The Utility of Serum IL-1β and CRP Together with Fractional Exhaled Nitric Oxide in the Diagnosis of Asthma in Adults

Hayder Abdul-Amir Makki Al-Hindy[1*], Ali Jihad Hemid Al-Athari[2], Mazin J. Mousa[3], Safa Jihad Hameed[4], Suhad Hafidh Obeed[4]

Abstract:

Background: Bronchial asthma (BrA), recognized lately as an umbrella, covers various subtypes rather than only one disease. Asthma is a chronic inflammation of the airways, in which cytokines could play a crucial role in its pathogenesis. Hence, labors to progress noninvasive markers for asthma had centered through this era. Presently, the fractional exhaled nitric oxide (FeNO), serum C-reactive protein (CRP), and interleukin levels are emerging analytical biomarkers in this field. FeNO is a noninvasive and practical tool even in mild asthma.
This study aimed to evaluate the utility of serum IL-1β and CRP together with fractional exhaled nitric oxide in the diagnosis of adult bronchial asthma.
Method: The study was a case control, including 150-patients and 100-healthy controls. FeNO tests, measurements of plasma levels IL-1β and HS-CRP had undertaken for all the participants. The statistical data had examined by SPSS (V/27) for Windows. Descriptive data of the variables had compatibly used. A significance lower than or identical to 0.05 had intended. ROC curve examination of FeNO tests, IL-1β, and HS-CRP, to predict asthma from healthy control had applied.
Results: there was a significant difference in the FeNo test, HS-CRP levels, and BMI, while no significant difference in all other variables between the groups. The FeNo results correlate positively, though not significantly, with the levels of IL-1β in asthmatic patients (> 0.05). There was a nonsignificant negative correlation between the FeNo results with the level of HSCRP. The accuracy, sensitivity, and specificity of the IL-1β to distinguish asthma were 68.6% and 58% at 95% CI [0.41-0.745], respectively, which was not significant (p>0.05). However, ROC analysis of HS-CRP revealed predictability for asthma patients (p-0.000), with higher accuracy, sensitivity, and specificity: 89.9%, and 68.1% at 95% CI [0.820-0.979], respectively. The FeNo tests revealed highly significant (0.000), high sensitivity, and specific (91% for both) with high 95% CI [0.938-1.000] predictability for asthma.
Conclusion: The utility of circulating HS-CRP is more valuable than IL-1β when combined with fractional exhaled nitric oxide in the diagnosis of asthma. Novel biomarkers could improve the precision of this field.

Key Words: Asthma, FeNO, IL-1β, and HS-CRP.

DOI Number: 10.14704/nq.2021.19.8.NQ21122 **NeuroQuantology 2021; 19(8):119-124**

Introduction

Bronchial asthma (BrA), recognized lately as an umbrella, covers various subtypes rather than only one disease. Asthma subtypes had classified into phenotypes and endotypes. Phenotypes mean the apparent features of the disease in a person.

Corresponding author: Hayder Abdul-Amir Makki Al-Hindy
Address: [1*]Assistant Professor, Department of Pharmacology and Toxicology, College of Pharmacy, University of Babylon, Iraq, https://orcid.org/0000-0001-6232-8501; [2]MSc. (Pharmacology and Toxicology), Department of Pharmacy, Al-Mustaqbal University College, Iraq; [3](Pathologist) College of Pharmacy, University of Babylon, Babylon, Iraq, https://orcid.org/0000-0003-2209-010X; [4]College of Pharmacy, University of Babylon, Babylon, Iraq.
[1*]E-mail: phar.hayder.abdul@uobabylon.edu.iq
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 12 June 2021 **Accepted:** 20 July 2021

Endotypes are the definite pathophysiological pathways causing the detected features of any given phenotype. Bronchial asthma is a long-lasting inflammation distressing over 315 million persons worldwide, triggering a chief source for illness and substantial burden on societies (Qasim J., 2020). Determining a phenotype/endotype of BrA becomes critical, mainly for asthma management.

Henceforth, the need for biomarkers will help to distinguish among these subtypes (Tadao Nagasaki, 2017, Carr and Kraft, 2018).

A single biomarker approach may be unsatisfactory to get a comprehensive analytical picture for the spectrum (diagnosis, treatment, prognosis, and response) of BrA. Nevertheless, data concerning multi-markers usefulness to identify asthma phenotype severity is infrequent (Heaney et al., 2016). Hence, labors to progress noninvasive markers for asthma have centered through this era. Presently, the fractional exhaled nitric oxide (FeNO) (Amjed H., 2021), serum C-reactive protein (CRP) (Qasim J., 2020), and interleukins (Tadao Nagasaki, 2017, Amjed H. Abbas, 2021) levels are emerging analytical biomarkers in this field.

In mild BrA (in particular), the airway obstruction is often not insistent, which might cause a diagnostic ambiguity (Kim et al., 2015). Cytokines play a crucial contribution in the persistent inflammation and the pathogenesis of BrA, even though little had known in the link between circulating cytokine concentrations and BrA outcomes (Bai et al., 2019).

Interleukin (IL)-1β is a proinflammatory cytokine involved in inflammation and resultant hyperresponsiveness in BrA (Scott et al., 2010). IL-1β is an essential cytokine largely involved in both local and systemic inflammatory responses (Liang et al., 2016). Likewise, a piece of cumulative evidence displaying that IL-1β modifies bronchial constriction and relaxation via direct action on the airway's smooth muscles (Clerisme-Beaty et al., 2009). Inclusively, this evidences highpoints the imperative role of IL-1β in the pathobiology of BrA (Novosad et al., 2013).

C-reactive protein manufactured by hepatic cells response to inflammatory reaction identified as a wide-ranging biomarker of systemic and vaso-inflammation (Amir Al-Mumin, 2020, Asseel et al., 2020, Hajir Karim Abdul-Husseein, 2020, Samer MM., 2020). Henceforth, it is rational to investigate the association between BrA (inflammatory state) and circulating HS-CRP levels.

FeNO is an accessible, noninvasive tool and proved beneficial even in mild asthma (De Abreu et al., 2019). The analytical precision of FeNO in BrA was investigated in large shreds of experimental studies, even though an indefinite cutoff for the decision on asthma was already described (Dweik et al., 2011b). This study aimed to evaluate the utility of serum IL-1β and CRP together with fractional exhaled nitric oxide in the diagnosis of adult bronchial asthma.

Subjects and Methods

Study Design and Sample Collection

The study was a case-control, including 150-patients and 100-healthy controls, was executed in Alimam-Alsadiq hospital and private clinic in Babylon province -during the period- from June to August 2020. The control group had recruited from patients' attendees being free from any asthma symptoms. Asthmatic subjects had assessed by the pneumologists at the hospital consultation clinics.

FeNO Tests Measurements

Asthma severity had evaluated with a FeNO test using (Medisoft®, Belgium) apparatus. FeNo measures have been estimated following the guidelines stated by the American Thoracic Society (ATS) by single breath practice (Dweik et al., 2011a, Amjed H., 2021). Repeated expirations were taken to attain three NO values that agreed at the 5% level and the average depended. Body mass index (BMI) was deducted as weight/height2 (kg/m2). Consistent with the ATS recommendations, FeNo results divided into two groups either low [<25ppb] or intermediate-high [⩾25ppb].

Biochemical Analysis

Quantitative analysis of circulating IL-1β and CRP had achieved by ELISA technique using Human IL-1β (Interleukin 1-Beta) kit from Elabscience® and highly sensitive CRP from CALBIOTECH® kit for measurement of the levels of HS-CRP.

Statistical Analysis

The statistical data had examined by the SPSS package (V/27). Descriptive data of gained variables had compatibly used. A significance lower than or identical to 0.05 had intended. The sensitivity, specificity, AUCs, and the use of IL-1β and HS-CRP to predict bronchial asthma had estimated by ROC curves analysis.

Results

Table (1) displays characteristics of the study groups, which revealed a significant difference regarding the levels of FeNo test, CRP, and BMI, while no significant difference of all other variables between the groups.

Table 1. Characteristics and outcomes of asthmatic and control subjects and their significance

(Mean±SD)	Total (No=250)	Asthmatic patients (No=150)	Healthy control (No=100)	P-value
Age	34.1±12.7	33.3±1.2	34.8±1.1	> 0.05
Male sex No (%)	89 (35.6)	54 (36)	35 (35)	> 0.05
BMI	29.8±5.4	30.6±0.6	28.8±0.6	0.041
Interleukin-1β	138.2±7.2	134.8±22.9	60.4±18.5	> 0.05
FeNo	28.6±28.2	43.8±3.3	8.95±0.5	0.001
HS-CRP	4.5±0.5	5.3±0.8	3.3±0.5	0.05

The gender distribution of the study parameters in asthmatic patients has revealed in table-2. The study revealed a nonsignificant difference regarding all study variables between the two sexes, apart from the number of patients on regular treatment. Females were stickier on treatment than males in this study.

Table 2. Gender distribution of study parameters and their significance in asthmatic patients

(Mean±SD)	Males (No=64)	Females (No=86)	P-value
Age	33.7±1.0	34.4±1.2	> 0.05
BMI	28.9±0.6	30.7±0.6	> 0.05
Interleukin-1B	85.9±22.1	152.3±31.1	> 0.05
FeNo	28.5±3.7	28.8±3.0	> 0.05
HSCRP	5.3±0.8	4.8±0.5	> 0.05
On treatment (N %)	16 (24.5)	48 (55.6)	0.001

The FeNo results correlate positively, though not significantly, with the levels of IL-1β in the sera of asthmatic patients (> 0.05). There was a negative (nonsignificant) correlation of the FeNo results with the level of HS-CRP in the blood (table-3).

Table 3. Correlation of FeNo with hypersensitive C-reactive protein and interleukin-1β among asthmatic patients

		HSCRP	Interleukine-1β
FeNo	Pearson Correlation	-0.008	0.081
	Sig. (2-tailed)	0.9	0.5
HSCRP	Pearson Correlation	-	0.105
	Sig. (2-tailed)	-	0.4

The ROC-curve analysis had performed to study the predictive strength of both IL-1β and HS-CRP for BrA. The accuracy, sensitivity, and specificity of the IL-1β were 68.6% and 58% at 95% CI [0.41-0.745], respectively, which was not significant (p>0.05). However, ROC curve analysis of HS-CRP revealed good predictability (p-0.000) to distinguish asthma patients from healthy with higher accuracy, sensitivity, and specificity: 89.9%, and 68.1% (for both) at 95% CI [0.820-0.979], respectively. The FeNo tests revealed significant (0.000), highly sensitive and specific (both 91%) with high 95% CI [0.938-1.000] (figure-1).

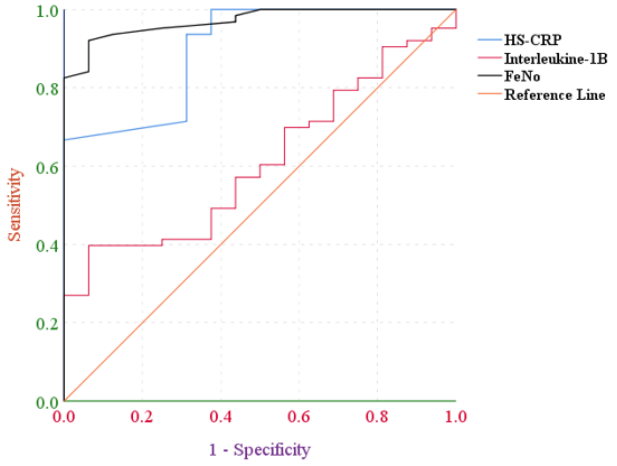

Figure 1. ROC of Hypersensitive C-reactive protein, Interleukine - 1B, and FeNo for Predicting asthmatic patients

Table 4. ROC curve analysis of HS-CRP, Interleukin-1β, and FeNo to predict bronchial asthma from healthier controls

Variables	AUC	Significance	Sensitivity	Specificity	95% Confidence Interval
HS-CRP	0.899	0.000	0.72	0.71	0.820 - 0.979
Interleukine-1β	0.610	0.18	0.58	0.58	0.474 - 0.746
FeNo	0.970	0.000	0.92	0.92	0.938 - 1.000

Discussion

Several markers had used for classifying asthma severity. Until recently, there were no specific biomarkers, which is pathognomonic to diagnosing asthma. Therefore, it essential to be use biomarkers introspectively or in combinations (Carr and Kraft, 2018). Clinicians now have access to a diversity of biomarkers that can practice for phenotyping BrA, e.g., age at onset, asthma duration, symptom triggers, in addition to obesity. In this work, we evaluate the utility of IL-1β and HS-CRP together with FeNo testing for diagnosing asthma phenotypes.

A closer look at the data indicates that FeNo tests raised significantly in asthmatic patients compared to controls. These elevated levels showed to vary with disease activity and in response to therapy. This finding is consistent with the outcomes reported by several current scholars (Amjed H., 2021, de Abreu et al., 2019). The awareness of FeNo had based on the convention that FeNo is a marker of both BrA and its control together, and it reflects eosinophilic airway inflammatory response (Taylor et al., 2008).

C-reactive protein is a ''nonspecific acute phase reactant'' manufactured by hepatic cells in response to inflammatory reaction identified as a wide-ranging biomarker of systemic and vaso-inflammation (Amir Al-Mumin, 2020, Asseel et al., 2020, Hajir Karim Abdul-Husseein, 2020, Raghdan Z. Al-Saad, 2020, Samer MM., 2020). Henceforth, it is rational to investigate the associations of BrA (inflammatory state) with circulating HS-CRP levels. Given the effect of inflammation in the pathophysiology of BrA, there has been a growing body of researchers that revealed a high level of circulating HS-CRP among asthmatics compared to controls (Qasim J., 2020, Maalej et al., 2012, Tiotiu, 2018). Increased concentrations of HS-CRP had linked with reduced pulmonary functions and respiratory hyperresponsiveness (Qasim J., 2020). Contrarily, other studies had failed to replicate our observations and had demonstrated that serum levels of C-reactive protein were not useful biomarkers of airway-hyperresponsiveness (Panaszek et al., 2007). This result was partially explained by the variation in the sampling of asthma patients or the state of atopy among asthma patients (Takemura et al., 2006).

IL-1β belongs to a family of particles (IL-1 axis) that possess both pro-and anti-inflammatory effects. IL-1β is the main cytokine principally intricated in local and systemic immune responses (Liang et al., 2016). Unlike our study about IL-1β levels in patients with BrA, other academics had published that the symptomatic asthma subjects display elevated IL-1β values compared to asymptomatic BrA (Mahajan and Mehta, 2006). The authors described such raised IL-1β values by increased IL-1β expression in asthmatic respiratory epithelium, besides higher counts of macrophages expressing IL-1β (Pospelova et al., 2013, Amjed H. Abbas, 2021). Similarly, IL-1β stimulates respiratory neutrophilia and hyperresponsiveness selectively to bradykinin (Souza et al., 2019).

The poor associations of BrA with IL-1β in our study are similar to the finding of Thomas et al. (Thomas and Chhabra, 2003). Patients that had higher FeNo measures are generally associated with eosinophilic asthma characterized by modest values of IL-1β. The IL-1B expression had boosted after the monocytes exposed to microbial endotoxin, and the existence of these endotoxins expected in airway passages instead of circulation. Hence, the release of IL-1B is estimated more in broncho-alveolar fluids instead of blood. Yet, there is high IL-1β expression in the monocytes (Whelan et al., 2004).

Moreover, transformíng growth ḟactor-β (TGF-β) is a pleiotropic-cytokine (Hayder AA. Al-Hindy, 2020, Fouad SD., 2020), formed by respiratory epithelium and stimulates fibroblasts growth which may induce pathological fibrosis of pulmonary tissue (Amjed H., 2021). Earlier revisions proved an elevated TGF-β1 in obstructive lung disorders (Judith C.W. Mak, 2009). As well, both TGF-β and IL-1B modify T-helper-17 cells that have a critical role in the pathobiology of chronic inflammation (Pourgholaminejad et al., 2016).

Moreover, both TGF-β and interleukins can stimulate platelet derived growth ḟactor (PDGF) release (Mehta, 2006, Bash H., 2021). PDGF is a forceful mitogen formed by different cells like fibroblasts (Fouad SD., 2020, Hayder AA Maki, 2020,

Raghdan Z., 2020) known to contribute an immune-regulatory effect in BrA by facilitating remodeling of respiratory airways (Kardas et al., 2020).

Conclusion

The utility of circulating HS-CRP is more valuable than IL-1β when combined with fractional exhaled nitric oxide in the diagnosis of asthma. The extent of FeNo levels is more diagnostic for asthma inflammation than IL-1β. Novel biomarkers could improve the precision of this field.

Financial support and sponsorship: Nil.

Conflicts of interest: The authors affirm that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

References

Al-Mumin A, Al-Hindy HAAM, Mousa MJ. Combined Assessments of Multi-panel Biomarkers for Diagnostic Performance in Coronary Artery Disease: Case-Control Analysis. *Systematic Reviews in Pharmacy* 2020; 11(6): 665-671.

Amjed HA, MAR, Hayder AA, Mazin JM, Hadeel AAA. The role of serum IL-1β in combination with fractional exhaled nitric oxide in the diagnosis of adult bronchial asthma. *NeuroQuantology* 2021.

Abbas AH, Al-Hindy HAA, Chabuk SK, Mousa MJ. Conicity Index as an Anthropometric Index of Central Obesity in the Prediction of Adult Bronchial Asthma; Correlation with Fractional Exhaled Nitrous Oxide Tests. *Medico Legal Update* 2021; 21(2): 1467-1473.

Shaker AK, Al-Saad R, Jasim R, Al-Hindy HAAM. Biochemical significance of cystatin-C and high-sensitive CRP in patients with acute coronary syndrome; any clinical correlation with diagnosis and ejection fraction. *Systematic Reviews in Pharmacy* 2020; 11(3): 301-308.

Bai C, Jiang D, Wang L, Xue F, Chen O. A high blood eosinophil count may be a risk factor for incident asthma in population at risk. *Respiratory medicine* 2019; 151: 59-65.

Bash H, HA, Basheer H, Mazin JM. The Study of Serum Ferritin Level as a Predictor of Growth Retardation in Thalassemia-Major. *Archivos Venezolanos de Farmacologia y Terapeutica* 2021.

Carr TF, Kraft M. Use of biomarkers to identify phenotypes and endotypes of severe asthma. *Annals of Allergy, Asthma & Immunology* 2018; 121(4): 414-420.

Clerisme-Beaty EM, Karam S, Rand C, Patino CM, Bilderback A, Riekert KA, Diette GB. Does higher body mass index contribute to worse asthma control in an urban population?. *Journal of Allergy and Clinical Immunology* 2009; 124(2): 207-212.

De Abreu FC, Da Silva Júnior JLR, Rabahi MF. The fraction exhaled nitric oxide as a biomarker of asthma control. *Biomarker insights* 2019; 14: 1177271919826550.

Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *American journal of respiratory and critical care medicine* 2011; 184(5): 602-615.

Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *American journal of respiratory and critical care medicine* 2011; 184(5): 602-615.

Dleikh FS, Al-Aaraji AJ, Mohin R, Mousa MJ, Al-Hindy HAAM, Abd Al-Ka'abi B. Possible cause-and-effect linkage of transforming growth factor-beta1 and platelets derived growth factor-AB with delayed anthropometric parameters in adolescent patients with Cooley's anemia: Cases vis control research strategy. *Eur Asian Journal of Bio Sciences* 2020; 14(1): 1119-1125.

Abdul_Husseein HK, Dleikh FS, Al-Aaraji AJ, Al-Hindy HAAM, Mousa MJ. Biochemical causal-effect of circulatory uric acid, and HSCRP and their diagnostic correlation in admitted patients with ischemic heart diseases. *Journal of Cardiovascular Disease Research* 2020; 11(2): 25-31.

Al-hindy HAAM, Mousa MJ, Shaker AK. No Significant Relationship of Ferritin Levels to the Levels of Platelet-derived Growth Factor (PDGF) in the Peripheral Blood of Transfusion-dependent β-Thalassemia Major Patients with Growth Retardation. *International Journal of Pharmaceutical Research* 2020; 12(3): 568-575.

Al-Hindy HAAM, Mousa MJ, Shaker AK, Al-Saad RZ, Al-Dujaili WHS. Relationship of levels of transforming growth factor-beta1 (TGF-β1) to the levels of ferritin in blood of transfusion dependent β-thalassemia major patients with growth retardation: A case-control study. *Eurasian Journal of Biosciences* 2020; 14(1): 521-527.

Heaney LG, Djukanovic R, Woodcock A, Walker S, Matthews JG, Pavord ID, Hardman T. Research in progress: medical research council united kingdom refractory asthma stratification programme (RASP-UK). *Thorax* 2016; 71(2): 187-189.

Mak JC, Chan-Yeung MM, Ho SP, Chan KS, Choo K, Yee KS. Hong Kong Thoracic Society COPD Study Group. (2009). Elevated plasma TGF-β1 levels in patients with chronic obstructive pulmonary disease. *Respiratory medicine* 103(7): 1083-1089.

Kardas G, Daszyńska-Kardas A, Marynowski M, Brząkalska O, Kuna P, Panek M. Role of platelet-derived growth factor (PDGF) in asthma as an immunoregulatory factor mediating airway remodeling and possible pharmacological target. *Frontiers in pharmacology* 2020; 11: 47.

Kim RY, Pinkerton JW, Gibson PG, Cooper MA, Horvat JC, Hansbro PM. Inflammasomes in COPD and neutrophilic asthma. *Thorax* 2015; 70(12): 1199-1201.

Liang Z, Liu L, Zhao H, Xia Y, Zhang W, Ye Y, Cai S. A systemic inflammatory endotype of asthma with more severe disease identified by unbiased clustering of the serum cytokine profile. *Medicine* 2016; 95(25): e3774.

Maalej S, Yaacoub Z, Fakhfekh R, Yaalaoui S, Kheder AB, Drira I. Association of obesity with asthma severity, control and quality of life. *Tanaffos* 2012; 11(1): 38-43.

Mehta AA, Mahajan S. Role of cytokines in pathophysiology of asthma. *Iranian journal of pharmacology & therapeutics* 2006; 5(1): 1-14.

Novosad S, Khan S, Wolfe B, Khan A. Role of obesity in asthma control, the obesity-asthma phenotype. *Journal of allergy* 2013.

Panaszek B, Liebhart E, Liebhart J, Pawłowicz R, Fal AM. Serum concentration of C-reactive protein is not a good marker of bronchial hyperresponsiveness. *Archivum immunologiae et therapiae experimentalis* 2007; 55(5): 341-345.

Pospelova S, Sobchenko S, Kravtsov V. Use of interleukin-1β (IL-1β) and interleukin-1 receptor antagonist (IL-1Ra) contents in alveolar macrophages for estimation of inflammation activity in patients with different levels of asthma control 2013; 42: P3866.

Pourgholaminejad A, Aghdami N, Baharvand H, Moazzeni SM. Is TGFβ as an anti-inflammatory cytokine required for differentiation of inflammatory TH17 cells?. *Journal of immunotoxicology* 2016; 13(6): 775-783.

Jawad AL-Daami Q, Bash HS, Naji GH, AL-Hindy HAAM. High-Sensitivity C-reactive protein Assessment in Bronchial Asthma: Impact of Exhaled Nitric Oxide and Body Mass Index. *Systematic Reviews in Pharmacy* 2020; 11(3): 705-711.

Al-Saad RZ, Shaker AK, Dleikh FS, Al-Hindy HAAM. Is There Any Association Between Highly Sensitive C-Reactive Protein and Dental-Status in Ischemic Heart Diseases? Comparative-Study. *Biochemical and Cellular Archives* 2020; 20(2): 6069-6075.

Mohammed SM, Hasan AS, Al-Hindy HAAM, Mousa MJ. C-Reactive Protein is Associated with the Severity of Periodontal Disease? An Observational Study Among Acute Myocardial Infarction Patients. *Systematic Reviews in Pharmacy* 2020; 11(10), 252-257.

Scott M, Raza A, Karmaus W, Mitchell F, Grundy J, Kurukulaaratchy RJ, Roberts G. Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. *Thorax* 2010; 65(3): 258-262.

Souza PP, Lundberg P, Lundgren I, Magalhães FA, Costa-Neto CM, Lerner UH. Activation of Toll-like receptor 2 induces B 1 and B2 kinin receptors in human gingival fibroblasts and in mouse gingiva. *Scientific reports* 2019; 9(1): 1-11.

Nagasaki T, Matsumoto H, Izuhara K. Utility of serum periostin in combination with exhaled nitric oxide in the management of asthma. *Allergology International* 2017; 66(3): 404-410.

Takemura M, Matsumoto H, Niimi A, Ueda T, Matsuoka H, Yamaguchi M, Mishima M. High sensitivity C-reactive protein in asthma. *European Respiratory Journal* 2006; 27(5): 908-912.

Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008; 63(1): 14-20.

Thomas SS, Chhabra SK. A study on the serum levels of interleukin-1beta in bronchial asthma. *Journal of the Indian Medical association* 2003; 101(5): 282-284.

Tiotiu A. Biomarkers in asthma: state of the art. *Asthma research and practice* 2018; 4(1): 1-10.

Whelan R, Kim C, Chen M, Leiter J, Grunstein MM, Hakonarson H. Role and regulation of interleukin-1 molecules in pro-asthmatic sensitised airway smooth muscle. *European Respiratory Journal* 2004; 24(4): 559-567.

Gonçalves CP. Quantum robotics, neural networks and the quantum force interpretation. *NeuroQuantology* 2019; 17(2): 33-55.