Identifying clinical phenotypes for hospitalized patients with chronic obstructive pulmonary disease acute exacerbation

Mayar Mamdoh[a], Mohamed A.H. El Nady[a], Hebatallah H. Assal[a], Gihan Saad[a], Amira I.A. Eldin[a], May S. Soliman[b], Amani A. Elkholy[b], Sara E.E. Haddad[b], Noha S. Soliman[b], Gehan Hamdy[c]

Departments of [a]Chest Diseases, [b]Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, [c]Department of Internal Medicine, Medical Research and Clinical Studies Insitute, National Research Centre, Cairo, Egypt

Correspondence to Gehan Hamdy (MD), Department of Internal Medicine, Medical Research and Clinical Studies Insitute, National Research Centre, Dokki, Cairo 12622, Egypt. Tel: +201003057788; e-mail: dr_gehan2010@hotmail.com

Received: 28 July 2024
Revised: 9 September 2024
Accepted: 16 September 2024
Published: 24 December 2024

Journal of The Arab Society for Medical Research 2024, 19:109–118

Background/aim
Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is common and has clinical consequences, such as a decline in quality of life, reduction in lung functions, hospitalization, and death. This study aims to assess the clinical phenotyping of hospitalized patients with AECOPD, and the correlation between the phenotype of Chronic Obstructive Pulmonary Disease (COPD) exacerbation and clinical outcome.

Patients and methods
This is a prospective cross-sectional study which included thirty- nine patients from the Chest diseases department, Faculty of Medicine, Cairo University. Each patient was subjected to full history taking, clinical examination, plain chest radiography, bacterial culture, viral polymerase chain reaction, modified medical research council dyspnea scale, and COPD assessment test.

Results
Most of our patients were males (92.3%), mean age was 65.33±9.73 years, 92% of the study populations were smokers and the mean BMI was 25.94±5.04 kg/m^2. Four phenotypes were identified as bacterial, viral, co-infection, and noninfectious. Regarding the clinical outcome, the viral phenotype had the highest ICU admission rate (58.3%), while the co-infection phenotype had the highest mean duration of hospital stay (18.13±16.8 days), and in-hospital mortality of 37.5%.

Conclusion
Clinically important differences in outcomes suggest that a phenotyping strategy based on etiologies can enhance AECOPD management.

Keywords:
Acute exacerbation of chronic obstructive pulmonary disease, modified medical research council dyspnea score, phenotypes

J Arab Soc Med Res 19:109–118

1687-4293

Introduction

Chronic obstructive pulmonary disease (COPD) is a significant global health problem, with its increasing incidence and prevalence (affecting approximately 10% of the adult population), and substantial social, economic, and personal impacts. An exacerbation of COPD (ECOPD) is defined as a worsening of symptoms, including; cough expectoration and dyspnea within a period fewer than 14 days. This may be accompanied by tachypnea and/or tachycardia and is often linked to heightened local and systemic inflammation triggered by infection, pollution, or other airway irritants [1].

Exacerbations are mainly triggered by respiratory viral infections, bacterial infections and environmental factors such as pollution. Symptoms usually last between 7 to 10 days, but some events may last longer [2].

Defining the phenotypes in COPD patients is important to provide prognostic information and to identify those who could respond to specific treatments [3].

ECOPD symptoms are heterogeneous, raising the need to identify distinct phenotypes, incorporating traits of the acute event and patients who experience recurrent events, to develop targeted therapies. These characterizations offer a comprehensive clinical picture, with the severity determining the course of pharmacological therapy. They may also suggest the need for changes in maintenance therapy to prevent future exacerbations [4].

Studies showed adverse effects of ambient concentrations of air pollutants (sulphur dioxide, nitrogen dioxides, ozone, and particulate matter) on hospitalization rates for COPD, especially during the winter season. Therefore, efforts to improve air quality can influence the frequency of exacerbations [5].

There are seven COPD phenotypes: the Eosinophil driven exacerbations phenotype accounts for around 30% of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), and patients with increased blood eosinophil count respond better to steroid therapy at stable state and exacerbation [6]. Bacteria-driven exacerbations are the major cause of infective AECOPD, accounting for 30–70% of all cases [7]. COPD exacerbations associated with purulent sputum are more likely to produce a positive bacterial culture which is an important diagnostic marker [8]. The current Global Initiative for Chronic Obstructive Lung Disease guidelines recommend antibiotic therapy if patients present with increased dyspnea, sputum volume, and sputum purulence or those who require ventilation. The use of antibiotics to treat AECOPD showed a strong beneficial effect on reducing treatment failure, mortality, and length of hospital stay among ICU patients with AECOPD [9].

The viral infections driven exacerbations phenotype where exacerbations are triggered by upper respiratory tract viral infections. This phenotype is more common in the winter months [8]. Since the introduction of influenza immunization for patients with chronic lung disease, the viral infections have become a less prominent cause of exacerbation [10]. COPD is associated with substantial changes in immune responses. Tobacco smoking hinders mucociliary clearance, and in COPD, bronchial epithelial cells increase the expression of the rhinovirus-binding receptor, intercellular adhesion molecule 1 (ICAM-1) [11]. Sore throat, cough, dyspnea, and chills are more common in viral than in bacterial infections. Viral exacerbations are associated with higher interleukin-6 levels, and lower levels of C-reactive protein [12]. Exacerbations triggered by respiratory viral infections are more severe and are associated with longer recovery times than those triggered by other factors [13].

Frequent exacerbators phenotype is a subgroup of COPD patients who experience reater than or equal to 2 exacerbations/year [14]. Frequent exacerbators have a worse quality of life, increased mortality, rapid decline in lung function, increased risk of future exacerbations, myocardial infarctions, and cerebrovascular events [15]. The frequent exacerbators are further divided into two types: those with emphysema predominant and those with chronic bronchitis predominant type. For the emphysema phenotype, the treatment is pharmacological in the form of long-acting bronchodilators, and in some cases with inhaled corticosteroids. The bronchitis-predominant exacerbator patients may be treated with bronchodilators and inhaled corticosteroids, also they respond to treatment with Roflumilast, long-term treatment with macrolides, mucolytics may be effective in reducing exacerbations as well [16].

Depression and anxiety phenotype; The estimated prevalence of anxiety disorders in COPD ranges up to 96%. Both depression and anxiety and their interaction, have been shown to impact the quality of life, adherence to therapy, medical burden, and functional capacity of the patients [17]. There is a significant association between hospital admissions due to COPD exacerbations and the presence of depressive and anxious symptoms according to the Hospital Anxiety and Depression Scale [18]. Cardiac dysfunction phenotype: COPD and heart failure frequently coexist and share common risk factors, with prevalence rates reaching up to 25% in various COPD populations. Heart failure is often undiagnosed in COPD, there is an undiagnosed left-sided heart failure among stable COPD patients in 17–20.5% [19]. Patients experiencing COPD exacerbations exhibit more severe symptoms compared with those with stable disease and have physiological stress that may affect their cardiac function [20]. Among the patients who survive hospitalization due to COPD exacerbation, the risk of cardiovascular events increases 9-fold within 30 days, with an elevated, although reduced, risk persisting up to 1 year after discharge [15]. Diagnosing heart failure in these patients can be challenging, as emphysema negatively impacts the quality of imaging from echocardiography or cardiac MRI. However, brain-type natriuretic peptide and its N-terminal prohormone fragment, released by the cardiac ventricles in response to wall stress, serve as reliable screening tests for heart failure [21].

Comorbidity phenotypes: AECOPD is often accompanied by comorbidities, which can be pulmonary disease or extrapulmonary disease. Comorbidities during hospital admission are associated with increased length of stay, mortality, and poor outcomes in patients with AECOPD [22].

This study aims to evaluate the clinical characteristics and phenotyping of hospitalized patients experiencing AECOPD. Additionally, it seeks to explore the relationship between different phenotypes of COPD exacerbation and their associated clinical outcomes.

Patients and methods

Patients

A prospective cross-sectional study conducted in the Chest Diseases Department, Faculty of Medicine, Cairo University in collaboration with the Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University and The Internal Medicine Department, National Research Centre during the period between March 2023 and March 2024. 39 patients (36 males and three females) with AECOPD who fulfilled the selection criteria and formed the study population. The inclusion criteria including the hospitalized patients with acute exacerbation of COPD, while the exclusion criteria including patients with insufficient cognitive capacity and overt left ventricular failure or acute myocardial infarction.

Ethical consideration

This study received approval from the Ethical Committee of Cairo University, Cairo, Egypt, under approval number: MS-263-2023. It was conducted following the ethical guidelines with the World Medical Association's Code of Ethics and the principles outlined in the Declaration of Helsinki. Written informed consent was collected from all patients before they were included in the study.

Determination of the sample size

An analytical cross-sectional study proposing primarily to assess the clinical phenotyping of hospitalized acute COPD exacerbations and its relation to the outcome. A previous study showed that among the hospitalized acute COPD exacerbations, the mortality rate at 6 months was 10.3% [23]. So, the sample size to study the results of the current study with a significant P less than 0.05 is calculated. Accordingly, at least 39 patients should be recruited to this study.

Methods

All patients were subjected to the following: Written informed consent including the whole study description, and the acceptance to use his/ her data for publication and presentation after masking their names. Full history taking including: age, history of smoking, residence, occupational and family history of chronic diseases with particular attention to special habits, comorbidities, treatment received before admission. Detailed clinical examination, routine laboratory investigations and chest radiographic assessment were done including Chest X-ray and high resolution computed tomography (HRCT) for diagnosis of COPD using (Siemens, Gemany) scanner. Also, each patient had undergone modified medical research council dyspnea score and COPD assessment test 'COPD assessment test (CAT) score' upon admission.

The smoking index was determined by multiplying the number of cigarettes consumed daily by the number of smoking years [24]. The participants' weight and height were measured, and their BMI was calculated by dividing their weight in kilograms (kg) by the square of their height in meters (m^2) [25].

Bacteriological and viral study

Sampling

Oropharyngeal (throat) and nasopharyngeal (NP) swabs were obtained and collected, transported and preserved in viral transport media. As well as sputum samples were collected and performing semi-quantitative bacterial cultures on standard media.

Throat swabbing

A dry, sterile nylon fiber-tipped swab applicator was used to swab both the tonsils and the posterior pharynx. The swab was then placed in a 15 ml centrifuge tube, labeled with the patient's unique ID, containing 2 ml of viral transport media, which consisted of a sterile solution containing bovine albumin fraction V, HEPES buffer, penicillin, and streptomycin in Hank's balanced salt solution, the applicator stick was subsequently cut off [26].

Nasopharyngeal swabs

Measurement: the distance between the ear lobule and the ala nasi was measured using the NP swab and then divided by two. The swab was marked at this point to ensure proper insertion depth. The flexible, sterile, nylon fiber-tipped swab applicator was gently inserted into the nostril, reaching the nasopharynx, where it was held in place for a few seconds before being slowly withdrawn with a rotating motion. The swab was then placed into the same centrifuge tube as the throat swab, labeled with the patient's unique ID, and the shaft was cut. The 15 ml tube containing the swabs was promptly transported to the hospital laboratory [27].

Bacterial cultures for spontaneously expectorated sputum samples

The procedure involved performing semi-quantitative bacterial cultures on standard media. All recovered organisms were identified through biochemical tests, and their antibiotic susceptibility was evaluated using established techniques [27].

Materials for Viral Transport Media (VTM) [27]

(a) Hanks' Balanced Salts – 500 ml.
(b) 2% Penicillin/Streptomycin – 10 ml.
(c) 2.5% HEPES Buffer – 12.5 ml (Hydroxyethyl) piperazine-1-ethanesulfonic acid + N-(2-Hydroxyethyl) piperazine-N'-(2-ethanesulfonic acid).
(d) Bovine Serum Albumin – 2.5 gm.

Preparation steps

Add 10 ml of 2% Penicillin/Streptomycin, 12.5 ml of 2.5% HEPES Buffer, and 2.5 gm of Bovine Serum Albumin to 500 ml of Hanks' solution. Mix thoroughly until all components are completely dissolved. Next, filter the mixture through a 0.2 μm filter. Dispense 3 ml of the filtered mixture into sterile Falcon tubes and adjust the final pH to 7.3±0.2 at 25°C. Finally, store the prepared tubes at −20°C until needed.

Sample processing: The swabs, placed in a 15 ml tube, were subjected to vigorous agitation for 10 s using a vortex mixer. This process effectively dislodged and released the cells from the swab tip into the surrounding medium for further analysis.

Detection of respiratory viruses in nasopharyngeal swabs

Respiratory viruses were detected in NP swabs using multiplex real-time reverse transcriptase PCR (Anyplex II RV16 Detection Kit, Seegene, Korea), following the manufacturer's instructions.

Nucleic acid isolation: Nucleic acid extraction was performed using the Bosphore Manual Spin Column Viral RNA Extraction Kit, following the manufacturer's instructions (Cat# ABXVR1, Anatolia, Turkey).

Reverse Transcription: Reverse transcription was carried out using a cDNA synthesis kit with the cDNA Synthesis Premix (SGRT801) from Seegene for manual setup.

Real-time PCR: Viral testing was conducted using real-time multiplex PCR with the Anyplex II RV16 Detection Kit (V1.1, Cat. No. RV7G01Y) from Seegene, operated on the CFX96 Real-time PCR System (Bio-Rad laboratories, Hercules, California, USA). The CFX96 Real-time PCR System (Bio-Rad) was programmed and the PCR reaction was prepared according to the manufacturer's instructions.

Interpretation of Results: The interpretation of results was based on:

(a) Tube A or B.
(b) The fluorophore used (FAM, HEX, Cal Red, Quasar).
(c) Melting temperature, as per the provided table.

Alternatively, results can be automatically interpreted using the Seegene Viewer (Seegene Inc., Canada) software after exporting the run data.

Statistical analysis

The statistical analysis was conducted using SPSS version 23.0 (SPSS, IBM, Chicago, Illinois, USA). Quantitative data were presented as mean±standard deviation and range for parametric distributions and were compared using the independent *t*-test. The normality of the data was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests [28]. A P value of less than 0.05 was deemed statistically significant group comparisons were done using the χ^2 test for categorical data and one-way ANOVA for continuous data [29].

Results

The present study included 39 patients, most of them were males n= 36 (92.3%) and three females n=3 (7.7%), with mean ages 65.33±9.73 years. 92.3% were smokers and a mean smoking index of 30.32 ±14.94. The mean BMI was 25.94±5.04 kg/m^2. 38.5% of the study population had comorbidities, which included diabetes mellitus, systemic hypertension, ischemic heart disease, obstructive sleep apnea, atrial fibrillation, and hepatitis C infection. The mean CAT score was 24.79±6.54 and the modified medical research council (mMRC) dyspnea scale 2.79±0.83. 10.3% of the study population were on Long term oxygen therapy (LTOT). Regarding the clinical outcome results obtained, 48.7% of the patients required ICU admission. 17% needed invasive mechanical ventilation (IMV) and 41% needed noninvasive mechanical ventilation (NIV). The mean duration of hospital stay was 11.87±9.98 days, in-hospital mortality was 12.8%, 6 month mortality was 10.3%, and re-admission within 6 months was 5.1% (Table 1).

The results reported in Table 2, showed that the bacterial phenotype comprised of 15 (38.46% of study population) patients, viral phenotype comprised of 12 (30.8% of study population) patients, co-infection phenotype comprised of eight (20.5% of study population) patients, noninfectious phenotype comprised of four (10.26%) patients of study. Regarding the bacterial phenotype, majority

Table 1 Demographics characteristics and hospital course for the study population

Demographics characteristics		
	Number (n=39) (Percentage (%))	
Male	36 (92.3)	
Female	3 (7.7)	
Comorbidities	15 (38.5	
Smoking habit	36 (92.3)	
LTOT	4 (10.3)	
	Mean	SD
Age (years)	65.33	9.73
BMI (kg/m^2)	25.94	5.04
CAT score	24.79	6.54
mMRC dyspnea scale	2.79	0.83
Smoking index	30.32	14.94
Hospital course		
	Number (n=39) (Percentage (%))	
ICU admission	19 (48.7)	
IMV	7 (17.9)	
NIV	16 (41)	
In-hospital mortality	5 (12.8)	
6 months mortality	4 (10.3)	
Re-admission in 6 months	2 (5.1)	
	Mean	SD
Duration of hospital stay [days]	11.87	9.98

BMI, body mass index; **IMV,** Invasive mechanical ventilation; **LTOT,** long term oxygen therapy; **mMRC,** modified medical research council dyspnea score; **NIV,** noninvasive mechanical ventilation.

of the patients were males (93.3%), mean age was 64.4 ±9.89 years, 40% had comorbidities, 93.3% were smokers with mean smoking index of 30±13.76, and the mean BMI was 30±13.76 kg/m^2. The mean CAT score was 26.8±5.53 and mMRC dyspnea scale 3.07 ±0.82. 20% of the patients needed LTOT. Regarding the viral phenotype, the majority of the patients were males n= 11 (91.7%) and 1 female patient, the mean age was 68.33±9.15 years, 16.7% had comorbidities, 91.7% were smokers with mean smoking index of 26.88±16.35, and the mean BMI was 26.55±4.48 kg/m^2. Mean CAT score was 20.83±6.83 and mMRC dyspnea scale 2.42±0.67. None of the patients of the viral phenotype needed LTOT. Regarding co-infection phenotype, patients were seven (87.5%) males and one (12.5%) female, the mean age was 64.5±11.82 years, 75% had comorbidities, 87.5% were smokers with mean smoking index of 31.25 ±16.23, and the mean BMI was 24.25±5.57 kg/m^2. The mean CAT score was 26.25±5.02 and mMRC dyspnea scale 3±0.69. None of the patients with the co-infection phenotype needed LTOT. Regarding the noninfectious phenotype, 100% of the patients were males, the mean age was 61.5±7.85 years, 25% had comorbidities, 100% were smokers with a mean smoking index of 40±14.14, and the mean BMI was 28.83±5.83 kg/m^2. Mean CAT score was 26.25±8.73 and mMRC dyspnea scale 2.5±1.29. 25% of the patients with the non-infectious phenotype needed LTOT.

As for the clinical outcome of bacterial phenotype, 46.7% of the patients required ICU admission, 13.3% needed IMV and 33.3% needed NIV, as shown in Table 2. The mean duration of hospital stay was 12.47 ±7.65 days, in-hospital mortality was 6.67%, 6 month mortality was 20%, and readmission within 6 months was 13.3%. Regarding clinical outcome of the viral phenotype, 58.3% of the patient's required ICU admission, 8.3% needed IMV and 58.3% needed NIV. With mean duration of hospital stay was 9.08 ±6.91 days; there was no in-hospital mortality or readmission within 6 months. 6-month mortality was 20%. The clinical outcome of the co-infection phenotype was 50% of the patient's required ICU admission, 50% of the ICU admitted cases required IMV and 50% needed NIV. The mean duration of hospital stay was 18.13±16.8 days, in-hospital mortality was 37.5%, and there was no 6-month mortality or readmission.

Regarding the clinical outcome of the noninfectious phenotype, 25% of the patients required ICU admission, none of them needed IMV or NIV, the mean duration of hospital stay was 5.5±0.58 days, in-hospital mortality was 25%, there was no 6-month mortality or readmission. According to the results reported in Table 3, the majority of the frequent exacerbator phenotype was males (95.2%) and the mean age was 66.10±7.95 years. 33.3% had comorbidities and 95.2%were smokers with a mean smoking index of 29.4±11.96. The mean BMI was 26.84±5.14 kg/m^2. Mean CAT score was 27.29±5.19 and mMRC dyspnea scale 3.1±0.7. 19% of the patients with frequent exacerbations needed LTOT. The clinical outcome of the frequent exacerbators was: 61.9% of the patients required ICU admission, 19% needed IMV and 47.9% needed NIV, with a mean duration of hospital stay of 13.62±11.24 days, in-hospital mortality was 14.3%, 6 month mortality was 19%, and readmission within 6 months was 9.5%.

Figure 1 exhibited the bacterial species isolated from our patients. 31.25% of the patients had Acenitobacter spp., equally 31.25% had *Streptococcus pneumoniae*. Methicellin resistant *Staphylococcus aureus* were recovered in 25% of the patients, while *Pseudomonas aeruginosa*, *Streptococcus pyogenes,* and *Staphylococcus aureus* were in 6.25% of the patients. 12.5% had Klebsiella species.

Table 2 Demographics characteristics and hospital course for the different phenotypes

Demographics characteristics					
	Bacterial (*n*=15) Number (%)	Viral (*n*=12) Number (%)	Co-infection (*n*=8) Number (%)	Non-infectious (*n*=4) Number (%)	*P* value#
Sex					
Male	14 (93.3)	11 (91.7)	7 (87.5)	4 (100)	0.891
Comorbidities	6 (40)	2 (16.7)	6 (75)	1 (25)	0.007*
Smoking habit	14 (93.3)	11 (91.7)	7 (87.5)	4 (100)	0.891
LTOT	3 (20)	0	0	1 (25)	0.189
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*P* value[@]
Age (years)	64.4±9.89	68.33±9.15	64.5±11.82	61.5±7.85	0.598
BMI (kg/m^2)	25.21±5.18	26.55±4.48	24.95±5.57	28.83±5.83	0.564
CAT score	26.8±5.53	20.83±6.83	26.25±5.02	26.25±8.73	0.088
mMRC dyspnea scale	3.07±0.82	2.42±0.67	3±0.69	2.5± 1.29	0.159
Smoking index	30±13.76	26.88±16.35	31.25±16.23	40±14.14	0.525
Hospital course					
	Number (%)	Number (%)	Number (%)	Number (%)	*P* value#
ICU admission	7 (46.7)	7 (58.3)	4 (50)	1 (25)	0.711
IMV	2 (13.3)	1 (8.3)	4 (50)	0	0.059
NIV	5 (33.3)	7 (58.3)	4 (50)	0	0.179
In-hospital mortality	1 (6.67)	0	3 (37.5)	1 (25)	0.067
6 months mortality	3 (20)	1 (8.3)	0	0	0.397
Re-admission in 6 months	2 (13.3)	0	0	0	0.338
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*P* value[@]
Duration of hospital stay (days)	12.47±7.65	9.08±6.91	18.13±16.8	5.5±0.58	0.068

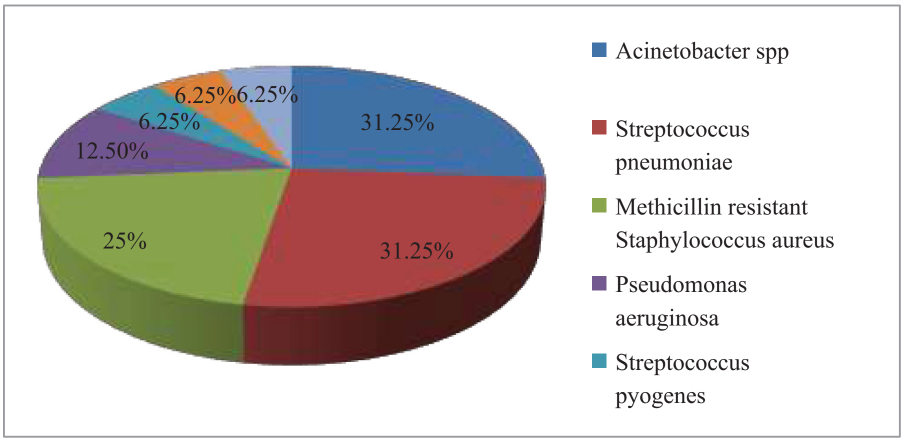
CAT score, COPD assessment test. the comparison between groups in the same raw was done using Chi-Square test; **IMV**, invasive mechanical ventilation; **NIV**, noninvasive mechanical ventilation. [#] or ANOVA test. [*]Significant difference at *P* valueless than 0.05, using Chi-square test.

Table 3 Demographics characteristics and Hospital course for the frequent exacerbator phenotype

Demographics characteristics	
	Number (*n*=21) (Percentage (%))
Male sex	20 (95.2)
Comorbidities	7 (33.3)
Smoking habit	20 (95.2)
LTOT	4 (19)
	Mean±SD
Age (Years)	66.10±7.95
BMI (kg/m^2)	26.84±5.14
CAT score	27.29±5.19
mMRC dyspnea scale	3.1±0.7
Smoking index	29.4±11.96
Hospital course	
	Number (*n*=21) Percentage (%)
ICU admission	13 (61.9)
IMV	4 (19)
NIV	10 (47.6)
In-hospital mortality	3 (14.3)
6 months mortality	4 (19)
Re-admission in 6 months	2 (9.5)
	Mean±SD
Duration of hospital stay [days]	13.62±11.24

BMI, body mass index; **IMV**, Invasive mechanical ventilation; **LTOT**, long term oxygen therapy; **mMRC**, modified medical research council dyspnea score; **NIV**, non-invasive mechanical ventilation.

Figure 1



Bacterial species isolated from the study population.

Figure 2 shows the viral species isolated from the patients, where 75% suffered from Respiratory syncytial virus infection. 20% had Influenza virus infection and 5% of the patients had Rhinovirus infection.

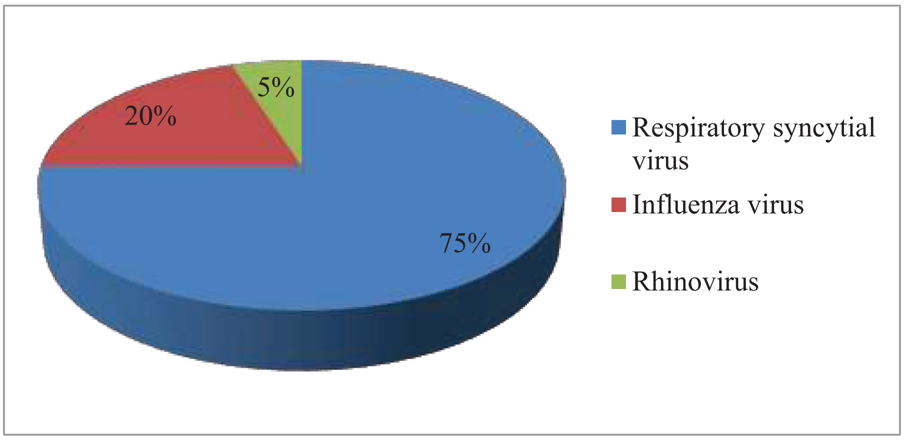
Discussion

Hospitalized AECOPD patients comprise a remarkably heterogeneous group of events, often featuring multiple distinct aetiological contributors. This heterogenecity is a barrier to progress in the field, since interventions targeting a specific aetiology or pathology may not show benefit if applied to an unselected group. Attention to exacerbation etiology and phenotyping AECOPD is a logical approach and may be the most suitable strategy to identify patients eligible for targeted interventions [23].

The aim of this study was clinical phenotyping of hospitalized patients with AECOPD, and correlation between phenotype of COPD exacerbation and clinical outcome. It was conducted in the Chest department, faculty of medicine, Cairo University; it included 39 patients with AECOPD.

The present study shows that most of our patients were males (92.3%), mean age was 65.33±9.73 years, 92% of the study population were smokers and the mean BMI was 25.94± 5.04 kg/m^2. This was in line with Donaldson *et al.* [30] who recorded mean age of 68.6±8.4 years, and Sethi *et al.* [31] with mean age 65.47± 4.6 years and 97% of the patients were males, also the results of Papi and co-authors [32] who reported the majority (87.5%) of the patients were males and the results of MacDonald *et al.* [23] with mean BMI 24.8±6.5 kg/m^2. AECOPD is often accompanied by comorbidities, which can be

Figure 2



Viral species isolated from of the study population.

pulmonary disease or extra-pulmonary, and are associated with increased length of hospital stay, mortality, and poor outcomes in patients with AECOPD [22]. In this study 38.5% of patients had comorbidities which included diabetes mellitus, systemic hypertension, ischemic heart disease, obstructive sleep apnea, atrial fibrillation, and hepatitis C infection Westerik *et al.* [33] showed that comorbidities are highly prevalent in COPD patients (88%), and the most common were hypertension, coronary heart disease, and osteoarthritis. Jeong *et al.* [34] stated that comorbidities prevalence in COPD exacerbation was (79.2%), the most common of which were hypertension, coexisting asthma, malignancy, followed by diabetes mellitus and ischemic heart disease.

In our study, the mean CAT score was 24.79±6.54 and mMRC dyspnea scale 2.79±0.83. These results agreed with Tu *et al.* [35] who found a mean CAT score 23.19 ±7.00 and mMRC dyspnea scale 2.73±0.99. Cigarette smoking is the most well-studied COPD risk factor, 92.3% of our patients were smokers, with mean smoking index of 30.32±14.94, and this percentage matches that of Jeong and co-authors [34].

In the present study Chest radiography (CXR) shadow was present in 25.6% of the patients, this agreed with Andreassen *et al.* [36] who found that CXR shadow was present in 29% of the patients. Williams *et al.* [37] reported that CXR shadow was present in 20.1% of the patients. In this study, 40% of patients with bacterial etiology had CXR shadow, and 50% of the patients with co-infection had CXR shadow, while none of the patients with viral infection alone or non-infectious phenotype had CXR shadow. Our study states that 43.6% of the patients used antibiotics prehospitalisation, this was similar to that reported by MacDonald and colleagues [23]. This study shows that 48.7% of the patients required ICU admission, 17% needed IMV and 41% needed NIV, however with MacDonald and colleagues [23] the percentages were 30.8, 3.4, and 12.3%, respectively. In our study patients with noninfectious aetiologies had the lowest rate of ICU admission 25%, in contrast with MacDonald *et al.* [23] who stated that patients with noninfectious etiologies had a higher rate of ICU admission (40%).

A significant portion of the economic burden of COPD is associated with exacerbations, in this study mean duration of hospital stay was 11.87±9.98 days, this matched with that of Piquet *et al.* [38], however, Ruparel and co-authors [39] reported a lower mean duration of hospital stay (8.7±8.3 days). According to our findings, patients with co-infection had the longest mean hospital stay of 18.13±16.8, and this agreed with MacDonald and colleagues [40].

In our study, in-hospital mortality was 12.8%, these results were matched with that of Echevarria *et al.* [41]. Higher in-hospital mortality was found by Spannella *et al.* [42] (18.2%), while Ringbaek *et al.* [43] reported lower results (5.4%). Co-infection phenotype had the highest rate of in-hospital mortality (37.5%) agreed with MacDonald *et al.* [40]. Mortality in the months following AECOPD is quite high, our 6 months mortality rate was 10.3%, this was close to that of Shin *et al.* [44] (13%), but Triantafyllidou *et al.* [45] found a higher 6-month mortality rate (27%). Acute exacerbation is one of the main reasons for hospital admission and re-admission of patients with COPD, with severe negative impacts both for the patient and the healthcare system according to Suissa *et al.* [46]. In this study, re-admission rate within 6 months was 5.1%, this rate is low compared with that of Roberts *et al.* [47] and Johannesdottir *et al.* [48] who reported readmission rate of 17.9 and 26.7%, respectively.

Our study exhibits that 38.46% of patients had bacterial etiology, these results agreed with that of MacDonald *et al.* [23] which showed that bacterial etiology was found in 40.4% of patients but Sethi *et al.* [31] stated that bacterial aetiology was found in 50% of the patients. Isolated bacteria included *Acinetobacter* spp. (31.25%), *Streptococcus pneumoniae* (31.25%), methicillin resistant *Staphylococcus aureus* (25%), *Pseudomonas aeruginosa* (12.5%), *Streptococcus pyogenes* (6.25), *Staphylococcus aureus* (6.25%), *Klebsiella* spp. (6.25%). Sethi *et al.* [31] reported that isolated bacteria included *Haemophilus influenzae* (25%), *Haemophilus parainfluenza* (33%), *Moraxella catarrhalis* (17%), and normal flora (25%). Dai *et al.* [49] reported that isolated bacteria included *Pseudomonas aeruginosa* (35%), *Acinetobacter baumannii* (29%), *Klebsiella* (24%), *Escherichia coli* (6%), and *Streptococcus pneumoniae* (6%). MacDonald *et al.* [23] reported that isolated bacteria included *Haemophilus influenzae* (36%), *Pseudomonas aeruginosa* (32%), *Streptococcus pneumoniae* (12%), *Moraxella catarrhalis* (12%), methicillin-resistant *Staphylococcus aureus* (4%), and methicillin-susceptible *Staphylococcus aureus* (4%). Patients of bacterial aetiology were more likely to be frequent exacerbators (52% of patients with frequent exacerbation) and had a rate of re-admission within

6 months 13.3%, this finding was in concordance with MacDonald *et al.* [23].

In this study, patients with viral infection were less commonly frequent exacerbators (23.8% of patients with frequent exacerbation) and there was no mortality at 6 months posthospital discharge. These findings were in concordance with MacDonald *et al.* [23] and Messous *et al.* [50]. Isolated viruses included: Respiratory Syncytial Virus (70%), Influenza (25%), and Rhinovirus (5%). MacDonald *et al.* [23] reported that isolated viruses included Rhinovirus (37%), Human Metapneumovirus (25%), Influenza (25%), Respiratory Syncytial Virus (8%), Parainfluenza Virus (5%), while Dai *et al.* [49] reported that isolated viruses included Influenza virus (36%), Enterovirus/Rhinovirus (19%), Coronavirus (16%), Bocavirus (10%), Metapneumovirus (9%), Parainfluenza Virus (5%), and Respiratory Syncytial Virus (5%).

In this study, patients with co-infection had the highest mean duration of hospital stay 18.13±16.8 days, and an in-hospital mortality rate of 37.5% compared with other phenotypes. These results agreed with MacDonald *et al.* [40] and Dai *et al.* [49].

Frequent exacerbators have worse quality of life, increased mortality, rapid decline in lung function and increased risk of future exacerbations, myocardial infarctions, and cerebrovascular events [15]. Our study shows that 53.85% of the patients had frequent exacerbations. Patients with frequent exacerbations had poor clinical outcomes with high rate of ICU admission (61.9%), usage of NIV (47.6%), and IMV (19%). They also had an increased rate of in-hospital mortality (14%), 6-month mortality (19%), and re-admission in 6 months (9.5%), duration of hospital stays (13.62 days), noting that all patients who did not survive within 6 months those who were re-admitted within 6 months were all frequent exacerbators. Zhang *et al.* [51] recorded that the majority (79.2%) of frequent exacerbators stayed in the hospital for less than 14 days.

Other important phenotypes may be identified in larger studies, e.g., patients with anxiety/depression. In this study, only three patients had high Hospital Anxiety and Depression Scale scores, small number in this phenotype precluded meaningful statistical analyses. Psychological distress is common in patients with COPD, and both depression/anxiety, and their interaction, significantly impact the quality of life, adherence to therapy, medical burden and functional capacity of patients [17].

Conclusion

From the previous results, we can conclude that bacterial infection is the main cause of acute exacerbation of COPD. Phenotyping of AECOPD may affect the clinical outcome and mortality.

Financial support and sponsorship

This research is a part from master degree titled 'Clinical phenotyping of hospitalized acute COPD exacerbations' and supported by the department of Chest Diseases, Faculty of Medicine, Cairo University.

Conflicts of interest

There are no conflicts of interest.

References

1 GOLD Report 2023 Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. Global initiative for chronic obstructive lung disease, Inc. https://goldcopd.org/2023-gold-report-2/

2 Liang L, Cai Y, Barratt B, Lyu B, Chan Q, Hansell A, *et al.* Associations between daily air quality and hospitalizations for acute exacerbation of chronic obstructive pulmonary disease in Beijing, 2013-17: an ecological analysis. Lancet Planet Health 2019; 3:e270–e279.

3 Barrecheguren M, Miravitlles M. COPD heterogeneity. Implications for management. Multidiscip Respir Med 2016; 11:14.

4 Bhatt S, Agusti A, Bafadhel M, Christenson S, Bon J, Donaldson G, *et al.* Phenotypes, etiotypes, and endotypes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2023; 28: 1026–1041.

5 Ko F, Tam W, Wong T, Chan D, Tung A, Lai C, Hui D. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. Thorax 2007; 62:780–785.

6 Walters J, Tan D, White C, Gibson P, Wood-Baker R., Walters E. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database System Rev 2014; 9:CD001288.

7 Moghoofei M, Jamalkandi S, Moein M, Salimian J, Ahmadi A. Bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Infection 2020; 48:19–35.

8 Wedzicha J, Seemungal T. COPD exacerbations: defining their cause and prevention. Lancet 2007; 370:786–96.

9 Vollenweider D, Frei A, Steurer-Stey C, Garcia-Aymerich J, Puhan M. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database System Rev 2018; 10:CD010257.

10 Falsey A, Formica M, Hennessey P. Detection of respiratory syncytial virus in adults with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173:639–643.

11 Leopold P, O'Mahony M, Lian X, Harvey B, Crystal R. Smoking is associated with shortened airway cilia. PloS one 2009; 4:e8157.

12 Dimopoulos G, Lerikou M, Tsiodras S, Chranioti A, Perros E, Anagnostopoulou U, *et al.* Viral epidemiology of acute exacerbations of chronic obstructive pulmonary disease. Pulm pharmacol therapeutics 2012; 25:12–18.

13 Buss L, Hurst J. Viruses and exacerbations of chronic obstructive pulmonary disease: unmet clinical need. J Virus Eradication 2015; 1:208–210.

14 Wedzicha J, Brill S, Allinson J, Donaldson G. Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. BMC med 2013; 11:1–10.

15 Kunisaki K, Dransfield M, Anderson J, Brook R, Calverley P, Celli B, *et al.* Exacerbations of chronic obstructive pulmonary disease and cardiac events. A *post hoc* cohort analysis from the SUMMIT randomized clinical trial. Am J Respir Crit Care Med 2018; 198:51–57.

16 Albert R, Connett J, Bailey W, Casaburi R, Cooper J, Criner G, *et al.* Azithromycin for prevention of exacerbations of COPD. N Eng J Med 2011; 365:689–698.

17 Cully J, Graham D, Stanley M, Ferguson C, Sharafkhaneh A, Souchekn J, Kunik M. Quality of life in patients with chronic obstructive pulmonary

disease and comorbid anxiety or depression. Psychosomatics 2006; 47:312–319.

18 Dahlén I, Janson C. Anxiety and depression are related to the outcome of emergency treatment in patients with obstructive pulmonary disease. Chest 2002; 122:1633–1637.

19 Macchia A, Rodriguez, Moncalvo J, Kleinert M, Comignani P, Gimeno G, Arakaki D, Laffaye N, *et al.* Unrecognised ventricular dysfunction in COPD. Eur Respir J 2012; 39:51–58.

20 Tung R, Camargo C, Krauser D, Anwaruddin S, Baggish A, Chen A, Januzzi J. Amino-terminal pro-brain natriuretic peptide for the diagnosis of acute heart failure in patients with previous obstructive airway disease. Ann Emerg Med 2006; 48:66–74.

21 Januzzi JrJL, Camargo CA, Anwaruddin S, Baggish A, Chen A, Krauser D, *et al.* The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency department [PRIDE] study. Am J Cardiol 2005; 95:948–954.

22 Almagro P, Cabrera F, Diez J, Boixeda R, Ortiz M, Murio C, *et al.* Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD. Chest 2012; 142:1126–1133.

23 MacDonald M, Osadnik C, Bulfin L, Leahy E, Leong P, Shafuddin E, *et al.* MULTI-PHACET: multidimensional clinical phenotyping of hospitalised acute COPD exacerbations. ERJ Open Res 2021; 7:00198–2021.

24 Zhou J-S, Li Z-Y, Xu X-C, Zhao Y, Wang Y, Chen H-P, *et al.* Cigarette smoke-initiated autoimmunity facilitates sensitisation to el astin-induced COPD-like pathologies in mice. Eur Respir J, 56: 2000404.

25 The Surveillance of Risk Factors Report Series (SuRF). World Health Organization. 2005. p. 22. Archived (PDF) from the original on 2022-10-09

26 American Society for microbiology. CLINICAL MICROBIOLOGY REVIEWS, Apr. 1990, p. 120–131 0893-8512/90/020120-12&02.00/0 Copyright C) 1990, American Society for Microbiology Vol. 3 No 2

27 Carroll K, Pfaller M, Karlowsky J, Landry M, McAdam A, Patel R, Pritt B. Manual of Clinical Microbiology. 13th Edition. USA: ASM Books; 2023.

28 Chan YH. Biostatistics 102: Quantitative Data Parametric & Non-parametric Tests. Singapore Med J 2003; 44:391–396.

29 Chan YH. Biostatistics 103: Qualitative Data –Tests of Independence. Singapore Med J 2003; 44:498–503.

30 Donaldson G, Law M, Kowlessar B, Singh R, Brill S, Allinson J, Wedzicha J. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015; 192:943–950.

31 Sethi S, Muscarella K, Evans N, Klingman K, Grant B, Murphy T. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. Chest 2001; 118:1557–1565.

32 Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 2006; 173: 1114–1121.

33 Westerik J, Metting E, van Boven J, Tiersma W, Kocks J, Schermer T. Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. Respir Res 2017; 18:31.

34 Jeong S, Lee H, Carriere K, Shin S, Moon S, Jeong B-H, *et al.* Comorbidity as a contributor to frequent severe acute exacerbation in COPD patients. Int J Chron Obstruct Pulmon Dis 2016; 11:1857–1865.

35 Tu YH, Zhang Y, Fei GH. Utility of the CAT in the therapy assessment of COPD exacerbations in China. BMC Pulm Med 2014; 14:42.

36 Andreassen S, Liaaen E, Stenfors N, Henriksen A. Impact of pneumonia on hospitalizations due to acute exacerbations of COPD. Clin Respir J 2014; 8:93–99.

37 Williams N, Ostridge K, Devaster J-M., Kim V, Coombs N, Bourne S, *et al.* Impact of radiologically stratified exacerbations: insights into pneumonia aetiology in COPD. Respir Res 2018; 19:143.

38 Piquet J, Chavaillon J-M., David P, Martin F, Blanchon F, Roche N, *et al.* High-risk patients following hospitalisation for an acute exacerbation of COPD. Eur Respir J 2013; 42:946–955.

39 Ruparel M, López-Campos J, Castro-Acosta A, Hartl S, Pozo-Rodriguez F, Roberts C, *et al.* Understanding variation in length of hospital stay for COPD exacerbation: European COPD audit. ERJ Open Res 2016; 2:00034–2015.

40 MacDonald M, Korman T, King P, Hamza K, Bardin P. Exacerbation phenotyping in chronic obstructive pulmonary disease. Respirol 2013; 18:1280–1281.

41 Echevarria C, Steer J, Wason J, Bourke S. Oxygen therapy and inpatient mortality in COPD exacerbation. Emerg Med J 2021; 38:170–177.

42 Spannella F, Giulietti F, Cocci G, Landi L, Lombardi FE, Borioni E, *et al.* Acute exacerbation of chronic obstructive pulmonary disease in oldest adults: Predictors of in-hospital mortality and need for post-acute care. J Am Med Dir Assoc 2019; 20:893–898.

43 Ringbaek T, Terkelsen J, Lange P. Outcomes of acute exacerbations in COPD in relation to pre-hospital oxygen therapy. Eur Clin Respir J 2015; 2:27283.

44 Shin B, Kim S, Yong S, Lee W-Y., Park S, Lee S, *et al.* Early readmission and mortality in acute exacerbation of chronic obstructive pulmonary disease with community-acquired pneumonia. Chron Respir Dis 2019; 16:1479972318809480.

45 Triantafyllidou C, Effraimidis P, Vougas K, Agholme J, Schimanke M, Cederquist K. The role of early warning scoring systems NEWS and MEWS in the acute exacerbation of COPD. Clin Med Insights Circ Respir Pulm Med 2023; 17:117954842311523.

46 Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012; 67:957–63.

47 Roberts M, Clerisme-Beaty E, Kozma C, Paris A, Slaton T, Mapel D. A retrospective analysis to identify predictors of COPD-related rehospitalization. BMC pulmonary med 2016; 16:1–13.

48 Johannesdottir S, Christiansen C, Johansen M, Olsen M, Xu X, Parker J, *et al.* Hospitalization with acute exacerbation of chronic obstructive pulmonary disease and associated health resource utilization: a population-based Danish cohort study. J med econ 2013; 16:897–906.

49 Dai M-Y, Qiao J-P, Xu Y-H, Fei G-H. Respiratory infectious phenotypes in acute exacerbation of COPD: an aid to length of stay and COPD assessment test. Int j chronic obstruct pulm dis 2015; 10:2257–2263.

50 Messous S, Elargoubi A, Pillet S, Rajoharison A, Hoffmann J, Trabelsi I, *et al.* Bacterial and viral infection in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease: implication for antimicrobial management and clinical outcome. COPD: J Chronic Obstruct Pulmon Dis 18:53–61.

51 Zhang Y, Zheng S-P., Hou Y-F., Jie X-Y., Wang D, Da H-J, *et al.* A predictive model for frequent exacerbator phenotype of acute exacerbations of chronic obstructive pulmonary disease. J Thorac Dis 2023; 15:6502–6514.