Zagazig University Medical Journal
www.zumj.journals.ekb.eg

Volume 29, Issue 1, January 2023, Page (361-367) Supplement Issue

Manuscript ID ZUMJ-1912-1635 (R1)

DOI **10.21608/zumj.2020.20412.1635**

ORIGINAL ARTICLE

The correlation between Chitinase-Like Protein YKL-40 and Childhood Asthma in Zagazig University Hospitals

Dina Mohammed Shokry [(1)], Asmaa Mohamed husny Esh [(2)], Yousif Mohammed Yousif [(3)], Mohamad Ahmad Belgasm Allbad [(4)*]

[(1)] Professor of Pediatrics, Faculty of Medicine - Zagazig University, Egypt
[(2)] Professor of Clinical Pathology, Faculty of Medicine - Zagazig University, Egypt
[(3)] Lecturer of Pediatrics, Faculty of Medicine - Zagazig University, Egypt
[(4)] Pediatrics Department, Faculty of Medicine, Aljabl Algharby University – Libya

***Corresponding author:**
Mohamad Ahmad Belgasm Allbad
Pediatrics Department, Faculty of Medicine, Aljabl Algharby University – Libya
Email:
drmab2017@gmail.com

Submit Date 2019-12-02
Revise Date 2019-12-29
Accept Date 2020-01-03

ABSTRCT

Background: Chitinase-Like protein YKL-40 is secreted from neutrophils, macrophages and airway epithelial cells of the respiratory tract mucosa. Therefore, it can act as a specific biomarker of granulocyte function and macrophage activation in patients with asthma. This study aimed to investigate the association between serum levels of YKL-40 and asthma in Sharkia Governorate.

Methods: This case-control study was carried on 60 children; 30 asthmatic child with confirmed reversible, expiratory airway obstruction with clinically and Spirometric-based diagnosis of asthma and were further classified into 3 subdivide group according to Levels of asthma control in children adopted from the Global Initiative for Asthma GINA 2015 and 30 healthy age and sex matched child as control group who were admitted to paediatrics pulmonology department and outpatient clinic at zagazig university hospital during the period from October (2018) to April (2019).

Results: There was a high statistical significant difference between asthmatic and non-asthmatic groups in YKL40 level which was higher in asthmatic group than non-asthmatic group and there was a significant correlation between the levels of serum YKL-40 with the ratio of peripheral blood eosinophils.

Conclusion: The high levels of serum YKL-40 correlated with the diagnosis of asthma in children.

Keywords: Chitinase-Like protein YKL-40, Asthma, GINA Guidelines, Childhood

INTRODUCTION

The chitinase-like protein YKL-40, considered a human cartilage glycoprotein 39 (HCgp-39) and chitinase 3-like 1 (CHI3L1), binds chitin but deficient in chitinase activity. [1]

It is produced at the inflammation sites in cells and secreted from vascular smooth muscle cells and macrophages. [2] Many studies have demonstrated that the level of YKL-40 was increased during T-helper cell (Th) type 2 inflammation. [3] Also, it was supposed that YKL-40 had a role in inflammation and tissue remodeling in human diseases including joint injury [4], liver fibrosis and type 2 diabetes. [5] As recent concepts that asthma is the result of exaggerated Th2 airway inflammation, and airway remodeling is an important pathological characteristic of asthma, YKL-40 is supposed to have a role in the asthma pathogenesis and attracts the attention of scientific centers.[6] A previous study by Chupp et al. [7] established that YKL-40 levels were increased in the lung and circulation of patients with severe asthma. Thereby, they reasoned that YKL-40 could either be a cause or marker for asthma.The concentrations of YKL-40 predominantly increased at the site of allergen deposition in response to allergen challenge. But, whether serum YKL-40 levels are stable or increased during exacerbations of asthma still need to be studied [8]. The aim of the current study was to investigate the correlation between serum YKL-40 levels and asthma in Sharkia Governerate.

METHODS

It was a case control study that was carried out on 30 asthmatic child who were recruited from Pediatric Pulmonology Clinic, Zagazig University

Children Hospital in a period between October 2018 to April 2019, 30 age and sex matched healthy child were recruited as a control group.

Inclusion criteria: Asthmatic children 5-15 years of age with clinically and Spirometric-based diagnosis of asthma, both gender (males and females). Diagnosis of asthma was done according of GINA guidelines **(GINA 2015)** [9]

Exclusion Criteria: Children younger than 5 years, patients with severe co-morbidities such as organ failure , cancer , sever infection , autoimmune diseases , patients with significant pulmonary disease other than asthma , patients on regular systemic or oral anti-inflammatory drugs and patients who refuse to share in the study were excluded from the study.

All participants were divided in two groups as follow: Group A: Included 30 asthmatic children was divided into three subgroup according to level of asthma control according to GINA guidelines 2015. [9]

Group A1 Included 10 children as controlled asthmatic

Group A2 Included 10 children as partly controlled asthmatic

Group A3 Included 10 children as uncontrolled asthmatic

Group B: Control group included 30 healthy non-atopic children; age, sex, and ethnic matched to the asthmatic.

All patients participants subjected to the following:

Full history taking including: history of allergic rhinitis or eczema, history of respiratory symptoms in childhood, family history of asthma or allergy, which suggested that the respiratory symptoms are due to asthma.

Careful clinical examination and full examination (Physical examination in asthmatic people usually normal).

Pulmonary function testing including measurement of both FEV1, FVC

Complete blood count with differential count for eosinophil's Total IgE assay Serum YKL-40 levels assay using ELISA Pulmonary function test [10]: At the time of participation in the study, all asthmatic patients underwent Spirometric assessment to determine their lung function. Accurate Measurement of lung function is necessary to assess and manage asthma.

Normal value (95% confidence interval), FEV1 80% to 120%, PEFR >80%.

Written informed consent was obtained from all children' parents, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

STATISTICAL ANALYSIS

Data were collected, tabulated and analyzed by SPSS 20 software. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance;. difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test. Kruskal-Wallis test was used instead of a one-way ANOVA to find out if two or more medians are different. Ranks of the data points are used for the calculations, rather than the data points themselves and Mann-Whitney test was used to compare differences between two independent groups when dependent variables are either ordinal or continuous.

RESULTS

Table (1), showed that there was no statistical significant difference between groups regarding age. The mean ± SD ages of patients and controls were (7.76 ± 2.48) years and (9.30 ± 2.21) years, respectively. Out of the 30 patients, 17 (55.7%) were males and 13 (43.3%) were females; where in control group they were 12 (40%) males and 18 (60%) were females. There was no significant difference between studied groups regarding sex. **Table (2),** showed that there was a high statistical significant difference between asthmatic and non-asthmatic groups in FEV_1 and FVC where they were lower in asthmatic group than non-asthmatic (86 versus 99.80) and (87.53 versus 96.40) respectively. **Table (3),** showed that There was high statistically significant difference between groups regarding mean YKL40 (pg/ml), where it was 421.25 ± 145.3 in control group, and 3914±1350 in controlled asthma group, while in partly controlled asthma group it was 2993±998.1 and in uncontrolled asthma group it was 3193±1072, The serum YKL-40 levels in patients with asthma were higher than those in controls. The levels of serum YKL-40 in asthmatic patients were higher than patients in control group. **Table (4 and figures 1,2,3),** showed that there was a significant correlation between the serum YKL-40 levels and total serum immunoglobulin (Ig) E, there was a significant correlation between serum YKL-40 levels and the ratio of peripheral blood eosinophils (r .273, p .012) and there was a significant negative correlation between the serum YKL-40 levels with FEV_1 (r -0.384, p .021). **Table (5) and Figure (4)** showed that there was good discriminatory power (AUC 0.953), for diagnose a bronchial asthma, the accuracy of YKL40 in asthma detection was (92.5%), sensitivity was (93.3%) and specificity was (90%). **Table (6),** showed that there was no

statistical significant correlation between IgE with other study parameters. **Table (7)**, showed that there was a statistical significant negative correlation between pulmonary function tests (FEV1 and FVC) with Peripheral blood eosinophils level (higher eosinophils was associated with lower FEV1 and FVC). Otherwise, there was no statistical significant correlation between eosinophils with other study parameters.

Table (1): Demographic and baseline characteristics of the study population**.**

Demographic data	Control group (N=30)	asthmatic (N=30)	t- test	P value
Age (yr) Mean ± SD Range	 9.30 ± 2.21 6-13	 7.76 ± 2.48 5-12	1.741	0.379
Sex (%) Male Female	 12 (40%) 18 (60%)	 17 (٥5.7%) 13 (٤3.3%)	χ^2 (fisher)	0.361

Data is shown as number (percentage) or mean ± standard deviation.
Chi-square and student-t tests were used.

Table (2): Comparison between non asthmatic and asthmatic regarding pulmonary function tests**.**

Pulmonary function tests	Control group (N=30)	asthmatic (N=30)	Test	p-value
FEV1				
• **Mean ± SD**	99.80 ± 3.39	86 ± 17.14	2.471	0.008*
• **(Range)**	98.50 (96 – 105)	89.50 (41 – 118)		
FVC				
• **Mean ± SD**	96.40 ± 2.01	87.53 ± 15.51	1.491	0.002*
• **(Range)**	96.50 (93 – 100)	91 (36 – 112)		

P < 0.05 is significant.

Table (3): Comparing YKL40 (pg/ml) between the studied groups:

Mean ±SD	**Control group**	**Group A1 Controlled asthma**	**Group A2 Partly Controlled asthma**	**Group A3 Uncontrolled asthma**
YKL40 (pg/ml)	421.25 ± 145.3	3914±1350	2993±998.1	3193±1072
The univariate tests for the mean of YKL40 (pg/ml) among different groups				
		F-value		p-value
YKL40 (pg/ml)		6.931		0.001* (HS)
Multiple pairwise comparison tests (Post hoc tests) for the YKL40 (pg/ml)among different groups				
	Mild Vs. Partly Controlled	Controlled Vs. sever	Partly Controlled Vs. sever	Sever Vs. Partly Controlled
YKL40 (pg/ml)	0.005*	0.003*	0.404	0.816

*Significant at alpha level (P-value <0.05).

Table (4): Correlation between YKL40 findings and the percentage of peripheral blood eosinophils and IgE (iu/ml) and lung function test.

YKL40 (pg/ml)	r	P
IgE level (iu/ml)	**0.223**	0.014
Blood eosinophils (%)	**0.273**	0.012 (S)
FEV1 %	**-0.384**	0.021 (S)
FVC %	**-0.151**	0.331 (NS)

r Pearson Correlation

Table (5): YKL40 as a diagnostic test for bronchial asthma

Variable	AUC	Best cut off	Sensitivity	Specificity	NPV%	NPV %	Accuracy	p-value
YKL40	0.953	>813 pg/ml	92.3	91%	95.3%	80.1%	92.5%	<0.001 (HS)

Table (6): Correlation between IgE (iu/ml) and other study parameters.

	IgE (iu/ml)	
	R	p-value (Sig.)
Age (years)	+0.033	0.832 (NS)
Sex	+0.038	0.812 (NS)
Body weight (kg)	-0.005	0.977 (NS)
Length (cm)	+0.028	0.864 (NS)
BMI (kg/m^2)	+0.005	0.987 (NS)
Eosinophils (/mcL)	+0.110	0.563 (NS)
FEV1	-0.215	0.254 (NS)
FVC	-0.106	0.576 (NS)

r Correlation coefficient
p< 0.05 is significant.
Sig.: significance.

Table (7): Correlation between Eosinophils (/mcL and other study parameters.

	Eosinophils (/mcL	
	r	p-value (Sig.)
Age (years)	-0.103	0.521 (NS)
Sex	- 0.126	0.421 (NS)
Body weight (kg)	-0.160	0.321 (NS)
Length (cm)	.139	0.389 (NS)
BMI (kg/m^2)	+0.389	0.392 (NS)
FEV1	-0.215	0.013 (S)
FVC	-0.461	0.003 (S)

r Correlation coefficient
p< 0.05 is significant.
Sig.: significance.

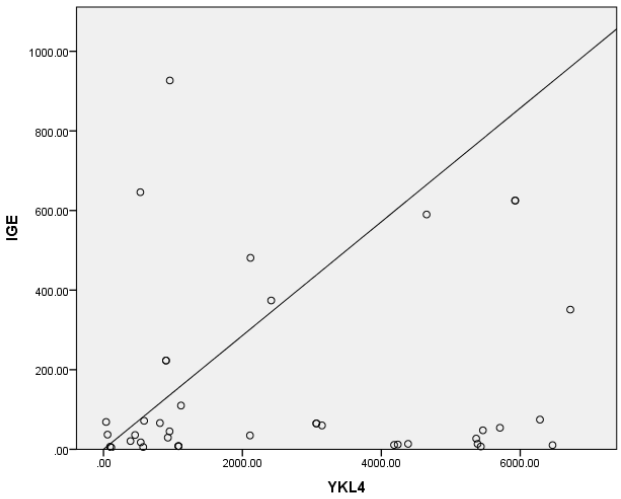

FIG (1): Correlation between YKL40findings and IgE (iu/ml)

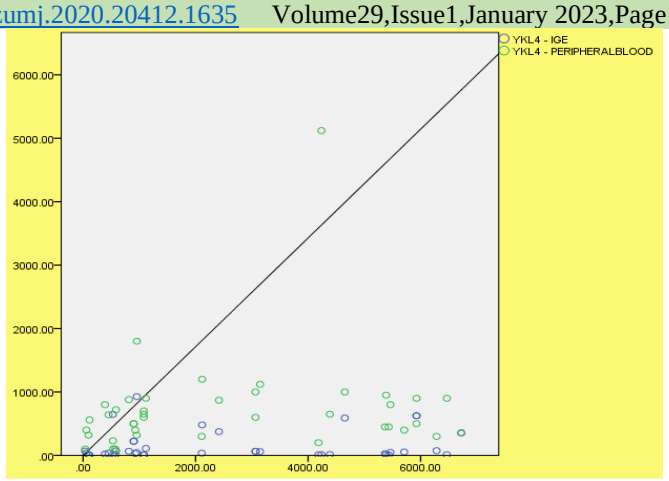

FIG (2): Correlation between YKL40findings and the percentage of peripheral blood eosinophils

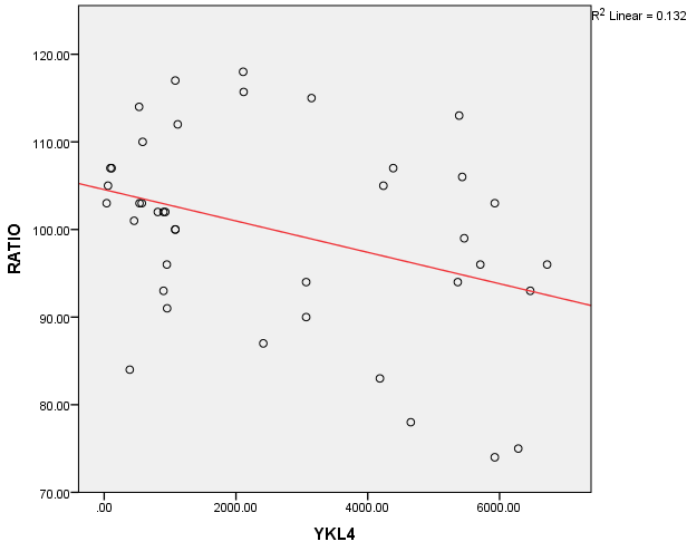

FIG (3): Correlation between YKL40findings and FEV1/FVC ratio

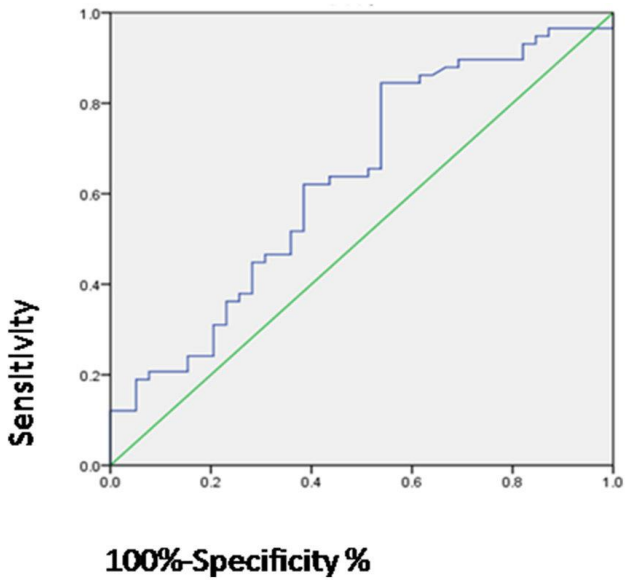

Figure (4): Receiver operating characteristic (ROC) curve of YKL40 as a diagnostic test for bronchial asthma**.**

DISCUSSION

YKL40 may cause asthma-associated inflammation through activation of interleukin-13 pathway that enhances airway hyper-reactivity, a key feature of bronchial asthma. [11]

The present study showed that there was no statistical significant difference between the studied groups as regarding sex and age, where the mean ages of patients and controls groups were (7.76± 2.48) years and (9.30 ± 2.21) years, respectively. Out of the 30 patients, 17 (55.7%) were males and 13 (43.3%) were female; where in control group they were 4 (40%) males and 6 (60%) were females. This was in agreement with the study of **El Basha et al. [11]** , who studied the increased expression of serum YKL40 in children with severe asthma, he found that the mean age was (7.67±2.40 years), (63.3%) were males and (36.7%) were females in the studied group. Also similar finding reported by **Chung [12],** who examined 103 patients diagnosed with asthma they were 56 males and 47 females.

Our study showed that the circulating levels of YKL-40 were increased in asthmatic patients compared to healthy subjects. There was a high statistical significant difference between asthmatic and non-asthmatic groups in YKL40 level which it was higher in asthmatic group than non- asthmatic (3366.96 versus 421.25). In addition, there was a positive correlation between the serum YKL-40 levels and the total serum IgE levels and the ratio of peripheral blood eosinophils, while it correlated inversely with lung functions. This was in agreement with study of **El Basha et al. [11]** who found on his study on 120 asthmatic children that there was a significant increase in the serum YKL40 levels in asthmatic children compared with healthy controls and there was positive correlation between serum YKL40 levels and asthma severity, also, he found a significant rise in the serum YKL40 levels during acute asthma exacerbation compared with stable asthma state. Also the study of **Chupp et al. [7]**, who found that there was a significant increase in the serum YKL40 levels in asthmatics patients compared with healthy controls, also, there was a positive correlation between serum YKL40 levels and asthma severity Also, the current study showed a significant relationship between the levels of serum YKL40 and acute asthma in children ($p<0.001$), which in agreement with the study of **Specjalski et al. [13]** who found that in asthmatic patients, the serum YKL40 level was significantly higher in the subgroup with poor symptoms control compared to the stable asthmatic patients. And also with the study of **Tang et al. [14]** who found that their was a higher serum YKL40 levels in patients with more severe or uncontrolled asthma, also he found that the levels of serum YKL-40 correlate positively with the levels of total serum IgE (r50.298, p50.018) .The present study revealed that there was a significant negative correlation between the levels of serum YKL-40 and FEV1/FVC ratio (r- .367, p .021). Also a significant correlation between the levels of serum YKL-40 and the ratio of peripheral blood eosinophils (r .273, p .012). Similar finding reported **by Lai et al. [15]**, who found that their was a negative correlations between the levels of serum YKL-40 level and the %FEV1 ($r = -0.37$, $p < 0.001$) The current study showed that the serum YKL-40 levels correlate positively with total serum IgE levels and the percentage of peripheral blood eosinophils, and correlate inversely with lung functions. This in agreement with study conducted by **El Basha et al., [11]** who reported that from 120 children with asthma show significant increases in the serum levels of YKL40 as compared with healthy controls. Also it correlate with asthma severity. Also, this study recorded a more significant rise in the serum levels YKL40 during acute asthma exacerbation compared with stable asthma state .Also this coped with **Tang et al., [14]** who showing the comparison of serum YKL-40 levels between asthma and healthy subjects, and the correlation between the protein levels and lung functions coincide finding, (Chupp et al.,2007) reported that there are significant increases in the serum levels of YKL40 in asthmatics compared with healthy controls, also, their levels correlate with asthma severity.

The current study revealed that there was a significant negative correlation between the serum YKL-40 levels with FEV1/FVC ratio (r- .367, p .021). also a significant correlation between the serum YKL-40 levels with the percentage of peripheral blood eosinophils (r .273, p .012). Similar finding reported **by Lai et al. [2015]** who concluded that the serum YKL-40 level was negatively correlated with %FEV1 ($r = -0.37$, $p < 0.001$). The present study found a statistical significant negative correlation between pulmonary function tests (FEV_1 and FVC) with Peripheral blood eosinophils level (higher eosinophils is associated with lower FEV_1 and FVC). There was a negative correlation between FEV_1 and the ratio of activated eosinophils to total eosinophils in endobronchial biopsies from COPD patients, which in agreement with the study of **Rogliani et al. [16]** found that there was a negative correlation between FEV_1, sputum eosinophils and eosinophilcationic protein (ECP)**.** The present study showed that exhibited good discriminatory power (AUC 0.953), respectively to diagnose a bronchial asthma, the accuracy of YKL40 in

detection of asthma was (92.5%), its sensitivity was (93.3%) and specificity was (90%).

CONCLUSION

The high levels of serum YKL-40 correlated with the diagnosis of asthma in children.

No conflict of interest

No financial disclosures

REFERENCES

1. Rathcke CN, Johansen JS, Vestergaard H. YKL-40, a biomarker of inflammation, is elevated in patients with type 2 diabetes and is related to insulin resistance. Inflamm Res. 2006; 55: 53–59.
2. Xie F, Qian Q, Chen Z, Ma G., Feng Y. Chitinase 3-like 1 gene-329G/A polymorphism, plasma concentration and risk of coronary heart disease in a Chinese population. Gene 2012, 499: 135–138.
3. Park HY, Jun CD, Jeon SJ, Choi SS, Kim HR, Choi DB. Serum YKL-40 levels correlate with infarct volume, stroke severity, and functional outcome in acute ischemic stroke patients. PLoS One 2012, 7 (12): e51722.
4. Kelleher TB, Mehta SH, Bhaskar R, Sulkowski M, Astemborski J, Thomas DL. Prediction of hepatic fibrosis in HIV/HCV co-infected patients using serum fibrosis markers: the SHASTA index. J Hepatol 2005; 43: 78–84.
5. Lee JH, Kim SS, Kim IJ, Song SH, Kim YK, Kim JI. Clinical implication of plasma and urine YKL-40, as a proinflammatory biomarker, on early stage of nephropathy in type 2 diabetic patients. J. Diab. Complicat. 2012, 26 (4): 308–312.
6. James AJ, Reinius LE, Verhoek M, Gomes A, Kupczyk M, Hammar U. Increased YKL-40 and chitotriosidase in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2016, 193 (2): 131-142
7. Chupp GL, Lee CG, Jarjour N, Shim YM, Holm CT, He S. A chitinase-like protein in the lung and circulation of patients with severe asthma. N Engl J Med. 2007, 357 (20) : 2016-2027
8. Kuepper M, Bratke K, Virchow JC. Chitinase-like protein and asthma. N Engl J Med. 2008, 358 (10): 1073-5.
9. Horak F, Doberer D, Eber E, Horak E, Pohl W, Riedler J. Diagnosis and management of asthma–Statement on the 2015 GINA Guidelines. Wien Klin Wochenschr 2016, 128(15-16), 541-554.
10. Fraire JA, Keens TG. Pulmonary function tests in children: guidelines for interpretation. J Resp Dis Pediatr. 2003, 5 (5): 211-218.
11. El Basha NR, Osman HM, Abdelaal AA, Saed SM, Shaaban HH. Increased expression of serum periostin and YKL40 in children with severe asthma and asthma exacerbation. J Investig Med. 2018, 66 (8): 1102-1108.
12. Chung KF. Personalized medicine in asthma: time for action: Number 1 in the Series "Personalised medicine in respiratory diseases" Edited by Renaud Louis and Nicolas Roche. Eur Respir Rev. 2017, 26 (145) : 170064.
13. Specjalski K, Chełmińska M, Jassem E. YKL-40 protein correlates with the phenotype of asthma. Lung 2015 ;193:189–94.
14. Tang H, Fang Z, Sun Y, Li B, Shi Z, Chen J. YKL-40 in asthmatic patients, and its correlations with exacerbation, eosinophils and immunoglobulin E. Eur Respir J. 2010, 35(4) : 757-760.
15. Lai T, Chen M, Deng Z, Lǔ Y, Wu D, Li D. YKL-40 is correlated with FEV 1 and the asthma control test (ACT) in asthmatic patients: influence of treatment. BMC Pulm Med. 2015, 15(1) : 1.
16. Rogliani P, Puxeddu E, Ciaprini C, Ora J, Onorato A, Pezzuto G. The Time Course of Pulmonary Function Tests in COPD Patients with Different Levels of Blood Eosinophils. Biomed Res Int. International 2016, 2016: 1–7.

To Cite:

Shokry, D, Esh, A, Yousif, Y, Allbad, M., The correlation between Chitinase-Like Protein YKL-40 and Childhood Asthma in Zagazig University Hospitals. Zagazig *University Medical Journal*, 2023; (361-367): -.doi: 10.21608/zumj.2020.20412.1635.