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Original article

A PROSPECTIVE STUDY OF THE LONG-TERM EFFECTS OF HYPEROXEMIA DURING COPD EXACERBATION: A PROSPECTIVE COHORT STUDY.

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Abstract

Objectives
This study aimed to examine the prolonged impact of hyperoxemia during acute exacerbations of chronic obstructive pulmonary disease (AECOPD), focusing on patient outcomes over 1 year. The investigation explored associations with 1-year all-cause mortality, three-month all-cause fatality, and frequent hospitalizations.

Methods
This prospective cohort study carried out between March 2022 to March 2023 investigates factors associated with hyperoxemia in acute exacerbations of COPD (AECOPD) at Bhima Bhoi Medical College and Hospital in Balangir, Odisha, India. A sample of 122 AECOPD patients, categorized into hyperoxemic and nonhyperoxemic groups based on their initial ED ABG, is followed for a year post-discharge.

Results
In this study involving 122 patients, baseline characteristics of hyperoxemic and nonhyperoxemic groups were largely similar, differing primarily in initial AECOPD PaO_2 values. The primary outcome, assessing one-year all-cause fatality, revealed no prominent difference between hyperoxemic and nonhyperoxemic (19.0 % vs 12.8 %) cohorts. Secondary outcomes indicated higher three-month all-cause mortality in the hyperoxemic group (10.9 % vs. 4.3 %), while repeat hospitalizations within one year were comparable between groups.

Conclusion
The study found no statistically significant difference in one-year all-cause mortality amongst hyperoxemic and nonhyperoxemic cohorts among 122 AECOPD patients. The results suggest that hyperoxemia may not be a major determinant of long-term mortality in AECOPD, emphasizing the need for further investigation.

Recommendation
This study recommends further research to explore additional factors influencing long-term outcomes in AECOPD. Specifically, investigating the impact of hyperoxemia on short-term mortality and repeat hospitalizations may provide valuable insights for refining treatment strategies.

Keywords: *COPD, Acute Exacerbation, Hyperoxemia, Mortality*
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Introduction
The prevalence of Chronic Obstructive Pulmonary Disease (COPD) has positioned it major cause of global fatality, as projected by the World Health Organization (WHO) for 2020 [1]. COPD, comprising short-term aggravations, necessitates oxygen therapy during both acute episodes and periods of stability to counter hypoxemia [2, 3]. Studies have validated this with long-term oxygen therapy (LTOT) demonstrating good efficacy in reducing mortality for stable COPD patients over a 5-year follow-up [4, 5].

However, the use of oxygen therapy for such aggravations, despite its potential benefits, has been linked to detrimental effects, such as increased fatality during hospitalization and need for mechanical ventilation [6-8]. Furthermore, guidelines outlined by the British Thoracic Society (BTS) in 2017 emphasizes the importance of titrating oxygen levels to specific ranges based on pulse oximetry (SpO2) and arterial blood gas (ABG) measurements [9, 10].

Severe AECOPD have been associated with elevated long-term fatality rates following the exacerbation event [11-15]. However, there is a scarcity of literature exploring the impact of hyperoxemia during AECOPD on these fatality rates. Previous research has extensively

examined the enduring consequences of oxygen therapy and hyperoxemia during short-term phases in other medical conditions, particularly myocardial infarction (MI) and stroke [16-18].

In our investigation, we aimed to explore the enduring outcomes linked to hyperoxemia during AECOPD. For this purpose, we conducted a prospective observational study designed to generate hypotheses. The study sought to compare the long-term patient-centric outcomes between individuals experiencing hyperoxemia (> 65 mm of Hg) and those without hyperoxemia (≤ 65 mm of Hg) during AECOPD, particularly in cases managed by emergency medical services (EMS) and emergency departments (ED).

Materials and Methods

Study design

A prospective cohort study was conducted. This study included a follow-up period of the patients, which represents the exploratory component of the research. During this phase, the study examined significant factors associated with hyperoxemia (PaO_2 >65mmHg) in AECOPD patients, aiming to gain insights into this specific aspect of the condition.

Study setting

The study was conducted at Bhima Bhoi Medical College and Hospital in Balangir, Odisha, India, from March 2022 to March 2023.

Participants

AECOPD patients were recruited with categorization into hyperoxemic and nonhyperoxemic cohorts based on their initial arterial blood gas result when admitted to the ED. Patients were tracked for a year post-discharge, and data collection included baseline information, weekly follow-ups, and outcomes such as all-cause mortality and repeat hospitalizations. Patients were grouped into hyperoxemic (PaO_2 >65 mm of Hg) and nonhyperoxemic (PaO_2 ≤65 mm of Hg) cohorts based on their first ED ABG result. Following discharge from ED or inpatient care, patients were under surveillance for a year.

Inclusion and exclusion criteria

The inclusion criteria for this prospective cohort study encompassed AECOPD patients, particularly those aged 35 years or older with AECOPD as the primary cause of dyspnea, confirmed by respiratory physicians. Inclusion required individuals to have undergone at least one arterial blood gas (ABG) test at the Emergency Department (ED) during their exacerbation. Conversely, exclusion criteria encompassed individuals below the age of 35, those lacking a confirmed COPD diagnosis, cases where AECOPD was not identified as the primary cause of dyspnea, absence of an ED ABG during exacerbation, presence of other medical conditions impacting outcomes, and individuals unwilling or unable to participate in the one-year follow-up post discharge from hospital.

Study size

The study employed 122 patients, anticipating 73 hyperoxemic and 49 non-hyperoxemic patients for analysis after a 1-year follow-up, considering mortality, repeat attendances, and potential incomplete data.

For this exploratory investigation, the sample size began with 350 patients based on the initial study, where the allocation ratio was 1.5 hyperoxemic patients to 1 non-hyperoxemic patient. It was anticipated that 3% of the initial cohort would pass away during their index AECOPD, and 20% of them would have repeat attendances. Factoring in a 2% rate of incomplete data during the 1-year follow-up, an estimated 122 patients were available for this current study, comprising 73 hyperoxemic and 49 non-hyperoxemic patients.

The expected all-cause mortality within 1 year following AECOPD typically ranges from 15% to 35%. Assuming a 15% 1-year mortality rate for the non-hyperoxemic group, the projected sample size of 122 patients could only detect a difference of 15% or more in delayed all-cause mortality between the groups, with a significance level (α) of 0.05 and a power (β) of 0.2.

It was also anticipated that the number of patients with delayed mortality in the less frequent (non-hyperoxemic) group would be at most 20. This limited the ability to include only two highly impactful predictors of delayed mortality in the Cox PH model, following guidelines that recommend at least 10 events per degree of freedom. Importantly, the predefined predictors, age≥ 70 years and repeat AECOPD hospitalization, were not rare events, ensuring the stability and reliability of the model.

Data collection

The collection of data involved general information of the group, tracked prospectively by investigators at weekly intervals for a year after discharge. Databases stored from hospital were used to monitor disease progression, with extracted data entered into a pre-designed form. The data collected included frequent hospitalizations for AECOPD, need for long-term oxygen therapy, as well as delayed fatality. The primary outcome aimed to explore all-cause fatality a year after AECOPD discharge in both cohorts. Secondary results included all-cause fatality within 3 months as well as number of frequent hospitalizations within a year post-discharge.

Bias

There was a chance that bias would arise when the study first started, but it was avoided by giving all participants the identical information and hiding the group allocation from the nurses who collected the data.

Statistical Analysis

Descriptive statistics included proportions and medians with IQRs, while Fischer's exact test compared the primary outcome. Kaplan–Meier curves and the Cox PH model analyzed time to delayed mortality, providing adjusted and crude hazards ratios for 1-year all-cause mortality.

Ethical considerations

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

Results/Outcomes

Participants

Around 122 patients were analyzed in this study, and the general traits of the hyperoxemic and nonhyperoxemic cohorts were compared. The groups exhibited largely similar baseline features, with the primary distinction being observed in the initial AECOPD PaO_2 values (Table 1). Regarding the primary outcome, which focused on all-cause mortality rates within one-year post-discharge, the difference between the hyperoxemic (19.0 %) and nonhyperoxemic (12.8 %) cohorts, were of no statistical significance. Kaplan–Meier survival curves visually indicated consistently low probability of survival in the hyperoxemic group throughout the follow-up period; however, the log-rank test did not reveal a significant difference (Table 1).

Table 1: General characteristics of both groups

	Hyperoxemic group (*n* = 73)	**Non-hyperoxemic group (*n* = 49)**
Demographics		
Men (%)	66 (90.5 %)	44 (89.4)
Average age (yrs)	74 (64–81)	73 (64–77)
Respiratory support for COPD (%)		
Home LTOT	14 (19.0 %)	13 (26.6 %)
Mechanical Ventilation in Exacerbations (past 5 Years)	23 (32.1 %)	16 (33.0 %)
Co-existing illness		
Respiratory illness		
Sleep apnea syndrome	3 (4.4 %)	1 (3.2 %)
Bronchiectatic lung disease	7 (10.2 %)	8 (16.0 %)
Lung tumor	2 (2.2 %)	0 (0 %)
Cardiovascular		
Heart failure syndrome	6 (8.8 %)	5 (9.6 %)
Persistent atrial fibrillation	8 (10.9 %)	3 (6.4 %)
ABG results at initial AECOPD		
Median pH (interquartile range)	7.32 (7.28-7.39)	7.32 (7.28-7.39)
Median PaO_2 (interquartile range) mm of Hg	81.5 (70.5-97.8)	54.2 (47.3-59.7)
Median $PaCO_2$ (interquartile range) mm of Hg	41.2 (38.2-53.9)	41.6 (38.2-52.9)
Median bicarbonate (interquartile range) mmol per litre	24.9 (22.8-28.1)	23.8 (23.1-27.9)
Do-not-resuscitate order (%)	24 (32.8%)	16 (33.0%)

The Cox proportional-hazards (PH) model, which was employed to analyze the time to delayed mortality, affirmed that the assumption of proportional hazards was not violated, indicating consistent hazard ratios over time. Detailed scrutiny of the crude and adjusted hazard ratios for one-year fatality showed no differences between the two groups.

For secondary outcomes, the hyperoxemic group demonstrated higher all-cause fatality rates in the first three months after discharge compared to the other group (10.9 % vs. 4.3 %). However, when examining frequent admission to hospitals for AECOPD within the one-year follow-up, the median number was comparable between the hyperoxemic and nonhyperoxemic groups.

Discussion

The preliminary investigation revealed no discernible disparities in both the primary outcome, one-year all-cause fatality, and the secondary outcomes, encompassing 3-month all-cause mortality and frequent admission to hospitals for AECOPD within the first year, between the hyperoxemic and nonhyperoxemic groups [6]. It is important to note that our study lacked sufficient statistical power to draw definitive conclusions regarding these outcomes.

The adverse consequences of hyperoxemia during acute exacerbations of COPD, such as increased in-hospital deaths and the need for ventilatory support, have been

documented in earlier studies [6-8]. Individuals experiencing AECOPD coupled with hyperoxemia demonstrated a higher likelihood of developing respiratory acidosis and hypercapnia, both factors linked to unfavorable outcomes, notably in-hospital mortality [8, 19, 20].

To date, no prior investigation has examined the prolonged consequences of hyperoxemia during acute exacerbations of COPD. The preliminary study stands as the inaugural exploration into these long-term effects. The observed delayed all-cause fatality rates, with 19.0% in the hyperoxemic group and 12.8% in the nonhyperoxemic group, align with the lower spectrum of the 15% to 35% range reported for one year fatality in previous studies [11, 12, 15]. The estimation suggested a potential variation in one year fatality amongst the cohorts, falling within the 5 to 10% range. It is essential to note that our study may not have the power to identify this nuanced variation.

Unregulated administration of oxygen therapy in short-term aggravations of COPD induces hypercapnia through mechanisms such as ventilation/perfusion mismatch, dead space ventilation, or the Haldane effect [21]. While the immediate effects can be mitigated by removing oxygen, the prolonged exposure to oxygen and resulting hyperoxemia also elevates the burden of free radicals. This oxidative stress may contribute to pathological developments, including inflammation of the bronchi, augmented cellular senescence, activation of immune cell system, and fibrosis of airways [22-24]. These subsequent pathological processes might be linked to extended impacts on patient-centered outcomes post-AECOPD, warranting further studies.

The present study hints at nuanced one-year fatality variations in hyperoxemic versus nonhyperoxemic COPD exacerbations. Despite limitations, it underscores the importance of investigating long-term impacts and developing targeted interventions for improved patient outcomes.

Conclusion

The exploratory study focussing on “long-term effect of hyperoxemia during chronic obstructive pulmonary disease exacerbation managed by emergency medical service and emergency department” found no significant differences in 1-year all-cause mortality and secondary outcomes between hyperoxemic and nonhyperoxemic groups in AECOPD. However, the study was underpowered to draw definitive conclusions. The prolonged effects of hyperoxemia in AECOPD, including potential contributions to adverse outcomes, warrant further investigation, considering the study's acknowledged limitations.

Limitations

The study faced limitations such as an uncertain vulnerable period for hyperoxemia post-discharge and the use of a 1-year follow-up, which may not capture shorter-term mortality peaks. Additionally, confounding factors like cardiac diseases and COPD intensity markers were challenging to adjust for due to sample size constraints.

Recommendations

The present investigation recommends future studies to identify the optimal duration of vulnerability to hyperoxemia post-AECOPD discharge. Additionally, exploring shorter follow-up periods and adjusting for more confounding factors in larger cohorts would enhance the robustness of future investigations.

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List of Abbreviations

COPD – Chronic Obstructive Pulmonary Disease
AECOPD - Acute Exacerbations of Chronic Obstructive Pulmonary Disease
LTOT - Long-Term Oxygen Therapy
WHO – World Health Organization
ABG – Arterial Blood Gas
MI - Myocardial Infarction
EMS - Emergency Medical Services
ED - Emergency Departments

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Conflict of interest

The authors have no competing interests to declare.

References

1. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187:347–365.
2. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002; 57:847–852.
3. Halpin DM, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. Int J Chron Obstruct Pulmon Dis 2012; 7:653–661.
4. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1981; 1:681–686.
5. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980; 93:391–398.
6. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ 2010; 341:c5462.
7. Wijesinghe M, Perrin K, Healy B, Hart K, Clay J,

Weatherall M, Beasley R. Pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. Intern Med J 2011; 41:618–622.
8. Joosten SA, Koh MS, Bu X, Smallwood D, Irving LB. The effects of oxygen therapy in patients presenting to an emergency department with exacerbation of chronic obstructive pulmonary disease. Med J Aust 2007; 186:235–238.
9. O'Driscoll BR, Howard LS, Earis J, Mak V; British Thoracic Society Emergency Oxygen Guideline Group; BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 2017; 72:ii1–ii90.
10. Lim BL, Cheah SO, Goh HK, Francis Lee CY, Ng YY, Guo WJ, et al. Most impactful predictors for hyperoxaemia in exacerbation of chronic obstructive pulmonary disease managed by Emergency Medical Services and Emergency Department. Clin Respir J 2019; 13:256–266.
11. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012; 67:957–963.
12. Schmidt SA, Johansen MB, Olsen M, Xu X, Parker JM, Molfino NA, et al. The impact of exacerbation frequency on mortality following acute exacerbations of COPD: a registry-based cohort study. BMJ Open 2014; 4:e006720.
13. Fazekas AS, Aboulghaith M, Kriz RC, Urban M, Breyer MK, Breyer-Kohansal R, et al. Long-term outcomes after acute hypercapnic COPD exacerbation: first-ever episode of non-invasive ventilation. Wien Klin Wochenschr 2018; 130:561–568.
14. Esteban C, Castro-Acosta A, Alvarez-Martínez CJ, Capelastegui A, López-Campos JL, Pozo-Rodriguez F. Predictors of one-year mortality after hospitalization for an exacerbation of COPD. BMC Pulm Med 2018; 18:18.
15. Genao L, Durheim MT, Mi X, Todd JL, Whitson HE, Curtis LH. Early and long-term outcomes of older adults after acute care encounters for chronic obstructive pulmonary disease exacerbation. Ann Am Thorac Soc 2015; 12:1805–1812.
16. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al.; AVOID Investigators. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 2015; 131:2143–2150.
17. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, et al.; DETO2X–SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2017; 377:1240–1249.
18. Hofmann R, Witt N, Lagerqvist B, Jernberg T, Lindahl B, Erlinge D, et al.; DETO2X-SWEDEHEART Investigators. Oxygen therapy in ST-elevation myocardial infarction. Eur Heart J 2018; 39:2730–2739.
19. Jeffrey AA, Warren PM, Flenley DC. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease: risk factors and use of guidelines for management. Thorax 1992; 47:34–40.
20. Denniston AK, O'Brien C, Stableforth D. The use of oxygen in acute exacerbations of chronic obstructive pulmonary disease: a prospective audit of pre-hospital and hospital emergency management. Clin Med (Lond) 2002; 2:449–451.
21. Abdo WF, Heunks LM. Oxygen-induced hypercapnia in COPD: myths and facts. Crit Care 2012; 16:323.
22. MacNee W. Oxidants and COPD. Curr Drug Targets Inflamm Allergy 2005; 4:627–641.
23. Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. Lancet 2009; 374:744–755.
24. Beasley R, Patel M, Perrin K, O'Driscoll BR. High-concentration oxygen therapy in COPD. Lancet 2011; 378:969–970.

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