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THE ASSOCIATION BETWEEN PHOSPHOLIPASE A2 ACTIVITY, PROSTAGLANDIN I2 AND LEUKOTRIENE B4 CONCENTRATION 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. PLA2 catalyzes the hydrolysis of membrane phospholipids, releasing arachidonic acid, which is a precursor for the synthesis of pro-inflammatory eicosanoids, such as leukotrienes and prostaglandins.
Methods: we performed Case-Control study compressing (n=120) including asthmatic patients (n=30) and COPD patients (n=30) with apparently healthy control subject group (n=60).
Results: The mean ± SD age of patients with Asthma were (34.60± 8.47 years) and in the Chronic Obstructive Pulmonary Disease were (41.83± 8.36 years) there was no a significant difference between groups patients. The mean PLA_2 levels with standard deviation (Mean± SD) are (44.29± 15.41) for Asthma, (55.50± 16.48) for COPD, and 22.13± 6.67 for Control. The statistical significance (Pr > F(Model)) is highly significant for Asthma ($p < 0.000001$), indicating a strong association between Asthma and PLA_2 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 LTB_4 levels with standard deviation (Mean± SD) are (116.39± 35.72) for Asthma, (148.47± 41.18) for COPD, and (55.16± 22.26) for Control. The statistical significance based on ANOVA ($p < 0.000001$) is highly significant for Asthma, suggesting a strong association between Asthma, COPD and Control groups. The mean PGI_2 levels with standard deviation (Mean± SD) are (93.84± 16.66) for Asthma, (82.87± 13.58) for COPD, and (124.74± 20.10) for Control. The statistical significance based on ANOVA ($p < 0.000001$) is highly significant for Asthma, suggesting a strong association between Asthma, COPD and Control groups.
Conclusion: Both serum levels of Phospholipase A2 and LTB_4 a significant increased in patients with Asthma and Chronic Obstructive Pulmonary Disease compared with control and level decreased in patients with Asthma and Chronic Obstructive Pulmonary Disease compared with control, this finding supporting role of Phospholipase A_2, LTB_4 and PGI_2 in patients with Asthma and Chronic Obstructive

CAHIERS MAGELLANES-NS
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Pulmonary Disease, and suggesting that Phospholipase A_2, LTB_4 and PGI_2 have an important role as Asthma and Chronic Obstructive Pulmonary Disease.

Keywords: Phospholipase A2 Activity, Prostaglandin I2, Leukotriene B4, Concentration, Asthma, Chronic Obstructive Pulmonary Disease

1. Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are both chronic inflammatory diseases of the airways, though they have distinct pathophysiological mechanisms and clinical manifestations. Phospholipase A2 (PLA2), leukotriene B4 (LTB4), and prostacyclin (PGI2) play significant roles in the inflammation and pathogenesis of both diseases ***(Kudo and Murakami, 2002)***. PLA2 enzymes are crucial in the production of arachidonic acid, a precursor for eicosanoids, including prostaglandins and leukotrienes. In asthma, PLA2 activity is often elevated, leading to the increased production of pro-inflammatory mediators that contribute to airway hyperresponsiveness and inflammation ***(Dennis and Norris, 2015)***. In COPD, PLA2 is also upregulated, contributing to chronic inflammation. The enzyme's activity is associated with the release of arachidonic acid, which is metabolized into various inflammatory mediators, exacerbating lung injury and inflammation ***(Pniewska and Pawliczak, 2013)***. LTB4 continues to be recognized as a potent chemotactic agent, particularly in neutrophil-dominated inflammation. In asthma, LTB4's role in recruiting neutrophils, eosinophils, and other leukocytes to the lungs contributes to the chronic inflammatory state, airway hyperresponsiveness, and remodeling ***(Rothenberg and Bousquet, 2020).*** LTB4 is heavily involved in the pathogenesis of COPD. It is one of the key mediators that drives neutrophilic inflammation in COPD, contributing to the progressive nature of the disease and its associated symptoms such as chronic bronchitis ***(Barnes, 2016)***. PGI2 is known for its vasodilatory and anti-platelet aggregation properties. Recent research suggests that PGI2 might have a protective role in asthma by counteracting the bronchoconstrictive effects of other mediators like thromboxane A2 (TXA2). However, the role of PGI2 in asthma remains complex, with some studies suggesting a dual role depending on the phase of the disease ***(Mitchell et al., 2015)***. In COPD, PGI2 is involved in modulating vascular tone and has potential therapeutic implications in managing pulmonary hypertension, a common complication in advanced COPD. PGI2 analogs are being explored for their ability to reduce pulmonary vascular resistance and improve symptoms in COPD patients with associated pulmonary hypertension ***(Alqarni et al., 2023).***

2. Materials and Methods

The present work included case control study, participant numbers 120, including (n=30) patients asthmatic, COPD (n=40) with healthy control (n=60). 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, 18-50 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

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collected between 08.00-12.30 am. Blood was allowed to clot at 37°C for 10-15 minutes and then 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: PLA2 activity and LTB4 and PGI2 concentration.

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, 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.

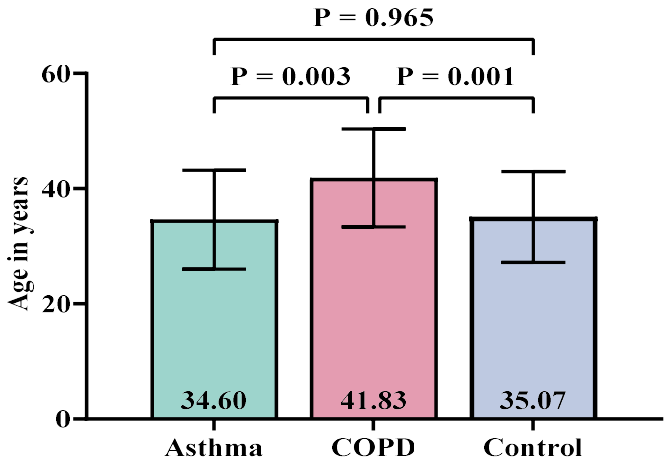

Figure Error! No text of specified style in document.**-1 Means of Age by groups**

Table *Error! No text of specified style in document.****-1 Descriptive statistics and comparison between***

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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**
PLA_2 Asthma	60.00	40.62	44.29± 15.41	2.86	**< 0.000001**	**B**
PLA_2 COPD	54.53	53.92	55.50± 16.48	3.06		**A**
PLA_2 Control	25.65	21.34	22.13± 6.67	0.87		**C**
LTB_4 pg\ml Asthma	120.61	112.47	116.39± 35.72	6.63	**< 0.000001**	**B**
LTB_4 pg\ml COPD	123.30	153.32	148.47± 41.18	7.65		**A**
LTB_4 pg\ml Control	82.13	49.95	55.16± 22.26	2.90		**C**
PGI_2 pg\ml Asthma	74.20	93.85	93.84± 16.66	3.09	**< 0.000001**	**B**
PGI_2 pg\ml COPD	51.70	82.15	82.87± 13.58	2.52		**B**
PGI_2 pg\ml Control	90.15	125.26	124.74± 20.10	2.62		**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.

Phospholipase A_2

For Asthma group, The standard deviation of the mean value was (44.29 ±15.41). with ANOVA p-value < 0.000001, which is statistically significant, indicating that the mean PLA_2 level in is significantly different from at least one of the other groups. For COPD group, The mean value was 55.50 ± of 16.48. For Control, The mean value was 22.13 ±6.67. The Tukey's multiple comparisons test was employed to analyze the mean differences between groups, The results revealed significant distinctions among these groups, In the comparison between Asthma and COPD, Asthmatic patients tends to have lower values compared to COPD. This difference was found to be statistically significant $p < 0.001$, Conversely, the comparison between Asthma and Control groups showed higher values for Asthma compared to the Control group. This difference was also statistically significant $p<0.001$.

ISSN:1624-1940
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Similarly, in the comparison between COPD and Control, statistically significant higher values for COPD compared to the Control group was and observed. These results suggest that there are significant differences in the levels of PLA_2 between the Asthma, COPD, and Control groups. Specifically, the Asthma and COPD groups are significantly different from each other and from the Control group, and from each other. This could indicate that PLA_2 levels are associated with these conditions. The results are presented in Figures (3.2), Tables (3.1).

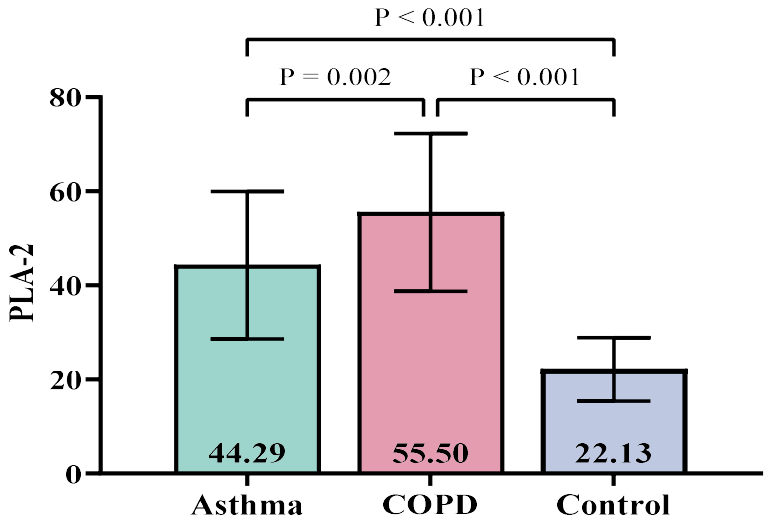

Figure 3.2. Mean values of PLA_2 inthe three studied groups

Leukotriene B_4

Table (3.1) delineates the outcomes derived from ANOVA and subsequent Tukey-Kramer test, focusing on pairwise comparisons of Leukotriene B4 (LTB4) levels across three distinct groups: Asthma patients, COPD patients, and a control groups. Specifically, the LTB4 level within the Asthma group is recorded at approximately (116.39 ± 35.72) pg/ml. This value markedly differs ($P < 0.05$) from both the Control group's LTB4 level of (55.16 ± 22.26) pg/ml and the COPD group's LTB4 level of (148.47 ± 41.1) pg/ml ($P < 0.001$). Furthermore, the LTB4 level observed in the COPD group significantly varies ($P < 0.001$) from both the Asthma group and the Control group ($P < 0.001$).

The summarized results indicate a significant variance in LTB4 levels across all three groups. Both the Asthma and COPD groups exhibit significantly higher LTB4 levels compared to the Control group. These findings hint at a possible involvement of LTB4 in the context of these respiratory conditions.

Figure (3.3) visually represents these findings, providing a graphical depiction of the distinct LTB4 level patterns observed within the study groups. This graphical representation reinforces the significant differences observed in LTB4 levels among the Asthma patients, COPD patients, and the Control groups, thereby accentuating the potential role of LTB4 in contributing to these respiratory conditions.

CAHIERS MAGELLANES-NS
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http://magellanes.com/

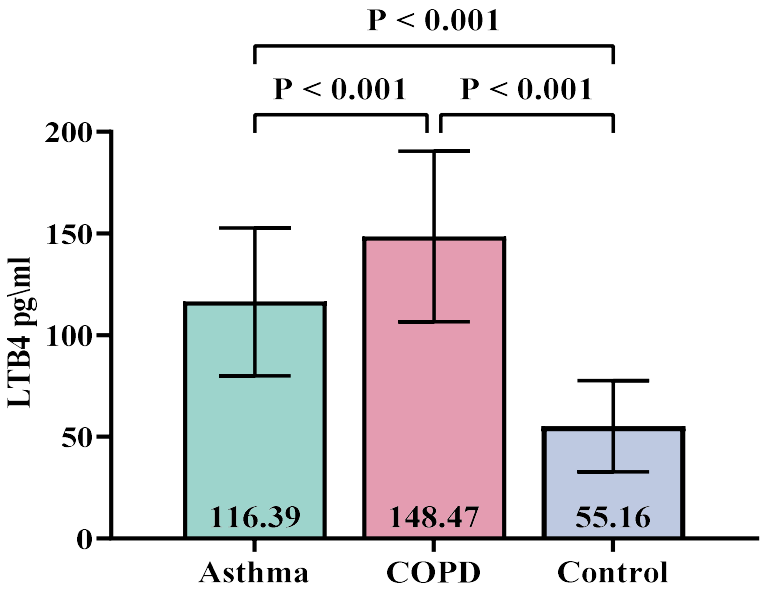

Figure 3.3. Mean of LTB_4 for three studied groups

Prostaglandin I_2

The outcomes of ANOVA and Tukey-Kramer test for pairwise comparisons of Prostacyclin (PGI_2) levels across three distinct groups are depicted in Table (3.1) and visually represented in Figure (3.6) Specifically, the PGI_2 level within the Asthma group is noted at approximately (93.84 ± 16.66) pg/ml. This value significantly differs ($P < 0.05$) from the Control group's PGI_2 level of (124.74 ± 20.10) pg/ml. Similarly, the PGI_2 level observed in the COPD group is recorded at (82.87 ± 13.58) pg/ml, also displaying a significant difference ($P < 0.05$) from the Control group's PGI_2 level.

These findings collectively indicate a significant variance in PGI_2 levels across all three groups. Both the Asthma and COPD groups exhibit markedly lower PGI_2 levels compared to the Control group. Such differences suggest a potential role of PGI_2 in contributing to these respiratory conditions.

The graphical representation in Figure (3.4) further accentuates these findings, providing a visual insight into the distinct PGI_2 level patterns observed within the study groups. This graphical depiction reinforces the significant differences observed in PGI_2 levels among the Asthma patients, COPD patients, and the Control group, thereby underscoring the potential significance of PGI_2 in relation to these respiratory conditions.

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
http://magellanes.com/

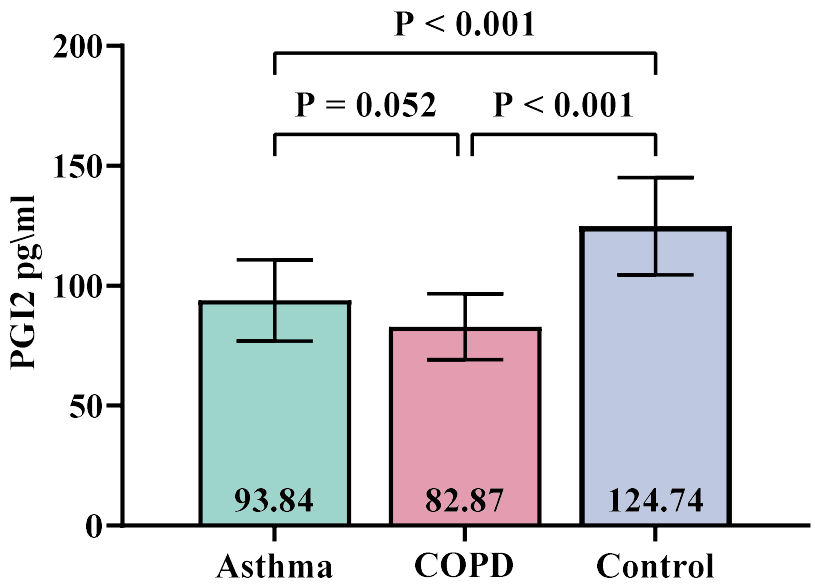

Figure 3.4. Mean of PGI_2 for three studied groups

The Pearson Correlation analysis

The correlation analysis conducted within this study, as illustrated in Tables (3.2) to (3.4), delves into the Pearson correlation coefficients across various parameters within three distinct groups: Asthmatic patients, COPD patients, and a Control group. Within the Asthmatic Patients group, the correlation between Age and PLA2 and Age and PGI2 displaying positive correlations but lacking statistical significance. Contrastingly, in the COPD Patients group, a significant positive correlation of 0.395 is found between LTB4 and PGI2, supported by a P-value of 0.0307 at the 0.05 significance level. Other correlations within this group, such as LTB4 and PLA2, LTB4 and Age, exhibit weak or non-significant associations. These findings underscore the nuanced correlation patterns observed within each group, highlighting potential areas of association and emphasizing the importance of context-specific analyses in understanding the interplay between different parameters within respiratory conditions such as Asthma, COPD, and Control subjects.

CAHIERS MAGELLANES-NS
Volume 06 Issue 2
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ISSN:1624-1940
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http://magellanes.com/

Table 3.2. The Pearson correlation coefficient and significance level between different parameters within Asthmatic patients

1.0 → -1.0				
Age	1			
LTB4 pg\ml	0.356 P=0.0538	1		
PLA-2	0.297 P=0.1109	0.079 P=0.6782	1	
PGI2 pg\ml	0.203 P=0.2829	-0.007 P=0.9723	0.225 P=0.2322	1
	Age	**LTB4 pg\ml**	**PLA-2**	**PGI2 pg\ml**

Table 3.3. The Pearson correlation coefficient and significance level between different parameters within COPD patients

1.0 → -1.0				
LTB4 pg\ml	1			
PGI2 pg\ml	0.395 P=0.0307	1		
PLA-2	0.226 P=0.2308	0.188 P=0.3198	1	
Age	-0.048 P=0.8006	-0.105 P=0.5804	-0.049 P=0.7958	1
	LTB4 pg\ml	**PGI2 pg\ml**	**PLA-2**	**Age**

Pearson correlation coefficient

CAHIERS MAGELLANES-NS
Volume 06 Issue 2
2024

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
http://magellanes.com/

Table 3.4. The Pearson correlation coefficient and significance level between different parameters within Control group

1.0 ——— -1.0				
Age	1			
LTB4 pg\ml	-0.090 P=0.4959	1		
PGI2 pg\ml	-0.109 P=0.4055	-0.073 P=0.5794	1	
PLA-2	0.018 P=0.8903	-0.074 P=0.5741	-0.219 P=0.0934	1
	Age	**LTB4 pg\ml**	**PGI2 pg\ml**	**PLA-2**

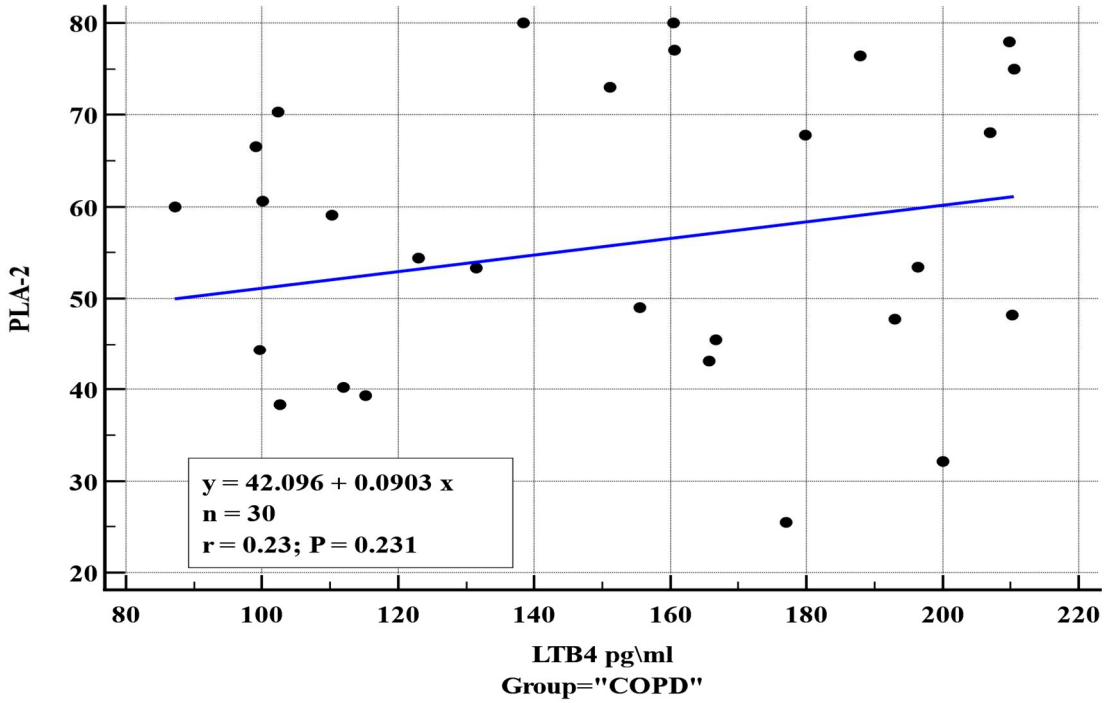

Figure 3.5. Scatterplot showing correlation between PLA_2 and LTB_4 in COPD group

Receiver Operating Characteristics (ROC) curve

Receiver operating curve, or ROC curve, is a graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied**.** Table (3.5) presents ROC analysis comparing different biomarkers in distinguishing between different the study groups: Asthma vs Control, COPD vs Control, and COPD vs Asthma.

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
http://magellanes.com/

Asthma vs Control group

The biomarkers PLA_2, LTB_4 pg/ml, and PGI_2 pg/ml have AUC values ranging from 0.881 to 0.928. PLA2 stands out with the highest AUC of 0.928, followed closely by PGI_2 at 0.88. The cutoff values for these biomarkers range from >35.41 to >109.7, indicating the threshold above which a sample is classified as belonging to the Asthma group.

COPD vs Control

All biomarkers exhibit high AUC values ranging from 0.963 to 0.993, The cutoff values for PLA2, PGI2 and LTB_4 pg/ml are >35.41, ≤93.1, and >92.4, 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 0.692 to 0.71. LTB4 shows the highest AUC of 0.71, indicating its potential in distinguishing between COPD and Asthma. However, PLA_2, and PGI_2 pg/ml show lower AUC values, suggesting limited discriminative ability in this particular comparison.

Table 3.5. The Receiver Operating Characteristic Curve performed in this study focuses on elucidating the discriminative capabilities of various biomarkers in distinguishing between different combinations of groups.

Combinations	parameters	AUC	SE	95% CI	Cutoff	Sens	Spec	+LR	-LR
Asthma vs Control	PLA_2	0.928	0.0300	0.854 to 0.972	>35.41	80.00	100.00		0.20
	LTB4 pg\ml	0.924	0.0274	0.849 to 0.970	>83.03	80.00	88.33	6.86	0.23
	PGI2 pg\ml	0.881	0.0377	0.796 to 0.940	≤109.7	83.33	78.33	3.85	0.21
COPD vs Control	PLA 2	0.977	0.0134	0.920 to 0.997	>35.41	86.67	100.00		0.13
	LTB4 pg\ml	0.993	0.00513	0.947 to 1.000	>92.4	96.67	96.67	29.00	0.034
	PGI2 pg\ml	0.963	0.0167	0.901 to 0.992	≤93.1	80.00	98.33	48.00	0.20

CAHIERS MAGELLANES-NS
Volume 06 Issue 2
2024

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
http://magellanes.com/

COPD vs Asthma	PLA_2	0.692	0.0698	0.559 to 0.805	>53.18	56.67	80.00	2.83	0.54
	LTB4 pg\ml	0.716	0.0657	0.585 to 0.825	>149.87	53.33	80.00	2.67	0.58
	PGI2 pg\ml	0.692	0.0691	0.560 to 0.805	≤83.4	56.67	76.67	2.43	0.57

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

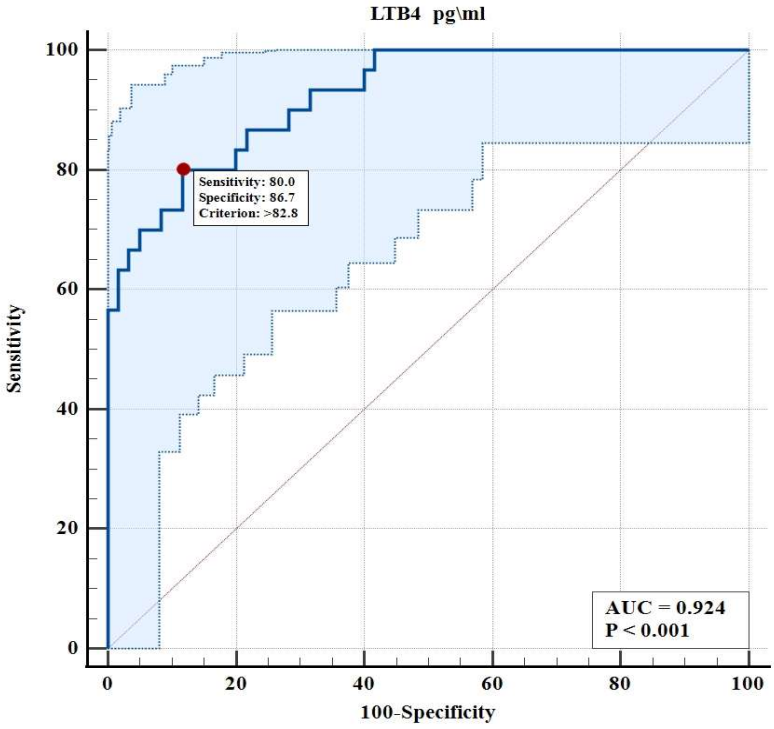

Figure** Error! No text of specified style in document..**6. ROC Curve showing AUC Area under

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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curve and Cutoff value for LTB4 as diagnosing Asthmatic patients from control subjects

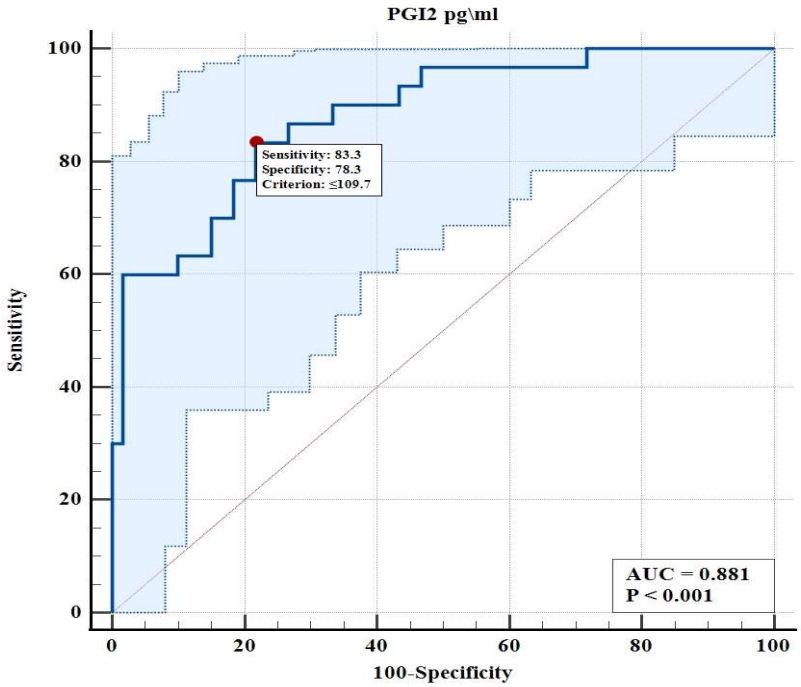

***Figure** Error! No text of specified style in document..7. ROC Curve showing AUC Area under curve and Cutoff value for PG1$_2$ as diagnosing Asthmatic patients from control subjects*

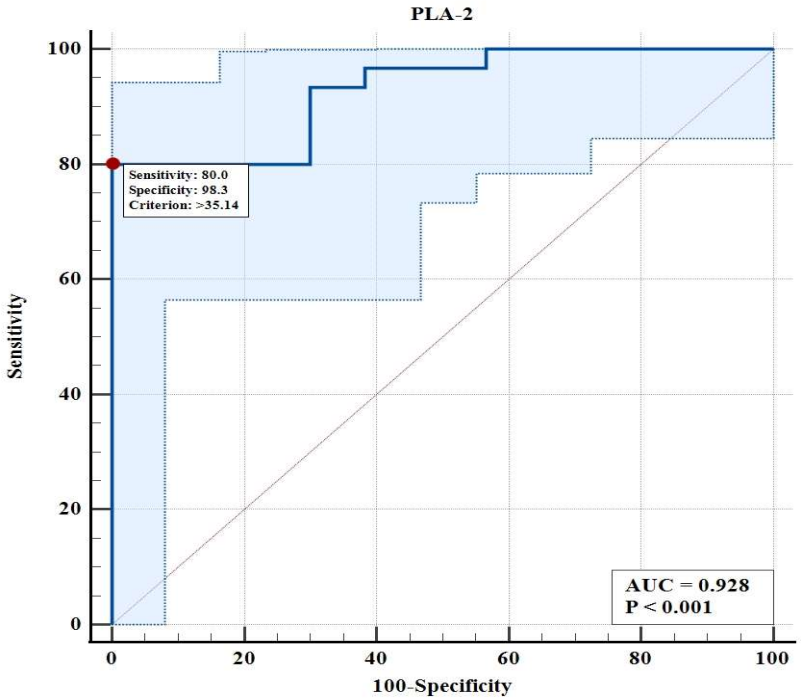

***Figure** Error! No text of specified style in document..8. ROC Curve showing AUC Area under curve*

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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and Cutoff value for PLA_2 as diagnosing Asthmatic patients from control subjects

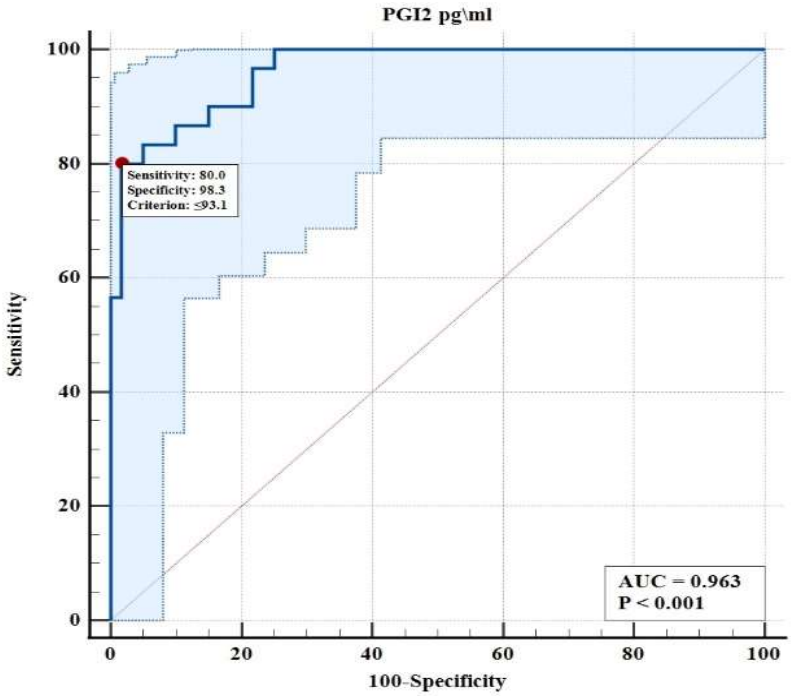

Figure** Error! No text of specified style in document..**9. ROC Curve showing AUC Area under curve and Cutoff value for PGI_2 as diagnosing COPD patients from control subjects

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
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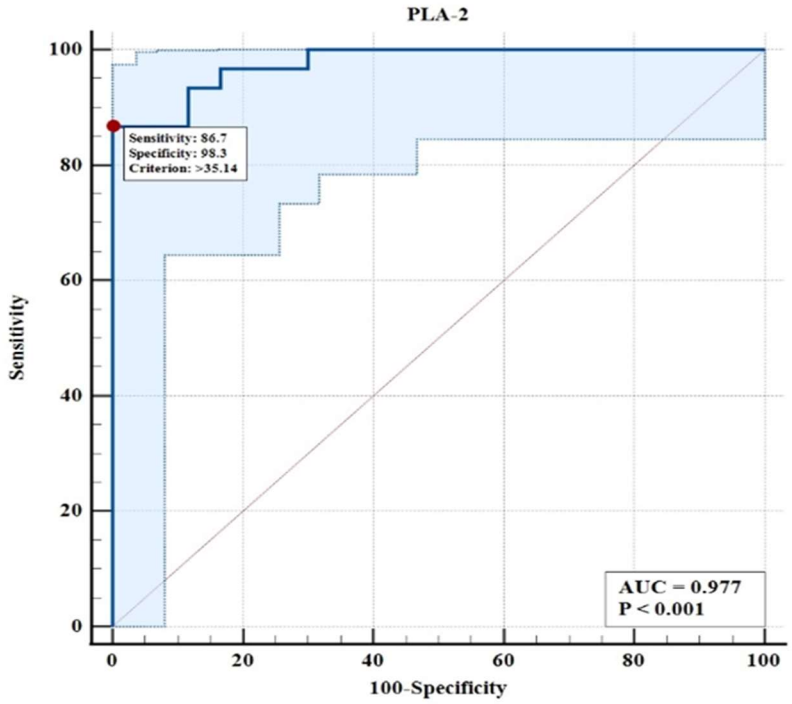

Figure** Error! No text of specified style in document.**.10. ROC Curve showing AUC Area under curve and Cutoff value for PLA_2 as diagnosing COPD patients from control subjects

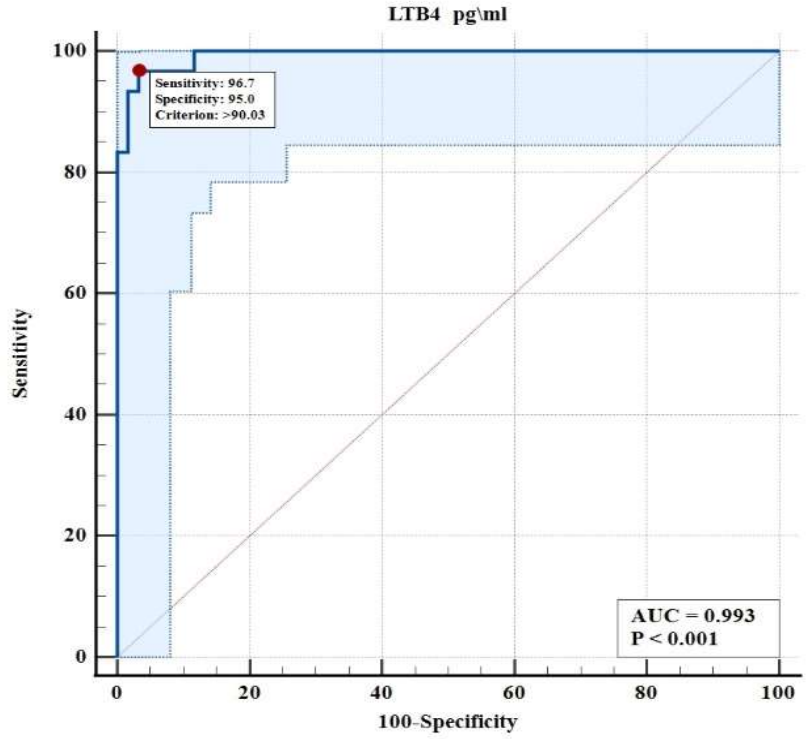

***Figure** Error! No text of specified style in document.**.11. ROC Curve showing AUC Area under*

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curve and Cutoff value for LTB_4 as diagnosing COPD patients from control subjects

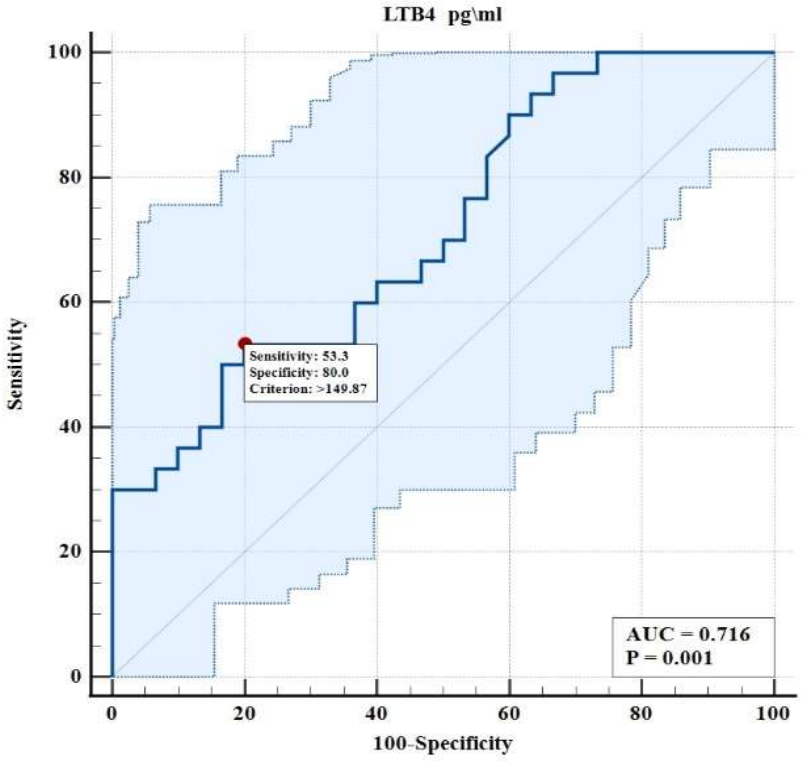

Figure 3.12. ROC Curve showing AUC Area under curve and Cutoff value for LTB_4 as diagnosing

ISSN:1624-1940
DOI 10.6084/m9.figshare.2632574
http://magellanes.com/

COPD patients from Asthma patients

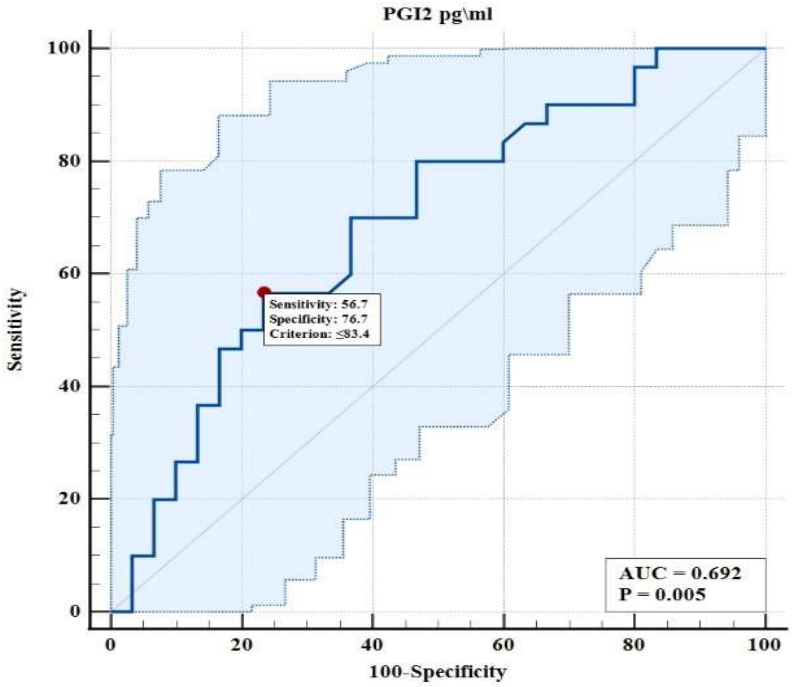

Figure** Error! No text of specified style in document..**13. ROC Curve showing AUC Area under curve and Cutoff value for $PG1_2$ as diagnosing COPD patients from Asthma patients

CAHIERS MAGELLANES-NS
Volume 06 Issue 2
2024

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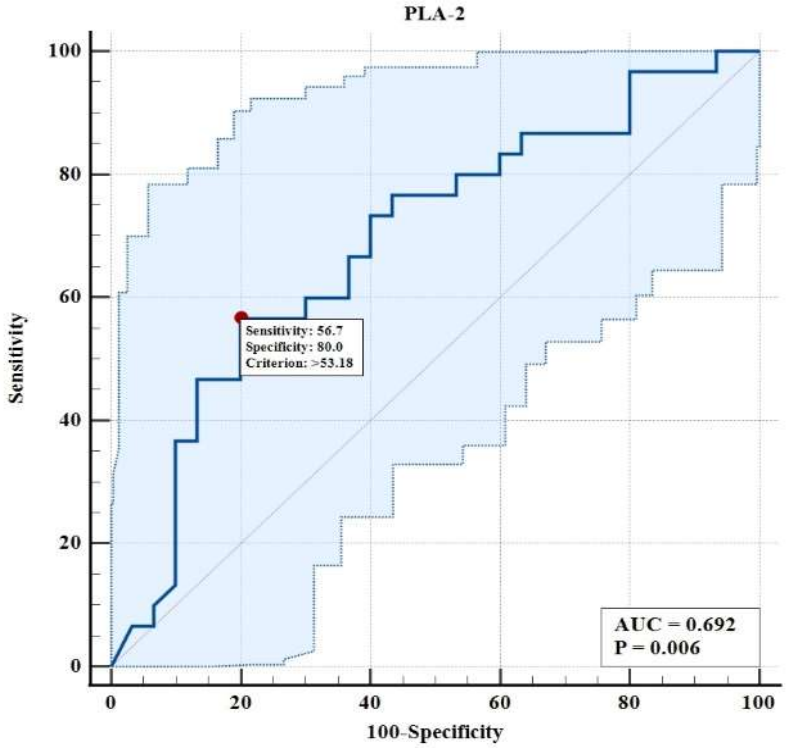

Figure** Error! No text of specified style in document..**14. ROC Curve showing AUC Area under curve and Cutoff value for PLA_2 as diagnosing COPD patients from Asthma patients

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 bronchodilator .All of these factors appear through knowing the parameters levels that indicate these factors, and then a significant distinction was made between their levels in both diseases and knowing the strongest correlation with age. The Receiver Operator Characteristic were studied and the most efficient tool for clinical diagnosis and discrimination between two diseases was determined through specificity and sensitivity.

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 of age (34.60±8.47) years. Likewise, the COPD group shows a wider age range from 33 to 42 years, with a mean of age (41.83 ± 8.36) years. The Controls range in age from 28 to 34.50 years, mean of age (35.07 ± 7.82). Significantly increase age groups in people with COPD compared to Control (p value=0.001) may be result of several factors, the most important of which is environmental factors, as

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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).** 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, Liao et al., 2024).**

Significantly increase age groups in people with Asthma compared to Control (p value=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).** The study of meta-analysis of Middle Eastern countries differs from the direction of the current study, as mentioned Among the 514,468 children and adolescents included in this meta-analysis, the overall prevalence of Asthma was 10.61%, as synthesized from 95 studies. Out of the countries analyzed, Qatar had the highest prevalence rate at 16.69%, closely followed by Saudi Arabia at 16.57%, Iraq at 16.22%, Oman at 15.20%, and Afghanistan at 14.90%. Adolescents exhibited a slightly higher incidence of Asthma at 10.10% in comparison to children at 9.70% **(Taherian et al., 2024).**

4.2. The difference in parameters level between Asthma, Chronic Obstructive Pulmonary Disease and Control groups.

4.2.1. The difference in parameters level of serum Phospholipase A_2 between Asthma, Chronic Obstructive Pulmonary Disease and Control groups.

4.2.1.1. The difference in the level of serum Phospholipase A_2 between Chronic Obstructive Pulmonary Disease and Control groups.

The mean value for the COPD group was (55.50 ± 16.48) and the mean value for Control was (22.13 ±6.67). A statistical analysis was conducted using the Tukey's multiple comparisons test to examine the mean differences between groups. The findings indicated significant variations among these groups $p<0.001$.

This difference may be due to smoking, stress, or taking excessive non-steroidal medications which causes an imbalance in the prostaglandin pathway, which causes the creation of an inflammatory environment and there are studies that support the findings of this study as Kang, Liu et al. 2024 noted that COPD exhibits significantly higher activity of PLA_2s compared to a control group **(Kang et al., 2024).** where noted that sPLA2 through either its pro-inflammatory role might be involved in the pathogenesis of several critical respiratory diseases **(Mitri et al., 2024).** O'Callaghan, Tarling et al. 2024 also noted imbalance in the $sPLA_2$ pathway due to different production of its modulators may account for increased surfactant degradation or lung tissue inflammation**s (O'Callaghan et al., 2024).**

Pniewska and Pawliczak 2013 agreed with the current study in most accepted causes in explaining

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high PLA_2 values in COPD than Control, the golden study and the association of pulmonary obstruction with smoking, oxidative stress, and inflammation **(** The Global Initiative for Chronic Obstructive Lung Diseases) **(Pniewska and Pawliczak, 2013)**

4.2.1.2. The differences in the values of serum PLA_2 Activity between Asthma and control groups

The comparison between Asthma and Control groups showed higher values of serum PLA_2 for Asthma compared to the Control group. The mean value was (44.29 ±15.41). ANOVA test showed a significant difference among the Asthma group when compared to the Control group $p<0.001$. Pniewska and Pawliczak 2013 study supports the current study were it found that $sPLA_2$ a secretory phospholipase, is most important among secretory phospholipases and is correlated with Asthma features like lung function and neutrophil recruitment **(Pniewska and Pawliczak, 2013).**

Hallstrand, Lai et al. 2011 Study have shown elevated of $sPLA_2X$ and $sPLA_2XII$ in induced sputum cells of Asthma patients **(Hallstrand et al., 2011).**

4.2.1.3. The differences in Phospholipase A_2 Activity values between Asthma and Chronic Obstructive Pulmonary Disease

In the comparison between patients (Asthma and COPD), Asthmatic patients tends to have lower values compared to COPD. This difference was found to be statistically significant $p < 0.001$.

Several independent studies have reported that significantly lower levels of phospholipase A_2 and thus LXs are observed in severe Asthmatics compared to patients with COPD **(Aljaroof, 2024)** . The difference in the roles of proinflammatory and apoptotic cells between the two diseases could be a main reason for the difference in PLA_2 levels between the two respiratory diseases. Elevated PLA2 levels, particularly sPLA2, are associated with acute exacerbations of asthma, often triggered by allergens or viral infections. These exacerbations are characterized by a rapid increase in eosinophilic inflammation and bronchoconstriction ***(Nolin et al., 2019)***. In COPD, sPLA2 contributes to the chronic inflammation, oxidative stress, and tissue damage, but the inflammatory mediators involved (e.g., prostaglandins) differ from those in asthma ***(Taketomi and Murakami, 2016).***

4.2.4. The differences in the level of serum Leukotriene B_4 between Asthma, Chronic Obstructive Pulmonary Disease and control groups

4.2.4.1. The differences in the level of serum Leukotriene B_4 between Asthma and control groups

delineates the outcomes derived from ANOVA and subsequent Tukey-Kramer test, focusing on pairwise comparisons of Leukotriene B4 (LTB4) levels across three distinct groups: asthma patients, and a control group. Specifically, the LTB4 level within the Asthma group is recorded at approximately 116.39 ± 35.72 pg/ml. This value markedly differs ($P < 0.05$) from Control group's LTB4 level of 55.16 ± 22.26 pg/ml.

Leukotriene B4 serum concentrations were reported to be higher in asthmatic patients than control may be due to clotting, “corticosteroid sensitive” inhibition of LPS, bronchoconstrictive effect. severity of inflammation, fluid leakage, and increased mucus All of these phenomena are confirmed by the

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following studies**.**

Paone, Leone et al. 2016 in his study agrees with the present study leukotriene B4 (LTB4) serum and plasma concentrations were reported to be higher in some asthmatic patients than in normal subjects, reported suggested that blood clotting causes the increased LTB4 concentration ***(Paone et al., 2016).***

In agreement with current study, Al-Azzam and Elsalem 2020 says that high leukotriene levels are a major cause of asthma influenced by various mediators, including prostaglandin , platelet activating factor, and leukotrienes causing bronchoconstrictive effects and potentially causing lung swelling by attracting white blood cells ***(Al-Azzam and Elsalem, 2020)*.**

Conway, White et al. 2024. It works to increase the cycle of inflammation and bronchoconstriction by contributing to allowing fluids outside the tissues to leak into tissues that are not internalized to them, which carry with them irritants that can increase mucus and increase severity of asthma.***(Conway et al., 2024)*.**

4.2.4.2 The differences in the level of serum Leukotriene B_4 between Chronic Obstructive Pulmonary Disease and control groups

delineates the outcomes derived from ANOVA test and subsequent Tukey-Kramer test, focusing on pairwise comparisons of Leukotriene B4 (LTB4) levels across three distinct groups: COPD patients, and a control group. Specifically, the LTB4 level within the COPD group is recorded at approximately 148.47 ± 41.18 pg/ml. This value markedly differs ($P < 0.05$) from Control group's LTB4 level of 55.16 ± 22.26 pg/ml.

Leukotriene B4 (LTB4) serum and plasma concentrations were reported to be higher in COPD patients compare to control liked to several allergic or Volatile organic compounds bacterial and toxins stimuli.

In a promising and in-depth study consistent with the current study conducted by Shaw, Vaughan et al. in 2014, it has been suggested that elevated levels of LTB4 and eosinophil counts, along with the presence of Volatile organic molecules, could potentially serve as indicators for the severity or progression of COPD ***(Shaw et al., 2014).***

Elevated LTB4 concentrations have been reported in various body fluids in several allergic and inflammatory conditions ***(Butola et al., 2021)*.**

Bronchial epithelial cells and fibroblasts are also able to generate LTB4 indicating that these cells may contribute to the inflammatory response in lungs. Peritoneal macrophages, monocytes and dendritic cells may produce LTB4 in response to several stimuli including N-formyl-methionyl-leucyl-phenylalanine peptide, zymosan particles, complement complex, bacterial components and endotoxins ***(Golenkina et al., 2024).***

Le Bel, Brunet et al. (2014) found that LTB4's immune modulatory capabilities increase its levels in lung cells. Its chemoattractive and proinflammatory effects are mainly mediated by the BLT1 receptor,

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http://magellanes.com/

while its signaling is mediated by the G protein-coupled receptor family, triggering kinase cascades and cytokine gene transcription.**(Le Bel et al., 2014).**

4.2.4.3. The difference in the level of serum Leukotriene B_4 between Chronic Obstructive Pulmonary Disease groups and asthma groups

delineates the outcomes derived from ANOVA and subsequent Tukey-Kramer test, focusing on pairwise comparisons of Leukotriene B4 (LTB4) levels across three distinct groups: asthma patients, and a COPD group. specifically, the LTB4 level within the Asthma group is recorded at approximately 116.39 ± 35.72 pg/ml. This value markedly differs ($P < 0.05$) from COPD group's LTB4 level of 116.39 ± 35.72 pg/ml.

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)*.**

In agreement with current study Dong, Xie et al. 2016 conclude that serum LTB4 concentrations are higher in COPD than in asthma due to allergic, inflammatory conditions, smokers, Long-term cigarette smoke exposure induced SOCS1 degradation and LTB4 accumulation, which was associated with emphysema and inflammation. COPD ***(Dong et al., 2016).***

Seggev, TThornton Jr et al 1991 believes in his study that Serum LTB4 concentrations were higher in COPD patients than in asthmatic subjects, which were higher than in normal controls. The reason for this increase is unclear, but increased LTB4 production by neutrophils and alveolar macrophages has been reported in asthmatic subjects. Clotting did not affect serum LTB4, and there was no correlation between neutrophil counts and concentrations. Increased production of LTB4 by neutrophils prior to cell separation cannot be excluded ***(Seggev et al., 1991).***

4.2.5. The differences in the level of serum Prostaglandin I_2 between Asthma, Chronic Obstructive Pulmonary Disease and control groups

4.2.5.1. The difference in the level of serum Prostaglandin I_2 between Asthma and control groups

The outcomes of ANOVA test and Tukey-Kramer test for pairwise comparisons of Prostacyclin levels across to distinct groups the PGI2 level within the Asthma group is noted at approximately 93.84 ± 16.66 pg/ml. This value significantly differs ($P < 0.05$) from the Control group's PGI2 level of 124.74 ± 20.10 pg/ml

In view of the abundance of inflammatory biomarkers and their interaction with each other in the development of asthma and pulmonary obstruction, it is necessary to study the effectiveness of prostacyclin and its characteristics, to shed light on the reason for the discrepancy in its proportion between the two diseases and the control.

Baker and Shaw's 2023 study found Prostacyclin, linked to inflammation, directly affects nerves,

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hypothalamus, and microvasculature, inhibiting inflammatory cell functions through increased intracellular cAMP and Prostacyclin signaling, and attenuating eosinophils and Prostacyclin levels in asthma patients**.** ***(Baker and Shaw 2023).***

May, Mitchell et al. 2023 mentioned that the levels of prostacyclin are low due to its multiple use in repelling many of the problems that face the lung as a result of chronic infections and pulmonary wound closure, survival, proliferation, collagen synthesis ,and myofibroblast differentiation46 in lung fibroblasts. Studies in this field have varied between modern and ancient, which are consistent with the results of the current study ***(May et al., 2023).***

4.2.5.2. The differences in the level of serum Prostaglandin I_2 between Chronic Obstructive Pulmonary Disease and control groups

The outcomes of ANOVA and Tukey-Kramer test for pairwise comparisons of Prostacyclin levels across tow distinct groups the Prostaglandin level within the COPD group is noted at approximately 82.87 ± 13.58 pg/ml. This value significantly differs ($P < 0.05$) from the Control group's Prostaglandin level of 124.74 ± 20.10 pg/ml**.**

Chronic bronchitis and emphysema are marked by excessive mucus production and thickening of the bronchial walls, leading to the collapse of the airways due to the destruction of the alveolar walls. COPD are characterized by persistent inflammation caused by activated macrophages, neutrophils, and lymphocytes, specifically CD8 T cells. ***(Chilosi et al., 2012)***

Contrasting with the current study, Verma, Pandey et al. 2022 found that serum levels of MMP-9, COX-2, and PGE-2 were significantly higher in COPD patients compared to healthy subjects. These levels were also higher with GOLD scores and CAT scores. Patients with a greater clinical history showed enhanced levels. The study suggests that these levels can be used as indicators to understand disease progression in COPD patients ***(Verma et al., 2022)*.**

In the same approach as Verma, Pandey et al. 2022, the following studies were in contradiction with what was reported by the current study, as Uzan, Borekci et al. 2020 found that Prostaglandin levels increase in respiratory secretions from COPD patients, indicating overexpression of COX-1 and EP2/4 receptors in fibroblasts. This overexpression is inversely related to idiopathic pulmonary fibrosis, a condition characterized by mesenchymal excess. ***(Uzan et al., 2020).***

4.3. Correlation

4.3.1. The correlation coefficient between study biomarkers and Age for Asthma

Within the Asthmatic Patients group, the correlation between Age and LTB4 yields a positive coefficient of 0.356; however, the non-significant P-value of 0.0538 suggests an absence of statistical significance at the 0.05 level. A similar pattern is observed across other parameters within this group, such as Age and PLA-2, Age and PGI2 all displaying positive correlations but lacking statistical significance.

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There is no clear reason and it have not found a study that agrees or confirms this association between Age and parameters, but it is possible A current study suggests that prolonged exposure to polluted environments, including smoking, the presence of the genetic factor in childhood is greater than in other stages of life, in addition to the fact that irritants and chemical agents can cause damage to the pulmonary alveoli can cause damage to the lungs at any age and this reduces the chances of ansignificant association between asthma disease and age.

4.3.1. The correlation coefficient between study biomarkers and Age for Chronic Obstructive Pulmonary Disease

Contrastingly, in the COPD Patients group, a significant positive correlation of 0.395 is found between LTB4 and PGI2, supported by a P-value of 0.0307 at the 0.05 significance level. Other correlations within this group, such as LTB4 and PLA-2, LTB4 and Age exhibit weak or non-significant associations

According to Ashraf's study, exposure to polluted environments for a long period, including smoking, can cause damage to the tennis system in any age group. Ashraf, Beishan, and Muhammad Ashraf's study confirmed that individuals with a history of smoking have a higher risk of developing chronic obstructive pulmonary disease (COPD) after 40. Other risk factors include chronic chemical exposure, spending time in environments causing lung damage, and younger individuals experiencing faster recovery from irritants.

In the COPD Patients group, a significant positive correlation is found between LTB4 and PGI2, Sharif 2023 mentioned that prostaglandins and leukotrienes are potent eicosanoid lipid mediators derived from phospholipase-released arachidonic acid that are involved in numerous homeostatic biological functions and inflammation ***(Nawata et al., 2024).*** They are generated by cyclooxygenase isozymes and 5-lipoxygenase, respectively, and their biosynthesis and actions are blocked by clinically relevant nonsteroidal anti-inflammatory drugs, the newer generation coxibs (selective inhibitors of cyclooxygenase-2), and leukotriene modifiers. The prime mode of prostaglandin and leukotriene action is through specific G protein-coupled receptors, many of which have been cloned recently, thus enabling specific receptor agonist and antagonist development. Important insights into the mechanisms of inflammatory responses, pain, and fever have been gleaned from our current understanding of eicosanoid biology ***(Sharif, 2023).***

The current study acknowledges that the connection between PGI2 and LTB4 came as a result of the tendency of each of them towards its pathological physiological action, where LTB4 a strong inflammatory mediator, while the role of PGI2 comes as an anti-inflammatory. According to the Montuschi, Kharitonov et al. 2003 study findings, individuals with COPD exhibit elevated levels of LTB4 and PGE2 in their esophageal blood, indicating that LTB4 may play a significant role in the development of COPD ***(Qian et al., 2024).*** there is a significant increase in PGE2 levels observed in COPD patients, indicating a potential mechanism that helps mitigate lung inflammation. Nevertheless,

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the significance of elevated PGF2α-LI levels in individuals with COPD may be minimal given the limited number of cases and low detection rates ***(Montuschi et al., 2003)*** **,** According to Aradhyula , Vyas et al. 2024 study revealed a noteworthy disparity in the levels of leukotriene B4 (LTB4) and prostaglandin I2 (PGI2), which are arachidonic acid metabolites, between patients with COPD , suggests a potential link between LTB4 and PGI2 levels, indicating that LTB4 may contribute to the damage of vascular endothelial cells, ultimately resulting in severe illness ***(Aradhyula et al., 2024)*.**

Finley Several studies show a positive correlation between Asthma, COPD and other parameters but they included children or those taking steroids with those who did not take them, or other lung diseases other than Asthma and COPD, and they were not taken into consideration, and since these correlations are weak, there were no studies to agree with them.

4.4. Determination the normal range (cutoff value) by The Receiver Operator Characteristic

4.4.1. Determination the normal range (cutoff value). Among the three group Asthma, Chronic Obstructive Pulmonary Disease and Control

The biomarkers PLA2, LTB4 pg/ml, and PGI2 pg/ml have AUC values ranging from 0.881 to 0.928. PLA2 stands out with the highest AUC of 0.928, followed closely by PGI2 at 0.881. These values suggest that PLA2 and PGI2 have excellent discriminatory power in distinguishing between Asthma and Control groups. The cutoff values for these parameters range from >35.41 to >109.7, indicating the threshold above which a sample is classified as belonging to the Asthma group.

Biomarkers that have shown high sensitivity and specificity such as PLA2 and PGI2 may be very important in developing the clinical tool and being within the correct criteria to actually diagnose patients, know the development of the disease at its beginning, and remove healthy people from the circle of suspicion of the disease for example symptomatic smokers with a FEV1/FVC ratio below 0.7 are diagnosed with COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ***(Vogelmeier, Criner et al. 2017),*** this cutoff is too low in younger persons and too high in older adults, therefore it's often contested this is especially critical when “normal” values range widely, especially in “early” disease phases when major pathological change in the small airways can affect spirometry-detected forced expiratory values ***(Hogg, Paré et al. 2017).***

Many COPD biomarker studies have compared patients with illness to healthy controls to identify a difference with little or no overlap in measures. In COPD, indicators including PLA2 and LTB4 are elevated due to the inflammatory nature of the disease ***(Emre, 2021)*** **,** while PGI2 are decreased due to the protection nature against the disease after accounting for all confounding factors, such biomarkers show statistically significant differences between groups, but individual subjects usually overlap, reducing some biomarker's sensitivity and specificity for COPD diagnosis ***(Arrighi et al., 2024).*** This may be due to assay variability, time-dependent disease activity fluctuations in a small percentage of patients, or distinct clinical morphologies, especially in low-grade inflammatory patients, where the illness noise-to-signal ratio may be difficult to identify. This uncertainty can only be resolved by test characterization, comprehensive phenotyping, or longitudinal follow-up ***(Stockley et al., 2019).***

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Due to the large normal range, people can experience excessive or minimal physiological decline before the "disease threshold**"** ***(Miller et al., 2011)*** producing a deceptive picture of disease activity. Recent investigations have also shown patients with regular symptoms and periodic deterioration that resemble COPD exacerbations and those with substantial emphysema on CT scans who do not match the spirometric threshold for COPD diagnosis ***(Woodruff et al., 2016, Regan et al., 2015).***

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