ORIGINAL ARTICLE

Unraveling the Complexities of Coagulation Dysfunction in Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Investigating the Interplay between Infection, Hypercapnia and Hemostatic Abnormalities

Bilal Ahmed[1*], Muhammad Imran[2], Nimra Naeem[3], Usman Haider[1], Muhammad Atif Rauf[4], Qaiser Iqbal[5]

ABSTRACT

Objective: To understand how the acute exacerbations of chronic obstructive pulmonary disease (COPD) can lead to coagulation dysfunctions causing hemostatic abnormalities (prolonged prothrombin time, slightly longer activated partial thromboplastin time, higher fibrinogen levels, higher D-dimer levels, and slightly lower platelet counts).

Study Design: Comparative cross-sectional.

Place and Duration of Study: The study was conducted at the Department of Internal Medicine Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan during the period of July 2023 to December 2023.

Methods: The current study utilized patients with a confirmed diagnosis of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) who were hospitalized in the respiratory care unit and were above 50 years of age. A total of 200 patients were accessed including their demographic characteristics (age, gender, residence, and job), clinical parameters (spirometry results (Forced expiratory volume in one second/Functional vital capacity ratio), complete blood counts, fibrinogen, prothrombin, activated partial thromboplastin time, D-dimers and arterial blood gas analysis. The intricate relationship between coagulation dysfunction and acute exacerbations of chronic obstructive pulmonary disease was analyzed using SPSS 26.

Results: The results obtained that; patients with acute exacerbation of chronic obstructive pulmonary disease had prolonged prothrombin time (13.5 ± 1.2 seconds, $P < 0.001$) slightly longer aPTT (32.1 ± 2.5 seconds, $P = 0.014$), along with higher fibrinogen levels (350.2 ± 45.8 mg/dL, $P < 0.001$) and D-dimer levels (550.4 ± 120.3 ng/mL, $P = 0.002$), as compared to patients with stable chronic obstructive pulmonary disease. The platelet counts of Acute exacerbation of chronic obstructive pulmonary disease patients obtained were slightly lower (260.3 ± 45.4x10^3/µL, $P = 0.009$) compared to stable chronic obstructive pulmonary disease patients. Furthermore, results provided that coagulation dysfunction was significantly associated with infection, hypercapnia, and acute exacerbation of chronic obstructive pulmonary disease. The prevalence of coagulation dysfunction markers was higher among patients with acute exacerbation of chronic obstructive pulmonary disease.

Conclusion: Coagulation dysfunction and its associated risk factors are higher in patients with acute exacerbation of chronic obstructive pulmonary disease and are elevated with increased exposure to air pollution.

Keywords: *Chronic Obstructive Pulmonary Disease (COPD), Exacerbation, Fibrinogen, Hemostatic, Hypercapnia, Infection.*

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Introduction

Being one of the leading respiratory disorders and with a higher contribution to the increased mortality rate worldwide, chronic obstructive pulmonary disease (COPD) has a worldwide prevalence rate of 13%.[1] Aiding to this, a report by World Health

[1]Department of Medicine/Pulmonology[2]/Gastroenterology[5]
Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan
[3]Department of Psychology
Riphah International University Islamabad, Pakistan
[4]Department of Electrophysiology
Armed Forces Institute of Cardiology (AFIC) Rawalpindi, Pakistan
Dr. Bilal Ahmed
Department of Medicine
Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan
E-mail: bilalahmed2955@gmail.com
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Organization in 2022, termed the disease to be the fifth leading cause of death globally, indicating that the disease can further prevail and will be the fourth leading disease globally with highest mortality rate.[2] While COPD can be characterized as increased airflow limitation and persistent inflammation, the disease when exposed to certain environments or stimuli exacerbates with abrupt worsening of respiratory symptoms, often necessitating hospitalization. Such acute exacerbation of the COPD often entails elevated levels of acute phase reactants (C-reactive protein (CRP), Fibrinogen, D-dimer) and pro-inflammatory cytokines {Interleukin-6 (IL-6), Tumor necrosis factor-alpha (TNF-alpha), Interleukin-8 (IL-8), Interleukin-1 beta (IL-1β), Interleukin-17 (IL-17)} in the blood leading coagulation pathways to become active and cause thrombosis.[3,4] This further hinders the hemostatic state between procoagulant and anticoagulant factors, leading to an increase in platelet adhesion and activation. Aiding to this, oxidative stress, the key feature of COPD pathogenesis, induces oxidative protein and lipid alteration, which impairs fibrinolysis in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) patients. A study by Rahaghi and Pistenmaa (2021) associated elevated D-dimer levels, impaired fibrinolysis, and the imbalance of procoagulant and anticoagulant factors in AECOPD patients with the impaired ability of the body to control blood clotting a condition termed as coagulation dysfunction.[5] Clinically, coagulation dysfunction can increase the risk of blood clot formation, leading to conditions such as deep vein thrombosis (DVT) or pulmonary embolism.[6] When observed in laboratory settings, the clotting time and levels of another acute phase reactant can be determined. The consequences of elevated markers of coagulation dysfunction vary depending on the individual and the underlying condition but often result in an increased risk of thrombotic events and potential complications.

Coagulation dysfunction is often associated with AECOPD patients, as previous studies reported that the key markers of coagulation dysfunction as aforementioned are found to be higher in AECOPD patients. A study by Hesham and Heba found the D-dimer levels to be 2348 μg/mL, highlighting the elevated risk of coagulation dysfunction.[7] Another study[8] provided that AECOPD patients had higher fibrinogen as compared to patients with stable COPD (mean ±SD: 399±82 mg·dL−1 versus 346± 65 mg·dL−1).

While studies have highlighted the higher prevalence of coagulation dysfunctions in patients with AECOPD, the risk factors of AECOPD and coagulation dysfunctions seemed to vary considerably across regions.[9,10] Within developing countries like Pakistan with a high prevalence of infectious diseases, the lack of access to healthcare facilities, socioeconomic factors, indoor smoke exposure, and air pollution, AECOPD is one of the leading causes of mortality.[11] In individuals with COPD, coagulation dysfunctions, hypercapnia, and hemostatic abnormalities can all be made worse by air pollution and indoor smoking exposure. Pakistan is ranked the 4th most polluted country with 44.73(μg/m3) particulate pollution in the air, the country faces significant environmental health concerns due to air pollution and smoke exposure, which contribute to respiratory diseases like COPD and acute exacerbations of COPD.[12,13] Outdoor air pollution, primarily in urban areas, is exacerbated by industrial emissions, vehicular exhaust, construction activities, and agricultural burning. Indoor smoke exposure, particularly from household fuel combustion, is a significant concern, particularly in rural areas where solid fuels such as dung crap and crop residue, are commonly used for cooking and heating.[14] The combination of these factors significantly contributes to the burden of COPD in Pakistan, with COPD prevalence rising, particularly among older adults and individuals with occupational exposure. Moreover, adults particularly males in Pakistan are involved in Smoking which creates oxidative stress and systemic

inflammation, which are key risk factors for the onset and progression of COPD. A report by the World Health Organization reported the smoking rate to be 12.4% in Pakistan with an average of 27 million adults involved in smoking.[15] Thus, keeping in view the aforementioned statistics, the current study helped identify the increased prevalence of coagulation dysfunction in patients with AECOPD in Pakistan due to their increased exposure to air pollution, respiratory infections, and smoke. In addition to exploring the prevalence of coagulation dysfunction in AECOPD cases in Pakistan, the study unraveled the complexities of coagulation dysfunction in COPD patients. The presence of coagulation dysfunction in patients with AECOPD further increases the risk of other cardiovascular and respiratory diseases. For instance, increased exposure to air pollution, smog or smoke can elevate the PaCO2 levels leading towards respiratory and systematic acidosis, this can further enhance the coagulation cascade and create thrombosis.[16] Such exposure further worsens the course of AECOPD by decreasing endothelial function, platelet activation, and fibrinolysis. Moreover, hypercapnia and acidosis also aggravate endothelial dysfunction and platelet activation.[17] Thus, it is pertinent to gain an understanding of these complexities associated with the coagulation cascade, the current study highlights these complexities to enhance management strategies and improve patient outcomes in cases with AECOPD. It provides a framework for future studies to utilize while investigating further facets if COPD. The study findings can be inferred for drafting reports related to the prevention and mitigation of AECOPD. It further helps understand the underlying mechanisms of AECOPD and develop targeted interventions for better patient care and a reduction in the burden of AECOPD on individuals and the healthcare system of Pakistan.

Methods

The comparative cross-sectional study was conducted at Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan during the time period of July 2023 to December 2023 after obtaining permission from the Ethical Review Committee of the hospital dated: 19th July 2023 vide letter no: A/28/ER/1528/23. 200 patients with a confirmed diagnosis of COPD were selected, utilizing a purposive sampling technique. The patients were above the age of 50 and were hospitalized with acute exacerbation of COPD, exhibiting worsening respiratory symptoms including coughing, dyspnea, and production of sputum. Furthermore, the patients' data entailed complete medical information, including coagulation profiles, microbiological data, laboratory results, and arterial blood gas analyses. Any patient record with a diagnosis of other known respiratory issues or significant comorbidities affecting hemostasis, such as liver disease or hematologic disorders, were not included in the study and further, the study data was kept confidential and the patient's right to privacy was maintained.

The study included the demographic characteristics of the patients, their COPD severity, smoking habits, their residence, and their jobs. The medical records were reviewed for the laboratory results, including arterial blood gas analysis, complete blood count, coagulation profiles, and microbiological data (respiratory pathogen identification). The patients identified with respiratory infections were further analyzed based on their medical reports of microbiological analysis (e.g., viral PCR, positive sputum culture). Coagulation dysfunctions were evaluated based on abnormalities in coagulation profiles, such as delayed prothrombin time, activated partial thromboplastin time, and high D-dimer levels. Hypercapnia was defined as arterial carbon dioxide tension (PaCO2) > 45 mmHg measured during arterial blood gas analysis.

IBM SPSS 26.00 was utilized to analyze the data obtained. The demographic and clinical characteristics of the data were analyzed using mean, standard deviation, frequency, and percentages, while to identify the association between coagulation dysfunction and risk factors, including infection, hypercapnia, and AECOPD, multivariate regression analysis was performed.

Results

Among the 200 patient records accessed, 80 patients had stable COPD while other 120 patients were admitted to acute exacerbations of COPD. The stable COPD patients entailed 60 males and 20 females. While most of the patients with AECOPD were males.

The results showed that most of the patients with AECOPD belonged to urban areas and had outdoor jobs. The patients with AECOPD were habitual chronic active smokers and exhibited chain smoking. Aiding to this, most of the patients were hospitalized with stage III COPD severity. Table-1 (n=200) demonstrated the demographic characteristics of and also the clinical parameters of the patients.

Furthermore, the laboratory results were also analyzed. Table-2 (n=200) demonstrates the laboratory examination parameters including the complete blood counts, c-reactive protein, and blood gas analysis. The results provided that patients with AECOPD had lower values of hemoglobin with high levels of white blood cell count. Aiding to this, the patient with AECOPD had elevated levels of CRP with lower levels of pH and PaO2. Patients with AECOPD further had low oxygen saturation, with increased PaCO2 and increased levels of bicarbonate (HCO3), indicating respiratory acidosis.

Table-1: Demographic and clinical parameters of Chronic Obstructive Pulmonary Disease

Variables	AECOPD (n =120)	Stable COPD (n =80)	Total (n = 200)
Age (M, ±SD)	70.1 ±8.1	65.2 ±10.2	68.3 ± 9.6
Gender (n%)			
Male	90 (75.0)	60 (75.0)	150 (75.0)
Female	30 (25.0)	20 (25.0)	50 (25.0)
Residence (n%)			
Urban	80 (66.7)	60 (75.0)	140 (70.0)
Rural	40 (33.3)	20 (25.0)	60 (30.0)
Job type (n%)			
Outdoor job	70 (58.3)	50 (62.5)	120 (60.0)
Indoor job	50 (41.7)	30 (37.5)	80 (40.0)
Smoking (M, ±SD)			
Habitual smokers	60 (50.0)	40 (50.0)	100 (50.0)
Passive smokers	20 (16.7)	20 (25.0)	40 (20.0)
Chain smokers	40 (33.3)	20 (25.0)	60 (30.0)
COPD severity (Gold Stage), (n%)			
Stage I	10 (8.3)	20 (25.0)	30 (15.0)
Stage II	30 (25.0)	30 (37.5)	60 (30.0)
Stage III	50 (41.7)	20 (25.0)	70 (35.0)
Stage IV	30 (25.0)	10 (12.5)	40 (20.0)

To analyze the coagulation dysfunction across both patients with AECOPD and stable COPD, multivariate regression analysis was performed. The analysis determined that patients with AECOPD had prolonged prothrombin time (13.5 ± 1.2 seconds, $P < 0.001$), along with slightly longer aPTT (32.1 ± 2.5 seconds, $P = 0.014$). Aiding to this, patients with AECOPD further exhibited higher fibrinogen levels (350.2 ± 45.8 mg/dL, $P < 0.001$) and D-dimer levels (550.4 ± 120.3 ng/mL, $P = 0.002$), as compared to patients with stable COPD. However, the platelet count of AECOPD patients was slightly lower (260.3 ± 45.4x10^3/µL, $P = 0.009$) compared to stable COPD patients. Table-3 demonstrates the comparative parameters of coagulation dysfunction across patients with AECOPD and stable COPD.

To obtain the association between coagulation dysfunction and infection, hypercapnia, and AECOPD, multivariate regression analysis was performed, the results of the analysis exhibited a slightly significant association of coagulation dysfunction with infection and hypercapnia, however, its association with AECOPD was strong. Table-4 demonstrates the association values for coagulation dysfunction with infection, hypercapnia, and AECOPD. Furthermore, the prevalence of

Table-2: Laboratory Reports Examination Parameters of thePatients of Chronic Obstructive Pulmonary Disease

Variables	AECOPD (n=120)	Stable COPD (n=80)	Total (n=200)
Blood Routine			
Hemoglobin (g/dL), mean ± SD	13.5 ± 1.3	14.2 ± 1.6	13.8 ± 1.5
White Blood Cell Count (x10^9/L), mean ± SD	10.5 ± 2.6	8.8 ± 1.8	9.7 ± 2.4
Platelet Count (x10^9/L), mean ± SD	260.3 ± 45.4	290.6 ± 35.2	268.5 ± 40.3
CRP (mg/L), mean ± SD	32.4 ± 15.6	18.7 ± 9.2	25.6 ± 12.8
Blood Gas Analysis			
pH, mean ± SD	7.34 ± 0.05	7.38 ± 0.03	7.36 ± 0.04
PaO2 (mmHg), mean ± SD	68.5 ± 9.2	72.8 ± 7.4	70.2 ± 8.7
PaCO2 (mmHg), mean ± SD	52.3 ± 7.1	44.7 ± 5.2	48.9 ± 6.3
HCO3- (mmol/L), mean ± SD	26.8 ± 3.2	23.6 ± 2.5	25.4 ± 2.8
SaO2 (%), mean ± SD	92.7 ± 2.1	94.2 ± 1.6	93.5 ± 1.9

Table-3: Comparison of Coagulation Dysfunction markers across patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease and stable Chronic Obstructive Pulmonary Disease (n= 200)

Coagulation Parameter	AECOPD (n=120)	Stable COPD (n=80)	*P*-value
Prothrombin Time (s), mean ± SD	13.5 ± 1.2	12.8 ± 1.0	<0.001
Activated Partial Thromboplastin Time (s), mean ± SD	32.1 ± 2.5	31.2 ± 2.0	0.014
Fibrinogen (mg/dL), mean ± SD	350.2 ± 45.8	325.6 ± 40.2	<0.001
D-dimer (ng/mL), mean ± SD	550.4 ± 120.3	480.6 ± 90.1	0.002
Platelet Count (x10^3/µL), mean ± SD	280.8 ± 50.2	310.4 ± 60.5	0.009

Table-4: Association of Coagulation dysfunction with infection, hypercapnia andAcute Exacerbation of Chronic Obstructive Pulmonary Disease across patients with Chronic Obstructive Pulmonary Disease (n = 200)

Variables	Beta Coefficient (95% *CI*)	*P*-value
Infection	0.72*(0.58 - 0.86)	<0.001
Hypercapnia	0.45*(0.36 - 0.54)	<0.001
AECOPD	0.63**(0.52 - 0.74)	<0.001

Table-5: Prevalence of Coagulation dysfunction markers in patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (n = 200)

Coagulation Parameter	Prevalence in AECOPD (%)
Prothrombin Time (PT) prolongation	75
Activated Partial Thromboplastin Time (aPTT) prolongation	60
Elevated Fibrinogen levels	80
Increased D-dimer levels	85
Platelet count abnormalities	55

coagulation dysfunction was analyzed across patients with AECOPD. The results presented in Table 5, provided that the markers of coagulation dysfunction such as prothrombin time (PT) prolongation was 75%, and aPTT prolongation was 60%. Moreover, the patients with AECOPD had elevated fibrinogen levels (80%) and D-dimer levels (85%). They also had low platelet count and 55% of patients showed platelet count abnormalities.

Discussion

While the world has advanced and the field of medicine has evolved, the Global health problems have also amplified with the worsening of existing illnesses brought on by the increase in smoking and

air pollution emissions. Increased urbanization, industrialization, and vehicle traffic have led to high levels of outdoor air pollution, further aiding to this the indoor pollution has also elevated due to the use of biomass fuels.[7,9] Such aversive consumption of air causes the toxins to enter the respiratory system and lead to immunological dysfunctions, oxidative stress, and inflammation, collectively contributing towards acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Additionally, the consistent exposure to the aforementioned toxins leads towards coagulation dysfunction, altogether worsening the health condition. The current study explores the complex link between coagulation malfunction and Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD). The study findings showed that activated partial thromboplastin time (APTT), fibrinogen (FIB), prothrombin time (PT)[10], and D-dimer levels were among the coagulation measures that were in abnormal levels in the patients with COPD. These abnormalities have been highlighted by studies to be especially noticeable during acute exacerbations of COPD (AECOPD).[10,11] Zhang et al. (2016) reported that d-dimer levels were higher in both patients with stable COPD and AECOPD, however in patients with AECOPD there ratio was significantly higher and had a significant association with the inflammatory markers.[12] Further parallel to the current study, a longitudinal study[13] reported that fibrinogen was one of determinants of AECOPD when observed in 15,792 patients presenting symptoms of COPD. The current study further obtained elevated white blood cell (WBC) count, elevated C-reactive protein (CRP) and serum HCO3 levels while platelet count, pH, PaO2, PaCO2 and oxygen saturation (SaO2) decreased in patients with AECOPD. Previous studies linked these abnormal levels with systemic inflammation, gas exchange abnormalities, and acid-base disturbance characteristic of AECOPD.[14] In addition to these elevated levels, the association of coagulation dysfunction with infection, hypercapnia and AECOPD was obtained significant. Aligning with the current study findings, Zheng et al. (2023) provided a significant relation of coagulation function with infection further leading towards thrombosis.[15] Additionally, studies have shown that the elevated levels of arterial carbon dioxide were positively associated with coagulation dysfunction.[17] Aiding to this, abnormal activation of coagulation system increases the likelihood of the presence of infection highlighting the imbalance between the production and clearance rate of intravascular fibrin.[18] Additionally, the prevalence of coagulation dysfunction is observed to be higher across patients with AECOPD[19], specifically in Pakistan where the prevalence of infectious diseases is higher and further the country is reported to be 4th ranked among the country with highest air pollution.[20] While the country reports higher prevalence of AECOPD cases and shares the economic burden due to the prevalence of the disease, there is a literature gap regarding the prevalence and examination of AECOPD and other factors associated with it. The current study provides an insight into all the multifaceted factors associated with AECPD, it further establishes the association between coagulation dysfunction and other hemostatic biomarkers with AECOPD, providing a base for future studies to explore the interactions of inflammatory markers, environmental factors with AECOPD. The study findings are further baseline for the development of therapeutic interventions, and for the medical specialist for COPD patient management. Additionally, the findings provide an insight to the policy makers to establish primary preventive care systems and emergency response plans, promoting preventive healthcare, thus aiming to lower the economic burden on country inflicted by the higher prevalence of AECOPD.

The study provided a thorough understanding of the study variables, however, the study is subjected to the limitations of study design. The current study utilizes a cross-sectional research method, it is recommended for future studies to explore the construct of AECOPD using longitudinal study, as longitudinal study would provide further insight into the complexities associated with coagulation dysfunction. Furthermore, the sample of the data is limited to 200 patients, a study encompassing a more generalizable sample from different provinces of Pakistan will enable a deeper understanding of the complexities associated with AECOPD.

Conclusion

While keeping in view the literature gap regarding coagulation dysfunction and AECOPD, the current study unravels the issues associated with constant exposure to air pollution and smoke, shedding light on the complexities of coagulation dysfunction. The study highlights the need for targeted interventions to optimize patient care and improve the outcomes, ultimately diminishing the economy.

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Authors Contribution

BA: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing and proofreading

MI: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing and proofreading

NN: Study designing, data collection, data analysis, results and interpretation, manuscript writing and proofreading

UH: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing and proofreading

MAR: Idea conception, data analysis, results and interpretation, manuscript writing and proofreading

BA: Study designing, data collection, data analysis, results and interpretation