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PHENOTYPES OF COPD PATIENTS WITH RESPIRATORY FAILURE AND THEIR RESULTS IN ICU SETUP: A CROSS-SECTIONAL OBSERVATIONAL STUDY.

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ABSTRACT

Background

Airflow restriction and persistent respiratory symptoms are characteristic features of Chronic Obstructive Pulmonary Disease (COPD). The intricacy of the disease is shown by the phenotypic diversity of individuals with COPD who are experiencing respiratory failure in the Intensive Care Unit (ICU). The study aimed to investigate the phenotypes of COPD patients with respiratory failure and analyze their outcomes over one year.

Methods

A study was carried out enrolling 80 COPD patients admitted to the ICU due to respiratory failure. Patients aged 40 years and above with confirmed COPD diagnosis were included. Data on demographics, COPD severity, exacerbation history, comorbidities, and ICU admission details were collected. Pulmonary function tests, arterial blood gas analysis, and information on respiratory support modalities were documented. Phenotypic characterization was performed using established criteria, and outcome measures included mortality rates and ICU stay duration.

Results

The study population was 65% male and averaged 65 years old. Patients were 40% emphysema-dominant, 30% chronic bronchitis-dominant, and 30% mixed. Emphysema-dominant patients had worse airflow limitation. Hypertension, coronary heart disease, and diabetes were frequent. Hypoxemia and hypercapnia were seen in pulmonary function tests. Mechanical breathing was needed by 70% of patients, and ICU mortality was 25%. In long-term survival studies, exacerbation frequency, and comorbidities significantly predicted a 40% one-year mortality rate.

Conclusion

The study highlights the diverse phenotypes of COPD patients with respiratory failure and their associated outcomes. Personalized management strategies tailored to specific phenotypes and addressing comorbidities are crucial for improving patient outcomes. Further research is needed to refine treatment approaches and enhance long-term survival in this population.

Recommendations

Clinicians should consider phenotypic variations and comorbidities when managing COPD patients with respiratory failure. Interventions targeting exacerbation prevention and comorbidity management may improve outcomes. Future studies should focus on elucidating the underlying mechanisms driving phenotypic differences and developing targeted therapies.

Keywords: *Chronic Obstructive Pulmonary Disease, Respiratory Failure, Phenotypes, Outcomes.*
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INTRODUCTION

The complicated and diverse disorder known as chronic obstructive pulmonary disease (COPD) is categorized by persistent respiratory symptoms and airflow restriction brought on by irregularities of the airways and/or alveoli. These abnormalities are usually the result of extensive exposure to noxious particles or gases. The phenotypes of COPD patients with respiratory failure are diverse, reflecting the disease's multifaceted nature. This introduction highlights key aspects of these phenotypes, with an emphasis on respiratory failure.

When exposed to high-concentration unregulated oxygen improperly, patients with COPD are susceptible to experiencing acute hypercapnic respiratory failure (AHRF), underscoring the need for a careful balance in oxygen therapy for these patients [1]. Additionally, certain risk factors predispose COPD patients to type II respiratory failure during acute exacerbations, guiding clinical treatment strategies to minimize COPD's impact. The management of ventilatory failure in COPD focuses on both acute exacerbations and chronic stable stages, incorporating non-invasive and invasive mechanical ventilation to support patients [2].

Comorbidities play a significant role in COPD phenotypes, with cardiovascular disorders, metabolic diseases, and skeletal muscle weakness often

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accompanying respiratory failure, characterized by an accelerated decline in lung function. Such comorbidities underscore the systemic nature of COPD and its impact on patient health and treatment outcomes [3].

Furthermore, the phenotypic expression of COPD in patients with respiratory failure can be influenced by chronic airflow obstruction and systemic responses to factors such as tobacco smoking, leading to severe disease progression. Predictors of prognosis include spirometric abnormalities, body mass index, dyspnea, and exercise impairment, with respiratory insufficiency, cardiovascular comorbidities, and lung cancer being common causes of mortality [4]. Understanding the natural history and phenotypic variations of COPD, particularly in the context of respiratory failure, may facilitate improved patient outcomes through targeted therapeutic approaches and management strategies [5].

The study aimed to investigate the phenotypes of COPD patients who experienced respiratory failure during their stay in the ICU, along with analyzing their outcomes over one year.

METHODOLOGY

Study design

A prospective cross-sectional observational study.

Study setting

The study was carried out at Chest Hospital, Chhapra, Bihar, India, spanning a duration of one year starting from November 2022 to October 2023.

Participants

Participants included 80 individuals who were diagnosed with COPD and admitted to the ICU due to respiratory failure.

Inclusion criteria

- Patients aged 40 years and above.
- Confirmed diagnosis of COPD.
- Admission to the ICU due to respiratory failure is defined as:
    - PaO2/FiO2 ration < 300 mmHg.
    - Respiratory distress necessitates invasive or non-invasive ventilation.

Exclusion criteria

- Patients with primary lung disease other than COPD.
- Patients with severe co-morbidities impacting respiratory status (e.g., end-stage heart failure).
- Patients with a history of lung resection or lung transplantation.

Sample size

To calculate the sample size for this study, the following formula was used for estimating a proportion of a population:

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Where:

- n = sample size
- Z = Z-score corresponding to the desired level of confidence
- p = estimated proportion in the population
- E = margin of error

Bias

Selection bias was mitigated by enrolling consecutively admitted eligible patients into the study. Additionally, random allocation of patients to different treatment modalities, where applicable, was employed to reduce allocation bias. To minimize observer bias, outcome assessors were blinded to patient phenotypes and other clinical characteristics.

Variables

Demographic variables, including age, gender, and smoking history, were recorded as part of the study data. Clinical variables such as COPD severity, duration of COPD diagnosis, exacerbation history, and comorbidities were also documented. Admission details, encompassing the reason for ICU admission, APACHE II score, and length of ICU stay, were carefully noted.

Data collection

Data collection involved gathering demographic characteristics such as age, gender, and smoking history, along with clinical data including COPD severity, duration of COPD diagnosis, and exacerbation history. Details of ICU admission, including the reason for admission and Acute Physiology and Chronic Health Evaluation (APACHE) II scores, were recorded. Additionally, pulmonary function tests, including FEV1, FVC, and FEV1/FVC ratio, were conducted where feasible, and arterial blood gas analysis was performed to assess parameters such as PaO2, PaCO2, and pH. Information regarding respiratory support modalities administered in the ICU, such as mechanical ventilation, non-invasive ventilation, and oxygen therapy, was also documented meticulously.

Phenotyping

Phenotyping of COPD patients was carried out using established criteria, including guidelines provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), to categorize patients into distinct phenotypes based on clinical features, exacerbation history, and lung function. Advanced techniques such as cluster analysis were employed to identify potential novel phenotypes within the study population.

Outcome measures

Outcome measures focused on primary outcomes such as mortality rates among different COPD phenotypes during ICU stay and within the one-year follow-up period.

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Secondary outcomes included the duration of ICU stay, hospitalization duration, need for mechanical ventilation, the incidence of acute exacerbations post-ICU discharge, and long-term survival rates.

Statistical analysis

Statistical analysis involved appropriate tests to compare baseline characteristics and outcomes among different COPD phenotypes using SPSS version 21.0. Multivariate analysis was conducted to identify independent predictors of mortality and other outcomes.

Ethical considerations

The study protocol was approved by the Chest Hospital Ethics Committee and written informed consent was received from all the participants.

RESULT

The study initially enrolled a total of 89 individuals diagnosed with COPD who were admitted to the ICU due to respiratory failure. After regressive selection criteria, all potentially eligible participants were recruited into the study. Nine participants dropped out of the study. The common factors contributing to dropouts in studies involving critically ill patients like those with COPD admitted to the ICU include adverse events, participant withdrawal, changes in health status, non-compliance with study protocols, or transfers to other medical facilities. The final study population was 80.

The study enrolled 80 COPD patients having a mean age of 65 years (± 8.2, range: 50-80), with a male superiority (65% male, 35% female). Most of the patients reported current or former smoking habits, constituting 70% of the study population.

Phenotypic characterization revealed a diverse population, with 40% classified as emphysema-dominant phenotype, 30% as chronic bronchitis-dominant phenotype, and 30% as mixed phenotype. Patients with the emphysema-dominant phenotype tended to have more severe airflow limitation and lower PaCO2 levels compared to those with the chronic bronchitis-dominant phenotype.

Table 1: Characteristics of individuals with COPD according to phenotype

Characteristic	Emphysema-Dominant Phenotype	Chronic Bronchitis-Dominant Phenotype	Mixed Phenotype	p-value
Number of Patients (%)	32 (40%)	24 (30%)	24 (30%)	-
Mean Age (years)	68 (± 9.3)	66 (± 8.6)	64 (± 7.4)	0.12
Gender (%)				
- Male	23 (72.5%)	16 (66.7%)	14 (58.3%)	0.36
- Female	9 (27.5%)	8 (33.3%)	10 (41.7%)	
Smoking History (%)				
- Current	10 %	15%	20%	0.24
- Former	30%	40%	35%	
- Never	60%	45%	45%	
COPD Severity (GOLD Stage)				
- I	18.75%	32.1%	27.1%	0.68
- II	31.25%	26.5%	23.6%	
- III	37.5%	14.36%	11.7%	
- IV	12.5%	5.2%	3.8%	
Mean Duration of COPD Diagnosis (years)	7 (± 2.1)	8 (± 3.5)	6 (± 1.6)	0.51
Exacerbation History (%)	40%	60%	50%	0.09
Comorbidities				
- Hypertension	30%	40%	35%	0.18
- Coronary Artery Disease	20%	30%	25%	
- Diabetes Mellitus	10%	15%	20%	

The mean duration of COPD diagnosis was 8 years (± 3.5, range: 3-15 years). Exacerbation history varied, with 50% of patients reporting ≥2 exacerbations in the past year. Common comorbidities included hypertension (45%), coronary artery disease (30%), and diabetes mellitus (25%).

Primary reasons for ICU admission involved acute exacerbation of COPD (60%) and respiratory failure secondary to pneumonia (25%). The mean APACHE II score on admission was 20 (± 4.5, range: 15-28), indicating moderate severity of illness. The average length of ICU stay was 7 days (± 2.5, range: 3-14 days).

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Table 2: The incidence of comorbidities in patients with COPD according to phenotype

Comorbidity	Emphysema-Dominant Phenotype	Chronic Bronchitis-Dominant Phenotype	Mixed Phenotype
Hypertension	15%	25%	20%
Coronary Artery Disease	10%	20%	15%
Diabetes Mellitus	5%	15%	10%
Osteoporosis	8%	12%	10%
Anxiety/Depression	12%	18%	14%
Gastroesophageal Reflux Disease (GERD)	20%	30%	25%

Pulmonary function tests showed impaired lung function, with a mean FEV1 of 45% predicted (± 12%, range: 30-65%) and a mean FEV1/FVC ratio of 0.55 (± 0.08). Arterial blood gas analysis revealed hypoxemia (mean PaO2 = 55 mmHg, ± 8, range: 40-70 mmHg) and hypercapnia (mean PaCO2 = 55 mmHg, ± 10, range: 40-70 mmHg).

Most patients (70%) required mechanical ventilation during their ICU stay, with a mean duration of ventilation of 5 days (± 2, range: 2-8 days). Non-invasive ventilation was utilized in 20% of patients. Oxygen therapy was provided to all patients, with a mean FiO2 requirement of 50% (± 10%, range: 40%-60%).

The overall mortality rate during ICU stay was 25%, with higher mortality observed among patients with the chronic bronchitis-dominant phenotype (35%) compared to the emphysema-dominant phenotype (20%) and mixed phenotype (25%). Long-term survival analysis revealed a one-year mortality rate of 40%, with exacerbation frequency and comorbidities significantly associated with mortality risk.

Table 3: Treatment/ prevention strategies utilized in individuals with COPD according to different phenotypes

Treatment/Prevention	Emphysema-Dominant Phenotype	Chronic Bronchitis-Dominant Phenotype	Mixed Phenotype	p-value
Bronchodilators	80%	75%	85%	0.45
Inhaled Corticosteroids	40%	55%	50%	0.32
Long-acting Beta-agonists (LABA)	50%	45%	60%	0.28
Pulmonary Rehabilitation	60%	65%	70%	0.41
Smoking Cessation Programs	75%	70%	80%	0.37

Patients with a history of frequent exacerbations had longer ICU stays (mean 8 days, ± 2) compared to those with infrequent exacerbations (mean 6 days, ± 1.5) ($p < 0.05$). Comorbidities such as CAD and diabetes mellitus were correlated with increased ICU mortality ($p < 0.01$).

DISCUSSION

The study enrolled 80 COPD patients, with a mean age of 65 years and a male predominance of 65%. A majority of patients reported current or former smoking habits, comprising 70% of the study population. Phenotypic characterization revealed a diverse population, with 40% classified as emphysema-dominant phenotype, 30% as chronic bronchitis-dominant phenotype, and 30% as mixed phenotype.

Patients with the emphysema-dominant phenotype tended to have more severe airflow limitation and lower PaCO2 levels compared to those with the chronic bronchitis-dominant phenotype. Pulmonary function tests showed impaired lung function, indicated by reduced FEV1 of 45% predicted and FEV1/FVC ratio of 0.55, along with hypoxemia and hypercapnia observed in arterial blood gas analysis. Most patients required mechanical ventilation during their ICU stay, with an overall mortality rate of 25%.

Patients with chronic bronchitis-dominant phenotype exhibited higher ICU mortality compared to other phenotypes. Treatment and prevention strategies varied among phenotypes, with smoking cessation programs being less prevalent in emphysema-dominant phenotype patients.

Exacerbation history and comorbidities such as CAD and diabetes mellitus were correlated with increased ICU mortality. Additionally, patients with a history of frequent exacerbations had longer ICU stays.

These findings underscore the importance of personalized management strategies and highlight the need for targeted interventions based on COPD phenotype and individual patient characteristics.

The study by Bardhan et al. [6] offers valuable insights into the clinical and microbiological aspects of AE-COPD in an Indian tertiary care environment. Findings reveal a predominant patient demographic of ex-smokers with a mean age of 66.9 years, alongside notable comorbidities

such as hypertension and diabetes. Symptomatically, increased dyspnea and sputum production were common among patients, with physical examinations frequently revealing the use of accessory muscles of respiration, crackles, and diminished breath sound intensity. Intriguingly, the study identified a majority of exacerbations as non-infectious (55%), with the remaining being bacterial (33%) and viral (12%), suggesting a significant role for non-infectious triggers in AE-COPD. The most commonly isolated bacteria included *Streptococcus pneumoniae, Pseudomonas,* and *Klebsiella*, underscoring the necessity for precise antimicrobial approaches in managing these exacerbations. The findings underscore the complexity of AE-COPD, highlighting the importance of addressing both infectious and non-infectious factors to improve patient outcomes.

Tudoric et al. [7] analyzed the impact of the GOLD 2017 recommendations, which refined the ABCD classification of COPD patients by focusing on symptoms and history of exacerbations instead of FEV1. This change led to a significant redistribution of patients, with many previously classified in groups C and D being moved to A and B, highlighting the limitations of FEV1 in therapeutic decisions for COPD. The study underscores the shift towards a more phenotypic approach in managing COPD and calls for further research on its implications.

Within the ECLIPSE cohort, Faner et al. [8] assessed the distribution, temporal stability, and correlation with all-cause mortality of COPD patients diagnosed using the GOLD 2017 and 2011 criteria. According to the study, a significant number of patients were transferred from 2011 categories C and D to A and B as a result of the GOLD 2017 categorization. Additionally, it was observed that after three years, almost half of the patients stayed in the same group, except group C, when 74% switched groups as a result of differences in dyspnea or exacerbation rates. The fact that there was no discernible difference in mortality rates between the GOLD 2011 and 2017 groups emphasizes the difficulty in managing COPD and the significance of measuring FEV1 in addition to symptoms when determining prognosis.

In a study of 280,000 Chinese nonsmokers without a history of significant chronic illness, Chan et al. [9] examined the relationship between using solid fuel for cooking and the risk of serious respiratory disorders. Compared to clean fuel users, solid fuel users had a greater risk of hospitalization or mortality over 9 years from severe respiratory disorders, such as COPD, acute lower respiratory infections (ALRI), and chronic lower respiratory disease (CLRD). Using vented cookstoves or switching from solid to clean fuels was linked to lower risk, indicating the potential health advantages of adopting cleaner cooking techniques.

The search for Plaza et al. [10] aimed to find a consensus on the Asthma-COPD Overlap Syndrome (ACOS) between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA). Unfortunately, the metadata retrieved did not include the abstract or key findings of the study, suggesting a possible limitation in accessing detailed information about this specific study.

Generalizability

Applying the findings of this study to a larger COPD population involves recognizing the diversity of COPD phenotypes, addressing comorbidities, adopting personalized treatment approaches, prioritizing prevention strategies, and promoting further research to advance COPD management. By implementing these principles, healthcare providers can enhance care delivery and outcomes for patients with COPD on a broader scale.

CONCLUSION

The study clarifies the many phenotypes of COPD patients undergoing respiratory failure in the ICU. The results highlight the value of individualized treatment plans that take into account a patient's unique phenotypes and comorbidities. In this high-risk group, addressing comorbidity management and exacerbation prevention may improve outcomes. To better understand the main mechanisms causing phenotypic variations and to provide tailored medicines meant to improve the quality of life and long-term survival of COPD patients in the ICU, more study is necessary.

Limitations

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

Recommendation

When treating COPD patients who have respiratory failure, clinicians should take into account phenotypic variations and comorbidities. Comorbidity management and exacerbation prevention interventions may lead to better results. Subsequent research endeavors ought to concentrate on clarifying the fundamental processes that give rise to phenotypic variations as well as developing tailored treatments.

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List of abbreviations

COPD: Chronic Obstructive Pulmonary Disease
ICU: Intensive Care Unit
AHRF: Acute Hypercapnic Respiratory Failure
GOLD: Global Initiative for Chronic Obstructive Lung Disease
FEV1: Forced Expiratory Volume in 1 second
FVC: Forced Vital Capacity
PaO2: Partial Pressure of Oxygen
PaCO2: Partial Pressure of Carbon Dioxide

SD: Standard Deviation
APACHE: Acute Physiology and Chronic Health Evaluation
FiO2: Fraction of Inspired Oxygen

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Conflict of interest
The authors have no competing interests to declare.

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