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Review

Randomized Controlled Trials on Chronic Obstructive Pulmonary Disease in Africa: A Systematic Review

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Abstract

Background: The rising burden of chronic obstructive pulmonary disease (COPD) in African countries is attributed to the growing and aging of the populations, lifestyles, and environmental changes. This systematic review aims to map the available evidence on COPD interventions in Africa.

Methods: We performed a systematic search in 6 databases (including local African databases) and registries with updates through January 2022. We included randomized controlled trials (RCTs) that included patients diagnosed with COPD and were conducted in Africa, studying outcomes on acute respiratory episodes and rates, physical and functional abilities, and adverse events. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The study quality was assessed using the Cochrane risk of bias tool. We primarily summarized the results in narrative form.

Results: Out of 1594 identified publications, we included 18 studies with a total of 1504 participants, conducted in Egypt, South Africa, and Tunisia. Eight studies investigated interventions for patients in stable phases treated in outpatient settings, and 10 included patients with acute COPD exacerbations treated in emergency or intensive care settings. The interventions mainly included ventilatory support and pharmacological and rehabilitative interventions. Reported treatment effects were heterogeneous, ranging from no beneficial effects to clinically relevant benefits.

Conclusions: The included studies were conducted in countries with high infrastructural development and half of them were set in intensive care units. Despite the paucity of RCTs on COPD management, research activities have been increasing over the last several years.

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Abbreviations:

6MWD=6-minute walk distance; **AECOPD**=acute exacerbation of COPD; **ALT**=alanine aminotransferase; **ARF**=acute respiratory failure; **AST**=aspartate aminotransferase; **ATS**=American Thoracic Society; **AUC**=area under curve; **AVAPS**=average volume-assured pressure support; **BiPAP**=biphasic positive airway pressure; **CENTRAL**=Cochrane Central Register of Controlled Trials; **CG**=control group; **CI**=confidence interval; **CINAHL®**=Cumulative Index to Nursing and Allied Health Literature; **COPD**=chronic obstructive pulmonary disease; **CRQ**=Chronic Respiratory Disease Questionnaire; **ERS**=European Respiratory Society; **FEV_1**=forced expiratory flow in 1 second; **FVC**=forced vital capacity; **GOLD**=Global initiative for chronic Obstructive Lung Disease; **ICU**=intensive care unit; **IG**=intervention group; **IQR**=interquartile range; **IV**=inverse variance; **IWI**=integrative weaning index; **MD**=mean difference; **MIP**=maximal inspiratory pressure; **MPT**=metronome-paced tachypnea; **NPPV**=non-invasive positive-pressure ventilation; **NR**=not reported; **PACTR**=Pan African Clinical Trials Registry; **PEF**=peak expiratory flow; **PEN**=package of essential noncommunicable diseases; **PI_{max}**=maximal inspiratory pressure; **PRISMA**=Preferred Reporting Items for Systematic Review and Meta-Analysis; **RCT**=randomized controlled trial; **WHO**=World Health Organization

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide.[1,2] Of the 3.23 million COPD-related deaths in 2019, 80% occurred in low- and middle-income countries.[3] With a mean prevalence of 11.7%,[4] COPD affects the lives of over 150 million people in Africa.[5] The reported prevalence of COPD greatly varies across the continent, ranging from 8.4% in Cape Verde to 24.8% in South Africa.[6] These variations are attributed to differing local determinants, risk factors, diagnostic criteria, and procedures.[7]

The varying and increasing burden of non-communicable diseases such as COPD in African countries is attributed to the aging of the populations and lifestyle changes.[8] Major risk factors for COPD are cigarette smoking[9] and air pollution.[10] Despite several measures to raise awareness and tobacco-control policies,[11,12] cigarette consumption is increasing[2,13-15] and COPD prevalence is high even among non-smoking young people.[7,14,16,17] Major contributing factors include the use of biomass fuels for cooking and heating in enclosed spaces, environmental pollution, exposure to dust in occupational settings, tuberculosis, childhood respiratory infections,[7,16,18] and exposure to ambient air pollution in the megacities.[19]

COPD is an umbrella term describing chronic lung diseases that cause limitations in pulmonary airflow, with common symptoms such as shortness of breath, wheezing, excessive sputum production, and a chronic cough.[20] These symptoms persist with only small day-to-day variations, usually starting in middle age and slowly worsening over time.[21] Due to the high individual health and financial burdens of acute exacerbations of COPD (AECOPDs), interventions in stable phases and effective tertiary prevention are crucial.[21,22] Currently, there are no national guidelines on the diagnosis and treatment of COPD in African countries except in South Africa.[7,8,23] Well-established international guidelines[24,25] are rarely applicable due to the low availability of diagnostic tools and affordable treatment, especially in rural areas.[14,17]

The primary aim of this systematic review is to map the best available evidence of interventions for secondary and tertiary prevention, diagnosis, and treatment to achieve symptom control and to prevent exacerbations in African patients.

Methods

We registered a protocol for a systematic review to summarize studies on chronic obstructive respiratory diseases conducted in Africa on PROSPERO (CRD42020145057), an international prospective register of systematic reviews. This systematic review summarizes a subsample of studies on patients diagnosed with COPD from studies found in the systematic search. All steps were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Figure S1 in the online supplement).[26]

Inclusion and Exclusion Criteria

We included full-text publications of randomized controlled trials (RCTs) with COPD patients from African countries in stable or acute phases of COPD that reported results on our predefined primary or secondary outcomes. Included RCTs focused on any preventive, diagnostic, or treatment interventions for patients with COPD. Studies on primary COPD prevention that included participants without COPD, as well as international multi-center studies with fewer than 50% of centers in African countries, were excluded. Table 1 details our inclusion criteria.

Systematic Search

We performed a systematic search in electronic databases, including MEDLINE®, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and specialized African databases such as African Journals Online and African Index Medicus, without time restrictions until January 2022. Furthermore, we checked publications from studies registered in the World Health Organization (WHO) Pan African Clinical Trials Registry (PACTR),

Table 1. Inclusion and Exclusion Criteria

Design/Setting	Randomized Controlled Trials
Population	Adult patients >18 years from African countries with a COPD diagnosis (ICD-10 code: J44) in stable or acute phases (treatment of exacerbation) from African countries in secondary and tertiary prevention, diagnosis and treatment of COPD
Intervention	All secondary or tertiary prevention interventions (e.g., rehabilitation) versus diagnostic interventions or curative treatment options interventions (e.g., pharmacological interventions, ventilation support)
Control	Another or no intervention
Outcome	Primary outcomes: • Acute exacerbations, acute respiratory episodes (reported as rate, number or frequency of acute exacerbation respiratory episodes or COPD-related hospitalizations or emergency care) • Exacerbation rate Secondary outcomes: • Results of pulmonary function test (reported as, e.g., FEV_1, FVC, FEV_1/FVC ratio, PEF) • Level of dyspnea (reported as validated measures related to dyspnea, e.g., modified Borg scale) (shortness of breath) • Functional capacity (reported as walking tests, e.g., 6MWD) • Quality of life (assessed using validated scales on health-related or general quality of life) • Duration of mechanical ventilation, length of ICU stay, hospital stay • Mortality (reported as number of all-cause or disease-specific deaths) • Adverse events (as defined by the trial authors) • Adverse events only for patients in acute COPD exacerbation: reported duration of treatment (e.g., lengths of mechanical ventilation, intensive-care-unit, stay in-hospital stay) Within the longest reported follow-up period
Publication	Full-text publication (no protocols, conference abstracts, or preliminary results) in English or German language

COPD=chronic obstructive pulmonary disease; ICD-10=*International Classification of Diseases*, revision 10; FEV_1=forced expiratory flow in 1 second; FVC=forced vital capacity; PEF= peak expiratory flow;

screened reference lists, and contacted corresponding authors of included studies as well as members of Guidelines International Network Africa. Search strings based on the National Library of Medicine's Medical Subject Headings included terms on chronic obstructive lung diseases, including COPD, Africa, all 54 African countries, and terms related to RCTs (see full search strategy in the online supplement).

Study Selection and Data Extraction

Two authors independently screened titles and abstracts of all references as well as potentially eligible full-text articles. Data extraction was done by one author and checked by another author. Disagreements were solved by discussion.

Risk of Bias Assessment

Two authors independently judged the risk of bias for each study using the Cochrane risk of bias tool in 7 specific categories: (1) sequence generation, (2) allocation concealment, (3) blinding of participants/personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. They rated the risk of bias as low, high, or unclear.[27] Discrepancies were resolved by discussion.

We defined the risk of bias due to incomplete outcome data as high if more than 10% of randomized participants dropped out from analysis. We judged the risk of bias due to selective outcome reporting as low if study protocols with predefined primary and secondary outcomes were available, and high if any results of pre-planned outcomes were missing. Other sources of bias were judged as high risk in cases in which there were missing descriptions of, or relevant deviations from, a pre-planned sample size calculation, no description of a primary endpoint, or relevant differences in main baseline characteristics between the intervention and control groups.

Data Synthesis

We initially subdivided interventions according to the included patients' conditions (stable versus acute), and then narratively summarized studies according to the type of intervention. We did not perform a pre-planned meta-analysis due to the substantial heterogeneity of interventions and outcomes. We produced forest plots with Cochrane RevMan software[28] to visualize treatment effects.

Results

We identified 1819 references, screened 1594 references, read 161 potentially eligible articles, and included 18 studies (reported in 19 articles) on African patients diagnosed with COPD. We excluded 51 articles reporting on asthma patients and 5 articles on patients with other chronic obstructive

lung diseases (Figure 1 and "the Included Studies" list in the online supplement). We grouped patients into 2 groups: stable patients in outpatient settings, and patients with AECOPDs treated in intensive care units (ICUs) or emergency care settings. The interventions mainly included ventilatory support and pharmacological and rehabilitative interventions.

Study Characteristics

Setting

All studies were conducted either in Egypt,[29-37] Tunisia,[38-44] or South Africa.[45,46] Ten studies were conducted in ICUs,[29-31,36,38,43,44] emergency units,[40] or specialized chest disease departments[37] of tertiary hospitals, and included patients in acute conditions. Eight studies were set in outpatient departments and included patients in stable condition.[32-35,39,41,42,45,46]

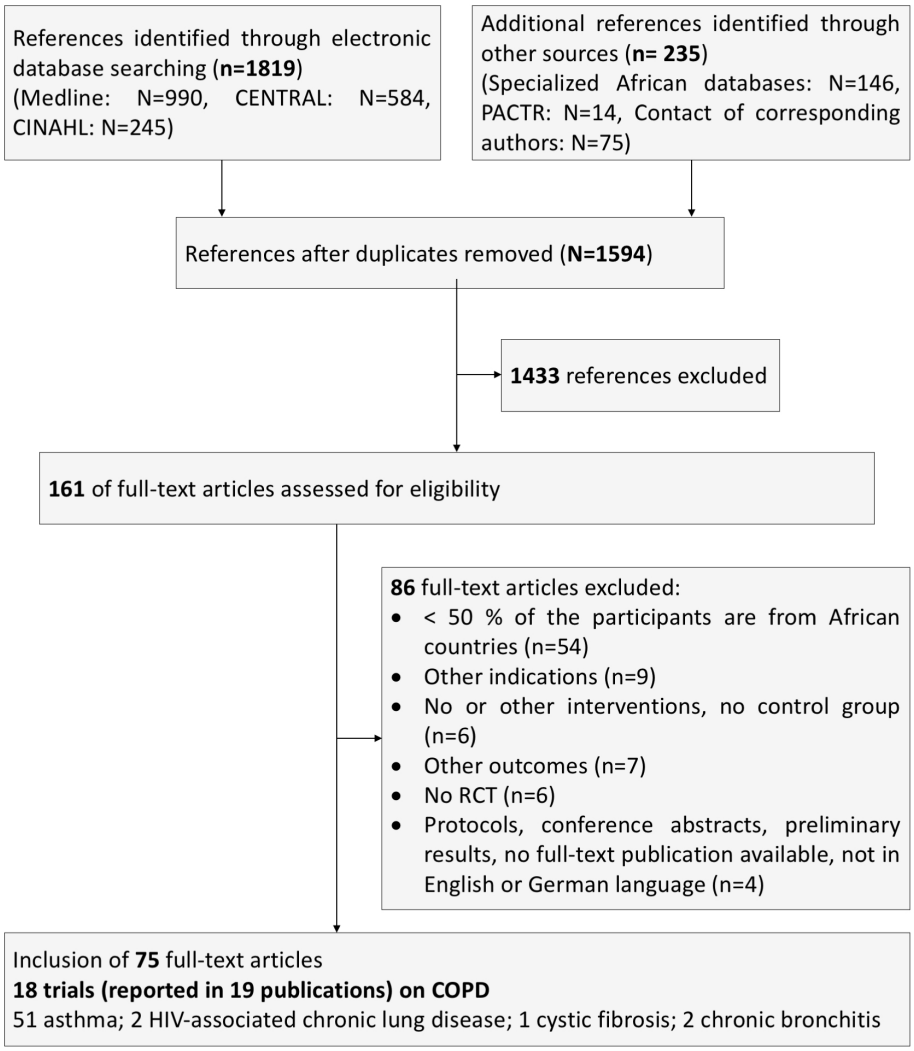
Population

A total of 17 RCTs involved 1480 participants, and one crossover RCT that randomized an additional 24 participants to 6 diagnostic procedural variants.[46] Eleven studies reported the inclusion of women (between 9% and 45%). The participants' mean age ranged from 47 to 69 years. Over 90% of the participants had a smoking history, 3 studies excluded recent smokers.[29,39,41] Most studies utilized the 2020 Global initiative for chronic Obstructive Lung Disease (GOLD) criteria[47] to diagnose COPD,[30,38,40,41] and classified airflow limitation as moderate,[35,46] moderate to severe,[32,34,36,37] or severe.[42] Other studies based the diagnosis on the criteria[48] of the American Thoracic Society,[35,36] pulmonary function testing,[39] or a clinical diagnosis and pulmonary function testing.[29,31,33,43-45]

Interventions and Results

Two studies reported results on our planned primary

Figure 1. Study Selection Flow Chart



Preferred reporting items for systematic reviews and meta-analyses flow chart describing the process of study selection.

CENTRAL=Cochrane Central Register of Controlled Trials; CINAHL®=Cumulative Index to Nursing and Allied Health Literature; PACTR=Pan African Clinical Trials Registry; RCT=randomized controlled trial

outcomes of acute respiratory episodes and exacerbation rates. Magdy et al[34] compared the effects of 2 nightly ventilation support regimens: spontaneous-timed average volume-assured pressure support (AVAPS), and biphasic positive airway pressure (BiPAP), in stable outpatients with hypercapnic respiratory failure over 6 months. The interventions showed no difference in treatment effects on the change in the number of exacerbations (mean difference [MD] -0.9; 95% confidence interval [CI] -0.9 to 0.7), hospitalizations (MD -0.1; 95% CI -0.6 to 0.4), or hospital days (MD -1.5; 95% CI -5 to 2) over a 6-month period with different support systems. However, patients in the AVAPS group showed slightly better exercise tolerance with a higher change in the 6-minute walk distance (6MWD) of 9.2m (95% CI -1 to 15) and quality of life (QoL) scores. Nouira et al[44] compared the effects of the antibacterial agents trimethoprim-sulfamethoxazole and ciprofloxacin in the treatment of severe exacerbations in ICUs, finding no difference in exacerbation-free intervals (14 days; 95 % CI -15 to 43).

Interventions for Patients in Stable Phases of COPD

Eight studies included stable patients[32,34,35,37,39,41,42,46] with moderate to severe COPD (if reported)[34,35,37,41,46] where interventions were prescribed and conducted in outpatient settings or at home (Table 2).

Rehabilitative Interventions

Six studies tested rehabilitative interventions including physical activity, balance training, home-based pulmonary rehabilitation, neuromuscular electrical stimulation, inspiratory muscle training, and nightly spontaneous-timed AVAPS ventilation,[32,35,39,41,42] and compared these interventions to usual care or other active component (Figure 2).

All these studies reported on exercise tolerance (all studies reported on 6MWD) showing beneficial, yet very heterogeneous treatment effects, with an MD between 5.3m (95% CI -14.0 to 24.6) and 73.2m (95% CI 54.0 to 92.2) (Figure 2). A clinically relevant difference in the 6MWD of over 25m, which was judged as clinically relevant for patients with COPD,[49] was gained in 3 studies.[32,35,41]

The highest exercise tolerance benefit was reported from a home-based pulmonary rehabilitation program that included educational lectures and muscle training, MD 73.2m (95 %CI 54.1 to 92.2). The study also described improved health-related QoL scores.[32] Two studies trialing neuromuscular electrical stimulation[39,41] in addition to standard pulmonary rehabilitation programs, showed improved balance and exercise parameters. Finally, a comparison of training inspiratory versus training expiratory muscles[35] showed improved pulmonary function parameters and 6MWD in both groups but showed little to no between group differences. Magdy et al tested 2 nightly breathing support regimens in stable COPD outpatients with chronic hypercapnic failure.[34] Both interventions had beneficial outcomes with AVAPS showing additional improvements in exercise tolerance and in several QoL domains.

Other Pharmacological and Diagnostic Interventions

Two studies compared pharmacological interventions with comparable results in pulmonary function and dyspnea parameters.[37,45] Calligaro et al tested ways to provoke dynamic hyperinflation showing the feasibility of metronome-paced tachypnea as an alternative to exercise testing.[46]

Treatment of Patients in Acute Exacerbation Phases of COPD

Ten studies studied patients with AECOPDs in the ICU[29-31,36,38,43,44] or in emergency departments[40] requiring mechanical ventilation or included outpatients.[33,45] Seven studies[29,33,38,40,43-45] investigated the efficacy of medication, and 3 studies compared different ventilation treatments.[30,31,36] The studies reported results on ventilation support outcomes,[30,31,38,43,44] length of ICU[31,36,38,43,44] or hospital stay,[30,31,40,43,44] mortality,[29,31,36,38,40,43,44] and adverse events including hyperglycemic episodes, ventilator-associated pneumonia, nausea, tremors, and headaches[29,36,38,40,43,44] (Table 2 and Table 3 and Figures S1 to S4 in the online supplement).

Pharmacological Interventions

Three studies[33,43,44] investigated the effects of antibiotics. Two of them stated the benefit of antibiotic therapy for patients with exacerbations Nouira et al[43] compared ofloxacin to placebo and stated reduced mortality, time on mechanical ventilation, and hospital stay. Additional treatment with quinolone or amoxicillin resulted in a shorter treatment time and a higher treatment success rate.[33] No differences were shown between distinct antibacterial agents (trimethoprim-sulfamethoxazole and ciprofloxacin).[44]

Only one of the other pharmacological studies[29,38,40] showed some benefit for patients with exacerbations. A small study including 80 patients with COPD exacerbations showed that intravenous supplementation of the trace elements selenium, manganese, and zinc during mechanical ventilation can reduce the length of ventilation by 8.4 days (95% CI 5.1 to 11.7) and slightly reduce mortality and adverse events in the ICU[29] (Table 2).

Table 2. Characteristics of Studies Involving Patients in Stable Phases of COPD

	Setting	Population		Intervention (IG) vs. Control (CG)	Results
Design	Place and Time	Inclusion Criteria	Baseline Characteristics	Description and Patient Number	Longest Follow-up Period (IG vs. CG); 95%-CI or *p*-value
Rehabilitative Interventions					
Acheche 2020 RCT 01/2016 to 09/2016	Tunisia NR Outpatients	Clinically stable COPD diagnosed by pulmonary function testing, recent fall, or fall in the past 5 years, 40-70 years	N=49 (100% males) Age (years): 63±5 Ex-smokers: 100%; Pack years: 48±6	IG (n=25): neuromuscular electrical stimulation+endurance & resistance training CG (n=24): endurance & resistance training	Berg balance scale: no differences 53.68±1.78 vs. 55.10±1.07 6MWD (m): better in IG: IG:542±136 vs. CG: 523±68
Ghanem 2010 RCT 07/2008 to 03/2009	Egypt Urban (44% vs. 14.3%) Home-based	Outpatients, recovery from AECOPDs, moderate to severe COPD (GOLD), local district residency, ability to complete the CRQ in 1 session, first language Arabic, age >40 years	N=39 (NR) Age (years): 56.77±10.76 Non-smokers: 5.13%	IG (n=25): home-based pulmonary rehabilitation program CG (n=14): usual care	Primary not defined Exemplary outcome: 6MWD (m): better in IG IG: 141.7±23.1 vs. CG: 68.6±32.1
Magdy 2020 RCT 02/2018 to 11/2019	Egypt Urban Outpatients	Stable COPD stage 3 or 4 (GOLD), chronic hypercapnic respiratory failure; age >18 years; sufficient social support for initiation of NPPV at home	N=40 (55% males) Age (years): 65.6±9.1 Ex-smokers+current smokers: 97.5%	IG (n=20): nightly spontaneous-timed AVAPS support CG (n=20): nightly bilevel positive airway pressure	No differences in Exacerbations: IG: n=1.5±0.3 vs. CG: n=1.5±0.2 Hospitalizations: IG: n=1.1±0.1 vs.CG: n=1.2±0.1 Hospital days: IG: n=3.4±2.1 vs. CG: n=3.5±2 6MWD (m): 260.5±32.2 vs. 255.2±30.2
Mehani 2017 RCT	Egypt NR Outpatients	Male outpatients, moderate COPD (ATS criteria), mild to moderate smokers, 50-60 years	N=50 (100% males) Age (years): 60±3.3 Smoking (years): 12.7±2.54 Pack years: 15	IG1 (n=25): inspiratory muscle training IG2 (n=25): expiratory muscle training	6MWD (m): higher increase (better) in IG 1 vs. 68.4±7.38 vs. 33.5±8.81
Mekki 2019 RCT 03/2015 to 08/2015	Tunisia Urban Outpatients	Outpatients with COPD (GOLD criteria), postbronchodilator $FEV_1/FVC < 0.7$	N=45 (NR) Age (years): 59.6±4.1 100% males	IG (n=25): neuromuscular electrical stimulation+pulmonary rehabilitation+endurance training CG (n=20): pulmonary rehabilitation program+endurance training	6MWD (m): better in IG IG: 116.1±27 vs. CG:73.4±11.7
Mkacher 2015 RCT	Tunisia Outpatients	Clinically stable severe COPD (GOLD), recent fall, or fall in the last 5 years	N=68 (100% males) Age (years): 60±4	IG (n=35): balance training+standard pulmonary rehabilitation CG (n=33): standard pulmonary rehabilitation	Balance outcomes: better in IG; e.g., Timed Up and Go Test: 10.9±1.1 vs.13.2±1.5 6MWD (m): no differences 511.2±19.3 vs. 505.6±31
Breathing Support Interventions					
Magdy 2020 RCT 02/2018 to 11/2019	Egypt Urban Outpatients	Stable COPD stage 3 or 4 (GOLD), chronic hypercapnic respiratory failure; age >18 years; sufficient social support for initiation of NPPV at home	N=40 (55% males) Age (years): 65.6±9.1 Ex-smokers+current smokers: 97.5%	IG (n=20): nightly spontaneous timed average volume-assured pressure support CG (n=20): nightly bilevel positive airway pressure	No differences in Exacerbations: IG: n=1.5±0.3 vs. CG: n=1.5±0.2 Hospitalizations: IG: n=1.1±0.1 vs.CG: n=1.2±0.1 Hospital days: IG: n=3.4±2.1 vs. CG: n=3.5±2 6MWD (m): 260.5±32.2 vs. 255.2±30.2
Pharmacological Interventions					
Bateman 2008 RCT	South Africa NR Outpatients	Outpatient, clinical diagnosis: moderate to severe COPD, airflow limitation, smoking history of >10 pack years, age ≥40 years	N=107 (71% males) Age (years): 62.4±8.1 Pack years: 42.8±19.2	IG (n=56): tiotropium CG (n=51): salmeterol+fluticasone	FEV_1 (L): no differences AUC over 12 hours 1.55±0.22 vs. 1.57±0.28
Mostafa 2021 RCT 11/2016 to 12/2018	Egypt - NR Chest Disease Department	Moderate to severe COPD (GOLD criteria), age ≥50 years, FEV_1/forced vital capacity <0.70, FEV_1 30% to 80% of predicted	N=60 (76% males) Age (years): 63.6±8,60 Ever smokers: 73% Smoking (years): 22.7±8.2	IG 1 (n=20): inhaled corticosteroid IG 2 (n=20): inhaled corticosteroid+budesonide IG 3 (n=20): long-acting beta2-agonist+long-acting muscarinic antagonist+tiotropium	FEV_1 as a% of predicted: No differences: IG 1: 77.61±21.34 vs. IG 2: 72.60±13.31 vs. IG 3: 73.83±15.97 (p=0.710)
Diagnostic Interventions					
Calligaro 2014 Crossover-RCT	South Africa NR Outpatients	Moderate COPD (stage ≤2, GOLD criteria), smoking history of ≥10 pack years, total lung capacity >80% of predicted, age ≥40 years	N=24 (67% males) age (years): 61±8 Pack years: 37.7±18.9	IG (n=24): salbutamol+ipratropium CG (n=24): placebo MPT (n=24): metronome-paced breathing Exercise testing (n=24): cycle ergometry	Dynamic hyperinflation: greater decline of total lung capacity (in mL) during MPT with higher breathing frequencies and I:E ratio of 1:1 versus 1:2 (p=0.032):

IG=intervention group; CG=control group; CI=confidence interval; RCT=randomized controlled trial; COPD=chronic obstructive pulmonary disease; 6MWD=6-minute walk distance; AECOPDs=acute exacerbations of COPD; GOLD=Global initiative for chronic Obstructive Lung Disease; CRQ=Chronic Respiratory Disease Questionnaire; NR=not reported; NPPV=non-invasive positive-pressure ventilation; AVAPS=average volume-assured pressure support; ATS=American Thoracic Society; FEV_1=forced expiratory flow in 1 second; FVC=forced vital capacity; AUC=area under curve; MPT=metronome-paced tachypnea

Breathing Ventilatory Support

Weaning was more often successful with proportionally assisted ventilation than with pressure support ventilation, resulting in shortened duration of mechanical ventilation and hospital stay (relative risk: 1.35; 95% CI 1.02 to 1.79).[31] Due to the importance of successfully weaning patients from mechanical ventilation, El-Daim et al[30] investigated different predictors of successful weaning and stated sensitive parameters. Another study[36] investigated the therapeutic utility of fiber-optic bronchoscopy to suction retained secretions in patients with noninvasive ventilation as an alternative to intubation and was able to reduce stay in the ICU by 30.5 hours (95% CI 14.4 to 46.6) without major complications.

Risk of Bias

Adequate information on sequence generation and allocation concealment was reported for 8 studies. Most studies analyzed more than 90% of randomized participants in their primary analyses. The risk of selective outcome reporting was checked in 7 studies with published protocols and judged as low. Other sources of bias were identified in 10 studies, either due to missing descriptions of primary endpoints or pre-planned sample sizes, relevant deviations from the pre-planned sample sizes, or missing descriptions of main baseline characteristics (Figure 3).

Discussion

This systematic review aims to map the available high-quality evidence of management options for patients with COPD conducted in Africa. The included studies investigated patients in stable phases of COPD treated in outpatient settings and those experiencing AECOPDs treated in emergency or intensive care settings. The interventions involved ventilatory support and pharmacological and rehabilitative interventions. At present, RCTs are sparse and heterogeneous, but the number of studies and the frequency of publications have grown over the last 2 decades. As of today, all RCTs were conducted in 3 countries with comparably high infrastructural development. No studies have been conducted in Central, East, or West Africa.

Early Detection, Diagnosis, and Initial Assessment and Diagnosis of COPD

Reliable diagnostic interventions are crucial to initiate adequate treatment, inform patients about their condition, monitor the disease, and prevent exacerbations.[50] Diagnostic studies with patient-related outcomes are generally rare.[51] We identified only 1 small crossover trial that tested a simple standardized alternative to usual exercise testing for early diagnosis and assessment.[46] The WHO recommends spirometrically measuring the peak expiratory flow rate for patients presenting typical COPD symptoms. Underutilization due to high costs and the need for trained staff is a major reason for the under- and over-diagnosis of COPD.[52] There is a need for implementation research on how to effectively implement high-quality diagnostic infrastructure, especially spirometry, for chronic lung diseases in Africa.[53,54]

Treatment of Patients in Stable Phases of COPD

The 6 included studies that tested rehabilitative interventions in the management of COPD[32,34,35,39,41,42] all showed some beneficial results as an additional component to usual care. Even though the studies were very heterogeneous in both intervention type as well as outcomes, these rehabilitative efforts are diverse and are showing promising results, offering a first glimpse into a future where COPD interventions that have been trialed in African countries can be used in continent-specific guidelines. Stating this positive trend, it has to be said that these 6 studies are currently only being conducted in Tunisia and Egypt, and 4 of them were conducted solely with male participants in urban areas,[35,39,41,42] leaving out vulnerable groups such as women and people living in rural areas, who have a higher exposure to indoor air pollution and the associated increased COPD risk.[55-57] This leaves a big leap to be taken to implement research structures that represent different African populations more distinctly.

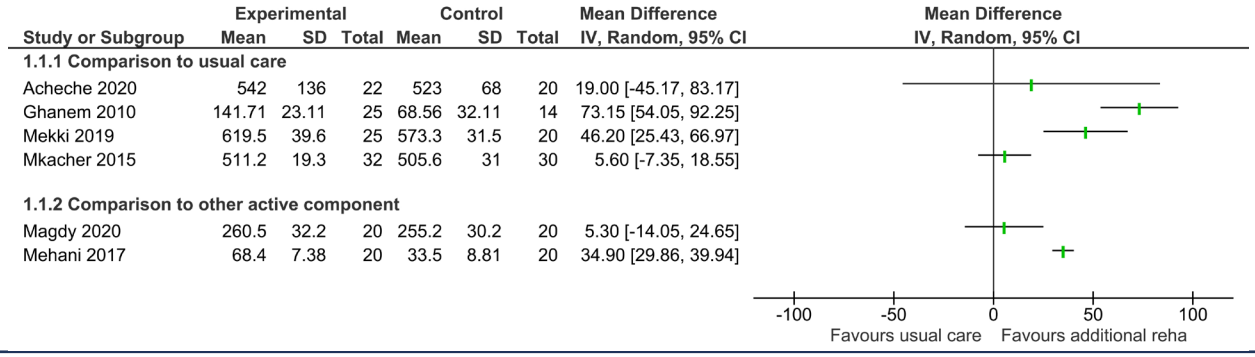
Treatment of Patients in Acute Exacerbation Phases of COPD

Most of the included studies stated at least one beneficial change in clinically relevant outcomes in the intervention group.[29,31-36,39,41,43] The existing evidence is mainly concentrated on different pharmacological interventions (Table 3). Since ICU treatment is cost- and infrastructure-intensive, there are considerable hurdles to its implementation and utilization in many low-resource settings. Self-management interventions with prescribed drugs for AECOPDs are proven to reduce the delay in seeking treatment, lower the risk of hospitalization, and improve QoL.[22,58]

Association Between Prevalence and Research

The geographic distribution of the randomized studies we included does not reflect the distribution of COPD prevalence with the highest rates in the southern and eastern African regions.[4] Only 2 of the included studies were conducted in South Africa, where it is known that prevalence rates are high, while most studies were conducted in Tunisia and Egypt, where prevalence rates are comparably low.[4,59] Despite the increase in COPD prevalence research in recent years, and

Figure 2. Summary of Treatment Effects of Rehabilitative Interventions for Stable Patients on 6-MinuteWalk Distance



Visualization of treatment effects without meta-analysis due to substantial heterogeneity of both interventions and outcomes.

SD=standard deviation; IV=inverse variance; CI=confidence interval

Table 3. Characteristics of Studies Involving Acute Patients in Acute Exacerbation Phases of COPD

Study Name	Setting	Population	Intervention (IG) vs. Control (CG)	Primary Outcome Results	Results
Design, Time	Place	Inclusion Criteria	Baseline Characteristics	Description and Patient Number	Longest Follow-up Period (IG vs. CG); 95%-CI or *p*-value
Pharmacological Studies, Interventions					
Abroug 2014 RCT 2008-2011	Tunisia, Urban ICU	ICU admission, AECOPD, hypercapnic ARF requiring ventilatory support, >10 pack years, known or strongly suspected COPD (GOLD criteria), age ≥40 years	N=217 88 % males Age (years): 70 (IQR 63-75) vs. 68 (IQR 63-75)	IG (n=111): daily prednisone CG (n=106): usual care.	ICU mortality: no differences shown 15.3% vs. 14.2% Length of ICU stay (median days with IQR): no differences shown Mechanical ventilation: 6 (4–12) vs. 6 (3.8–12) ICU: 9 (6–14) vs. 8 (6–14) Adverse events including hyperglycaemic episodes (49.5% vs. 33.0 %) were more prevalent in IG
Beltaief 2018 RCT 07/2013 to 12/2016	Tunisia Urban Emergency Department	COPD (GOLD criteria) with exacerbation, cough, sputum production or dyspnea and/ or history of exposure to risk factors	N=232 81.9 % males Age (years): 63.5±11 Smokers: 75.9 %	IG (n=115): terbutaline+ipratropium bromide+saline solution CG (n=117): terbutaline sulfate+saline solution	No difference shown in Admission to hospital: 65.2% vs. 59.8%, ICU: 32.2% vs. 25.6% Length of hospital stay (days): 6.5±2.1 vs. 5.5±2.4 7-day mortality: 1.3% vs. 11.9% No differences in adverse events including tachycardia, No differences in adverse events (20% vs. 24.8 %) including tachycardia, tremor, dizziness, headache, or dry mouth
El-Attar 2009 RCT 01/2008 to 09/2008	Egypt Urban ICU	Respiratory failure due to COPD exacerbation, required > 48 hrs of mechanical ventilation, ex-smokers, smoked ≥ 3 months, age:18-65 years	N=80 76.2 % males Age (years): 46.9±8.2 (24–60)	Usual care + IG (n=40): trace elements (sodium selenite, zinc, and manganese) CG (n=40): placebo	Length of stay on mechanical ventilation (days): benefit for IG 9.4±7.3 vs. 17.8±7.6 (p=0.013) ICU mortality: 2.9% vs. 5.6 % No differences in adverse events including ventilator-associated pneumonia (13.9% vs. 20.6 %)
El-Daim 2020 RCT 11/2017 to 08/2018	Egypt Urban ICU	Ventilated COPD (GOLD criteria) with acute respiratory failure diagnosis	N=30	IG (n=15): rapid shallow breathing index, respiratory rate, IWI CG (n=15): respiratory rate, vital capacity, Pimax	MIP and IWI were the most sensitive parameters Length of stay (days): Mechanical ventilation: Successful weaning: 8.1±1.45 vs. 9.0±3.0 Failed weaning: 15.4±4.2 vs. 17.7±3.2 In-hospital: Successful weaning: 11.8±1.93 vs. 13.2±3.0 Failed weaning: 32.6±1.8 vs. 29.0±7.9
Hassan 2015 RCT 04/2013 to 10/2014	Egypt Urban: 43 % Outpatients	Type 1 exacerbation of COPD (defined as increase in dyspnea, sputum purulence and increased sputum volume)	N=100 83 % males Age (years): 61.8±6.5 (39-77) Active smokers:	Bronchodilators & corticosteroids + IG (n=50): antibiotic treatment group (quinolone or amoxicillin). CG (n=50): placebo.	Primary not defined: Exemplary outcome Treatment success rate: 88 vs. 70 % (p=0.006) No differences in adverse events including nausea (10 vs. 8 %), vomiting, abdominal cramps, diarrhea, or skin rash

(continued on the next page)

			43 %; Ex-smokers: 38 %		
Nouira 2001 RCT 01/1996 to 12/1999	Tunisia Urban ICU	Inclusion: age ≥40 years, AECOPD (diagnosed based on clinical history, physical examination, and chest radiograph), ARF requiring mechanical ventilation within the first 24 hours of admission	N=93 90.3 % males Age (years): 66.4±8.3 Smoking (pack year): 54.52±7.56	IG (n=47): oral ofloxacin CG (n=46): placebo	Length of stay (days): benefit for IG Mechanical ventilation: IG 6.4±3.1 vs. 10.6±5.1 ICU: 9.4±5.2 vs. 14.5±6 In-hospital: 14.9±7.4 vs. 24.5±8.5 Mortality: benefit for IG ICU: 4.2 vs. 17.4 %, In-hospital: 4.2 vs. 21.7 % No differences in adverse events (11 vs. 9%) including diarrhea, rash or facial edema
Nouira 2010 RCT 07/2002 to 06/2005	Tunisia NR ICU	Inclusion: age ≥40 years diagnosis of severe AECOPD (history of COPD with clinical evidence of a purulent bronchitis+ARF requiring mechanical ventilation maximum 24 hours after ICU admission)	N=170 91.2 % males Age (years): 67.5±9.9 Pack years: 58.25±25.35	IG1 (n=85): trimethoprim-sulfamethoxazole IG2 (n=85): ciprofloxacin	Length of stay (days): no differences shown mechanical ventilation: 6±4.2 vs. 5.6±4.3 ICU: 10.2±7 vs. 9.4±4.8 In-hospital: 12.9±7.4 vs. 13.1±8.4 Mortality: no differences shown ICU: 8.2 vs. 8.2%, In-hospital: 8.2 vs. 9.4% Exacerbation-free intervals: 83±51 vs. 69±50 days 6MWD after 6 months: 260.5±32.2 vs. 255.2±30.2 m No differences in adverse events (5.9% vs. 7 %) including diarrhea, cutaneous reaction, or abnormal AST/ALT levels
Diagnostic Studies					
El-Daim 2020 RCT 11/2017 to 08/2018	Egypt Urban ICU	Ventilated COPD (GOLD criteria) with acute respiratory failure diagnosis	N=30	IG (n=15): rapid shallow breathing index, respiratory rate, IWI CG (n=15): respiratory rate, vital capacity, P_{Imax}	MIP and IWI were the most sensitive parameters Length of stay (days): mechanical ventilation: Successful weaning: 8.1±1.45 vs. 9.0±3.0 Failed weaning: 15.4±4.2 vs. 17.7±3.2 In-hospital: Successful weaning: 11.8±1.93 vs. 13.2±3.0 Failed weaning: 32.6±1.8 vs. 29.0±7.9
Ventilatory Support Studies					
Elganady 2014 RCT n.r.	Egypt Urban ICU	AECOPD, indicated for invasive mechanical ventilation	N=60 81.7% males age (years): 59.7±6.9	IG (n=30): Weaning with proportional assist ventilation CG (n=30): Weaning with pressure support ventilation	Success of weaning: 90% vs. 66.7% Length of stay (days): benefit for IG ICU: Success: 3.70±0.94 vs. 5.45±1.43 Failure: 8.33±0.58 vs. 10.0±1.05 In-hospital: Success: 4.81±1.24 vs. 6.65±1.57 Failure: 9.67±0.58 vs. 11.5±1.60 28-day mortality: no difference shown: 3.3% vs. 6.7 %
Mohamed 2018 RCT 06/2016 to 03/2017	Egypt NR ICU	Inclusion: moderate to severe COPD (ATS/ERS & GOLD), AECOPD due to respiratory tract infection, hypercapnic ARF, dyspnea at rest, bronchial hypersecretion, loose cough, inability to clear airways	N=40 65 % males age (years): 47.5±11.6 (27–68)	Non-invasive ventilation, usual care + IG (n=20): fiberoptic bronchoscopy for suctioning the retained secretions CG (n=20): no additional therapy	Length of ICU stay (hours): Better for IG: 23.35±17.53 vs. 53.85±32.28. No major complications/no differences ICU mortality: no differences 0% vs. 5 % No differences in adverse events including sinus tachycardia (5% vs. 0 %)

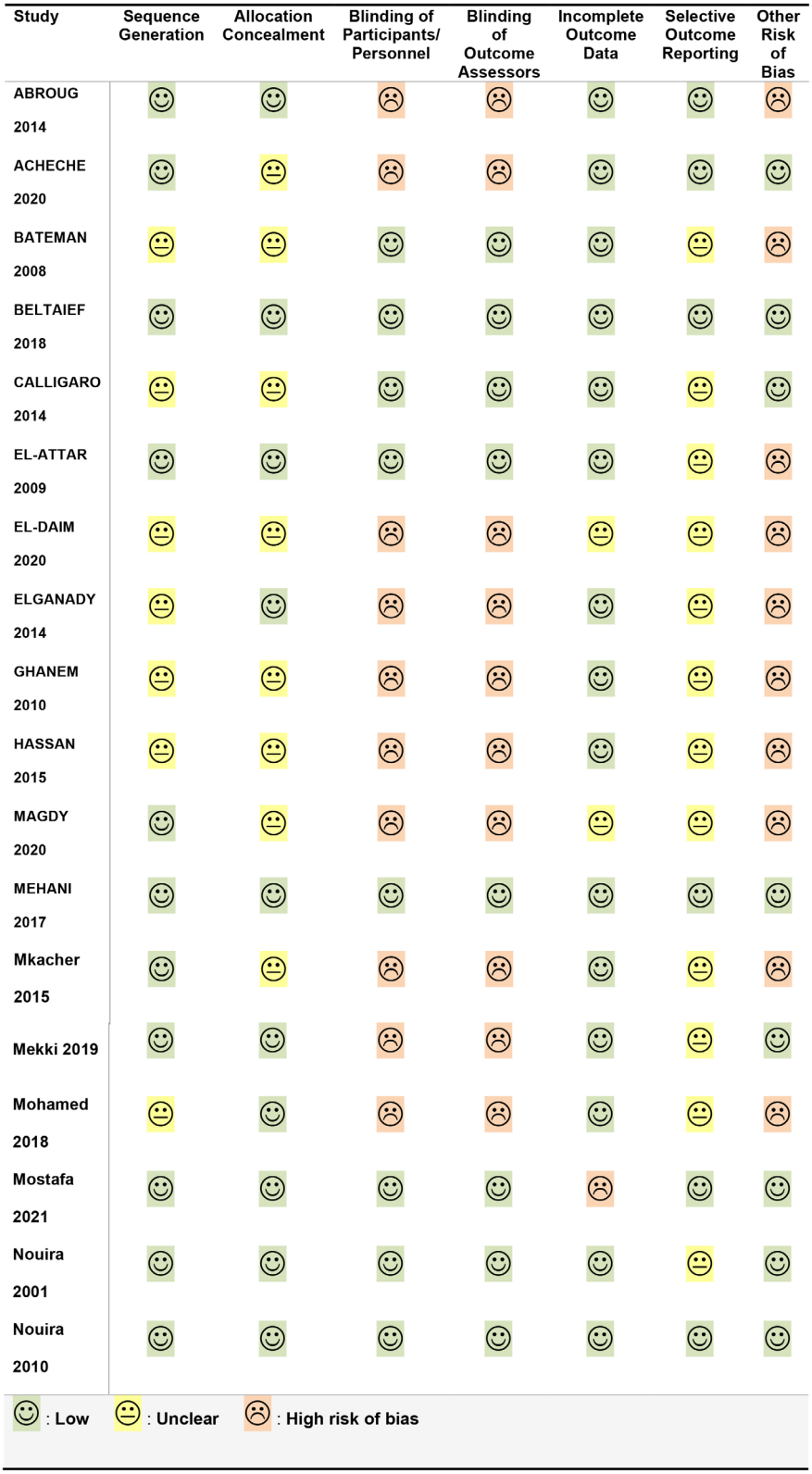
COPD=chronic obstructive pulmonary disease; IG=intervention group; CG=control group; CI=confidence interval; RCT=randomized controlled trial; ICU=intensive care unit; AECOPD=acute exacerbation of COPD; ARF=acute respiratory failure; GOLD=Global initiative for chronic Obstructive Lung Disease; IQR=interquartile range; IWI=integrative weaning index; PImax=maximal inspiratory pressure; MIP=maximal inspiratory pressure;; NR=not reported; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ATS=American Thoracic Society; ERS=European Respiratory Society

COPD being considered a relevant health problem, there is a lack of awareness of the ongoing burden of COPD that exists in many African countries.[4,6,60,61] Research activities are affected by infrastructural conditions including access to essential medications, ICU capacities, research-supportive environments, funding, or trained personnel than by the burden of disease.[62-64]

Infrastructural Aspects of COPD Research

Hospital care for COPD is often costly due to acute medical treatment in ICUs.[65] Egypt, South Africa, and Tunisia rank

Figure 3. Risk of Bias Assessment Based on the Cochrane Risk of Bias Tool 1



second, fourth, and sixth, respectively on the 2018 African Infrastructure Development Index.[66] About half the studies were set in ICUs, studying AECOPD interventions. On average, there are 3.1 ICU beds per 100,000 capita throughout the African continent,[64] whereas the European mean is 11.5. Egypt, South Africa, and Tunisia have an estimated 11.2, 5.7, and 4.3 ICU beds, respectively, per 100,000 capita. Other African countries have much lower ICU capacities (e.g., Nigeria: 0.2; Ethiopia: 0.5). Moreover, the availability of standard treatment options such as salbutamol in public health facilities varies greatly on the African continent, ranging from 81% to 100% availability in Tunisia, to below

5% in countries like Mali and Nigeria.[63] The improvement of medical infrastructure, including ICU capacities, access to medication, funding, and training of research personnel is required to support high-quality research.[62,67,68]

Low-Resource Contexts

Six out of 7 studies trialing pharmacological treatments[33,38,40,43-45] tested management options from the WHO essential medicines list[69] and from the WHO Package of Essential Noncommunicable (WHO PEN) Disease Interventions for Primary Health Care[50] that can be used in low-resource settings. There is a strong need to provide effective and affordable long-term primary care treatment to prolong the duration of stable clinical periods, manage and provide rehabilitation from AECOPDs, and prevent adverse events.[50]

Strengths and Limitations

The main aim of this review was to map, describe, and discuss the characteristics and results of all RCTs related to the prevention, diagnosis, and treatment of chronic obstructive respiratory diseases in African countries. We initiated, registered, and used all methods of a systematic review and visualized treatment effects. Due to this broad question, a scoping review with no synthesis of findings from individual studies might have been an alternative.[70] We, therefore, decided to visualize, but not synthesize, treatment effects.

This review is the first to summarize RCTs on the management of patients with clinically diagnosed COPD in African countries. We did not include studies on individual and community-based primary prevention of COPD, since these are generally not COPD-specific.[71-73] Nevertheless, these interventions clearly have a large impact on tackling the burden of COPD and should be considered when implementing care. However, the more specific focus on RCTs maps the current research landscape on high-quality quantitative research for COPD patients.

This review aims to emphasize research primarily initiated, planned, and conducted in African countries. We excluded several multinational studies with few African centers that provide training for researchers to improve skills in scientific methodology, study design, and study conduction. The small number of included studies, as well as the heterogeneity of interventions and outcomes, limits the current possibility of building specifically adapted COPD guidelines in African countries.

Conclusion

This systematic scoping review summarizes heterogeneous COPD interventions with a wide range of outcomes and results. The available evidence was compiled in 3 countries with comparably high infrastructural development, highlighting the urgent need for comprehensive technical infrastructure implementation and capacity building in African countries. Due to the increasing COPD burden, studies on early identification approaches and preventive primary care for high-risk populations are highly needed.

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Kathleen Denny corrected and proofread the manuscript.

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Declaration of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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