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STUDY THE ACTIVITY OF ENDOTHELIN CONVERTING ENZYME-1 AND ANGIOTENSIN CONVERTING ENZYME-2 IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract:
Background: Asthma is a chronic inflammatory disease of the airways, it results from a combination of genetic predisposition and environmental factors. Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease characterized by persistent respiratory symptoms and airflow limitation. Endothelin Converting Enzyme-1 (ECE-1) is an enzyme involved in the activation of endothelin-1 (ET-1), a potent vasoconstrictor and pro-inflammatory peptide. ET-1 plays a significant role in the pathophysiology of both asthma and COPD. Angiotensin-Converting Enzyme (ACE) plays a pivotal role in the renin-angiotensin system, converting angiotensin I to the potent vasoconstrictor angiotensin II, and inactivating bradykinin, a vasodilator. This enzyme is implicated in the pathophysiology of both asthma and COPD.
Methods: we performed Case-Control study compressing (n=160) including asthmatic patients (n=40) and COPD patients (n=40) with apparently healthy control subject group (n=80).
Results: The mean ± SD age of patients with Asthma were (167.19± 19.66 years in ECE-1), (28.13± 5.12 years in ACE_2) and in the Chronic Obstructive Pulmonary Disease were (213.75± 15.27 years in ECE-1), (24.36± 5.25years in ACE_2) there was no a significant difference between groups patients. The mean ECE-1 levels with standard deviation (Mean± SD) are 167.19± 19.66 for Asthma, 213.75± 15.27 for COPD, and 101.43± 18.04 for Control. The statistical significance ($Pr > F(Model)$) is highly significant for Asthma ($p < 0.000001$), indicating a strong association between Asthma and ECE-1 levels. However, for COPD and Control groups, the p-value is not provided, necessitating further analysis or interpretation to understand the significance of these results. The mean ACE_2 levels with standard deviation (Mean± SD) are 28.13± 5.12 for Asthma, 24.36± 5.25 for COPD, and 52.48± 13.36 for Control. The statistical significance based on ANOVA ($p < 0.000001$) is highly significant for Asthma, suggesting a strong association between Asthma and ACE_2 levels. However, for the COPD and Control groups.
Conclusion: serum activity of, Endothelin Converting Enzyme-1 a significant increase in patients with Asthma and Chronic Obstructive Pulmonary Disease compared with control, and Angiotensin

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Converting Enzyme-2 activity decreased in patients with Asthma and Chronic Obstructive Pulmonary Disease compared with control**.**

Keywords: Endothelin, enzyme-1, Angiotensin, enzyme-2, asthma, Chronic Obstructive Pulmonary Disease

1. Introduction

Asthma is a chronic lung disease which cause inflammation in the bronchioles, narrow the airways and characterized by airflow obstruction and bronchospasm, coughing, chest tightness, wheezing, shortness of breath referred as asthma attack **(Kuruvilla et al., 2019)**. These episodes are usually associated with widespread but variable air flow obstruction that is often reversible either spontaneously or with treatment **(Holguin et al., 2020)**.

Chronic obstructive pulmonary disease (COPD) is a progressive condition characterized by irreversible airflow limitation. In general, this condition results from an abnormal inflammatory response after exposure of the lung to noxious particles and/or gases **(Vogelmeier et al., 2020)**.
A worldwide increase in smoking has led to a dramatic rise in the prevalence of this condition. However, while cigarette smoke remains the most significant risk factor for developing COPD, up to one-quarter of those with COPD are nonsmokers. Individuals with COPD typically complain of nonspecific symptoms that include chronic cough, mucus hypersecretion, and shortness of breath **(Fiore, 2009)**. In asthma and COPD , there is an increased production of endothelin-1, which contributes to airway inflammation and bronchoconstriction. ECE-1 is involved in the processing of big ET-1 to its active form, and its upregulation may lead to increased levels of ET-1 in the airways, exacerbating inflammation and airway hyperresponsiveness **(Snell and Newbold, 2008).**
ACE_2 is responsible for the degradation of bradykinin. Inhibition of ACE_2 can lead to increased levels of bradykinin **(Arya et al., 2020)**. Bradykinin is a vasodilator peptide that plays a role in inflammation and bronchoconstriction. In asthma and COPD, increased levels of bradykinin can contribute to airway hyperresponsiveness and bronchoconstriction, leading to symptoms such as wheezing and shortness of breath. Bradykinin can also stimulate the release of inflammatory mediators, contributing to airway inflammation and remodeling in asthma and COPD **(Ricciardolo et al., 2018).**

2. Materials and Methods

The present work included case control study, participant numbers 160, including (n=80) patients asthmatic, (n=40) and COPD (n=40) with healthy control (n=80). Were selected from respiratory Consultation Unit and at Al Hussein Teaching medical city/Karbala/ Iraq.
The sociodemographic aspects of the patents were collected through the self-reported technique (questionnaire). Inclusion criteria for patients included asthma and COPD diagnosis, 20-50 age range.
The exclusion criteria was all patients with chronic liver disease, thyroid problem, cardiac disease, renal disease, diabetic mellitus, hypertension, pregnant and postmenopausal women, and COVID-19.

Blood samples (5ml) were collected from each patient. The collected blood as stored in gel tube (contain a special gel that separates blood cells from serum to cause blood to clot quickly). The samples were collected between 08.00-12.30 am. Blood was allowed to clot at 37°C for 10-15 minutes and then

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centrifuged at 2000xg for approximately 10-15 minutes. After, stored at -20°C, the collected serum from patients and controls were used for the measurements of the following parameters: ECE-1 activity and ACE_2 activity.

Statistical Analysis:

The Statistical Analysis IBM SPSS Statistics 26 program was used to detect the effect of different factors on study parameters. One-way ANOVA and T-test was used to significantly compare between means. Chi-square test was used to significantly compare between percentage (0.05 and 0.01 probability). Correlations between quantitative variables were carried out using Spearman correlation coefficient. P values less than 0.05 were considered statistically significant.

3. Results

Participant Characteristics

it is essential to give an overview of the participants' characteristics in the study. including demographic details such as age, gender distribution, medical history, as well as any specific inclusion or exclusion criteria that were applied. Having a clear understanding of the participant profile is crucial as it provides context and background information that helps interpret the analysis of biochemical markers.

The statistics for age in three groups, namely Asthma, COPD, and Control, reveal important insights. In the Asthma group, ages range from 31 to 33.50 years, with a mean age of 34.60 ±8.47years. Similarly, the COPD group exhibits a wider age range of 33 to 42 years, with a median and mean age of 41.83± 8.36 years. In contrast, the Control group has an age range of 28 to 34.50 years, with a mean age of 35.07 ± 7.82.

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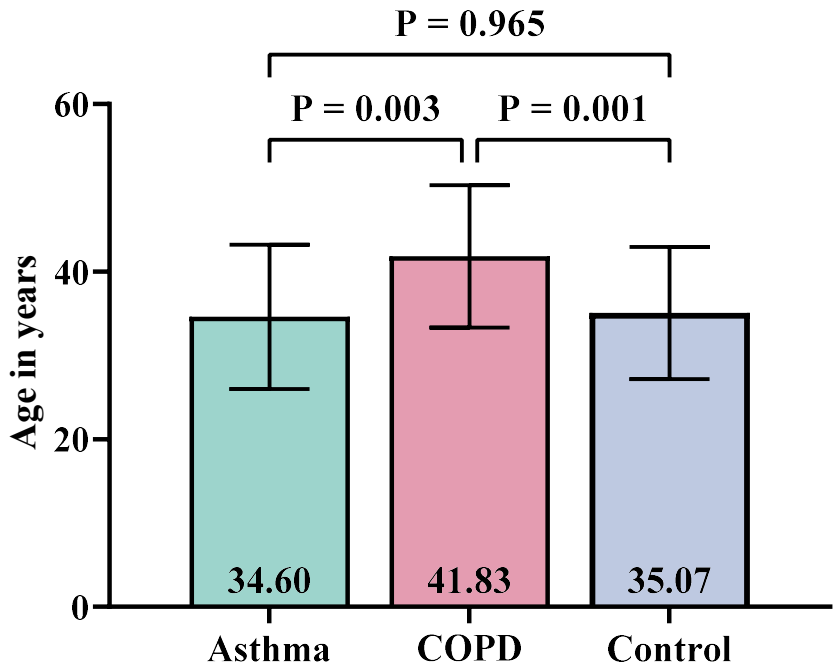

Figure** Error! No text of specified style in document.**-1 Means of Age by groups

Table** Error! No text of specified style in document.**-1 Descriptive statistics and comparison between the three groups of the biomarkers and Age

Statistic	Range	Median	Mean± SD	SEM	Pr > F(Model)	Groups*
Age | asthma	31.00	33.50	34.60± 8.47	1.57	**< 0.000001**	**B**
Age | COPD	33.00	42.00	41.83± 8.36	1.55		**A**
Age Control	28.00	34.50	35.07± 7.82	1.02		**B**
ECE-1 asthma	77.74	167.49	167.19± 19.66	3.65	**< 0.000001**	**B**
ECE-1 COPD	68.17	210.58	213.75± 15.27	2.84		**A**
ECE-1 Control	78.13	103.69	101.43± 18.04	2.35		**C**
ACE_2 asthma	26.13	28.44	28.13± 5.12	0.95	**< 0.000001**	**B**
ACE_2 COPD	19.70	25.15	24.36± 5.25	0.97		**B**

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ACE_2 Control	59.54	48.74	52.48± 13.36	1.74		**A**

Biochemical Analysis

The core of this chapter focuses on the analysis of biochemical markers measured in both patient and control groups. Each marker is evaluated individually, with a detailed description of the methodology used for measurement and analysis.

ECE-1

Figure 3-2 illustrates the ECE-1 concentrations in three distinct groups. Individuals diagnosed with Asthma and COPD exhibited notably elevated ECE-1 levels, registering 167.19± 19.66 and 213.75± 15.27 respectively, when compared to the Control group which recorded 101.43± 18.04. The difference is statistically significant as indicated by the P-value of less than 0.001. Notably, the ECE-1 levels in the COPD group were significantly different from those in the Asthma group

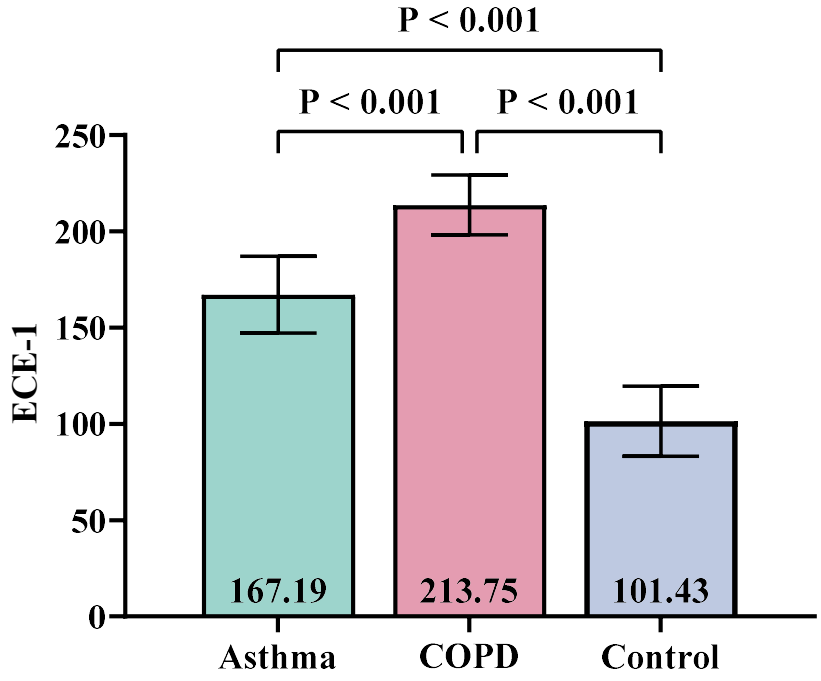

Figure** Error! No text of specified style in document.**-2 Bar graph comparing the mean levels of Endothelin Converting Enzyme-1 (ECE-1) with 95% CI of means among individuals with Asthma, Chronic Obstructive Pulmonary Disease (COPD), and a Control group

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Angiotensin Converting Enzyme-2

The results pertaining to Angiotensin-Converting Enzyme-2 (ACE_2) are outlined in Table 3-1, which presents the outcomes of ANOVA and subsequent Tukey-Kramer test pairwise comparisons regarding ACE_2 levels across various study groups. Specifically, in the asthmatic group, the mean ACE_2 level was measured at 28.1263 ± 5.2083. Notably, this ACE_2 level significantly differs ($P < 0.05$) from that of the Control group, which recorded an ACE_2 level of 52.4762 ± 13.4746. Within the COPD group, the mean ACE_2 level was 24.3567 ± 5.3402, also exhibiting a significant difference ($P < 0.05$) from the Control group's ACE_2 level.

These findings collectively indicate a significant variance in ACE_2 levels across all three groups. Both the Asthma and COPD groups display notably lower ACE_2 levels compared to the Control group. Such observations suggest a potential role of ACE_2 in the context of these respiratory conditions.

The summarized depiction of these findings can be observed in Figure 3-4, encapsulating the distinct ACE_2 level patterns observed within the study groups and reinforcing the significance of ACE_2 in relation to the respiratory conditions under investigation.

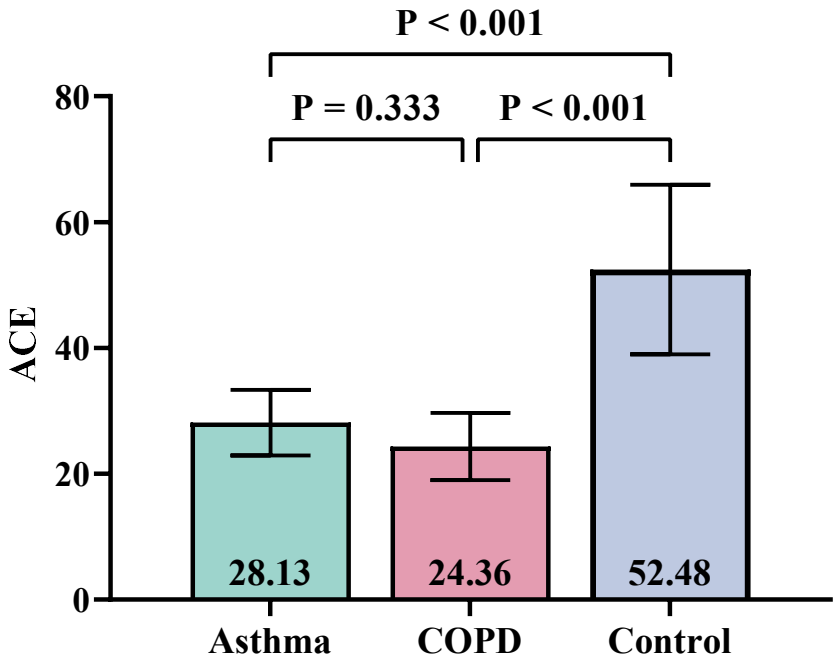

Figure** Error! No text of specified style in document.**-2 bar chart comparing the ACE_2 (Angiotensin-Converting Enzyme-2) levels in three groups: asthma patients, COPD patients, and a control group.

Correlation analysis

the correlation between Age and ECE-1 yields a positive coefficient of 0.254; however, the non-

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significant P-value of 0.1761 suggests an absence of statistical significance at the 0.05 level, as well as Age and ACE_2, all displaying positive correlations but lacking statistical significance.
Contrastingly, in the COPD Patients group, a non-significant correlation between Age, ECE-1 and ACE_2.
Lastly, within the Control Group, correlations between ECE-1 and ACE_2, ECE-1 and Age, are all characterized by weak or very weak positive or negative coefficients, with none displaying statistical significance.

Table** Error! No text of specified style in document.**-2 correlogram showing the Pearson correlation coefficient and significance level between parameters within Asthmatic patients

1.0		-1.0
Age	1	
ECE-1	0.254 P=0.1761	1
ACE_2	-0.212 P=0.2616	-0.299 P=0.1082
	Age	**ECE-1**

Table** Error! No text of specified style in document.**-3 correlogram showing the Pearson correlation coefficient and significance level between parameters within COPD patients

1.0		-1.0
ECE-1	1	
Age	-0.050 P=0.7949	1
ACE_2	0.166 P=0.3814	0.007 P=0.9728
	ECE-1	**Age**

Pearson correlation coefficient

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Table** Error! No text of specified style in document.**-4 correlogram showing the Pearson correlation coefficient and significance level between different parameters within control group

1.0 → -1.0		
ECE-1	1	
ACE_2	0.026 P=0.8456	1
Age	0.081 P=0.5376	-0.076 P=0.5616
	ECE-1	**ACE_2**

Receiver Operating Characteristic analysis

Table 3-5 presents ROC analysis comparing biomarkers in distinguishing between the study groups: Asthma vs Control, COPD vs Control, and COPD vs Asthma.

Asthma vs Control group

the biomarkers ECE1, ACE_2 have AUC values ranging from 0.992 to 0.997. ECE-1 stands out with the highest AUC of 0.997, followed closely by ACE_2 at 0.992. These values suggest that ECE1 and ACE_2 have excellent discriminatory power in distinguishing between asthma and control groups. The cutoff values for these biomarkers range from >35.05 to >127.34, indicating the threshold above which a sample is classified as belonging to the asthma group.

COPD vs Control

The biomarkers exhibit high AUC values ranging from 0.998 to 1.000, with ECE-1 having a perfect AUC of 1.000. This indicates that ECE-1 is highly effective in differentiating COPD from control subjects. The cutoff values for ECE-1, ACE_2 are >133.03, ≤33.03 respectively. These cutoff values help in determining the optimal threshold for classifying samples into the COPD group.

COPD vs Asthma

the AUC values range from 0.704 to 0.973. ECE-1 again shows the highest AUC of 0.973, indicating its potential in distinguishing between COPD and asthma. However ACE_2 show lower AUC values, suggesting limited discriminative ability in this particular comparison.

In terms of sensitivity and specificity, ECE-1 consistently shows high values across all comparisons, indicating its robustness in correctly identifying true positives and true negatives. ACE_2 also demonstrates good sensitivity and specificity in the Asthma vs Control and COPD vs Control groups but shows lower performance in discriminating between COPD and Asthma.

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Table** Error! No text of specified style in document.**-5 The Receiver Operating Characteristic analysis performed in this study focuses on elucidating the discriminative capabilities of various biomarkers in distinguishing between different combinations of groups.

Combinations	Variable	AUC	SE	95% CI	Cutoff	Sens	Spec	+LR	-LR
Asthma vs Control	ECE 1	0.997	0.00299	0.953 to 1.000	>127.34	100.00	93.33	15.00	0.00
	ACE_2	0.992	0.00643	0.944 to 1.000	≤35.05	96.67	98.33	58.00	0.034
COPD vs Control	ECE 1	1.000	0.000	0.960 to 1.000	>133.03	100.00	100.00		0.00
	ACE_2	0.998	0.00191	0.957 to 1.000	≤33.03	100.00	98.33	60.00	0.00
COPD vs Asthma	ECE 1	0.973	0.0162	0.894 to 0.998	>185.3	96.67	86.67	7.25	0.038
	ACE_2	0.704	0.0688	0.573 to 0.815	≤25.7	56.67	83.33	3.40	0.52

AUC = (Area Under the Curve); SE (Standard Error); 95% CI (Confidence Interval); Sens (Sensitivity); Spec (Specificity) ;+LR (Positive Likelihood Ratio); -LR (Negative Likelihood Ratio)

this ROC analysis suggests that ECE-1 is a promising biomarker for distinguishing between asthma and control groups as well as COPD and control groups. However, its performance in discriminating between COPD and asthma needs further investigation, as other biomarkers may be more effective in this specific comparison.

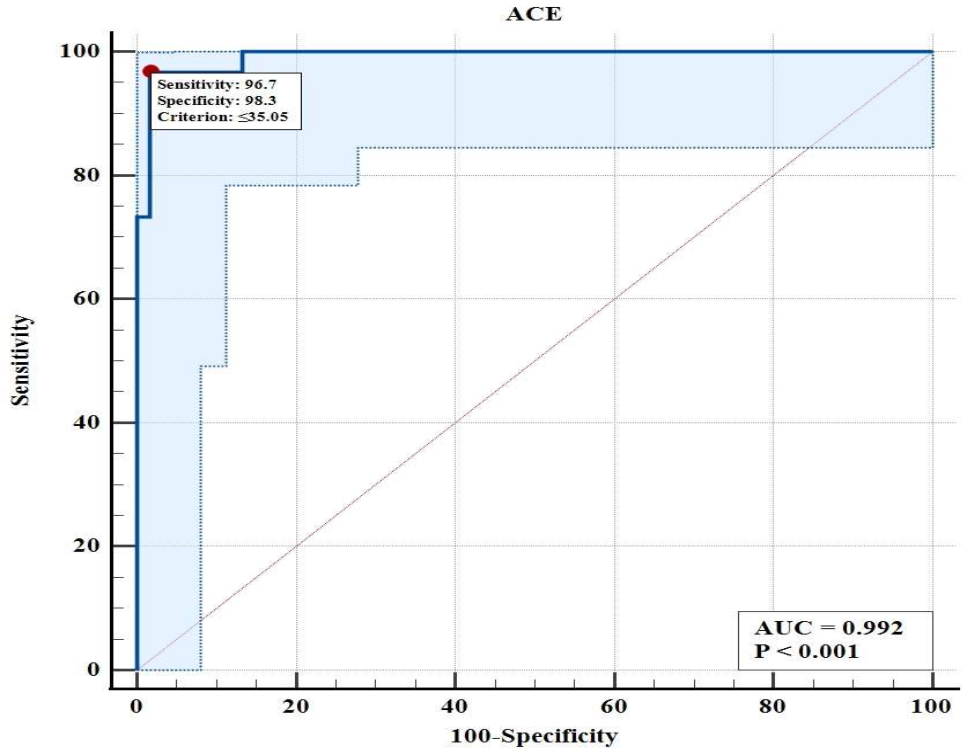

Figure** Error! No text of specified style in document.**-3 ROC Curve showing AUC Area under curve and Cutoff value for ACE_2 as diagnosing Asthmatic patients from control subjects

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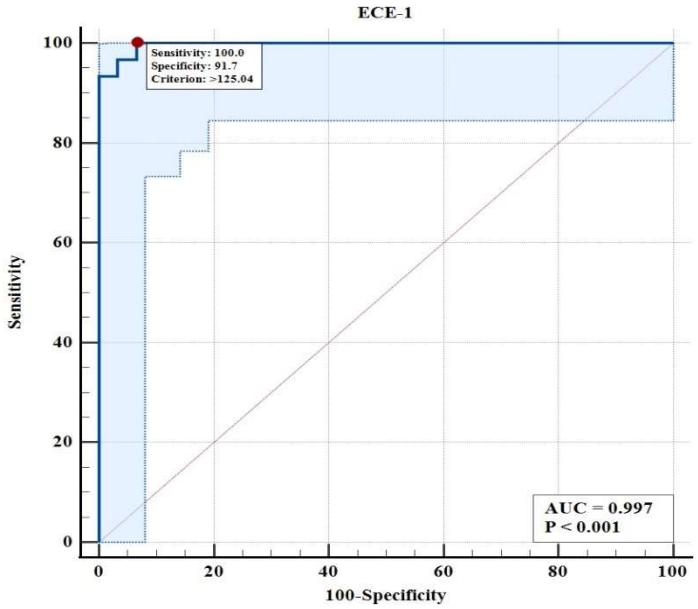

Figure** Error! No text of specified style in document.**-4 ROC Curve showing AUC Area under curve and Cutoff value for ECE-1 as diagnosing Asthmatic patients from control subjects

COPD

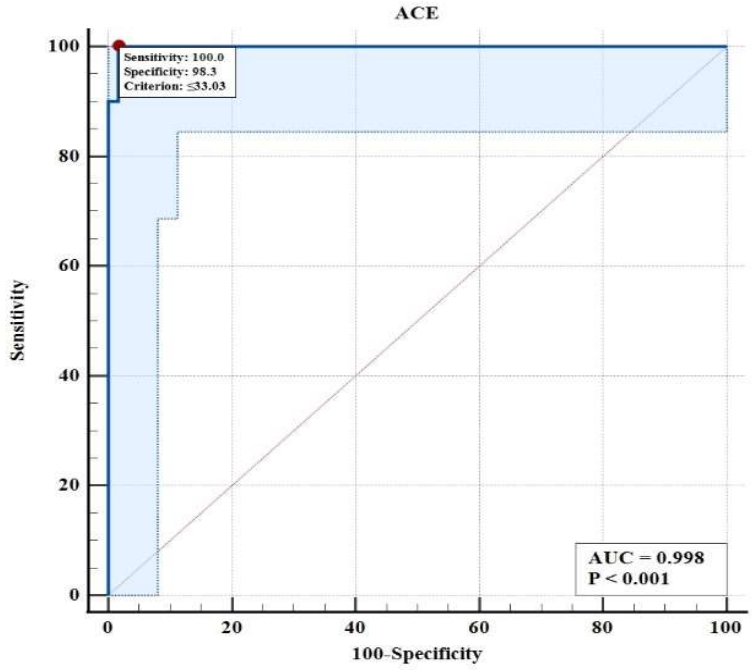

Figure** Error! No text of specified style in document.**-7 ROC Curve showing AUC Area under curve and Cutoff value for ACE as diagnosing COPD patients from control subjects

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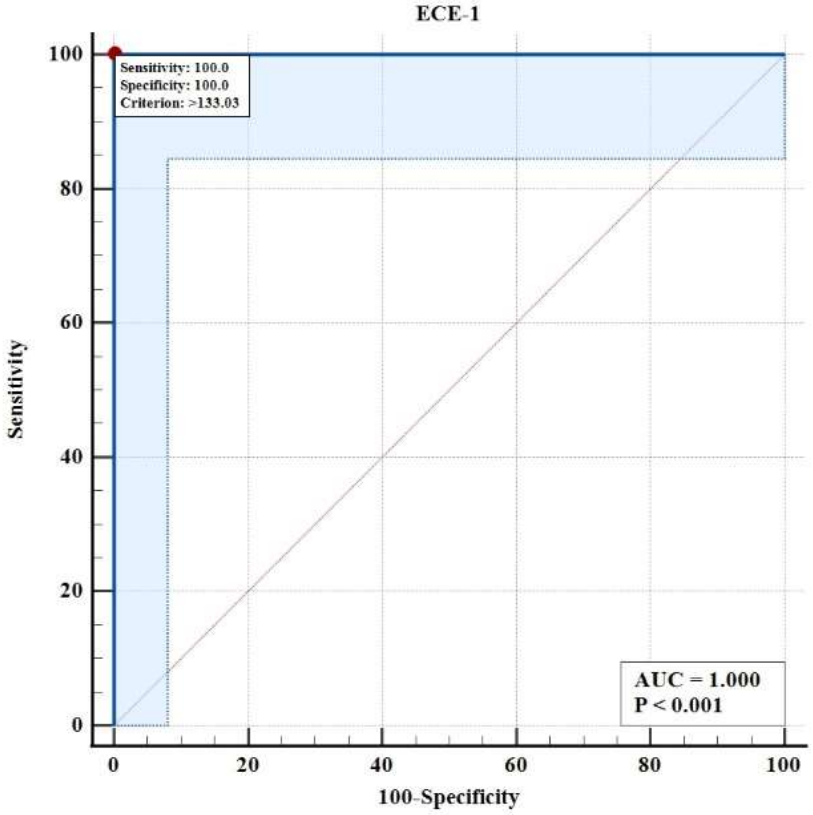

Figure** Error! No text of specified style in document.**-8 ROC Curve showing AUC Area under curve and Cutoff value for ECE-1 as diagnosing COPD patients from control subjects

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COPD vs Asthma

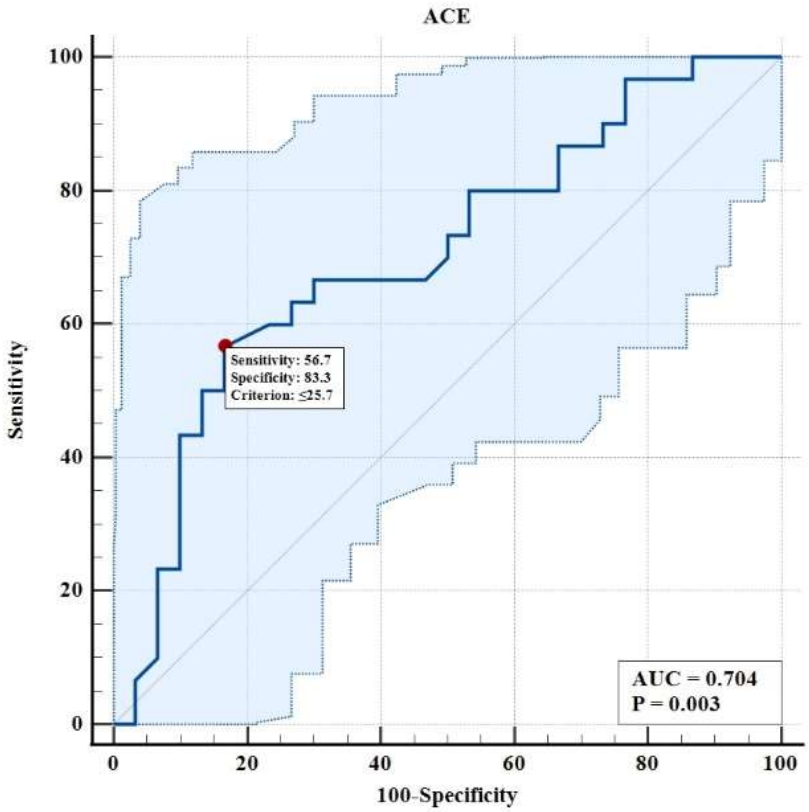

Figure** Error! No text of specified style in document.**-9 ROC Curve showing AUC Area under curve and Cutoff value for ACE as diagnosing COPD patients from Asthma patients

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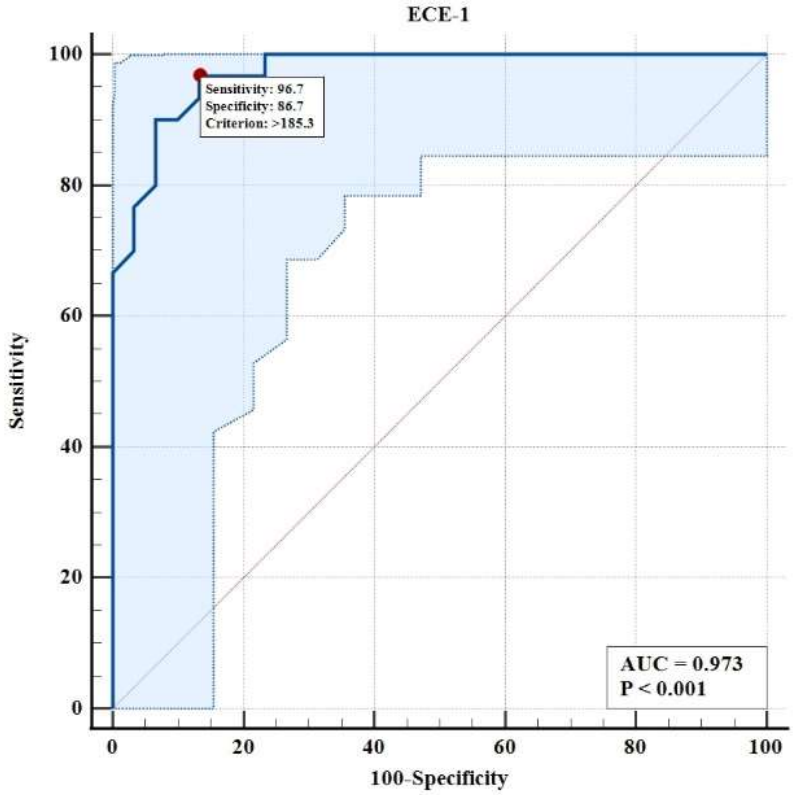

Figure** Error! No text of specified style in document.**-10 ROC Curve showing AUC Area under curve and Cutoff value for ECE-1 as diagnosing COPD patients from Asthma patients

4. Discussion

The study focused on the factors that cause the two respiratory diseases (asthma and Chronic obstructive pulmonary disease) in terms of the long-term inflammation, its triggers, the lack of anti-inflammatories and properties of some of them are bronchial constrictors and others are bronchodilators

4.1. Descriptive statistics and comparison between the three groups in the parameters and age.

The results for age in asthma and Chronic obstructive pulmonary disease, when compared to control, revealed important insights. Ages in the asthma group ranged from 31 to 33.50 years, with a mean age of 34.60±8.47 years. Likewise, the COPD group shows a wider age range from 33 to 42 years, with a mean age of 41.83 ± 8.36 years. The controls range in age from 28 to 34.50 years, mean age of 35.07 ± 7.82.

Significantly increase age groups in people with COPD compared to control (p=0.001) may be result of several factors, the most important of which is environmental factors, as smoke, industrial, and chemical pollutants have recently increased in Iraq 2023.

This results agrees with previous study done by **(Pauwels and Rabe, 2004)**Chronic obstructive pulmonary disease (COPD) builds up over a long period of time Over 40 is the average age of COPD patients **(Stratelis et al., 2004).**

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Ashraf, Zeeshan, and Muhammad Ashraf's agreed with result study that the smoking history, chronic chemical exposure, and other risk factors increase the age range of patients with chronic obstructive pulmonary disease (COPD) **(Ashraf and Ashraf, 2024)**

Significantly increase age groups in people with asthma compared to control (p=0.001) may be to various factors that contribute to the rise in asthma cases among individuals aged 34.60±8.47 years. A study goes on to say that asthma can occur at any age group, including the age range in the current study that present varying perspectives on the onset and progression of asthma. Previous studies demonstrated that Asthma can start at any age, but it is commonly seen in childhood when the immune system is still developing. The majority of children experience their first symptom of asthma by the age of 5 **(Kyvsgaard et al., 2024).**

4.2. The difference in parameters level between asthma, COPD groups and control groups.

4.2.1. The difference in the level of serum Endothelin Converting Enzyme-1 Activity between asthma, COPD groups and control groups

Asthma and COPD patients had significantly higher Endothelin Converting Enzyme-1 levels (167.19± 19.66 and 213.75± 15.27, respectively) compared to the Control group (101.43± 18.04). The P-value of less than 0.001 indicates a significant difference. COPD and asthma groups had significantly varied Endothelin Converting Enzyme-1 levels. The factor most closely related to and influencing the endothelial tissues and their contraction and relaxation, and since this enzyme is activated to regulate the work of these veins through its receptors, risk factors such as smoking, and stress can combine to increase the confusion and mitogenic effect in regulating the signals and receptors related to the endothelium **(Böhm and Pernow, 2007)**. There are several Studies are consistent with the present study and according to these defective mechanisms were an increase in Endothelin Converting Enzyme-1 is associated with an increase in Endothelin -1 The active with diverse biological activity that has been implicated in numerous diseases and its relationship to both lung diseases were , Chen, Su et al. (2020) In their study examined the process of Endothelin-1 (ET-1) cleavage by endothelial cells (ECs), resulting in the formation of proET-1 and big ET-1. ET-1 undergoes cleavage by the endothelin-converting enzyme 1/2 (ECE1/2) to produce its active form. It interacts with endothelin A or B receptors, enhancing ET-1 signaling. ET-1 has a significant impact on vasoconstriction and the growth of vascular smooth muscle cells **(Chen, Su et al. 2020).**

Park, Seo et al. 2024 consistent with present study as it mentioned that Endothelin -1 levels were shown to be significantly increased in patients with COPD and asthma **(Spiropoulos et al., 2003)**. demonstrated that cigarette smoke exposure increases ET expression in small intrapulmonary arteries **(Park et al., 2024).**

4.2.2. The significant differences in Endothelin Converting Enzyme-1 Activity values between asthma and COPD

The significant differences between the values, as mentioned previously, come in sPLA2 and the rest of the biomarkers, most of which are related to the severity of inflammation or the decline of Resolve (Dimitroglou et al., 2022).

The current study comes to its optimal explanation, which it adopted, about the inhibition of the intrinsic substance of vasodilation and relaxation nitric oxide (NO). were the severity of inflammation in COPD may be strongly linked to the strong stimulation of endothelin in smokers and those exposed to polluted

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substances for a long time **(Vilardi et al., 2024)**. As Park, Seo et al. 2024 said. or those exposed to a long-term inflammatory environment supported by interleukins and disintegrin and metalloprotease, and the endothelin in turn, if associated with receptors type A, that is, it has a negative impact on the work of nitric oxide, which is one of the tasks of vessels relaxation, and therefore with the intensity of inflammation and the severity of the narrowing that occurs in the ducts of the air sacs (Bronchoconstriction), reflex the severity of the COPD than asthma.

4.3. The difference in the level of serum angiotensin-converting enzyme between asthma, COPD groups and control groups

4.3.1. The difference in the level of serum angiotensin-converting enzyme between asthma groups and control groups

The results regarding Angiotensin-Converting Enzyme (ACE_2) are presented through ANOVA test and subsequent Tukey-Kramer test pairwise comparisons, which analyze ACE_2 levels across different study groups. In the group of individuals with asthma, the average ACE_2 level was recorded as 28.1263 ± 5.2083. It is worth mentioning that the ACE_2 level of this group differs significantly ($P < 0.05$) from that of the Control group, which had an ACE_2 level of 52.4762 ± 13.4746.

Angiotensin Converting Enzyme expression decreasing may be linked to increased eosinophil inflammation, endogenously produced kinins, chemotactic effect on eosinophils and the I/D polymorphism of ACE_2 as genetic cause.

In one study consistent with current study as Du, Xu et al. 2023 confirmed that Epithelial ACE_2 expression is downregulated and eosinophil inflammation is upregulated in asthmatic patients. Although we found ACE_2 in the major airways of both healthy and asthmatic individuals, we found much lower ACE_2 expression on the surface epithelium of non-corticosteroid-treated asthmatic patients **(Du et al., 2023).**

In another study, Baluk and McDonald 2020 confirmed that ACE_2 may regulate the effects of endogenously produced kinins and tachykinins released from intraepithelial C-fiber nerves, regulating proinflammatory effects and cough reflex. ACE_2's presence in airway endothelial cells may also account for the high frequency of coughing as an adverse effect of ACE_2 inhibitor treatment **(Baluk and McDonald, 2020)**.

This decline, which was observed in the current session, also agrees with Ashaolu, Zarei et al. 2023 , who stated that low ACE_2 may be due to toxic oxidizing effects of eosinophils or the limit of degradation of a bioactive peptide with a chemotactic effect on eosinophils **(Onyeaka et al., 2023).** The reasons for low ACE_2 expression in the surface epithelium of asthmatic subjects not treated with corticosteroids are unclear **(Hellings and Steelant, 2020).**

4.3.2. The difference in the level of serum angiotensin-converting enzyme between COPD groups and control groups

In the COPD group, the average ACE_2 level was 24.3567 ± 5.3402, which showed a significant difference ($P < 0.05$) compared to the ACE_2 level of the Control group which recorded an ACE_2 level of 52.4762 ± 13.4746.

The body has many mechanisms by which we try to repair the system, adapt and resolve inflammation. One of these mechanisms is that the alveoli try to reduce angiogenesis by reducing ACE_2 Low ACE_2 comes to prevent the destructive respiratory effect of Angiotensin II were it contribute to hypoxic

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pulmonary hypertension via its vasoconstrictor and growth-stimulatory effects on vascular smooth muscle cells (VSMCs). Therefore, the use of ACE_2 inhibitors might reduce hypoxic pulmonary hypertension by decreasing pulmonary vasomotor tone or vascular remodeling.

In recent study, Su, Li et al. 2024 confirmed that lower ACE_2 activity in Lung disease such as COPD, liked to angiotensin II mediates, improve oxygen , modulate impaired physical capability **(Lan et al., 2024).** , systemic inflammation ,the use of ACE_2 inhibitors, hypoxic pulmonary hypertension **(Su et al., 2024).**

Furthermore, mounting evidence suggests that COPD is characterised by systemic inflammation that might have an adverse impact on various extrapulmonary organs Interestingly, RAS blockade exerts an anti-inflammatory action in many systems **(Takeuchi et al., 2024).**

In contrast to the current study Gupta, Gupta et al 2020 mentioned that ACE_2 activity is increased by chronic hypoxia which worsens the condition of the lungs through successive events led to COPD by polycythemia, vasoconstriction, and pulmonary vascular remodeling. involves hyperplasia and hypertrophy of small pulmonary arteries, with angiotensin II potentially contributing to the development **(Gupta et al.).**

Finally in contrast to the current study, genetic causes play an important role in both respiratory diseases, as data suggest that elevated ACE_2 activity is not a major risk factor for asthma or COPD, or for ischemic heart disease, hypertension, and low physical activity in COPD patients. in meta-analysis provides strong evidence that the I/D polymorphism of ACE_2 is associated with asthma risk **(Zhou et al., 2024).**

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