advanced imaging, spirometry, and endoscopic services are mostly available and accessible in the tertiary health care system. These facilities, however, in western countries, can be easily accessed at the primary health care.^{19,20} For instance, patients with any x-ray abnormality (tuberculosis, cancer) or obstruction in spirometry (COPD) are readily diagnosed in the primary care without being referred to a specialist cough clinic which often deals with highly selective and challenging cases that may not be a true representation of chronic cough burden of the population. An alternative explanation is the geographical variations in the incidence of respiratory conditions and epidemiological risk factors like biomass, cigarette smoking, and infectious diseases that are responsible for the leading conditions.^{12,14} According to the National Tuberculosis Management Guidelines, PTB is endemic in our environment and is a risk factor for developing COPD.^{12,14} It can be argued that the contribution of PTB, and other factors, perhaps, are responsible for COPD as the leading cause of chronic cough, therefore, corroborating our findings.

Unexpectedly in this study, COPD was the leading cause of CC, accounting for a third of cases. Our observation might be attributed to indoor and outdoor pollution exposure as about 50% of the recruited subjects reported biomass fuel use for cooking. A significantly higher percentage of women reported the use of biomass fuels than men, and over 70% of them belong to lower socioeconomic status, which is associated with a high risk of exposure to biomass smoke.²¹ Even though smoking is decreasing in our country, efforts to ensure the domestic use of cleaner fuels and promote good air quality have failed due to the astronomical cost of cleaner fuels and massive pollution from diesel and gasoline power generators.²² Greenpeace's world air quality report ranks Nigeria as the 10th most polluted country globally, with an estimated average PM_{2.5} concentration of 44.8 micrograms per cubic meter, corroborating this study finding.²³

Furthermore, PTB was the second leading cause of chronic cough. The figure of 27.1% in this study is lower than the 48% reported in Zimbabwe.⁷ However, it is higher than 5% for PTB in India.²⁴ TB is an infectious disease that can be managed at a primary, secondary or tertiary level depending on the closeness of the health facilities to their patients abode. Munyati et al⁷ in Zimbabwe found TB as the most common diagnosis in patients with CC attending a primary care clinic. Almost half of the patients presented eight weeks after the symptoms, which is the cut-off duration used to classify chronic cough in this study and international respiratory societies. This finding can be adduced to patient delays in seeking health care. Previous studies have shown that 70–80% of patients with PTB are delayed in seeking treatment for their symptoms, and the median patient delay time is eight weeks.^{25,26} Insufficient money to pay out-of-pocket hospital bills, ignorance of the necessity for treatment, and the paucity of health facilities close to the home are responsible for the delays.²⁵

In this study, less than 1% of the chronic cough was due to GERC, and no upper airway cough syndrome was recorded, which contrasted with the reports from Western nations' cough clinics.^{7,16,17} The main reason can be the low diagnostic utility of the reflux symptoms. According to Irwin et al²⁷, in GERC, "GI symptoms can be absent up to 75% of the time, making the diagnosis more challenging". Besides, cough and GERD often co-exist, but their association does not imply a causative relationship in all cases. It was noted that GERC was unlikely due to only aspiration of intra-esophageal acid and that non-acid reflux, both liquid and gaseous, may be an etiological factor.^{5,27} From a clinical perspective, throughout the study duration, the team rarely encountered patients with extra-esophageal symptoms that warrant referral for 24-hr esophageal manometry, pH monitoring, and impedance-pH monitoring.

This study found that chronic cough was more frequent in males than in females, different from studies from Europe, the Americas, and local data from the population studied.^{4,28–30} In contrast, a hospital-based study in Malaysia and general population studies in Canada and Korea found a slightly higher male predominance.^{31–33} Similarly, a study in China found an almost equal proportion of females to males.³⁴ The female predominance is due to intrinsically heightened cough response.^{28–30} The male predominance in our study can be attributed to the two leading causes of CC identified in this study: COPD and PTB. Epidemiological studies worldwide have shown that men accounted for

a significant proportion of PTB³⁵ and COPD.^{14,36–39} Because the present study was conducted in a tertiary care setting, this observation might need to be validated in a future community-based study.

We found that the commonest cause of chronic cough in the male was COPD, as one in three male patients had COPD, while the leading cause of chronic cough in the female was asthma. Chronic cough is often the first symptom of COPD and is frequently disregarded by the patient as an expected consequence of smoking or environmental exposures.¹⁴ On the other hand, approximately one-third of female patients with chronic cough have asthma (35.5%). This association is because women have a high level of atopy, bronchial hyperresponsiveness, and exposure to indoor pollutants compared to men.¹³

Most cases of chronic cough with SOB result from COPD, followed by asthma and PTB. The three conditions together accounted for 72% of all cases of SOB. Previous studies have shown that COPD has a mixed pattern of chronic bronchitis and emphysema, with most patients presenting with chronic cough, chronic expectoration of sputum, and breathlessness.^{37–39} Therefore, physicians should consider these clinical patterns in their differential diagnoses.

Systemic hypertension (15.6%) was the most frequent comorbidity. It is not surprising that nearly half of those with high blood pressure have COPD. This observation agrees with previous studies.^{37–39} An earlier Canadian study found that cardiovascular disease was associated with a higher incidence of chronic cough.³² The condition often has many other disorders related to either smoking or aging that can lead to hypertension.¹⁴

Chest radiograph, sputum geneXpert for TB, spirometry, detailed history, and treatment trial were enough to establish a cause in 72% of patients with chronic cough. Some conditions like bronchogenic cancer and interstitial lung disease require additional tests like chest CT scan, bronchoscopy, and tissue biopsy to establish an etiology. For a population with a higher number of people living below poverty, this diagnostic approach and outcome can be cost-effective in diagnosing chronic and might warrant subsequent validation.

Limitations of the Study

This study has several limitations that warrant discussion. Firstly, the study was conducted in a chest clinic (general respiratory clinic) in tertiary care, and this might make it difficult to generalize the study to other settings. In as much as we tried to prevent misclassification using a multidisciplinary team, few cases might have occurred because of diagnostic challenges and logistics issues on the part of the patients and physicians. In addition, the study depends on patient self-report of symptom duration, which is subject to bias. Finally, the study was conducted before the COVID–19 pandemic, and there is a possibility of an evolving pattern of chronic cough that might warrant future investigation. Despite the limitations, the strength of this study is that we have adopted a classification of chronic cough that would make it easier to compare our findings and pattern with the other regions of the world.

Conclusion

The leading causes of chronic cough in this study are different from the etiologies in western countries. The causes of cough from a sub-Saharan Africa perspective can be quite different from those reported from other parts of the world, and it would be erroneous to draw any definitive conclusions from other regions. Clinicians working in sub-Saharan Africa and TB endemic countries should consider these geographical variations in epidemiology and clinical patterns when evaluating a patient presenting with chronic cough.

Disclosure

The authors report no conflicts of interest in this work.

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