COMPLICATION-PRONE COPD WITH ARTERIAL HYPERTENSION: INTEGRATED CLINICAL, INFLAMMATORY, PSYCHOSOCIAL, AND EDN1/ENOS ENDOTHELIAL-GENETIC PREDICTORS

Tilloeva Shakhlo Shavkatovna[1*], Yuldashova Rano Urinbaevna[1], Djurayeva Nozima Orifovna[1], Karimova Nilufar Nabijonovna[2], Bokieva Charos Sharofovna[3], Asrorov Akmal Aminjonovich[1]

[1*]Department of Retraining and Advanced Training of Family Doctors named after N.D. Sharipova, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan

[2]Department of Obstetrics and Gynecology, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan

[3]Bukhara Innovative University of Education and Medicine, Bukhara, Uzbekistan

[1]PhD, Head of Department (Tilloeva Shakhlo Shavkatovna) | ORCID: https://orcid.org/0000-0002-0327-650X | Email: tilloyeva.shahlo@bsmi.uz

[1]PhD, Associate Professor (Yuldashova Rano Urinbaevna) | ORCID: https://orcid.org/0000-0003-4936-6006 | Email: yuldashova.rano@bsmi.uz

[1]PhD, Associate Professor (Djurayeva Nozima Orifovna) | ORCID: https://orcid.org/0009-0008-4955-5054 | Email: djurayeva.nozima@bsmi.uz

[2]DSc (Karimova Nilufar Nabijonovna) | ORCID: https://orcid.org/0009-0007-9349-8029 | Email: karimova.nilufar@bsmi.uz

[3]PhD, Associate Professor (Bokieva Charos Sharofovna) | ORCID: https://orcid.org/0009-0000-4730-0279 | Email: tilloyeva.shahlo@bsmi.uz

[1]PhD, Associate Professor (Asrorov Akmal Aminjonovich) | ORCID: https://orcid.org/0009-0003-2264-2469 | Email: asrorov.akmal@bsmi.uz

***Corresponding Author:** Tilloeva Shakhlo Shavkatovna, PhD, Head of the Department of Retraining and Advanced Training of Family Doctors named after N.D. Sharipova, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan | ORCID: https://orcid.org/0000-0002-0327-650X | Email: tilloyeva.shahlo@bsmi.uz

Abstract

Background Chronic obstructive pulmonary disease (COPD) is becoming more and more recognised as a systemic disease with cardiovascular comorbidity. Arterial hypertension has been proposed to increase the instability of COPD by inflammatory activation and endothelial dysfunction, but prognostic markers that combine clinical scores, biomarkers, and endothelial-genetic susceptibility are not fully characterised in inpatient populations in real-life.

Aim: To explore pathogenetic processes and prognostic indicators of complication-prone course in COPD with comorbid arterial hypertension with a focus on systemic inflammation, psychoemotional state, and endothelial-related genetic polymorphisms.

Procedures: A prospective observational design was used in the study and involved 218 patients with spirometry-confirmed COPD who were hospitalised and treated in the Pulmonology Department of the Bukhara Regional Multidisciplinary Medical Centre (Uzbekistan) in 2023-2024. A detailed evaluation was conducted on the patients with check-ups, Pulmonary functional testing (spirometry and peak flowmetry), radiography, measuring the burden of symptoms at the COPD Assessment Test (CAT), psychoemotional screening at the Hospital Anxiety and Depression Scale (HADS), and laboratory testing (complete blood count, C-reactive protein, and fibrinogen). An endothelial-related polymorphism, EDN1 (Lys198Asn) and eNOS (T786C), was analysed genetically. Multivariate modelling was used to detect predictive independent variables of complication-prone course and incremental prognostic power.

Findings: COPD patients who had comorbid arterial hypertension exhibited a more severe clinical phenotype with increased symptom burden as well as psychoemotional distress and systemic inflammatory activation as revealed by increased CRP and fibrinogen. The hypertensive COPD phenotype showed more common variant carriage of EDN1 (Lys198Asn) and eNOS (T786C), which added extra prognostic effects to the clinical-functional indices. A combination of clinical scores, biomarkers and endothelial-genetic markers with integrated models enhanced exclusion of a complication-prone course in comparison with clinical-functional assessment.

Conclusion: COPD associated with arterial hypertension is a high-risk multidimensional phenotype in which systemic inflammation and endothelial vulnerability capabilities are central pathogenetic and prognostic factors. The use of CAT and HADS assessment together with inflammatory biomarkers and EDN1/eNOS polymorphism profiling can improve the risk stratification and can be applied as a supplement to more focused inpatient management approaches.

Keywords: Chronic obstructive pulmonary disease; arterial hypertension; systemic inflammation; C-reactive protein; fibrinogen; endothelial dysfunction; EDN1 (Lys198Asn); eNOS (T786C); CAT; HADS.

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Introduction

Chronic obstructive pulmonary disease is typically defined as a chronic respiratory disease, but in clinical practise it is actually a multisystem disease where airway blocking is just one of the aspects with which the disease is manifested in the pathophysiological process. With the advanced COPD, there is now chronic inflammation, oxidative stress, and hypoxaemia that will start to influence vascular regulation, autonomic balance and even metabolic pathways. Due to this, the long-term consequences of COPD are frequently characterised not by the changes in spirometric indices only, but by the formation of systemic complications and comorbidities accumulating gradually around the underlying primary pulmonary pathology. The reasons why COPD remains one of the most common causes of morbidity and mortality in the whole world, and why the disease is increasingly being talked of as a chronic ailment to be managed on an integrated basis rather than an organ-constrained one is explained by this systemic nature [1].

In the ordinary practise in the hospital, COPD patients are very challenging to treat, especially those individuals who do not exhibit any single pulmonary symptoms but have other chronic illnesses that affect the stability of the disease. Multimorbidity in COPD is no exception; it is the common trend, particularly in patients of middle age and old age. The cardiovascular diseases are in the middle of this spectrum, and in most cohorts of COPD, one of the most common and clinically relevant comorbidities is arterial hypertension. The coincidence of arterial hypertension and COPD results in a more complicated pattern of symptoms, a greater constraint of functional capacity and more frequent hospital admissions, especially in the context of exacerbation on the premises of an unstable blood pressure regulation [2].

The age and similarities in lifestyles are not sufficient explanation for the overlap between COPD and arterial hypertension. Even though smoking history, ageing, and sedentary behaviour lead to both of the conditions, there exists a finer biological connection between chronic lung pathology and systemic vascular disease. COPD is typified by chronic inflammatory stimulation, which starts in the airways, but it does not stay there. Molecules related to inflammation are circulated in the system and make possible the constant low-grade inflammatory activity that, in turn, leads to vascular injury and remodelling. Simultaneously, hypertension is not merely high blood pressure, but it is a condition that is accompanied by chronic stress of the endothelium and structural modifications of the vascular system. When the processes are combined, the outcome of such a combination is a more aggressive clinical syndrome that is more susceptible to complications [3].

One of the most important mechanisms by which COPD can affect the cardiovascular system is systemic inflammation, and it is of particular importance in the case of hypertension that is already in place. C-reactive protein and fibrinogen are inflammatory burden biomarkers, and they are clinically relevant as they reflect processes that transcend the perception of symptoms. CRP shows that there is active inflammatory signalling, and fibrinogen not only reflects inflammation, but also is associated with blood viscosity and thrombogenic practises, which is most applicable in cardiovascular stability. CRP and fibrinogen are high in COPD patients who have comorbid hypertension, and this could be indicative of a biological environment that predisposes their exacerbations to become more severe and their vascular complications to increase. Hence, the incorporation of these biomarkers in prognostic assessment is relevant in order to construct a clinically practical risk model instead of describing laboratory changes [4].

A second vial axis that connects COPD and hypertension is endothelial dysfunction and could represent one of the pathways by which inflammation is converted into clinical outcomes. The endothelium is a dynamic vascular organ that ensures the regulation of the vascular tone, the maintenance of the microcirculatory flow, and the regulation of the inflammatory and thrombotic processes. In the case of a decrease in endothelial performance, the equilibrium becomes abnormal in favour of vasoconstriction and lack of tissue perfusion. Oxidative stress and hypoxia in COPD impair the availability of nitric oxide, which weakens the process of vasodilatory protection. Parallel to that, hypertension causes mechanical stress of the vascular wall, which accelerates endothelial injury and stiffness of arteries. Endothelial malfunction may be further intensified when the two illnesses coincide, and this gives biological reasons as to why cardiovascular instability, pulmonary involvement and more likely chances of exacerbation complications will occur [5].

Biological rivalry of vasoconstrictive and vasodilatory systems is especially applicable in this case, and endothelin-1 and nitric oxide are the main elements of this interaction. One of the strongest endogenous vasoconstrictors is endothelin-1 that has been linked to hypertension and vascular remodelling as well as heightened vascular resistance. Nitric oxide, on the other hand, serves as a protective vasodilator and inhibits platelet aggregation and vascular inflammatory activation. Complications are more likely to happen in the chronic hypoxic stress and inflammatory environment in COPD with hypertension, which shifts the balance to endothelin dominance and nitric oxide deficiency, thereby establishing the kind of vascular environment. This process is clinically significant since it implies not only the correlation, but also the pathophysiological direction, i.e. endothelial regulatory processes are both markers and targets of therapy [6].

This endothelial susceptibility may also be further conspicuously replicated by genetic predisposition, which is believed to cause patient-to-patient variations in the course of disease. In the same clinical state, some patients experience more exacerbations, faster functional deterioration and cardiovascular destabilisation. This heterogeneity implies that there might be genetic variations that influence risk, which include endothelin activity and nitric oxide pathways. Variants that have been mentioned as functionally relevant in terms of polymorphisms and may cause a switch to vascular regulation being more inclined to vasoconstriction and less inclined to endothelial protection include EDN1 Lys198Asn and eNOS T786C. Such variants can enhance the dysfunction of the endothelium in COPD patients with hypertension, where inflammation and hypoxia have already stressed the endothelium and predisposed them to complications. The incorporation of genetic markers in the prognostic evaluation process may thus enhance the process of risk stratification and facilitate a more individualised method of clinical practise [7].

Meanwhile, the prognosis of COPD cannot be seen outside of the human aspect of the illness, namely, the symptom burden and psychoemotional vulnerability. Cat offers systematic observation of the impact of symptoms on everyday activity, quality of sleep, and energy levels, which is why it is a convenient measure of instability in the case of spirometry values. HADS can also be used to measure anxiety and depressive propensity, which frequently occurs in COPD and can greatly influence disease management by decreasing treatment adherence, increasing the perception of dyspnoea, and reducing physical activity. Psychoemotional stress can also disrupt autonomic balance and blood pressure regulation due to hypertension, thereby increasing the risk of complications even more. Thus, a more realistic prognostic framework that incorporates functional indices, inflammatory markers, genetic variants, CAT and HADS analysis could allow the development of more realistic prognostic models of complications in COPD patients with arterial hypertension [8].

Aim and objectives

The current research was conducted to explain the pathogenesis-related pathways and also to determine the prognostic indicators of complications in chronic obstructive lung disease in patients with accompanying arterial hypertension. This comorbid phenotype is so commonly encountered in the routine pulmonology wards that it may seem like an ordinary phenotype; nevertheless, it tends to behave like a clinically distinct pattern with increased clinical instability and increased likelihood of adverse outcomes. As such, the main objective of the research was to get beyond descriptive comparison and to create a clinically viable prognostic tool that can serve to assist in identifying high-risk patients at an early-stage in the inpatient care process in a tertiary-care environment [9].

In the pursuit of this goal, we established our goals in a multidimensional manner to reflect the multidimensional nature of COPD, hypertension interaction: to characterise the clinical course and functional impairment of hospitalised COPD patients with special consideration of the subgroup of patients with arterial hypertension; to quantify symptom burden and health-related quality-of-life impact by the use of COPD Assessment Test; to assess psychoemotional vulnerability by using Hospital Anxiety and Depression Scale as a clinically relevant determinant of symptom perception and disease [10].

Methods

The study was an observational one carried out in a hospital between 2023 and 2024 at the Bukhara Regional Multidisciplinary Medical Centre, which is a tertiary referral hospital located in the region, offering inpatient care to respiratory diseases. It was a study that aimed at maintaining the natural-life clinical profile of COPD admissions, such that the assessments were conducted using standard workflows of diagnosis, with the insertion of structured symptom and psychoemotional measures and molecular genetic tests whose main purpose was to enhance the pathogenetic interpretation and prognostic modelling [11].

The pulmonology department was able to enrol 218 consecutive patients who had confirmed COPD. The adoption of consecutive sampling was done with the objective of reducing selection bias, as well as the cohort being representative of the actual inpatient case-mix as opposed to a conveniently chosen subset. Diagnosis of COPD was done according to GOLD requirements and had to be confirmed by post-bronchodilator airflow restriction with a persistent airflow limitation with FEV1/FVC of less than 0.70 [12].

The definition of arterial hypertension was made according to the recorded history, the use of antihypertensive treatment, and the recurring inpatient blood pressure readings according to the modern guideline values. The patients had to be older than 40 years, they needed to be certain about COPD, they had to be treated in the inpatient pulmonology unit within the specified time, and they were to give written informed consent, including a further consent to genetic testing. Inclusion criteria were selected to minimise diagnostic overlap and biomarker confounding, and comprised acute infection with a transient obstruction without underlying COPD, active pulmonary tuberculosis, lung malignancy, bronchiectasis as the primary diagnosis and severe decompensated heart failure or end-stage renal or hepatic disease [13]

Structured clinical assessment was used on all participants, and its focus was on smoking exposure, occupational hazards, medication patterns, exacerbation history, and comorbidity profile. Measurement of blood pressure was done under resting conditions, and repeated measurements were made to enhance reliability. Inpatient records were used in the recording of exacerbations and past hospitalisation, and were cross-validated by structured

patient interviews so that there was consistent endpoint recording [14].

The test was conducted on pulmonary function through spirometry as per the ATS/ERS criteria, with FEV1, FVC and FEV1/FVC ratio recorded, and post-bronchodilator testing was done to confirm the result. Peak flowmetry was conducted as another functional measure that shows the intensity and variability of airflow limitation in a bedside format, which is practicable in inpatient settings. All participants were subjected to chest radiography to exclude other possible diagnoses and record structural patterns that are applicable in the COPD severity and complications related results [15].

The COPD Assessment Test (initially chosen due to its measurement of patient-centred impact of disease) was used to assess symptom burden and health-related quality of life as it is considered to complement spirometry (including daily functional impairment, sleep disturbance and reduced energy). The scale used to measure psychosomatic vulnerability was the Hospital Anxiety and Depression Scale, but the anxiety and depression subscales were assessed individually, because psychoemotional stress can mediate the perception of dyspnea, adherence to the treatment, and physiological reactions to stress, which is clinically significant in COPD and could be the cause of blood pressure fluctuations in hypertensive patients [16].

Laboratory studies consisted of complete blood count, C-reactive protein as a measure of an inflammatory activity on the systemic level, and plasma fibrinogen as a measure of the correlation between an inflammatory activity and a prothrombotic disposition. These were chosen based on their clinical availability in the conditions of a typical hospital environment and have pathogenetic significance to COPD hypertension comorbidity, where inflammatory vascular susceptibility should be augmented [17].

A molecular genetic test was done on endothelial regulation pathways, and also the genotyping of EDN1 (Lys198Asn) and eNOS (T786C) polymorphisms was done. These variants were chosen because they are biologically plausible. EDN1 is associated with endothelin-mediated vasoconstriction, and eNOS is involved in endothelial protection mechanisms involving nitric oxide. The results of genetic analysis were combined with clinical, functional, laboratory and psychoemotional data to assess their role in predicting complications in an applied prognostic scenario [18].

The main outcome was a course of exacerbation, a minimum of two moderate exacerbations in 12 months or one exacerbation which necessitated hospitalisation according to the medical registers and a structured history. Secondary endpoints were severe airflow limitation (FEV1 < 50 percent predicted), high symptom burden (CAT 20 or more), clinically important anxiety and/or depression (HADS subscale 8 or above) and high levels of inflammatory/procoagulant activity indicated by CRP and fibrinogen out of range [19]

They were statistically analysed by descriptive statistics with distribution analysis, between-group analysis by the use of parametric or non-parametric methods depending on the situation, correlation analysis between clinical and biomarker domains and multivariate logistic regression as independent predictors of complications. Predictive discrimination was assessed by ROC analysis with the calculation of the area under the curve, and the predicted probabilities were converted into a clinically relevant risk stratification method. The statistical significance was predetermined to be less than two-sided below 0.05. [20].

Ethical norms were followed strictly. The involvement was based on a voluntary basis; all participants were given informed consent, confidentiality was ensured during the entire data management process, and genetic testing was conducted after further consent in line with the ethics of biomedical research and the postulates of the Declaration of Helsinki [21].

Results

Two hundred and eighteen patients with spirometry-proven chronic obstructive pulmonary disease were studied, who presented a consecutive population of inpatients with COPD that had to be treated in the Pulmonology Department of the Bukhara Regional Multidisciplinary Medical Centre in 20232024. The apparent observation of this cohort was that COPD was hardly a solitary pulmonary disease but rather most commonly appeared as a complicated cardiopulmonary phenotype. Hypertension of the arteries was detected in 142 individuals, i.e. almost two-thirds of the cohort had both the clinically significant vascular burden and airway obstruction. This comorbidity was not an imaginary background diagnosis; it actually formed the clinical picture of instability, the intensity of the symptoms, and the biological picture of systemic stress, which is why a specific risk phenotype of COPD complicated by hypertension should be considered, but not a common comorbidity label.

Comparing the baseline profiles, the subgroup of hypertensive COPD patients showed a uniformly heavier entry phenotype, which is characterised by advanced age, increased metabolic load and an unstable history of diseases. Above all, COPD and hypertension patients reported and recorded a higher number of recent exacerbations and increased hospital use, which implies that comorbidity was followed by a more vulnerable course before the introduction of biomarker and genetic data. This difference in the baseline is essential in a prognostic situation in which a phenotype presenting to the hospital with recurrent destabilisation has increased inflammatory signalling, enhanced endothelial dysfunction and reduced adaptation capacity [23]. Table 1 shows the comparison of the baseline.

Table 1. Baseline characteristics (COPD+AH vs COPD only)

Variable	COPD + AH (n=142)	COPD only (n=76)	p-value
Age, years (mean ± SD)	66.4 ± 8.1	61.2 ± 7.9	<0.001
Male sex, n (%)	104 (73.2)	54 (71.1)	0.74
Smoking history, pack-years (median [IQR])	26 [18–38]	22 [14–31]	0.02
BMI, kg/m² (mean ± SD)	27.6 ± 4.8	25.8 ± 4.2	0.01
SpO_2 at admission, % (mean ± SD)	91.2 ± 3.4	92.4 ± 3.2	0.01
COPD duration, years (median [IQR])	9 [6–13]	7 [4–11]	0.03
≥2 exacerbations in past 12 months, n (%)	78 (54.9)	27 (35.5)	0.006
COPD hospitalisations in the past year, n (%)	49 (34.5)	16 (21.1)	0.04

Demographic and clinical characteristics of hospitalised COPD patients with comorbid arterial hypertension stratified at baseline. Continuous variables are represented as n (SD) or n (IQR) as mean on SD or median on IQR, respectively, depending on the spread. Categorical variables n (n) and (n). Parametric and non-parametric tests were appropriate where comparisons were to be made between groups.

The next important level of differentiation was pulmonary function testing. In spite of airflow limitation being the characteristic feature of COPD, there was a more intensive functional impairment of the spirometry and peak flow indices in the hypertensive subgroup, which indicated that comorbid hypertension was related to a more clinical manifestation of respiratory impairment. This can indicate a prolonged illness process, an accumulation of exposure load or a more susceptible systemic condition in which bronchial hindrance and vascular pressure reciprocally enhance each other. It was not just a statistical difference, but it was in agreement with the bedside practise in which hypertensive COPD patients tend to have worse tolerance to exertion, increased dyspnoea perception and exhibited greater variability in symptoms [24].

But the most persuasive aspect of the comorbid phenotype was that patient-centred experience correlated with functional decline. The results showed that COPD with hypertension had a significantly higher CAT score, which supports the argument that not only could symptom burden be quantified, but it was also functionally significant in the daily life aspect of daily life that includes mobility, quality of sleep and fatigue. Simultaneously, psychoemotional screening showed that the patterns of anxiety and depressive symptoms were more evident among hypertensive COPD patients. In practise in the real inpatient setting, this kind of psychoemotional burden cannot be a discrete mental health problem; more frequently, it can be an added destabilisation process that enhances dyspnoea perception, decreases adherence to medication and heightens physiological responsiveness to stress. This compounded picture of poorer functional performance and greater CAT/HADS load is summed up in Table 2 with systemic biomarkers. [25].

Table 2. Pulmonary function + CAT/HADS + biomarkers

Variable	COPD + AH (n=142)	COPD only (n=76)	p-value
FEV1, % predicted (mean ± SD)	47.8 ± 14.6	53.9 ± 15.2	0.004
FEV1/FVC ratio (mean ± SD)	0.52 ± 0.08	0.55 ± 0.09	0.03
Peak Expiratory Flow, L/min (mean ± SD)	214 ± 67	241 ± 71	0.01
CAT score (mean ± SD)	22.7 ± 6.1	19.4 ± 5.7	<0.001
HADS-A score (median [IQR])	9 [6–12]	7 [5–10]	0.01
HADS-D score (median [IQR])	8 [5–11]	6 [4–9]	0.008
CRP, mg/L (median [IQR])	12.6 [7.2–22.4]	8.9 [5.1–15.6]	0.002
Fibrinogen, g/L (mean ± SD)	4.38 ± 0.92	3.91 ± 0.81	<0.001

Performance of a comparative analysis of functional indices, patient-reported symptom burden (CAT), psychoemotional status (HADS) and systemic biomarkers (CRP and fibrinogen) of COPD patients with comorbid arterial hypertension and COPD patients.

The pathogenetic soundness of the findings was enhanced by systemic biomarker variations. CRP and fibrinogen were also increased in COPD and hypertension, suggesting that there is a biologically measurable inflammatory and prothrombotic condition that can potentially lead to complication propensity. Not an incidental occurrence, but a functional intermediary between bronchial blockage and vascular susceptibility, in the comorbid phenotype, inflammation is no longer an incidental occurrence. CRP indicates that it is a sign of systemic inflammatory signalling in action, whereas fibrinogen indicates that it is more coagulable and its viscosity is increased, which is clinically useful in hypertension because the strain on the endothelium is already established. The higher symptoms, worse functioning and high-biomarker congruence indicate the multidimensional instability phenotype where exacerbation and hospitalisation are more likely [26].

Genetic testing also brought in another dimension of explanation, especially to the COPD-hypertension overlap. The EDN1 Lys198Asn mutation is a possibility of transition to endothelin-based vasoconstrictive control, whereas eNOS T786C can undermine the abundance of nitric oxide and consequently endothelial protection. Genotype

distribution in the cohort showed a trend towards increased variant carriage in hypertensive COPD patients, indicating the possibility of the enrichment of the endothelial susceptibility in the subgroup where the vascular stress is persistent. Notably, it does not mean that the genetic predisposition is the sole determinant of prognosis; indeed, it is conducive to a model according to which the genetic predisposition moderates the extent to which inflammation and hypoxaemia are converted into endothelial dysfunction and clinical effects. Table 3 gives the genotype distribution [27].

Table 3. Distribution of EDN1 and eNOS polymorphisms

Genetic marker	Category	COPD + AH (n=142)	COPD only (n=76)	p-value
EDN1 (Lys198Asn)	Lys/Lys	63 (44.4)	42 (55.3)	0.04
	Lys/Asn	59 (41.5)	26 (34.2)	
	Asn/Asn	20 (14.1)	8 (10.5)	
eNOS (T786C)	TT	58 (40.8)	41 (53.9)	0.03
	TC	64 (45.1)	26 (34.2)	
	CC	20 (14.1)	9 (11.9)	

Genotype distribution of EDN1 (Lys198Asn) and eNOS (T786C) endothelial regulatory related polymorphisms in COPD patients stratified by the occurrence of presence of arterial hypertension.

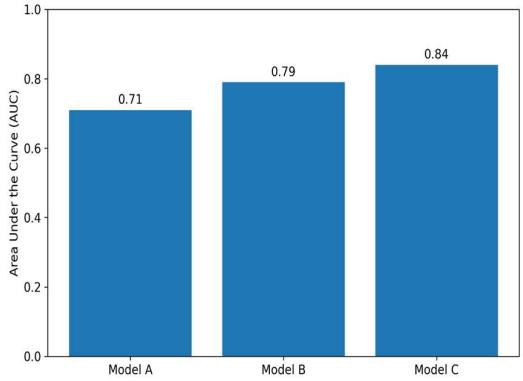
We left descriptive comparisons to multivariate modelling in which complication-prone course was used as the primary outcome to ascertain which markers were really independent prognosticators. The last model affirmed that the multidimensional risk architecture of COPD complicated with hypertension was complex in nature: age and pulmonary function were predictable factors, but patient-centred symptom burden and systemic biomarkers were among the strongest predictors even after correction. Interestingly, genetic variants did not lose their independent associations, implying that endothelial predisposition provides extra risk data as opposed to only being a manifestation of clinical severity. All multivariate model is at Table 4 [28].

Table 4. Independent predictors of complication-prone course (multivariable model)

Predictor	Adjusted OR	95% CI	p-value
Age (per +1 year)	1.04	1.01–1.07	0.01
FEV1 (% predicted, per -10%)	1.28	1.10–1.49	0.002
CAT score (per +1 point)	1.11	1.05–1.18	<0.001
CRP (per +5 mg/L)	1.22	1.08–1.39	0.001
Fibrinogen (per +1 g/L)	1.46	1.12–1.90	0.005
EDN1 Asn allele carrier	1.74	1.03–2.93	0.04
eNOS C allele carrier	1.69	1.01–2.81	0.046
Hypertension (present)	1.58	1.01–2.48	0.048

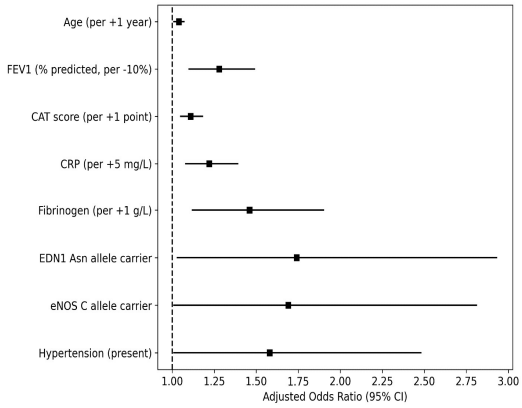
Multivariate logistic regression model of independent predictors of complication-prone course in COPD cohort. The confounders that are incorporated in the final model are adjusted; allele carriers are the heterozygous or homozygous forms of a variant.

Figure 1. Incremental prognostic performance of sequential models for complications in COPD with arterial hypertension (ROC analysis)



ROC curves that compare three sequential prognostic models that can forecast a complication-prone course in hospitalised COPD. Model A contains the variables of demographic and pulmonary function, Model B also contains the variable of systemic inflammatory biomarkers (CRP and fibrinogen), and Model C contains the variable of endothelial-related genetic polymorphism EDN1 (Lys198Asn) and eNOS (T786C). The gradual rise of AUC indicates the progressive prognostic benefits of incorporating systemic inflammation and endothelial-genetic susceptibility into the clinical-functional routine process, especially in the case of hypertensive COPD phenotype.

Figure 2. Independent predictors of complication-prone course in COPD: multivariable logistic regression (forest plot)



Forest plot showing adjusted odds ratios and 95% confidence intervals of independent predictors included in the final multivariable logistic regression model Predictors represent different domain of interaction between the hypertension and thelessness of the patient: pulmonary functional impairment, patient-reported symptom burden (CAT), systemic inflammation (CRP and fibrinogen), psychoemotional vulnerability (HADS) and polymorphisms of genes related to the endothelium. The relative strength of each determinant is highlighted and visually illustrates that the risk architecture of complications in hypertensive COPD is multidimensional and not due to one clinical marker.

Finally, according to model discrimination analysis, the predictive performance was improved when biomarkers and genetic indicators were added to clinical-functional variables. This supports the main practical message of the study, that in a hospitalised group of people with COP, the subgroup of patients with arterial hypertension benefits from risk assessment approaches that go beyond spirometry and include the presence of systemic inflammation, symptom burden and endothelial genetic vulnerability. In a real pulmonology ward, such multidimensional stratification is valuable as it will help clinicians to identify those patients who might need more intensive monitoring, better prevention of exacerbation triggers and more intensive cardiopulmonary stabilisation strategies [29].

Discussion

The results of this study support the opinion that chronic obstructive pulmonary disease complicated by arterial hypertension should be considered as a specific high-risk phenotype rather than a simple concurrence of two common chronic diseases. In our consecutive inpatient group of 218 patients with a diagnosis of chronic obstructive pulmonary disease, who were treated in Bukhara during 2023-2024, a high prevalence of hypertension was observed, which was consistently associated with a more unstable clinical course with increased frequency of exacerbations, higher burden of symptoms and wider functional limitation. Such clustering of respiratory and vascular pathology is clinically important because it represents a warning for decreased physiologic reserve and a propensity for systemic decompensation, which may not be adequately assessed by the interpretation of the severity of the disease process of COPD using spirometry alone. These observations are in line with current evidence that cardiovascular co-morbidity increases morbidity and mortality in patients with CVD related to their co-morbidity in asthma, but our data emphasise that this interaction is particularly evident in the hospitalised population, where the mechanisms of destabilisation accumulate and manifest with greater intensity [30].

A key message to be gleaned from our results is the unambiguous integration of patient-centred symptom burden, psychoemotional vulnerability, and functional impairment in the hypertensive subgroup of patients with obstructive sleep apnea. Elevated CAT scores in the comorbid group indicate that the disease is perceived as more disabling in everyday life, with the ability to move, to sleep and to feel tired being affected. Importantly, this symptom burden was not occurring in isolation; it was accompanied by higher levels of anxiety and depressive symptoms as measured by HADS. In clinical reality, such psychoemotional stress is rarely a separate phenomenon in the field of chronic obstructive pulmonary disease; it interacts with the perception of dyspnoea, the autonomic regulation, the sleep fragmentation, and the treatment adherence. In the presence of hypertension, this interaction may be even greater as the years of vascular strain and increased sympathetic activity may result in an underlying internal environment where both respiratory symptoms and blood pressure instability develop with greater ease during inflammatory flares or hypoxaemic episodes. Therefore, CAT and HADS combined give more than descriptive information: They reflect clinically meaningful vulnerability, which is associated with biological markers of systemic stress and helps to understand why the comorbid subgroup displays a more complication-prone pattern [31].

Systemic inflammatory and haemostatic markers offer a pathogenetic link between the two diseases (COPD and hypertension) in our cohort. The elevation of CRP and fibrinogen in hypertensive patients with COPD is suggestive that the comorbid phenotype is characterised not only by airway inflammation but also systemic inflammatory activation with prothrombotic characteristics. This combination is of special relevance in hypertension, where the integrity of the endothelium is chronically challenged and the tendency for vascular stiffness to progress over time is high. In such a setting, inflammatory mediators may cause an amplification of endothelial dysfunction, a disturbance of microvascular regulation and impair tissue oxygen delivery, while the increased fibrinogen may also increase blood viscosity and promote perfusion mismatch. This biological configuration provides a plausible mechanism for the observed exacerbation-prone clinical course, as episodes of increased inflammation can translate into respiratory destabilisation as well as vascular stress, which would increase the likelihood of complications and hospital readmissions. From an applied perspective, CRP and

fibrinogen are of great importance as they account for this systemic risk layer and may aid in early identification of patients who need to be more closely monitored than the spirometric classification would warrant [32].

The merging of endothelial genetic markers is the newest aspect of this study and is important to add biological depth to the prognostic interpretation. EDN1 (Lys198Asn) and eNOS (T786C) polymorphisms were chosen based on their role in vascular tone control and endothelial homeostasis: endothelin pathways are generally pro-vasoconstrictive and remodelling, whereas nitric oxide has protective anti-inflammatory and vasodilatory activities. In our analysis, variant carriage showed meaningful associations in the hypertensive phenotype of the comorbidity of chronic obstructive pulmonary disease and was relevant after adjustment in the multivariable modelling. This does not mean that genetic variants "cause" complications in their own right but supports a more realistic susceptibility model in which the endothelial-genetic predisposition has a modulating effect on the strength of inflammation/hypoxaemia in translating to vascular dysfunction. In patients having been exposed to recurrent exacerbations, systemic inflammation and oxygen fluctuation, such a predisposition can plausibly result in accelerated endothelial instability and increased cardiopulmonary stress response, with complications likely to occur in patients with even comparable spirometric severity [33].

An important strength of our results is that the prognostic concept is not only supported by associations, but also by improvements in predictive discrimination could be measured. ROC analysis showed a stepwise increase in AUC by the addition of inflammatory biomarkers for clinical-functional predicting factors and an additional increase by integrating genetic markers. This pattern suggests that biomarkers and genotypes are non-redundant sources of information and enhance risk stratification as opposed to merely reflecting the severity of the disease. Clinically, this means that two patients with similar FEV1 may have different chances of having a course with complications based on system inflammation, burden of symptoms and susceptibility of endothelium. Such a conclusion is of particular value for the practise of inpatient pulmonology, as identifying high-risk individuals early on may influence the intensity of monitoring, frequency of reassessment and cardiopulmonary stabilisation strategies during in-hospital stay and post discharge [34].

These results have direct practical implications for the clinical management, more so in settings similar to our regional inpatient setting. First, a priority subgroup for structured risk assessment at admission should be those patients with arterial hypertension among those with COPD. Second, the feasibility of a combined clinical-biomarker panel based on CAT score, CRP, and fibrinogen is feasible, relatively inexpensive and ready for transfer into routine practice - this can be used as an early warning system for which individuals are most likely to develop complications. Third, psychoemotional screening should not be considered optional, as symptoms of anxiety and depression are likely to affect clinical progression of dyspnoea, the behavioural response, adherence to medication and autonomic balance, issues that are particularly relevant in hypertensive subjects. Genotyping, where available, might be an added fine-tuning instrument, especially in the case of borderline or clinically unclear cases, and might aid in the more personalised management of prevention of exacerbation recurrence [35].

There are a number of limitations that should be recognised. The inpatient cohort design will enrich the sample with unstable and more severe cases; therefore, the extrapolation to outpatient populations should be done cautiously. Biomarker evaluation in the current analysis was constrained to CRP and fibrinogen, and broader panels used, such as those encompassing endothelial injury, oxidative stress, and vascular stiffness, could be used to further strengthen mechanistic interpretation. In addition, the analysis of the genetics was limited to 2 variants related to the endothelium and should be considered targeted, rather than holistic. Nevertheless, the study has important strengths that contribute to its clinical credibility: its recruitment of individuals consecutively in a real-world pulmonology setting, the multidimensional nature of the assessment with the inclusion of symptoms, the psychoemotional assessment and functional testing and an integrated approach to prognostic modelling based on biologically plausible pathways [36].

In conclusion, our study shows that the combination of arterial hypertension and COP represents a high-risk phenotype with an increased burden of symptoms, a psychoemotional vulnerability, a high level of systemic inflammation and endothelial susceptibility. The combination of clinical scores (CAT), inflammation (CRP and fibrinogen) and endothelial genetics (EDN1 and eNOS) enhances the prognostic stratification. It provides a rational basis for more specific inpatient management and post-discharge prevention strategies. These findings may support the development of pragmatic risk-adapted frameworks for the care of patients with COPD in comorbid populations, as well as contribute to the development of more personalised approaches in regions where repetitive exacerbations and cardiovascular comorbidity considerably affect clinical outcomes [37].

Conclusion

This study shows that chronic obstructive pulmonary disease complicated by arterial hypertension is a clinically and biologically distinct high-risk phenotype with greater instability and a higher tendency to develop complications. In a cohort of hospitalised patients with chronic obstructive pulmonary disease (n = 218) studied at the Bukhara Regional Multidisciplinary Medical Centre over the period 2023-2024, the presence of hypertension was

found to be consistently associated with a greater burden of symptoms, worse functional status and increased systemic inflammatory activation. Importantly, the results indicate that the determination of prognosis in hypertensive patients with clinically significant levels of CO2 can't be based solely on spirometric severity, as patient-centred outcomes and systemic markers add another clinically significant risk information.

The combination of symptom burden (CAT), psychoemotional vulnerability (HADS) and inflammatory biomarkers (CRP and fibrinogen) identified a coherent multidimensional profile of vulnerability likely to be at the root of the recurrent destabilisation and complication-prone course. Moreover, endothelial-related genetic polymorphisms EDN1 (Lys198Asn) and eNOS (T786C) provided a mechanistically based layer of susceptibility in support of the notion that endothelial dysfunction may serve as a central link between airway pathology and vascular instability in this comorbid population. The non-redundant prognostic value of the factors is further confirmed by the stepwise improvement in the predictive performance upon the addition of biomarkers and genetic markers. Overall, a multidomain strategy to improve early risk stratification by combining clinical-functional evaluation with biomarker and endothelial-genetic profiling may help to support a more targeted management approach for patients with arterial hypertension in patients with COPD and in particular in inpatient settings where burden of exacerbations and complications is the highest.

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