Serum YKL-40 as a Potential Diagnostic and Prognostic Biomarker in Asthma: Correlations with Exacerbation, Inflammatory Markers, and Disease Severity

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ABSTRACT

Background:YKL-40 is a new marker that plays a role in tissue remodeling and airway inflammatory processes.
Objective: The objective wasevaluatingYKL-40 serum levels in children with bronchial asthma, its predictive value for asthma exacerbation, and its correlation with other inflammatory parameters.**Patients and Methods:** 84 patients with bronchial asthma (34 acute, 50 stable) and 60 healthy children as controls were recruited. YKL-40 levels were measured using an ELISA kit, analyzing correlations with inflammatory parameters. **Results:**Serum YKL-40 levels in asthmatic patients were significantly higher than in non-asthmatic individuals ($p < 0.001$), demonstrating excellent diagnostic accuracy; the area under the curve (AUC) was 1. At a cutoff of 11.9 ng/mL, YKL-40 exhibited 100% sensitivity and 98% specificity. Higher levels were observed in patients with exacerbations ($p < 0.001$) and a history of hospitalizations or intensive care unit (ICU) admissions ($p = 0.03$, $p < 0.001$ respectively). Positive correlations were found with ICU admissions ($r = 0.34$, $p < 0.001$) and inverse correlations with asthma control test (ACT) score ($r = -0.62$, $p < 0.001$). YKL-40 was also associated with inflammatory markers and predicted exacerbations (AUC = 0.73, $p < 0.001$) at a cutoff of 20.2 ng/mL (sensitivity 79%, specificity 65%).**Conclusion:**YKL-40 could serve as a potential biomarker for asthma exacerbation prediction and may provide valuable insights into disease severity and inflammation.

Keywords: YKL-40, Severe Bronchial Asthma, Asthma exacerbation, ICU admission.

INTRODUCTION

Asthma is a complex condition caused by multiple factors, characterized by reversible obstruction of the airways due to chronic inflammation affecting the bronchi. Bronchial asthma can cause recurring cough episodes, wheezing with rhonchi, and difficulty breathing, especially during exhalation. These symptoms are common across all age groups and are often accompanied by increased bronchial responsiveness [(1)]. *Asthma* affects a significant portion of the world's population, with estimates ranging from 1% to 18%. In Egypt, the reported prevalence of asthma in school-aged children is approximately 9%, while 23.2% of infants with wheezy chests are suspected to have airway diseases such as asthma [(2)]. Studies show that bronchial asthma is the most prevalent chronic illness affecting the airways of infants and school-aged children [(3)]. A multifaceted interplay between genetic factors and environmental exposures influences the development of asthma in infants. Research indicates that asthma prevalence is higher in urban areas than in rural areas, and environmental tobacco smoke and air pollution are believed to be the main contributing factors to the disease [(4)].Asthma is characterized by bronchial inflammation, which significantly impacts its prognosis. Additionally, structural changes in the epithelium and subepithelial membrane, known as bronchial remodeling, can cause a decline in spirometry parameters [(5)]. However, the pathophysiology of asthma is multifactorial and complex [(6)]. Despite updated guidelines for asthma control, many subgroups and caregivers still struggle with poor asthma control, even with specialist care [(7)]. Clinical scientists have observed that improving disease outcomes in asthma involves diagnosing the condition earlier and monitoring it more closely with greater sensitivity. It is crucial to find new and specific biomarkers that can be used to evaluate and keep track of lung inflammation in patients with different levels of asthma control[(6-7)].

Lately, there has been an increasing interest in researching the distinct function of chitinase and chitinase-like proteins in the inflammation and alteration of tissues in different human illnesses [(8)]. Gaining knowledge about these roles could provide valuable perspectives in managing asthma.YKL-40 is a glycoprotein that weighs 40 kDa and can bind to heparin. It is known to attach to chitin, which is a polysaccharide consisting of N-acetylglucosamine, particularly in cells that are experiencing inflammation. It is secreted from macrophages, smooth muscle cells of blood vessels, neutrophils, chondrocytes, and cancer cells [(9)]. Previous research has shown its dual role in inflammation and tissue remodeling in human diseases like liver fibrosis, joint injury, and type II diabetes [(10)].

This study aimed to evaluate the serum levels of YKL-40 in children with bronchial asthma, its predictive value for asthma exacerbation, and its correlation with other inflammatory parameters.

PATIENTS AND METHODS

Study design and patient's selection: The current study included 84 patients with bronchial asthma.All data werecollected from files during routine patient's visits, Pediatrics Pulmonary Follow-up Clinic, Ain Shams University Hospital as well fromthoseadmitted in hospital. Diagnosis of asthma was according to GINA

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guidelines[1]. The extracted data included age, sex, BMI, disease onset, number of exacerbation that need hospital admission, number of exacerbation that need ICU admission and oral corticosteroid use. Additionally, the routine laboratory data as total leukocyte count (TLC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also collected.

Exclusion criteria were concomitant medical illness, current immunosuppressant or immunodeficiency, hepatic or renal insufficiency, and DM type 2. Additionally, individuals who had been administered oral corticosteroids or had suffered from pneumonia in the four weeks leading up to the study were not considered part of the study population. Such individuals were excluded from the study to ensure that these factors did not influence the results obtained and to maintain the integrity and accuracy of the study findings.

Sample size calculation

The first step was calculating sample size, which have been done using Minitab 17.1.0.0 for windows (MinitabInc., 2013, Pennsylvania, USA). As reported in structural demographic study[11]; 40% ofEgypt's populations are under 18, so the target populations exceed the millions.Moreover, in different Egyptian studies [2,4] that evaluating the prevalence ofasthma on children, it ranged from 8.2% to 9.4%. After considering the data mentioned earlier, we estimated that the average prevalence of asthma among children is 8.8%. We also set a margin of error of 5%, which means that the actual prevalence of asthma among children is likely between 3.8% and 13.8%. The confidence level we chose was approximately 90%. Lastly, we determined that a minimum of 87 participants was required to achieve accurate results.

Ethical approval and IRB number

During the study, the parents and caregivers of the participating children signed consent forms that included illustrations. The research followed the ethical guidelines for medical investigations involving human subjects, as outlined in the Declaration of Helsinki (1964). The Ethics Committee of the National Research Center granted its approval, and the study was assigned the ethical approval number 231110112021.

Outcome and measurements: The study included two groups of asthmatic patients: exacerbation and stable group. Exacerbation was defined as a rapid symptoms deteriorationthat required unscheduled medical care with lower FEV1 [12].Patients in the exacerbation group sought urgent medical care for acute asthma exacerbation, while those in the stable group were recruited during scheduled clinic visits with stable symptoms and FEV1 levels. During the study, neither of the groups received any changes in their treatment regimen for at least four weeks. As well, both groups did not experience any asthma exacerbations throughout this period. Moreover, 60 healthy children without asthma were included as controls.Asthma Control Test (ACT) questionnaires, including a shortened Arabic version (symptoms plus β2-rescue bronchodilator), were completed by all patients. Forced spirometry was performed using VIASYS HEALTH CareGmbh, IibnizStrasse 7 system (Jaeger, Germany), following standard ATS/ERS Recommendations [13].

In the morning, blood samples were collected from the veins to measure the serum YKL-40 levels using the enzyme immunoassay method in combination with the MicroVue YKL-40 test from Quidel, San Diego, CA, USA. This test uses specific antibodies and streptavidin-coated microplate wells. All measurements were duplicated and calibrated using the kit's calibrators.

Statistical analysis

The data analysis was done using Minitab 17.1.0.0 software (Minitab Inc., 2013). Continuous data were summarized using mean and standard deviation, whereas categorical data were presented as counts and percentages. The Shapiro-Wilk test was used to assess normalityof continuous data. Independent t-test was used to compare continuous data between two groups, and chi-square test was used to compare categorical data among groups. Pearson correlation coefficients were used to evaluate linear relationships. Receiver operating characteristic (ROC) curves were used to assess the effectiveness of YKL-40 in asthma and exacerbation. *Significance* was defined as $p \leq 0.05$, with two-sided tests.

RESULTS

Participant: **Table 1** shows that about 84 asthmatic patients, more than half of them were males and below the age of 10 years, were enrolled in the study with nearly matched control subjects (n=60) in age and sex, p=0.04 and 0.4, respectively. However, the BMI of asthmatic patients was significantly higher than the control group, p=0.003.

Table 1: Baseline characters of asthmatic patients and control

Factors	Asthma (n=84)		Control (n=60)		*p*
Age (≤10 years), n, %	56	66.67	30	50	0.04ɭ
Sex (Female), n, %	36	42.86	30	50	0.40 ɭ
Weight (Kg) (mean/SD)	35.6	14.9	36.2	12.7	0.87†
Height (cm) (median/IQR)	128	(110-142)	140	(135-145)	**0.006**††
BMI (Kg/m^2) (median/IQR	21.4	(16.8-27.4)	14.9	(14.7-19.8)	**0.003**††

BMI: body mass index, n: number, SD: standarddeviation, IQR: inter quartile range, ɭ: chi square test, †: independent t-test, ††: Mann-Whitney test, p<0.05 considered significant.

The level of serum YKL-40 was markedly higher in asthmatic patients than in control participants. Moreover, the diagnostic utility of this biomarker was excellent in distinguishing asthmatic patients from normal individuals; the AUCwas 1; the sensitivity and specificity were 100% and 98% respectively at the cutoff point above 11.9 ng/mL **(Fig.1)**

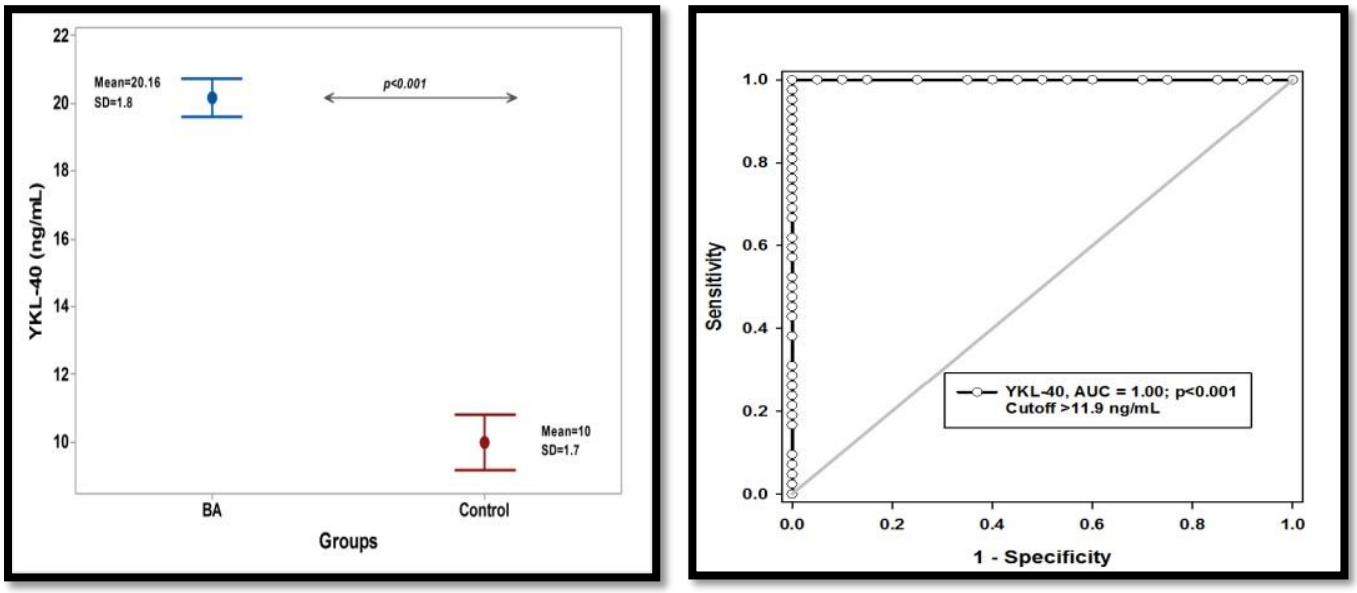

Fig.1: YKL-40 in asthmatic patients: a- Interval plot chart showscomparison of YKL-40 levels between asthmatic and control cases, b- ROC curve showsthe diagnostic parameters of YKL-40 regardingasthma.

Features of asthma exacerbation

Table 2 shows that patients on exacerbation status had significantly shorter duration of disease onset than those with stable asthma, p=0.04. Moreover, in one year before the study; exacerbating grouphad significantlymore patients who had exacerbations that needed hospital admission and higher frequency of hospital admissionthan the stable group, p<0.001 for both.Additionally;significantly more patients in theexacerbating group gave history of ICU admission in the last year, with a significant higher mean number of ICU admissions, p< 0.001 and 0.002, respectively. Unfortunately, all case in exacerbating group was uncontrolled, while 80% of the stable group was uncontrolled;the difference was significant, p=0.01.The use of oral steroids was significantly higher in exacerbating group one month before the study compared to the stable group, p=0.03. Additionally, regarding the laboratory data, the TLC, neutrophil, eosinophils, and CRP were significantly higher in the exacerbating group than the stable one, p<0.001 for all.

Table 2: Characteristic features of asthmatic patients

Factors	Exacerbation (n=34)		Stable asthma (n=50)		*p*
Age (≤10 years),n,%	24	70.59	32	64	0.53[l]
Sex (Female),n,%	18	52.94	18	36	0.12[l]
Weight (Kg), median, IQR	34	(25.5-45)	35	(27-36)	0.71[†]
Height (cm), mean, SD	128.90	23.90	120	24.60	0.11[†]
BMI (Kg/m^2), median, IQR	21	(16-25)	25	(15-31)	**0.11**[†]
Disease onset (Year), median, IQR	2	(1.5-3)	3	(2-6)	**0.04**[†]
ENHA, n,%	28.00	82.35	14.00	28.00	**<0.001**[l]
HAN, mean, SD	2.00	0.24	1.00	0.13	**<0.001**[†]
ICUA, n, %	16.00	47.06	4.00	8.00	**<0.001**[l]
ICUAN, median, IQR	2	(1-3)	1	(0-2)	**0.002**[†]
OCS (Yes), n, %	22	64.71	20	40	**0.03**[l]
ACT, median, IQR	11	(9-13)	14	(11-18)	**<0.001**[†]
Uncontrolled status (Yes), n, %	34	100	40	80	**0.01**[l]
TLC (10^9)/ml, mean, SD	14.39	1.58	9.51	1.55	**<0.001**[†]
Neutrophil (10^9)/ml, mean, SD	10.20	1.97	5.94	1.13	**<0.001**[†]
Eosinophils (10^9)/ml, median, IQR	3	(2-4)	1	(0.3-1.6)	**<0.001**[†]
PLT (10^9)/ml, median, IQR	234	(222-346)	283	(244-328)	0.32[†]
MPV (pg/mL), mean, SD	11.06	1.00	10.86	0.57	0.28[†]
CRP (mg/dL), median, IQR	35	(23-35)	5	(4-12)	**<0.001**[†]

BMI: body mass index, ENHA; exacerbation need hospital admission, HAN, hospital admission number, ICUA, ICU admission history, ICUAN, ICU admission number, OCS: oral corticosteroid, ACT: asthma control test, TLC: total leukocyte count, PLT: platelets, MPV: mean platelet volume, CRP: C-reactive protein, n: number, SD: standarddeviation, IQR: inter quartile range. l: chi square test, †: independent t-test, ††: Mann-Whitney test, p<0.05 considered significant

YKL-40 correlation with asthma exacerbation profile

In figure 2, the serum level of YKL-40 was significantly higher in exacerbating asthmatic patients, as well as in patients with a history of repeated hospital and ICU admission in the last year, plus, it showed a positive correlation with the number of admissions especially in ICU. On the contrary, YKL-40 revealed a significant reverse relationship with ACT score.

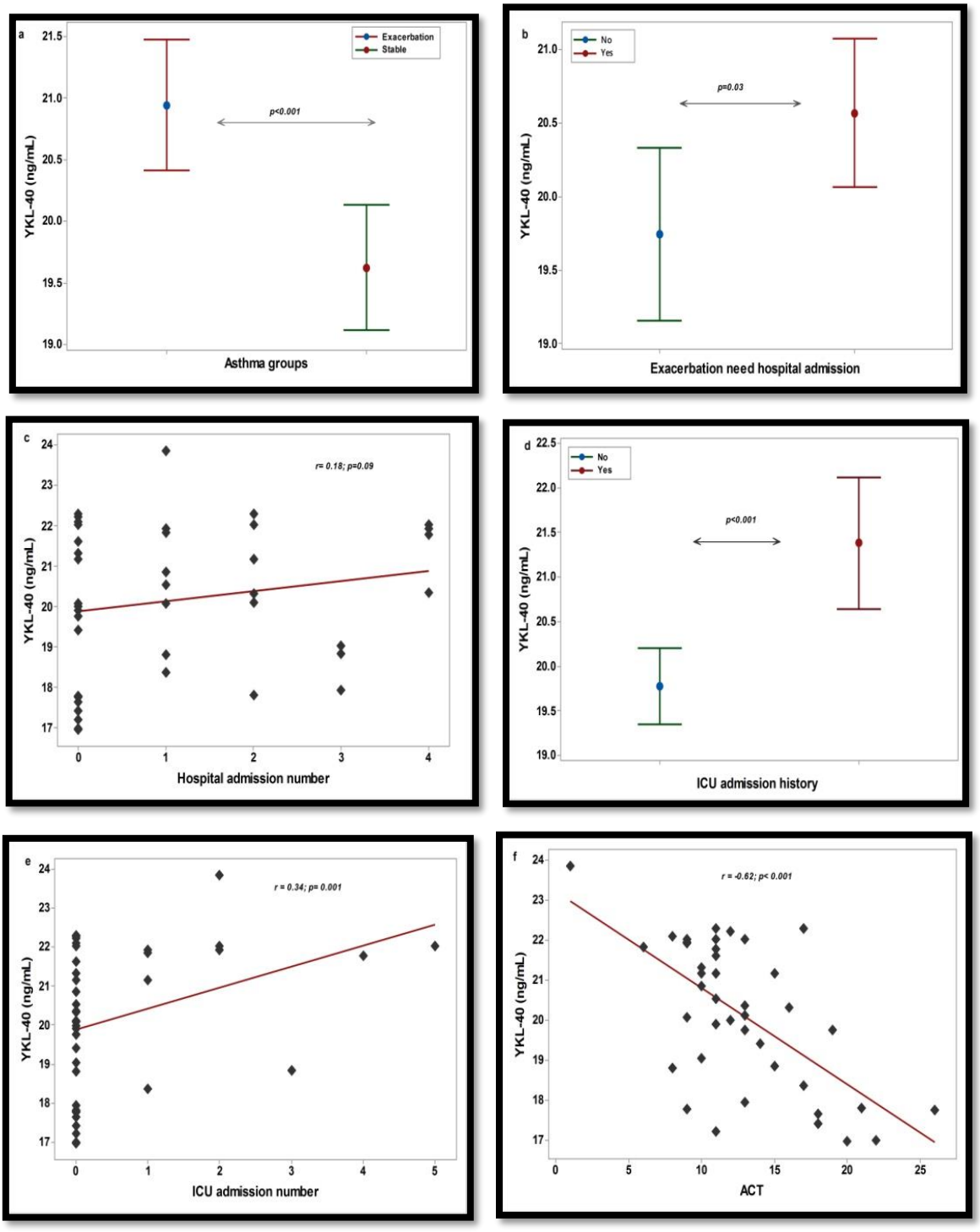

Fig.2: YKL-40 and exacerbation features.

ACT: asthma control test score, the test of significant: a, b and d: independent t-test, test of significant: c, e and f: Pearson correlation coefficient, the sign before the value of r denotes the direction of relationship.

However, considering the correlation with other inflammatory biomarkers, YKL-40 showed a significant positive correlation with TLC, neutrophils, eosinophils, CRP, and MPV**(Fig.3)**.

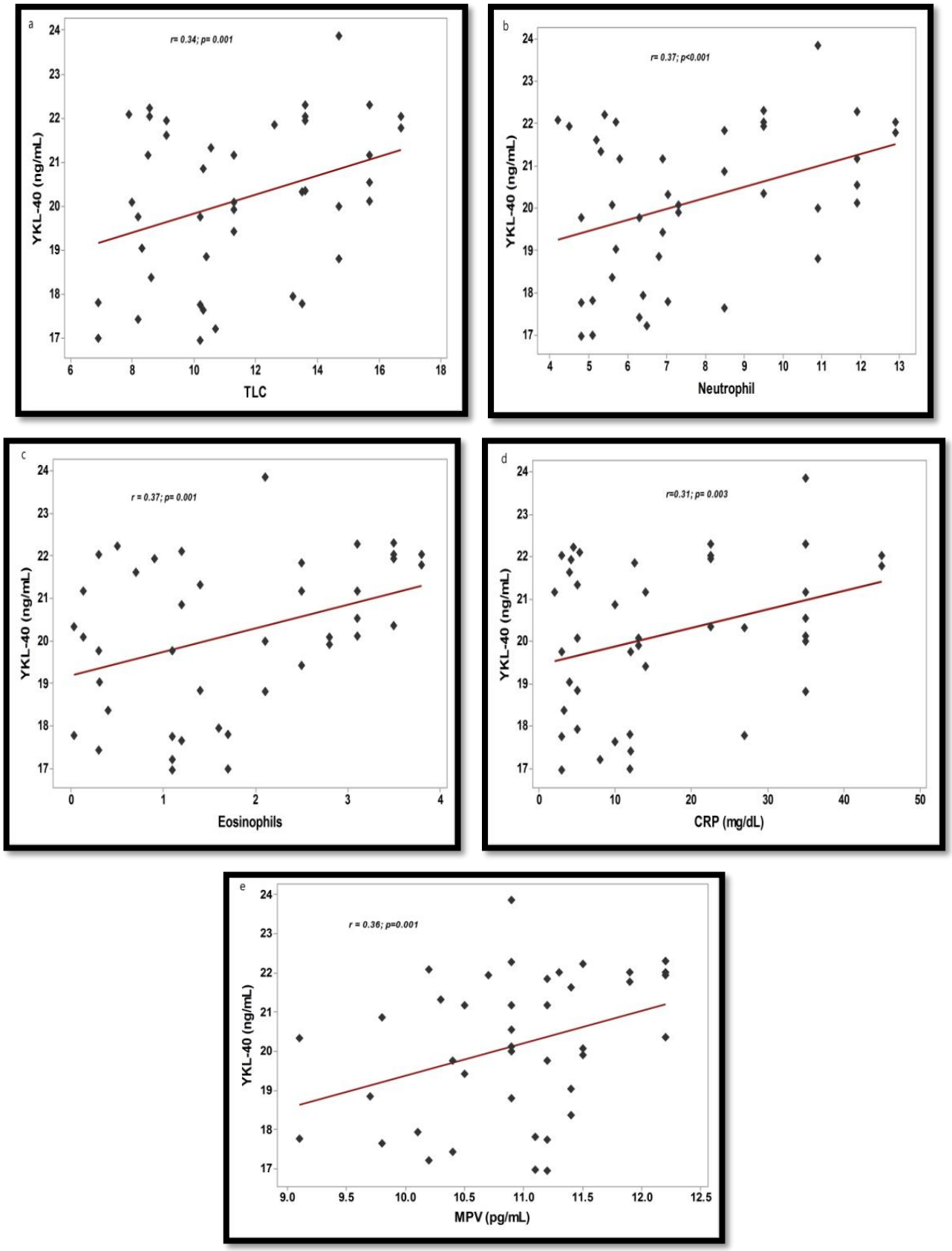

Fig.3: YKL-40 and other inflammatory profile.

CRP: C-reactive protein, MPV: mean platelet volume, test of significant: Pearson correlation coefficient, the sign before the value of r denotes the direction of relationship.

Moreover, the utility of YKL-40 in predicting asthma exacerbation was very good; the sensitivity and specificity at cutoff point >20.2 ng/mL were 79 and 65% respectively **(Fig.4)**.

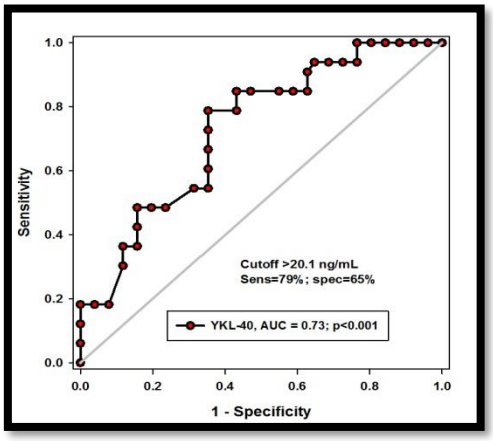

Fig.4: Utility of YKL-40 in predicting asthma exacerbation.

DISCUSSION

Asthma, a chronic respiratory disease, can significantly impair the quality of life of affected children and their families. When asthma is not adequately managed, it can lead to missed school days, academic difficulties, and other educational challenges[14]. Therefore, it is essential to control asthma to enable children to thrive academically and lead fulfilling lives. Caregivers may need to take time off work, resulting in financial difficulties[15]. Also, in severe cases, children may even experience life-threatening asthma attacks[16].

Asthma is a broad term that covers a range of symptoms, including wheezing, coughing, and shortness of breath. Healthcare providers often ask, "What kind of asthma is this?" because the condition has different subtypes, each requiring a unique treatment plan. Identifying asthma's characteristics and modifiable traits is just the first step in the diagnostic process[17].

Diagnosing asthma can be challenging because symptoms can come and go, and the type of asthma a patient may change over time. While wheezing is a critical sign of asthma, its absence in a child may reduce the likelihood of an asthma diagnosis. The sound during exhalation wheeze happens because of slight airway narrowing and inflammation[18]. It is essential to ensure that parents understand wheezing when they report it, as it can help with an accurate diagnosis. Regular symptom monitoring and treatment adjustments are necessary to manage this condition effectively[17]. The process of asthma diagnosis is challenging due to the high incidence of "preschool wheeze". Although many toddlers experience wheezing, not all of them develop asthma[17-18]. Regular asthma diagnosis reviews are essential to distinguish genuine asthma cases and accurately adjust treatment plans. A pivotal diagnostic factor involves observing a positive response to an appropriate asthma treatment trial. In children and adolescents, clinical examinations may appear normal, especially during symptom-free periods, necessitating a comprehensive approach to diagnosis. During acute asthma attacks, observable signs such as the use of accessory respiratory muscles and widespread wheezing may be present. In cases of chronic asthma, chest hyperinflation becomes evident. This inclusive approach to diagnosing asthma in the pediatric population involves monitoring symptoms, conducting diagnostic trials, carefully examining during acute episodes, and facilitating effective management in children and adolescents [19].

The results of the study demonstrated a significant difference in serum YKL-40 levels between asthmatic patients and the control group, which made YKL-40 a potential biomarker for asthma. Additionally, at a cutoff point above 11.9 ng/mL; the diagnostic accuracy of YKL-40 was found to be excellent, with the area under the curve (AUC) of 1 ($p<0.001$) and a sensitivity of 100%, and a specificity of 98%; the findings suggest that serum YKL-40 could be a reliable and sensitive marker for diagnosing and differentiating asthma from non-asthma conditions. These results align with previous research [20], showing elevated YKL-40 levels in asthmatic cases and a higher increase in patients with exacerbation history, highlighting its relevance in asthma episodes.

A promising diagnostic and prognostic role of YKL-40 in numerous inflammatory diseases affecting central nervous system, chest disease like pneumonia and lung cancer,rheumatoid illness such as arthritis, osteoarthritis, breastcancer, andlastly hepatic fibrosis [21,22] and tissue remodeling has beenintensively suggested years ago[23]. Furthermore, **Chupp*et al.*[23]**, have concluded that YKL-40 was statistically stronglyupregulated in the airway epithelium and alveolar macrophages of asthmatic patients with different ages, and that the monitored serum levels of YKL-40 were noticed to be increased in asthmatic cases.

Measuring inflammatory markers in the blood is an alternate way to comprehend airway inflammation and assess the effectiveness of treatments. Eosinophil levels in the blood can reflect the response to treatments such as inhaled corticosteroids and allergen immunotherapy. Although some inflammatory cytokines like IL-4, 5, and 13 have been suggested as potential markers, they need further evaluation before being used as indicators of treatment response[1,3].The circulated serum level of YKL-40 was correlated with different grades of asthma severity[24]. The measured thickness of subepithelial basement membrane and spirometry parameters (pulmonary function)are supporting that the serum level of YKL-40 might be having an influence as a vital biomarker in the chronic illness of asthma[24]. YKL-40 is pivotal in modulating inflammation and tissue remodeling processes within

biological systems. Its intricate functionalities unfold through interactions with diverse cellular entities, receptors, and signaling pathways. Although the precise mechanisms underlying the participation of YKL-40 in inflammatory and pathological processes remain subjects of ongoing investigation, discernible patterns have emerged linking elevated concentrations of this protein in the bloodstream to heightened inflammatory responses and a spectrum of associated diseases and conditions [24-25]. The complex web of interactions involving YKL-40 underscores its multifaceted involvement in orchestrating molecular events that contribute to the complexities of inflammatory cascades and tissue remodeling [24]. The ongoing research in this domain seeks to unravel the nuanced molecular interplay orchestrated by YKL-40, shedding light on its significance as a potential biomarker and therapeutic target in the context of various pathological states [23]. Moreover, there was a significant association between high body mass index in asthmatic group and the resulted outcome of high serum levelof YKL-40. This was in line with **Catalán*et al.*** [26]. Also, **Specjalski*et al.***,reported that the mean investigated serumYKL-40 level in obese asthmatic children was 135.6 ng/ml versus to 50.0 ng/ml in normal body weight cases with diagnosed asthma ($p<0.001$),but there were no correlations regarding theserum bloodCRP,neutrophilia or eosinophiliawere noticed [27]. While,**Tang *et al.***, and **Konradsen *et al.***,supported our finding regarding the significant higher eosinophils 'percentage in exacerbating group than the stable one, $p< 0.001$ for all, and positive correlation to the biomarker YKL-40 [28,29].

This association with obesity might be explained, that it is known that visceral adipose tissue plays an important role as a main source of YKL-40. The pro-inflammatory inclination observed in children grappling with both asthma and obesity serves as an additional manifestation of the heightened levels of serum YKL-40 [30]. This association underscores a potential interplay between the two conditions, implicating YKL-40 as a crucial mediator in the intricate web of inflammatory processes. Elevating serum YKL-40 levels in the context of asthma and obesity highlights its potential role as a biomarker. It suggests a plausible link between the pro-inflammatory milieu and the coexistence of these health conditions in pediatric populations. Further exploration of this relationship holds promise for a deeper understanding of the underlying molecular mechanisms and potential therapeutic interventions aimed at mitigating the inflammatory burden in children with concurrent asthma and obesity. However, there is controversy,asthe increased YKL-40 level was not known to be specific, and publishedresearches show no correlations in different asthmatic subgroups in pediatric population[31].Since asthma is a well-known heterogeneous disease[14], it may hypothesized that YKL-40 is solely increased in certain asthma phenotypes.Recent studies tracking children from birth or early childhood to adulthood have delineated three distinct asthma phenotypes. The first, transient wheezing, typically manifests during the initial 3-5 years of life and is often associated with maternal smoking during pregnancy and exposure to daycare environments. Notably, this phenotype lacks a typical association with a family history of asthma or allergies. The second phenotype, non-atopic wheezing, tends to persist in children who experience wheezing with respiratory syncytial virus early in life, irrespective of allergic predisposition. Finally, the third phenotype, IgE-mediated wheezing, represents the classic asthma phenotype linked to allergic sensitization. Early sensitization emerges as a significant risk factor for the persistence of asthma into later childhood and beyond [32].

A study conducted by **Gomez *et al.*** has shown that individuals with elevated levels of the biomarker YKL-40 in their serum are associated with two distinct asthmatic phenotypes. The first group exhibited irreversible airway obstruction, while the second group was prone to severe exacerbations. These two clusters, determined by their levels of YKL-40, can be used as a tool for identifying individuals with either severe or exacerbation-prone asthma [10]. This information can aid in developing more personalized treatment plans for individuals with these specific asthma phenotypes [10, 33].Previous study had mentioned thatby applying the measuring of YKL-40 levels with the routine asthma evaluation regarding the physiological and clinical assessment symptoms [33], this can categorize specific subgroups of patients with definite clinical symptoms and risk for suspected severe airflow limitation and even obstruction [10].

Recent years have seen significant advancements in asthma diagnosis, with a growing focus on identifying potential inflammatory markers. Historically, diagnosis relied heavily on clinical symptoms, pulmonary function tests, and bronchial provocation tests. However, the emergence of inflammatory markers like YKL-40 has brought a more precise dimension to asthma diagnosis. These markers provide critical insights into the type and extent of airway inflammation, which helps differentiate between different asthma phenotypes. They also play a crucial role in assessing treatment response and customizing therapies for individuals with asthma[32]. By leveraging these markers, clinicians can make more informed decisions, leading to better management and improved quality of life for asthma patients[33]. As research in this field progresses, we can expect even more accurate and personalized asthma diagnosis and management approaches.

CONCLUSION

In this study, kids with bronchial asthma have higher levels of YKL-40 compared to those who do not

have asthma. Moreover, among the asthmatic children, those with acute exacerbations had even higher levels of YKL-40 than those with stable asthma. These results imply that the severity of asthma is related to the level of YKL-40 in the serum. YKL-40 may be a valuable biomarker for diagnosing and predicting the development of bronchial asthma. It could also serve as a potential diagnostic tool and a prognostic indicator for assessing disease progression. However, a prospective study is recommended to obtain the outcome and prove whether the serum levels of YKL-40 would change (either decreased or even diminished) when those exacerbation subjects are reported to be well controlled after treatments.

DECLARATIONS

- ***Conflict of interest***
  The authors have no conflicts of interest.
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