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Evaluation of serum level of uric acid among patients with exacerbation of asthma and patients with controlled asthma

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Abstract

Introduction: Evidence of increased serum uric acid (UA) levels during asthma exacerbations is still unclear. High levels of UA may lead to increased inflammation; in this regard, we aimed to investigate the level of UA and associated factors in patients with exacerbation of asthma attacks and those with controlled asthma.

Materials and Methods: In this study, demographical and clinical data from 300 patients (150 outpatients and 150 hospitalized patients) with asthma who were referred to Razi Hospital, Rasht, Iran, from August 2018 to March 2019 were collected. Also, the UA and spirometry parameters (FEV1, FEV1/FVC) were assessed for patients. All data were analyzed using SPSS version 21 considering a significant level<0.05.

Results: Among 300 patients with asthma, 158 were male, and 142 were female. A significant association was reported between gender, body mass index (BMI), history of smoking, opium consumption, alcohol consumption, number of asthma attacks, family history of asthma, and history of atopy among hospitalized and outpatients (P<0.05). In addition, there was a significant difference between the level of UA in the two groups at the beginning of treatment (P<0.05). Also, a significant difference between the level of UA in hospitalized patients at the beginning and the end of treatment was observed (P<0.05). In addition, a significant difference between the oxygen saturation level among two groups of outpatients and hospitalized patients at the beginning of treatment was seen (P<0.001).

Conclusion: According to our results, the level of UA might be used as a relative predictive factor in the severity of asthma attacks.

Keywords: Asthma, Chronic obstructive pulmonary disease, Outpatients, Hospitalized patients, Uric acid

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Introduction

Asthma is a chronic inflammatory disease of the airways characterized by increased responsiveness of the tracheobronchial passages to various stimuli. Asthma occurs due to temporary blockage of airflow due to chronic inflammation of the airways, identified by periodic and reversible attacks of wheezing, shallow breathing, shortness of breath, and cough. From the etiological point of view, asthma is a heterogeneous disease that genetics, environment, and allergens contribute to the onset and continuation of it (1,2). The prevalence of asthma is increasing in many parts of the world, and it is estimated that 4-5% of the population of the USA has asthma. Bronchial asthma occurs at any age, with the most frequent onset at the early years of life (3).

Asthma is diagnosed according to some symptoms, physical examination, chest X-ray, and lung function diagnostic tests measuring FEV1, PEF, and most importantly, FEV1/FVC through spirometry (3,4). A disproportionate response of T-helper cells usually causes airway restriction in asthma type 2 (Th2) to allergens. Cytokines produced by Th2 are mainly responsible for regulating many features of asthma and lead to airway inflammation, excessive mucus secretion, and structural changes in the airway path (5,6).

Uric acid (UA) is a product of the purine metabolism pathway first recognized as a danger signal released from dying cells (7). It was reported that the level of UA was increased in the airways of asthmatic patients exposed to allergens. The administration of UA crystals with protein antigen leads to increased Th2 immunogenicity and clinical features of asthma through dendritic cell activation, splenic tyrosine kinase, and inositol triphosphate (IP3) kinase signaling (8).

These studies indicate that UA is an essential initiator and enhancer of Th2 immunogenetic in asthma, reflecting airway inflammation. In addition, strategies that target the inhibition of UA synthesis with allopurinol or the suppression of the uricase enzyme lead to a reduction in the production of Th2 progenitor cytokines, pulmonary inflammation, repair, and fibrosis (9,10). Hypoxia can explain the possible potential mechanism of the impact of UA on asthma during the exacerbation of asthma, which is induced by UA, oxidative stress, and inflammation-inducing lung tissue damage that leads to increased levels of UA. Also, high levels of UA may lead to increased inflammation that ultimately impairs lung function (11,12).

Previous studies have indicated that serum levels of UA increased in hypoxic conditions such as chronic heart failure, primary pulmonary hypertension, and chronic obstructive pulmonary disease (COPD) compared to hyperoxia/normoxia conditions (13–15). Moreover, the exact mechanism also occurs during the exacerbation of asthma and bronchospasm caused by it. However, evidence of increased serum levels of UA during asthma exacerbations is unclear; only a few studies have been conducted on this issue. In this regard, we aimed to compare the serum level of UA among patients with controlled asthma and patients with exacerbation of asthma attacks at the beginning of hospitalization and at the time of discharge from the hospital in Rasht, Iran.

Materials and Methods

Study design

This study collected demographical data and clinical characteristics of 300 patients (150 outpatients and 150 hospitalized patients) with asthma who were referred to Razi hospital, Rasht, Iran, from August 2018 to March 2019. Patients with incomplete data and a history of malignancies were excluded from the study. All data were recorded from the patients' archives. Asthma exacerbation was diagnosed based on GINA guidelines, which include a set of specific clinical findings, including relevant medical history, progressive increase in shortness of breath, cough, wheezing, chest tightness, pulse rate, respiratory rate, oxygen saturation, and peak flow measurement (16). The patients with lung diseases, in addition to asthma, suspected or confirmed malignancy, multiple disorders or infection, acute gastrointestinal bleeding, cardiovascular diseases, kidney failure, and consumption of foods containing large amounts of purine, were excluded from the study. This study was approved by the ethical committee at the Guilan

University of Medical Science [IR.GUMS.REC.1397.357].

Variables

Collected data included age, gender, body mass index (BMI) as low weight (BMI<18.5 kg/m^2), average weight (BMI=18.5–24.99 kg/m^2), overweight (BMI=25–29.9 kg/m^2), and obese (BMI≥30 kg/m^2), a family history of asthma, keeping pets, history of exposure to allergens, history of smoking, alcohol consumption, opium consumption, underlying diseases, asthma medication, obstructive symptoms, sinusitis, mental illness, history of reflux, atopy, level of serum UA, and spirometry indexes such as FEV1 and FEV/FVC. In addition, the level of UV was measured by kit (Bionik, Iran) with the BT3500 (Biotecnica Instruments. SpA -Italy) auto-analyzer.

Statistical analysis

All data were analyzed using SPSS software version 21. The quantitative data were reported as mean ± standard deviation (SD), and qualitative data were also described as numbers and percentages. The normality was measured using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The comparison of serum levels of UA in patients with exacerbation of asthma attacks and those with controlled asthma was measured using the independent t-test (Mann-Whitney if were non-parametric). The correlation between the serum level of UA and variables was measured using Pearson's correlation test (Spearman's if were non-parametric). The comparison of the level of UA in patients with exacerbation of asthma attack at the beginning of hospitalization and at the time of discharge was performed using paired t-test (Wilcoxon's if were non-parametric). Logistic regression was used to investigate the relationship between the level of UA and asthma considering the effects of other intervening variables. The statistical significance level of the data was defined as P<0.05.

Results

Demographical data and clinical characteristics of patients were demonstrated in Table 1. Of the 300 studied patients, 158 were male, and 142 were female, with a mean age of 60.19±16.48 years. The mean age of hospitalized patients was lower than outpatients, 56.96±17.15 years (24-90) and 60.19±15.16 years (27-86), respectively, but no statistically significant difference was reported (P=0.610) between the mean age of two groups. The mean BMI in hospitalized and outpatient groups was 78.78±18.98 kg/m^2 and 73.96±19.22 kg/m^2, respectively, representing a significant difference between the two groups (P=0.010). The average time of asthma diagnosis in outpatients and hospitalized groups was 88.19±117.71 months and 106.71±101.7 months, respectively (P=0.140).

Evaluating the presence or absence of daily exposure to occupational allergens among patients revealed that most hospitalized patients were exposed to allergens compared to the outpatients (P=0.001). Also, keeping pets was more frequent among hospitalized patients than outpatients (P<0.05). Most hospitalized patients had a history of opium consumption, and the frequency of smoking was significantly higher in hospitalized patients than in outpatients (P<0.001). There was a significant difference between the two groups based on alcohol consumption and a history of mental illness (P<0.05).

The average times of asthma attacks in hospitalized and outpatients were 2.02±1.27 months (0-8), and the mean age of 66.68±21.73 years old (1-50) during their lifetime (P<0.001). However, the frequency of hospital administration due to asthma attacks was significantly higher in the hospitalized group compared to the outpatients (57.12±87.78 vs. 2.09± 1.21, P=0.010). In addition, the prevalence of a family history of asthma and consuming asthma medication was higher among hospitalized patients (P<0.05). Also, pulmonary construction symptoms were highly reported in both groups, while the prevalence of atopy was significantly higher among hospitalized patients (P<0.001).

The mean serum level of UA was 4.82±1.19% mg/dL in the outpatient group; and in the group of hospitalized patients, at the beginning of the treatment, the mean serum level of UA was 7.31±1.85 mg/dL and at the end of treatment was 5.69±1.11 mg/dL (P<0.001), Figure 1. There was a significant difference between the serum level of UA in the two groups (P<0.001). The mean oxygen saturation level in the outpatient group was 91.14±1.81%, and in hospitalized patients at the

beginning and the end of treatment, were 78.13±2.95% and 90.65±1.91%, respectively (P<0.001).

Evaluation of the level of FEV1 illustrated that in the group of outpatients, it was 65.59 ± 3.3%. In the group of hospitalized patients, at the beginning of the treatment, the mean serum level of UA was 69.95±44.2 mg/dL, and at the end of treatment was 94.76±62.2 mg/dL (P<0.001). Also, the level of FVC in the group of outpatients was 65.05±2.99, and in hospitalized patients at the beginning and the end of treatment, were 44.2±13.9 and 57.2±46.5, respectively (P<0.001).

Table 1. Demographical data and clinical characteristics of outpatients and hospitalized patients with asthma.

Variables		Hospitalized patients n (%)	Outpatients n (%)	P value
Gender	Male	79 (52.7)	79 (52.7)	0.500
	Female	71 (47.3)	71 (47.3)	
Expose to allergen	Yes	124 (82.7)	34 (22.7)	0.001
	No	26 (17.3)	116 (77.3)	
Keeping pets	Yes	90 (60.0)	58 (38.6)	0.010
	No	60 (40.0)	92 (61.4)	
History of smoking	Yes	82 (54.6)	44 (29.3)	<0.001
	No	68 (45.4)	106 (60.7)	
History of underlying disease	Yes	97 (64.6)	85 (56.6)	0.180
	No	53 (35.4)	65 (33.4)	
History of opium consumption	Yes	68 (45.4)	26 (17.3)	<0.001
	No	82 (54.6)	124 (82.7)	
History of alcohol consumption	Yes	50 (30.0)	34 (22.7)	0.050
	No	150 (70.0)	116 (77.3)	
History of mental illness	Yes	16 (10.7)	30 (20.0)	0.030
	No	134 (89.3)	120 (80.0)	
History of sinusitis	Yes	73 (48.7)	21 (14.0)	<0.001
	No	77 (51.3)	129 (86.0)	
History of reflux	Yes	40 (26.7)	45 (30.0)	0.620
	No	110 (73.3)	105 (70.0)	
Family history of asthma	Yes	64 (42.7)	44 (29.3)	0.020
	No	86 (57.3)	106 (60.7)	
History of asthma medication	Yes	117 (78.0)	95 (63.3)	0.009
	No	33 (22.0)	55 (36.7)	
Presence of obstructive symptoms	Yes	115(76.6)	132 (88.0)	0.001
	No	35 (23.4)	18 (12.0)	
History of atopy	Yes	99 (66.0)	38 (25.4)	<0.001
	No	51 (34.0)	112 (74.6)	

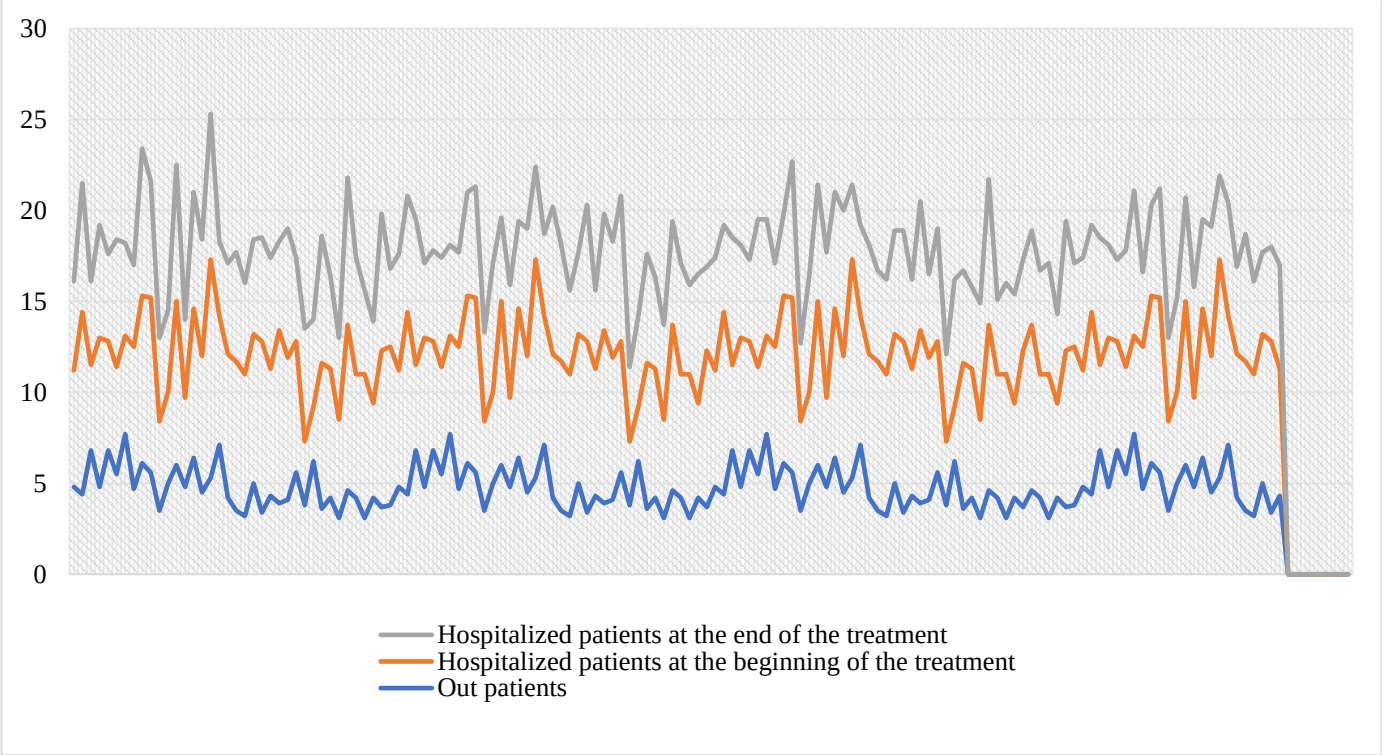

Figure 1. The level of uric acid in the outpatient group, and in the group of hospitalized patients at the beginning and end of the treatment.

No statistically significant association was reported between the serum level of UA and oxygen saturation among hospitalized patients with exacerbation of asthma attack at the time of administration and at the time of discharging (r=0.4, P=0.620 vs. r=0.06, P=0.410), respectively. While a significant association was reported between the level of UA and duration of hospitalization (r=0.92, P=0.008). Assessing the correlation of serum level of UA with spirometry indices (FEV1, FEV1/FVC) among hospitalized patients at the times of administration and discharge represented no statistically significant differences (r=-0.119, P=0.14 vs. r=0.05, P=0.540) for FEV1 and (r=-0.12, P=0.12 vs. r=-0.04, P=0.620) for FVC. In the multivariate logistic regression analysis of significant factors using the Backward method between two groups, the initial level of UA was significantly different (P<0.05). The results of the multivariable logistic regression demonstrated that among variables, only the consumption of medication was significantly associated with the level of UA in hospitalized patients (P<0.05) (Table 2).

Table 2. The results of multivariate logistic regression in the investigation of factors related to the initial UA level; and secondary UA levels in hospitalized patients.

Variables	Regression coefficient	Standard error	Standardized regression coefficient	Test statistics	P-value
Outpatients/Hospitalized patients	2.44	0.18	0.61	13.45	<0.001
Use of medication	-0.491	0.219	-0.182	-2.23	0.027

Discussion

The present study evaluated the serum level of UA among patients with exacerbation of asthma attacks and controlled asthma. Most of the patients in the current study were middle-aged males (52.6%). Due to our findings, the level of UA in hospitalized patients was significantly higher than in outpatients. Also, the level of UA at the beginning of hospitalization was

significantly higher than at the time of discharge, similar to other studies (17–19). In addition, our results illustrated that the level of UA was significantly different in the two groups regarding age, gender, BMI, a history of smoking and opium, alcohol consumption, and asthma medication ($P<0.05$).

This increase may be related to the asthma attack due to the inflammatory state caused by cell necrosis and apoptosis, followed by an increase in purine metabolites, including DNA and RNA. This increase in metabolites elevated the function of the xanthine oxidase (XO) enzyme, which results in higher levels of UA (20). Another mechanism that has been described as the increased UA following an asthma attack is the increase in the degeneration of adenosine three phosphates (ATP) and the increase in the production of UA by the XO enzyme following hypoxia that plays a diverse role in both acute and chronic lung inflammation (21,22). In addition, several studies have mentioned the relationship between the higher level of UA and the increase in the level of inflammatory cytokines such as C reactive protein (CRP), tumor necrosing factor (TNF), and interleukin-1 (IL-1), which are higher in the acute phase compared to the chronic phase (11,18,23).

The current study found no significant association between hospitalization frequency and UA level in the two groups ($P>0.05$). This finding suggests that UA levels may not be a reliable marker for predicting the likelihood of hospitalization in patients with asthma exacerbation or controlled asthma. While previous studies have suggested a potential link between UA and the incidence of asthma (24), our results indicate that other factors might play a more dominant role in determining hospitalization rates. This negative correlation implies higher UA levels may indicate poorer respiratory function and lower oxygen saturation levels. Moreover, there was a negative association between the level of UA and FEV1 and FVC. These findings align with previous research suggesting that UA could contribute to airway inflammation and obstruction, impairing lung function. While their result of the association between hospitalization frequency and UA level did not consistent with our study (18). However, it is essential to note that our study only establishes an association and does not establish a causal relationship.

A study by Lin et al. found a significant relationship between levels of UA and functional lung disorders (17). Other studies reported that the level of UA has an inverse association with spirometry indicators, primarily due to tissue hypoxia during the exacerbation of asthma that causes UA production, and secondly, because the increase in UA levels causes lung tissue inflammation and decreases lung function (25,26).

Recent studies illustrated the impact of the antioxidants such as vitamins E and C in reducing the level of UA, which can indicate that the level of UA may be changed due to cardiovascular diseases, diet patterns, lifestyle, kidney function, and familial purine metabolism problems (27,28). Moreover, the age of the patients can affect the level of UA, which explains the variety of results in different studies (27). Also, some studies have pointed out that vitamin D, E, and C deficiency affects the exacerbation of asthma attacks (29,30).

Limitations

One limitation of this study is referring to the recall bias of the patients to report the duration time of asthma. Also, the impact of consuming supplements was not investigated in the current.

Conclusions

According to our results, the level of UA at the beginning of hospitalization was significantly higher than outpatients and at the time of discharge, which might be used as a predictive factor for asthma severity assessment.

Author contribution

AT, **SAAF**, and **AJ** conceptualization, the original draft writing, investigation, and formal analysis; **AT** and **AJ** conceptualization, supervision, and project administration; **SAAF** and **AJ c**onceptualization, and project administration; **AT**, and **MGH** investigation; **AJ** and **MGH** writing including reviewing and editing and investigation.

Conflict of interest

The authors reported no potential conflict of interest.

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References

1. Price D, Fletcher M, Van Der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ Prim care Respir Med. 2014;24(1):1–10.

2. Hough KP, Curtiss ML, Blain TJ, Liu R-M, Trevor J, Deshane JS, et al. Airway remodeling in asthma. Front Med. 2020;7:191.

3. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's principles of internal medicine, 19e. Vol. 1. Mcgraw-hill New York, NY, USA:; 2015.

4. Burkhardt R, Pankow W. The diagnosis of chronic obstructive pulmonary disease. Dtsch Arztebl Int. 2014 Dec;111(49):834–45, quiz 846.

5. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nat Rev Immunol. 2008;8(3):183–92.

6. Hammad H, Lambrecht BN. The basic immunology of asthma. Cell. 2021;184(6):1469–85.

7. Kobayashi T, Kouzaki H, Kita H. Human eosinophils recognize endogenous danger signal crystalline uric acid and produce proinflammatory cytokines mediated by autocrine ATP. J Immunol. 2010;184(11):6350–8.

8. Kool M, Willart MAM, van Nimwegen M, Bergen I, Pouliot P, Virchow JC, et al. An unexpected role for uric acid as an inducer of T helper 2 cell immunity to inhaled antigens and inflammatory mediator of allergic asthma. Immunity. 2011;34(4):527–40.

9. Gasse P, Riteau N, Charron S, Girre S, Fick L, Pétrilli V, et al. Uric acid is a danger signal activating NALP3 inflammasome in lung injury inflammation and fibrosis. Am J Respir Crit Care Med. 2009;179(10):903–13.

10. Lee S, Suh G-Y, Ryter SW, Choi AMK. Regulation and function of the nucleotide binding domain leucine-rich repeat-containing receptor, pyrin domain-containing-3 inflammasome in lung disease. Am J Respir Cell Mol Biol. 2016;54(2):151–60.

11. Aida Y, Shibata Y, Osaka D, Abe S, Inoue S, Fukuzaki K, et al. The relationship between serum uric acid and spirometric values in participants in a health check: the Takahata study. Int J Med Sci. 2011;8(6):470.

12. Hong JW, Noh JH, Kim D-J. Association between serum uric acid and spirometric pulmonary function in Korean adults: The 2016 Korea National Health and Nutrition Examination Survey. PLoS One [Internet]. 2020 Oct 22;15(10):e0240987. Available from: https://doi.org/10.1371/journal.pone.0240987

13. Rahimi-Sakak F, Maroofi M, Rahmani J, Bellissimo N, Hekmatdoost A. Serum uric acid and risk of cardiovascular mortality: a systematic review and dose-response meta-analysis of cohort studies of over a million participants. BMC Cardiovasc Disord [Internet]. 2019;19(1):218. Available from: https://doi.org/10.1186/s12872-019-1215-z

14. Gonçalves DLN, Moreira TR, da Silva LS. A systematic review and meta-analysis of the association between uric acid levels and chronic kidney disease. Sci Rep. 2022;12(1):1–13.

15. Maulana S, Nuraeni A, Aditya Nugraha B. The Potential of Prognostic Biomarkers of Uric Acid Levels in Coronary Heart Disease Among Aged Population: A Scoping Systematic Review of the Latest Cohort Evidence. J Multidiscip Healthc. 2022;161–73.

16. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143–78.

17. Lin L, Chun W, Fuqiang WEN. An unexpected role for serum uric acid as a biomarker for severity of asthma exacerbation. Asian pacific J allergy Immunol. 2014;32(1):93.

18. Abdulnaby NK, Sayed AO, Shalaby NM. Predictive value of serum uric acid in hospitalized adolescents and adults with acute asthma. Ther Clin Risk Manag. 2016;1701–8.

19. Sayyah SG. Serum Uric Acid Level in the Blood of Asthmatic Patients in Basrah Governorate-Iraq. J Basrah Res. 2014;40(2).

20. Wu JT, Wu LL. Chronic systemic inflammation leading eventually to myocardial infarction, stroke, COPD, renal failure and cancer is induced by multiple risk factors. J Biomed Lab Sci. 2007;19(1):1.

21. Li X, Berg NK, Mills T, Zhang K, Eltzschig HK, Yuan X. Adenosine at the Interphase of Hypoxia and Inflammation in Lung Injury. Front Immunol. 2020;11:604944.

22. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med. 2011 Feb;364(7):656–65.

23. Zha X, Yang B, Xia G, Wang S. Combination of uric acid and pro-inflammatory cytokines in discriminating patients with gout from healthy controls. J Inflamm Res. 2022;1413–20.

24. Wang H, Jia Y, Yi M, Li Y, Chen O. High Serum Uric Acid Was a Risk Factor for Incident Asthma: An Open Cohort Study. Risk Manag Healthc Policy. 2020;13:2337–46.

25. Jeena J, Manhas S, Prasad R, Prasad S, Gupta R. Direct Relationship Between Uric Acid and C-Reactive Protein and Its Implication in the Chronic Kidney Disease. Indian J Clin Biochem. 2022;37(3):365–9.

26. Ahmad A, Shameem M, Husain Q. Relation of oxidant-antioxidant imbalance with disease progression in patients with asthma. Ann Thorac Med. 2012;7(4):226.

27. Peruzzolo TL, Pinto JV, Roza TH, Shintani AO, Anzolin AP, Gnielka V, et al. Inflammatory and oxidative stress markers in post-traumatic stress disorder: a systematic review and meta-analysis. Mol Psychiatry. 2022;1–14.

28. Al-Abdulla NO, Al Naama LM, Hassan MK. Antioxidant status in acute asthmatic attack in children. J Pak Med Assoc. 2010 Dec;60(12):1023–7.

29. Demirci-Çekiç S, Özkan G, Avan AN, Uzunboy S, Çapanoğlu E, Apak R. Biomarkers of oxidative stress and antioxidant defense. J Pharm Biomed Anal. 2022;209:114477.

30. Misso NLA, Brooks-Wildhaber J, Ray S, Vally H, Thompson PJ. Plasma concentrations of dietary and nondietary antioxidants are low in severe asthma. Eur Respir J. 2005;26(2):257–64.