

## Assessment of Tenascin C levels in the serum of patients with bronchial asthma

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### Abstract

Asthma is a heterogeneous disease that affects a large proportion of the global population and is distinguished by airway hyperresponsiveness to direct and indirect stimulations. It is a multifactorial disease that is triggered by heredity and environmental causes. Tenascin C (TNC) is an extracellular matrix glycoprotein that promotes inflammatory cell migration from the interstitium to the airways. Stimulation of TNC is through cytokines from T helper 2 (Th2) cells, in addition, it proliferates within basement membranes of the airways in asthmatic patients. This study aimed to determine whether serum TNC can be used as a novel biomarker for asthma diagnosis and to evaluate the association between serum TNC measurement and asthma severity. This case-control study included 64 patients with mild to severe bronchial asthma, diagnosed according to GINA 2022, referred to the Allergy and Clinical Immunology outpatient clinic at Ain Shams University Hospital, and 64 normal subjects as controls. Serum TNC levels were measured by ELISA. Serum TNC levels were significantly higher among bronchial asthma patients than controls ( $p < 0.001$ ). The sensitivity of serum TNC measurement in the diagnosis of bronchial asthma was 93.75%, the specificity 60.94%, and the negative predictive value 90.7%. Besides, a significant relation was found between serum TNC levels and the severity of bronchial asthma ( $p=0.004$ ), as elevated serum TNC levels were the highest among severe asthmatic patients. *In conclusion*, the results gained in this study revealed that serum TNC level could be proposed as a potential biomarker for the diagnosis of bronchial asthma and a potential predictor of disease severity.

**Keywords:** Bronchial asthma, serum Tenascin C (TNC), asthma severity.

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### Introduction

Asthma is a prevalent chronic respiratory disease affecting individuals of all age groups, with more than 300 million people worldwide suffering from this disease in 2021.<sup>1</sup> while in Egypt the prevalence of bronchial asthma was 6.7%.<sup>2</sup> Asthma is a disease characterized

by variable expiratory airflow obstruction and chronic airway inflammation.<sup>1</sup> Despite advances in our knowledge of the pathophysiology and management of asthma, the underlying mechanisms responsible for disease progression and severity are still not fully understood.<sup>3</sup>

Airway tissue remodeling is a secondary process caused by a persistent inflammatory process.<sup>4,5</sup> It interferes with the normal repair of airway tissue, which involves mucous hyperplasia, smooth muscle hyperplasia, mucosal neovascularization, myofibroblast hyperplasia, goblet cell hyperplasia, epithelial hypertrophy, and deposition of extracellular matrix protein (ECM), which cause thickening of the airway wall.<sup>4,6</sup>

ECM proteins, which play a crucial role in tissue remodeling and repair, have been the focus of current research efforts in asthma.<sup>7</sup> Tenascin C (TNC) is one of these proteins.<sup>8</sup> TNC, a large hexameric glycoprotein within the extracellular matrix, has emerged as a potential immunomodulatory ECM protein in the airways of asthmatic patients,<sup>8,9</sup> and it facilitates inflammatory cell migration from the interstitium to the alveolar space.<sup>10</sup> TNC deposition thickness in the basement membrane was shown to be correlated with T-lymphocyte, eosinophil, and macrophage counts.<sup>11</sup> The accumulation of TNC in asthmatic bronchi may be indicative of an incomplete healing process and airway remodeling. Consequently, it can be utilized as a marker to identify the activity of the disease.<sup>12</sup>

Several previous studies have investigated TNC expression in the airway tissues of asthmatic patients, revealing increased levels compared to healthy individuals.<sup>12-14</sup> However, the assessment of TNC levels in serum samples of asthmatic patients constitutes a promising option for non-invasive diagnosis and assessment of asthma severity. By measuring circulating TNC, it may be possible to identify patients at higher risk of asthma exacerbations and potentially develop novel therapeutic options targeting tenascin-related signaling pathways. Therefore, the aim of this study was to determine the serum levels of TNC in asthmatic patients and to assess its potential relation with asthma severity.

## Subjects and Methods

Our case-control study comprised 128 participants who visited the Allergy and Clinical Immunology outpatient clinic at Ain Shams University Hospital. They were divided into two

groups. Group 1: The control group comprised 64 apparently healthy persons who have never had asthma or any other allergic illnesses and matched the same exclusion criteria as the patients. They were medical workers chosen from the hospital team. Group 2: Asthmatic patients' group, included 64 adults (>18 years old) they were diagnosed as bronchial asthma individuals, in accordance with the Global Initiative for Asthma (GINA 2022).<sup>15</sup>

### *Inclusion criteria*

Asthmatic patients ranged in severity from mild to severe, in accordance with GINA 2022.<sup>15</sup>

### *Exclusion criteria*

It included patients diagnosed with chronic obstructive pulmonary disease (COPD) as defined by the Global Initiative for Chronic Obstructive Lung Disease guidelines (GOLD guidelines 2022).<sup>16</sup> Smoking patients, patients with any recent respiratory illness excluding asthma, as acute or chronic bronchitis, patients with a known cystic fibrosis case, or interstitial pulmonary fibrosis, patients with any other intercurrent allergic diseases such as allergic rhinitis, chronic urticaria, atopic eczema, or allergic conjunctivitis, patients on immune suppressants or immunotherapy, pregnant females were excluded from the study. Patients with end-organ failure such as liver cell failure, renal impairment, heart failure, or respiratory failure and patients rebuttal to contribute were also excluded from the study.

### *Study methods*

Each participants underwent a comprehensive medical history, thorough chest examination, pulmonary function testing via spirometry for evaluating the forced expiratory volume in one second (FEV1) and FEV1/forced vital capacity (FVC), chest x-ray to exclude any other pulmonary disorders. Total serum IgE by the enzyme linked immunosorbent assay (ELISA) as described below. Complete blood count (CBC) test with an eosinophilic count using an automated analyzer (Sysmex XN 1000 Hematology Analyzer, Japan), according to the manufacturer's instructions. *C-reactive protein* (CRP) was performed using a clinical chemistry analyzer (Cobas C, Roche Diagnostics, USA),

according to the manufacturer's instructions. Skin prick testing for common aeroallergens was done as shown below. Atopy was diagnosed by the existence of at least one positive skin prick test result. Asthma severity score, asthma symptom control was designed according to GINA 2022,<sup>15</sup> and Serum tenascin C level detected by ELISA.

#### *Skin prick test (SPT)*

SPT was performed for all the subjects by using common aeroallergen extracts (Omega Company, Canada), including house dust mites (HDM), pollen, animal epithelia, and molds. Saline was used as the negative control, and histamine dihydrochloride was employed as the positive control.<sup>17</sup> Participants were instructed to discontinue the use of antihistamines for one week prior to the skin testing. The SPT results were examined after 15 minutes. The wheal's maximum diameter was measured, and a positive reaction was defined as a wheal diameter of 3 mm or greater.<sup>18</sup>

#### *Asthma severity scoring*

According to GINA 2022,<sup>15</sup> severity was determined retrospectively based on the type of essential treatment needed to manage complaints and exacerbations: Mild asthma: maintained well with on-demand relief medications either alone or combined with low-dose inhaled corticosteroids (ICSs), leukotriene receptor antagonists, or chromones. Moderate asthma: controlled with low-dose ICS/long-acting beta2-agonists (LABA). Severe asthma, which necessitated high-dose ICS/LABA to keep it from getting out of control, or asthma that did not get better even with this treatment.

#### *Assessment of asthma symptom control*

According to the GINA 2022 asthma control evaluation, the patients' asthma symptom control was graded as well-controlled, partially controlled, or uncontrolled. Study subjects were questioned about asthma symptoms frequency during the previous 4 weeks, any waking at night owing to asthma or activity constraints, and patients' frequency of usage of short-acting beta-2 agonist (SABA) relievers to treat symptoms.<sup>15</sup>

#### *Pulmonary Function Test (PFT)*

The age, height, and weight of study patients and controls were documented. PFT was accomplished by a spirometer (Flowmate V Plus spirometer, Spirometrics, Gray, ME, USA) at the Pulmonary Functions Laboratory at Ain Shams University Hospital. All tests were carried out in the sitting position, and the best reading out of three successive readings was recorded. A ventilatory deficit that was obstructive was indicated by a FEV1/FVC ratio of a value lesser than 0.70. When the FEV1/FVC ratio was normal >0.70 and the FVC was reduced further than the FEV1, the respiratory defect was deemed to be restrictive.<sup>19</sup>

#### *Specimen collection and preparation*

A venous blood sample (5 ml) was collected from each study participant using an aseptic venipuncture technique. Serum samples were separated by centrifugation and kept frozen at -20°C until used for measurement of total IgE, and TNC.

#### *Serum Total IgE Level*

Serum total IgE was measured by commercial ELISA kits (G enzyme Diagnostics, Medix Biotech, San Carlos, Calif., USA), according to the manufacturer's instructions. Total serum IgE concentrations were reported in international units or nanograms per milliliter. Total serum IgE concentrations among non-allergic adults are below 100 IU/ml.<sup>20</sup>

#### *Serum TNC level*

Commercially available sandwich ELISA kits were utilized for quantitative measurement of the serum level of TNC (Cat. No: E1414Hu, Shanghai Crystal Day Biotech CO., LTD, China), according to the manufacturer's instructions. The outcomes were quantified in ng/l. The kit assay range was 20–6000 ng/l.

#### *Statistical Analysis*

Data were gained, revised, coded, and analyzed using the Statistical Package for Social Science (SPSS) IBM, version 23. For parametric quantitative data, means, standard deviations, and ranges were displayed; for non-parametric data, medians, and interquartile ranges (IQR)

were displayed. Qualitative variables were displayed as numbers and percentages. When comparing qualitative data, the Chi-square test was used. In order to compare two groups with quantitative data and a parametric dispersion, the independent t-test was applied. For comparison of two groups utilizing quantitative data and a non-parametric dispersion was done using the Mann-Whitney test. The One-Way ANOVA test was implemented to compare more than 2 distinct groups whenever measurable data and a parametric dispersion were present. The Kruskal-Wallis test was applied to compare more than two groups while employing quantitative data and a non-parametric distribution. The correlation between two numerical parameters within the same group was evaluated using the Spearman correlation coefficients. The receiver operating characteristic (ROC) curve analysis was utilized to quantify the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and area under the curve (AUC). We

considered a 5% acceptable margin of error and a 95% confidence interval, respectively. So, the  $p$ -value of  $< 0.05$  was considered significant.

## Results

### Study population

The case group in the present study involved 20 male patients and 44 female patients with mild to moderate asthma, with a mean age of 41.58 years. The control group involved 26 males and 38 females, with a median age of 43.75 years. There were no age or gender differences between the two research groups (Table 1). Mild asthmatics were 48.4%, moderate asthmatics accounted for 31.2% and severe asthmatics 20.3%. As regards asthma symptom control, 18.8% were uncontrolled 34.4% partially controlled and 46.9% well controlled. Patients with atopic asthma were 78.1% while patients with non-atopic asthma represented 21.9% (Table 2).

**Table 1.** Comparison of demographic data between the patient and the control groups.

|             |               | Control group     | Patients group    | $p$ value |
|-------------|---------------|-------------------|-------------------|-----------|
|             |               | No. = 64          | No. = 64          |           |
| Age (years) | Mean $\pm$ SD | 43.75 $\pm$ 11.99 | 41.73 $\pm$ 11.84 | NS*       |
|             | Range         | 19 – 60           | 18 – 60           |           |
| Gender      | Female        | 38 (59.4%)        | 44 (68.8%)        | NS*       |
|             | Male          | 26 (40.6%)        | 20 (31.2%)        |           |

SD: Standard deviation; \*: Chi-square test; •: Independent t-test.  $P > 0.05$  is not significant (NS).

**Table 2.** Clinical Characteristics of Asthma Patients.

|                               |                     | Patients group |
|-------------------------------|---------------------|----------------|
|                               |                     | No. = 64       |
| Asthma severity               | Mild                | 31 (48.4%)     |
|                               | Moderate            | 20 (31.2%)     |
|                               | Severe              | 13 (20.3%)     |
| Asthma control                | Uncontrolled        | 12 (18.8%)     |
|                               | Partly controlled   | 22 (34.4%)     |
|                               | Well-controlled     | 30 (46.9%)     |
| Atopic or non-atopic patients | Atopic patient      | 50 (78.1%)     |
|                               | Non atopic patients | 14 (21.9%)     |

### TNC serum level in cases and control group

Data in Table 3 demonstrates that serum TNC levels in patients with bronchial asthma were significantly greater than TNC values in the control group ( $p < 0.001$ ). To appraise the validity of the TNC serum level for the diagnosis of bronchial asthma, the ROC curve analysis was

utilized. It demonstrated a sensitivity of 93.75%, a specificity of 60.94%, negative predictive value of 90.7%, and positive predictive value of 70.6%. The serum TNC cutoff value was greater than 1632 ng/l, with an area under the curve of 0.679, as shown in Figure 1 and Table 4.

**Table 3.** Comparison of serum TNC level between the patient and control groups.

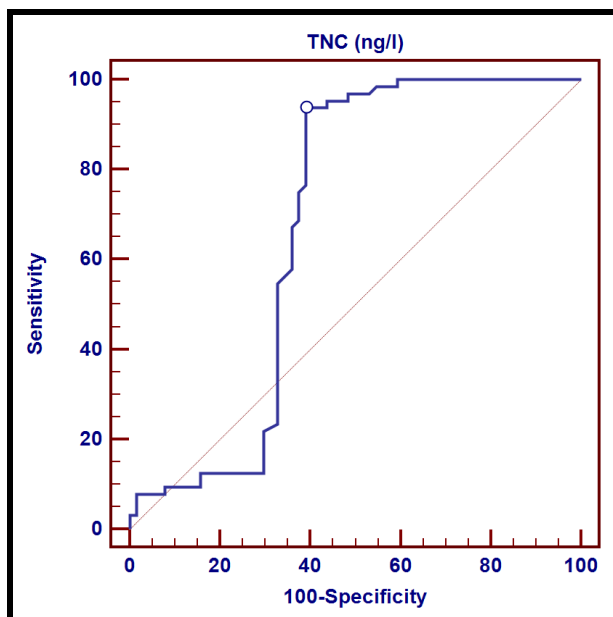
| TNC (ng/l)   | Control group        | Patients group           | p value |
|--------------|----------------------|--------------------------|---------|
|              | No. = 64             | No. = 64                 |         |
| Median (IQR) | 1429 (681.15 – 1795) | 1661.5 (1645.5 – 1677.5) | <0.001  |
| Range        | 233.1 – 4938         | 1230 – 5859              |         |

IQR: interquartile range; #: Mann-Whitney test.  $P \leq 0.05$  is significant.

**Table 4.** Accuracy of serum TNC for diagnosis of bronchial asthma.

| Cut off point | AUC   | Sensitivity | Specificity | PPV  | NPV  |
|---------------|-------|-------------|-------------|------|------|
| >1632         | 0.679 | 93.75       | 60.94       | 70.6 | 90.7 |

AUC: Area Under the Curve. PPV: Positive predictive value. NPV: Negative predictive value.



**Figure 1.** Receiver operating characteristic (ROC) curve analysis for TNC level to detect cases with bronchial asthma.

### Relation between asthma severity and different laboratory parameters and pulmonary function test results

There was a significant statistical difference between asthma severity and CRP level measurement ( $p=0.045$ ). While there was no difference in total IgE level measurement and asthma severities ( $p=0.808$ ). Besides, there was no difference between eosinophilia and asthma

severity levels ( $p=0.403$ ). There were no differences in pulmonary function tests including FEV1, FEV1/FVC ratio, and asthma severity, as shown in Table 5. Furthermore, serum TNC levels were significantly different between atopic and non-atopic asthma patients, with higher levels in atopic asthma patients than in non-atopic asthma patients ( $p=0.032$ ), as shown in Table 6.

**Table 5.** Relation between asthma severity and pulmonary function test results and laboratory data of the studied patients.

|                                       |               | Asthma severity    |                     |                    | <i>p</i> value |
|---------------------------------------|---------------|--------------------|---------------------|--------------------|----------------|
|                                       |               | Mild               | Moderate            | Severe             |                |
|                                       |               | No. = 31           | No. = 20            | No. = 13           |                |
| Eosinophils count ( $\times 10^9$ /L) | Median (IQR)  | 0.09 (0.06 – 0.5)  | 0.4 (0.07 – 0.7)    | 0.2 (0.07 – 0.58)  | NS*            |
|                                       | Range         | 0 – 1              | 0 – 1               | 0.04 – 3           |                |
| CRP (mg/L)                            | Median (IQR)  | 33 (22 – 45)       | 31.5 (19.35 – 45.5) | 17 (13 – 23)       | 0.045*         |
|                                       | Range         | 2 – 140            | 7.8 – 190           | 1.4 – 56           |                |
| FEV1                                  | Median (IQR)  | 2.94 (2.04 – 3.24) | 2.02 (1.78 – 3.05)  | 2.21 (1.36 – 3.14) | NS*            |
|                                       | Range         | 1.08 – 4.96        | 1.08 – 4.99         | 1.09 – 4.87        |                |
| FVC                                   | Mean $\pm$ SD | 3.74 $\pm$ 0.76    | 3.63 $\pm$ 0.87     | 3.84 $\pm$ 0.66    | NS*            |
|                                       | Range         | 2.03 – 4.94        | 1.96 – 5.81         | 2.49 – 4.99        |                |
| FEV1/FVC ratio                        | Mean $\pm$ SD | 79.49 $\pm$ 10.40  | 80.94 $\pm$ 9.44    | 80.97 $\pm$ 7.98   | NS*            |
|                                       | Range         | 52.8 – 97.97       | 52 – 96             | 66 – 98            |                |
| Total serum IgE (IU/L)                | Median (IQR)  | 135 (50 – 197)     | 117.15 (35.9 – 148) | 104 (62 – 221)     | NS*            |
|                                       | Range         | 17.6 – 360         | 6.5 – 946           | 8.3 – 539          |                |

SD: Standard deviation; IQR: interquartile range; CRP: C-reactive protein; FEV1: Forced expiratory volume in the first-second; FVC: Forced vital capacity. \* Kruskal-wallis test; • One Way ANOVA test.  $P \leq 0.05$  is significant.

**Table 6.** Comparison of serum TNC levels between Atopic and Non-atopic Asthma Patients:

|                   | TNC (ng/l)           |             | <i>p</i> value |
|-------------------|----------------------|-------------|----------------|
|                   | Median (IQR)         | Range       |                |
| Non-atopic asthma | 1653 (1636 – 1670)   | 1230 – 1683 | 0.032          |
| Atopic asthma     | 1664.5 (1648 – 1680) | 1474 – 5859 |                |

IQR: interquartile range. •: Mann-Whitney test.  $P \leq 0.05$  is significant.

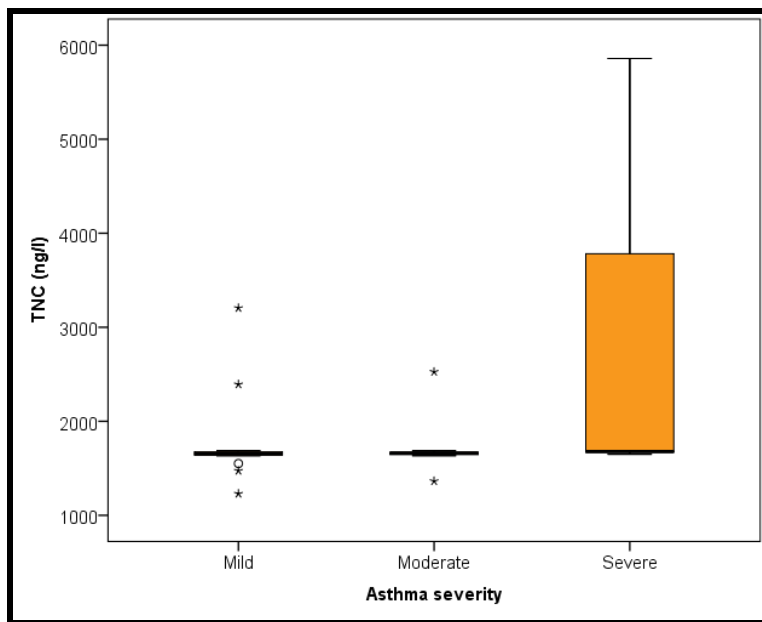
Data in Table 7 and Figure 2 illustrate that the serum TNC level is statistically significantly higher in patients with severe asthma than in patients with mild to moderate asthma ( $p = 0.004$ ). The median (IQR) value for TNC was 1679 (1670 – 3782) in severe asthmatic patients. Also, Table 7 shows that the serum

TNC level was elevated in patients with uncontrolled asthmatics compared to partially controlled asthmatic patients ( $p = 0.006$ ). The median (IQR) level of serum TNC in uncontrolled asthmatic patients was 1675.5 (1667.5 – 4275.5).

**Table 7.** Relation between serum TNC level and asthma severity, and asthma control among the patient's group.

|                 |                   | TNC (ng/l)               |             | <i>p</i> -value |
|-----------------|-------------------|--------------------------|-------------|-----------------|
|                 |                   | Median (IQR)             | Range       |                 |
| Asthma severity | Mild              | 1653 (1640 – 1676)       | 1230 – 3205 | 0.004           |
|                 | Moderate          | 1662.5 (1645.5 – 1671)   | 1364 – 2526 |                 |
|                 | Severe            | 1679 (1670 – 3782)       | 1649 – 5859 |                 |
| Asthma control  | Uncontrolled      | 1675.5 (1667.5 – 4275.5) | 1649 – 5859 | 0.006           |
|                 | Partly controlled | 166.4 (1648 – 1675)      | 1364 – 3782 |                 |
|                 | Well controlled   | 1652 (1640 – 1674)       | 1230 – 3205 |                 |

IQR: interquartile range. •: Kruskal-Wallis test.  $P \leq 0.05$  is significant.



**Figure 2.** Relation between asthma severity and TNC level.

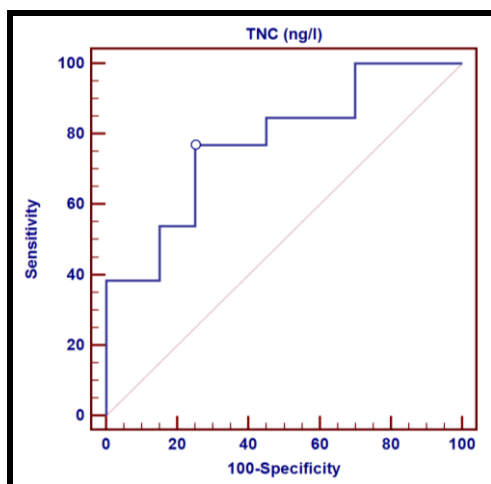
To evaluate the reliability of TNC level measurement for the determination of asthma severity, the ROC curve analysis was performed. It showed sensitivity and specificity of 76.92% and 75.00%, respectively. While the negative and positive predictive values were 83.3% and 66.7%, respectively. Such data were obtained at serum TNC cutoff value of >1669ng/l, and AUC

of 0.777, as shown in Table 8 and Figure 3. Finally, data in Table 9 shows no correlation between serum TNC and age, serum eosinophils, CRP, IgE, or pulmonary function test in the patient group.

**Table 8.** Accuracy of serum TNC level for diagnosis of Asthma severity.

| Cut off point | AUC   | Sensitivity | Specificity | NPV  | PPV  |
|---------------|-------|-------------|-------------|------|------|
| >1669         | 0.777 | 76.92       | 75.00       | 83.3 | 66.7 |

AUC: Area Under the Curve; NPV: Negative predictive value; PPV: Positive predictive value.



**Figure 3.** Receiver operating characteristic (ROC) curve analysis for TNC level to diagnose asthma severity.



**Table 9.** Correlation between TNC and other studied parameters among the patients' group.

|                                       | TNC (ng/l) |         |
|---------------------------------------|------------|---------|
|                                       | r          | p value |
| Age(years)                            | -0.021     | NS      |
| Eosinophils count ( $\times 10^9$ /L) | 0.095      | NS      |
| CRP (mg/L)                            | -0.223     | NS      |
| FEV1                                  | -0.151     | NS      |
| FVC                                   | 0.119      | NS      |
| FEV1/FVC ratio                        | 0.133      | NS      |
| Total serum IgE (IU/L)                | 0.101      | NS      |

CRP: C-reactive protein. FEV1: Forced expiratory volume in the first second. FVC: *Forced vital capacity*;  
r: Spearman correlation coefficient.  $P > 0.05$  is not significant (NS).

## Discussion

The present study aimed to determine the association between serum TNC level and diagnosis of bronchial asthma and to assess the relation between serum TNC level measurement and asthma severity. In the current study the serum TNC levels of patients with bronchial asthma were significantly higher than in the control group ( $p < 0.001$ ). Findings of a study in animal models by Nakahara et al., 2006, were consistent with our observations. They reported that TNC-deficient mice exhibited substantially diminished eosinophilic inflammation of the airways, less lung secretion of Th2 cytokines, MMP-9 (metalloproteinase-9), and MCP-1 (monocyte chemoattractant protein-1), and less hyperresponsiveness in the airways than WT (wild-type) mice, indicating the potential role of TNC in the pathogenesis of asthma. The same study revealed that adding exogenous TNC to the spleen lymphocytes of mice excites IgE release.<sup>21</sup>

Also, our findings are in agreement with those of a previous study by Donovan et al., 2023, performed in the lungs of mice, showed that TNC expression is higher in structural (fibroblast, endothelium, and bronchial smooth muscle) and immune (T lymphocyte cells and Natural killer cells) cells in patients with asthma compared to healthy controls.<sup>14</sup>

In the current study, serum TNC levels were significantly higher in patients with severe asthma than in patients with mild to moderate asthma ( $p = 0.004$ ). Also, serum TNC levels were higher in patients with uncontrolled asthma compared to those who are well- or partially

controlled asthmatics ( $p = 0.006$ ). These results agreed with findings of a study by Yasuda et al., 2018 which showed that patients with severe asthma had TNC serum levels substantially greater than mild to moderate asthma ( $p = 0.012$ ). TNC levels were considerably greater in the group of patients with GINA treatment steps 4+5 (severe, uncontrolled asthma) than the group of patients with GINA treatment steps 1-3 (mild to moderate, well controlled) ( $p = 0.002$ ), according to GINA 2016.<sup>22</sup> In addition, they concluded that asthmatic patients who possess elevated serum TNC levels might benefit better from omalizumab therapy due to the omalizumab-associated improvement in FEV1 of at least 12%, related to high serum TNC levels.<sup>23</sup>

In the present study, serum TNC levels were significantly higher in atopic asthmatics than in nonatopic asthmatics. This result agreed with that of study by Karjalainen et al., 2003, which included a total of 79 bronchial asthma patients and showed that atopic participants' subepithelial basement membrane tenascin layer was substantially thicker than nonatopic participants (7.6 vs. 6.3  $\mu\text{m}$ ,  $p = 0.007$ ). Only atopic asthmatics showed a correlation between tenascin thickness and eosinophil, T-lymphocyte, and macrophage numbers, in addition to an interleukin-4-positive number of cells. These results indicate that tenascin expression in patients with atopic asthma may be regulated by inflammatory cells.<sup>11</sup>

In our study, the ROC curve analysis estimated the accuracy of the measurement of serum TNC level for the diagnosis of asthma severity. It demonstrated a sensitivity of 76.92%



and specificity of 75.00 % at area under the curve of 0.777. These agreed with findings of a prior research investigation by Yasuda et al., 2018, which revealed sensitivity of 51.9%, specificity of 77.8% by ROC curve for serum TNC levels comparing the GINA step 4 + 5 groups with the GINA step 1-3 group, with the area under the curve of 0.665.<sup>23</sup>

Our study did not find a significant correlation between serum TNC and CRP or between serum TNC and the FEV1/FVC ratio ( $r = 0.133$ ,  $p = 0.293$ ) despite a correlation with asthma severity. These findings are in accordance with the results of the study by Yasuda et al., 2018. Also, we found no significant correlation between serum TNC and serum total IgE ( $r = 0.101$ ,  $p = 0.427$ ). This was inconsistent with the results of the previous study by Yasuda et al., 2018, which revealed a positive correlation between the levels of total IgE and serum TNC.<sup>23</sup> These contradictory results can be explained considering that TNC and IgE levels can be influenced by factors other than asthma, such as age, gender, and genetic factors. Also, total IgE levels are influenced by allergen exposure, which may be different.

One limitation of this study is that its findings are based on data from only a small number of patients, from a single study site. In conclusion, TNC serum level could be proposed as a biomarker for bronchial asthma diagnosis as well as in the assessment of asthma severity.

### Author Contributions

ME, HE, and AE designed the study. YH, AE, and HE shared in the sample collection, did the statistical analysis, and did the manuscript review. The final version was approved by all authors. The final manuscript was reviewed and approved by all authors.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of Faculty of Medicine, Ain Shams University (FMASU MS 60/2023).

### Informed consent

All study participants provided written informed consent before being included in the study.

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