# Effect of Asthma Exacerbation on Blood Coagulation Compared with Stable State in Children

**Running title:** Asthma Exacerbation effect on Blood Coagulation in Children

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**Abstract**

Paroxysmal airflow blockage, airway hyper-responsiveness to irritative stimuli, wheezing, chest tightness, and coughing are all signs of asthma, a condition characterised by persistent airway inflammation. The purpose of this research was to compare the effects of an asthma exacerbation on children's blood coagulation to those of a child's stable condition. Thirty paediatric asthma patients were included in this prospective observational research. In this study, patients were split into two groups: Thirty children with asthma who were experiencing an acute flare-up made up Group 1. Group 2 included the same asthmatic kids when they were in a stable condition. Comprehensive paediatric and neurological exams, as well as determination of asthma exacerbation, asthma evaluation, laboratory work-up, measurement of protein C, determination of D-dimer, and determination of C-reactive protein were performed on all patients. The results showed that the median levels of Protein C were substantially lower during an asthma exacerbation (p=0.0001) than they were during a stable condition (range, 44-124) (range, 85-140). Exacerbation length was strongly associated with an increase in the median Protein C during an asthma exacerbation (p0.0001). D-dimer and C-reactive protein median values were also not substantially different across exacerbation durations for those with asthma. Asthma exacerbations, as shown by our research, are accompanied with considerably reduced levels of Protein C compared to normal conditions.

**Keywords:** Asthma; Exacerbation; Blood Coagulation; Stable State; Children

**Introduction**

Paroxysmal airflow blockage, airway hyper-responsiveness to irritative stimuli, wheezing, chest tightness, and coughing are all signs of asthma, a condition characterised by persistent airway inflammation. Allergic inflammation, including the infiltration of mast cells, eosinophils, and T-helper 2 (Th2) lymphocytes into the airway wall, and mucus hypersecretion, are the underlying causes of these symptoms. The persistent loss in lung function, frequent exacerbations, and steroid resistance seen in many patients with chronic asthma pose a significant clinical challenge and health hazard (1). Asthma treatment options now available do not adequately address the underlying inflammation that precipitates attacks (2).

Asthma pathogenesis is reportedly involved with the protein C (PC) anticoagulant system.

When thrombin binds to thrombomodulin on the surface of the cell, a complex is formed that catalyses the conversion of prothrombin complex (PC) to active prothrombin complex (APC).

Several preclinical models of inflammatory illnesses, such as sepsis, acute lung damage, stroke, ischemia/reperfusion injury, and wound healing, have shown the efficacy of recombinant APC treatment (3).

Asthmatic patients' lungs seem to have defective PC system function. 4 hours after a bronchial allergen challenge, APC levels in individuals with moderate allergic asthma were considerably lower than in healthy controls. Asthma patients' induced sputum showed lower APC/thrombin and APC/PC ratios, indicating a dysregulation between the coagulation and PC systems (4).

It has been found that asthmatic people, when compared to healthy controls, had elevated C-reactive protein (CRP) levels, indicating systemic inflammation in addition to the inflammation of the airways (5).

Patients with asthma have been demonstrated to have elevated CRP levels during asthma exacerbations and exercise-induced bronchoconstriction. In systemic inflammatory disorders such sepsis, dengue virus infections, and acute respiratory tract infections, the relationship between inflammation and coagulation has been well established (6).

The systemic coagulation pathway is activated during an asthma exacerbation because of the increased airway and systemic inflammation. Clot creation from the activation of coagulation factors (including factors V, VII, VIII, and X), anticoagulants to inhibit clot formation, and fibrinolysis to lyse existing clots make up the three major elements of the coagulation system (7).

During an asthma exacerbation or a stable condition, the levels of endothelial activation, coagulation marker, anticoagulant, and fibrinolysis shift. As a result, the concentration of von Willebrand factor (vWF) was evaluated for signs of endothelial activation. Measurement of plasminogen activator inhibitor type 1 (PAI-1) was used to evaluate fibrinolytic activity. We evaluated protein C levels to check for anticoagulant properties. indicators of coagulation such as D-dimer, prothrombin fragment 1+2 (F1+2), and thrombin-antithrombin complex (TAT). D-dimer was utilised as a marker of coagulation and fibrinolysis since it is the smallest component of fibrin breakdown products. Clues to clot formation, such as F1+2 and TAT, were analysed (8).

The purpose of this study was to compare the effects of an asthma exacerbation on children's blood coagulation to those in a stable condition. As well as comparing the levels of blood coagulants protein C, D-dimer, and CRP in children with asthma during exacerbation and steady condition.

**Patients and methods**

Thirty children with asthma participated in this prospective observational research at Egypt's Benha University's Pediatric Department, Faculty of Medicine. From January to December of 2021, individuals under the age of 18 who suffer from asthma were recruited and given informed permission to participate in the research.

The research was conducted with the approval of an independent ethics committee (the "Institutional Review Board") and the parental permission of all minor participants.

The people that participated in this research were split into two categories: Thirty children with asthma who were experiencing an acute flare-up made up Group 1. Group 2 included the same asthmatic kids when they were in a stable condition.

Children of both sexes were eligible to participate as long as they were aged 3-13 and experiencing an acute episode of asthma.

Children older than 13 years of age, those with a history of thrombosis or coagulation disorders, those with cardiovascular disease, airway anomalies, systemic inflammatory diseases, severe infection, major trauma, and prior major surgery, those who had received blood transfusions within the previous three months, those who were taking medications that disturbed coagulation, those with systemic chronic diseases like chronic renal disease, diabetes, or hypertension, and those with autoimmune diseases were excluded.

All patients had extensive neurological and paediatric evaluations, which included the following: An exhaustive record of past events, including: Background information include identifiers and demographic details such as age, gender, and location. In the past (History of previous medical illness, History of medications the disease and Onset of asthmatic seizures). Current history [original symptom, illness start, duration, and progression (exacerbation), medications taken, including dosage and length of use, and any corticosteroid or non-steroidal anti-inflammatory drug usage]

Clinical and radiological examinations of the chest were performed on all research participants. Analysis of an Asthma Attack: An asthma exacerbation score was used to evaluate the severity of an asthma attack: Asthma exacerbation of mild severity has a total score between 1 and 4. Moderate asthma exacerbation is defined as a score between 5 and 8. The severity of an asthma exacerbation is defined as a score of 8 or above.

Evaluation of asthma according to the Global Initiative for Asthma Guidelines taking into account age, sex, asthma severity, and asthma control (9).

Evaluation in the Laboratory: White blood cell (WBC), neutrophil, and eosinophil counts are part of a CBC, or complete blood count. The coagulation rate in the blood was determined by taking two separate blood samples. The first sample was taken before the start of treatment with systemic corticosteroids for an asthma exacerbation. In this analysis, the length of an asthma exacerbation is defined as the time from the beginning of symptoms and the first time blood was taken. The second sample of blood was taken first thing in the morning during the stable condition, which is defined as having either fully or mostly under control asthma for at least three months following an asthma exacerbation according to the Global Initiative for Asthma Guidelines. Plasma was separated from the blood samples by centrifugation after being collected in sodium citrate coagulation tubes. When the plasma was collected, it was aliquoted and stored in a freezer at -80 degrees Celsius. No further freeze-thaw cycles were performed on the sample aliquots before analysis.

Protein C activity was determined using an automated functional clotting protein C test (Instrumentation Laboratory, Bedford, Mass., USA) based on the lengthening of activated partial thromboplastin time in the presence of active protein C on the ACL 200 automated coagulation analyzer (Beckman Coulter, Fullerton, California, USA). In order to construct the calibration curve, the manufacturer's standard activated protein C plasma concentration of 100% was employed.

To test for D-dimer, an enzyme-linked fluorescence assay (Biomérieux, Marcy l'Étoile, France) was used. A commercial latexenhanced immunoturbidimetric test (Siemens AG SYSMEX CS5100, Marburg, Germany) was used to determine D-dimer concentrations.

Non-fasting plasma samples were taken from all individuals for CRP determination. The samples were processed in under 30 minutes after being placed on ice. The samples have been frozen at -20 degrees until the CRP can be tested. All tests were conducted in accordance with the specifications provided by the manufacturer. Rate near-infrared particle immunoassay was used to test high-sensitivity CRP, and the Hitachi 7600 P module (Hitachi High-Technologies Corporation, Tokyo, Japan) was used to quantify CRP (IMMAGE Immunochemistry System, Beckman Coulter, Fullerton, CA). Improved immunoturbidimetric analysis will be used to determine CRP levels (Abbott Laboratories, Abbott Park, Ill., USA).

Analyzing the Data

IBM Corp. was used for all data collection, tabulation, and statistical analysis. 2015's release. IBM SPSS Statistics, Release 23.0 for Windows. Published by IBM (company) in Armonk, New York. Mean standard deviation and median (range) were used to describe quantitative data, whereas quantity and adjectives were used to describe qualitative data (percentage). When comparing two sets of data when one set has a normal distribution and the other doesn't, the t-test is performed. Mann Whitney We utilised the U test to compare two sets of data when one or both variables did not follow a normal distribution. In order to compare more than two groups of non-normally distributed data, the Kruskall Wallis test was utilised. F test Multiple sets of normally distributed variables were compared using Anova. It was determined by using a paired t-test to compare the means of two normally distributed variables that were assumed to be related. Sign of Wilcoxon Rank When comparing two paired, non-normally distributed variables, the t-test was applied. The strength of the relationship between the study's variables was evaluated using Spearman's correlation; a positive value indicates a direct correlation, a negative value indicates an inverse correlation, and a value close to 1 indicates a strong correlation, while a value close to 0 indicates a weak one. The questions on every exam were both multiple choice and true/false. When the probability value was less than 0.05, we knew it was significant.

**Results**

Thirty patients were enrolled in the study, and their ages varied from three to ten, with a mean of 5.5 2.1 years. The majority of the patients (18) were male. Seventeen percent of patients had an asthma exacerbation lasting less than seven hours; seventy-three percent had an exacerbation lasting between seven and twelve hours; and ten percent had an exacerbation lasting more than twelve hours. 66% of individuals had mild asthma and 33% had significant asthma. Median asthma score was 4, with a (1-7). The majority of patients (63.3%), who were treated with inhaled corticosteroids, had developed an upper respiratory tract infection as a precipitating factor (56.7 percent ). About two-thirds of persons with asthma have it under control. 20% of patients have just minimal control, and 16% have no control at all. Table 1 shows that the median levels of Protein C were considerably lower during an asthma exacerbation (90, range, 44-124) than during a stable condition (101, range, 85-140, p0.0001). When comparing the median D-dimer levels during an asthma exacerbation and during a stable condition, there was no significant difference (P>0. 05). When comparing the median CRP during an asthma exacerbation (6 mg/l, range: 6- 24) to the median CRP during a stable condition (4 mg/l, range: 3-6), p = 0.0001. Table 2 shows that the median levels of Protein C were considerably greater in asthma attacks triggered by an upper respiratory tract infection than in those triggered by any other causes (p=0.015). Both the D-dimer and C-reactive protein median values were not substantially different amongst asthma triggers (P>0.05). Table 3 shows that the median level of Protein C during an asthma exacerbation rises considerably with the length of the exacerbation (p0.0001). Median values of D-dimer and C-reactive protein did not change significantly across asthma exacerbation duration groups (P>0.05). Table 4 shows that the median levels of Protein C in patients with mild asthma were 97.5 (range: (76-124) vs 74.5 (range: 44-92), p=0.0001. There was no statistically significant difference in median D-dimer levels between asthma severity categories. P>0. 05. Median C-reactive protein levels were 6 mg/l (range, 6- 12) during mild asthma and 12 mg/l (range, 6- 24) during severe asthma (p 0.0001). As can be shown in Table 5, the median levels of Protein C in children with asthma who have been treated with inhaled corticosteroids are considerably lower than those in children who have not been treated with these medications (p=0.036). We found no statistically significant difference (P>0. 05) in the median D-dimer values of those who took or did not take inhaled corticosteroid treatment. When comparing children with asthma who used inhaled corticosteroids to those who did not, we found that the median CRP in the former group was considerably higher (p=0.021). According to Table 6, patients with well-controlled asthma had a median Protein C level that was considerably higher than those with moderately-controlled and uncontrolled asthma (p=0.002). The median D-dimer level was not different between those with and without asthma (P>.05). When comparing those with well-controlled asthma to those with moderately-controlled and uncontrolled asthma, the median CRP in the former group was considerably lower (p=0.0001). Table 7

Protein C has a substantial inverse relationship with asthma severity, whereas C-reactive protein (CRP) has a significant direct relationship with asthma severity. D dimer is not related to asthma severity in any other way. Protein C and C-reactive protein (CRP) have a strong negative correlation. Protein C and D dimer do not interact with one another in any other way. D-dimer levels and C-reactive protein (CRP) levels are directly correlated. Table 8

**Discussion**

Variable airway obstruction due to persistent eosinophilic and T-helper type 2 (Th2) airway inflammation characterises asthma. More and more data suggests that allergen exposures activate coagulation in the airways of asthmatic individuals (10).

According to the clinical features given by Manuyakorn et al. (6), sixteen patients (73%) experienced mild asthma exacerbation and six patients (27%). Upper respiratory tract infection (67%) and noncompliance with, or incorrect medicine administration, were the leading triggering factors (33 percent ). Viral infections and contributing variables, such as airway bacteria and allergens, triggered the asthma attack. Some studies have linked respiratory viruses to as much as 85% of paediatric asthma exacerbations and 80% of adult ones. Evidence suggests that viral infection and allergen exposure both contribute to the development of fibrin in the lungs (11).

Median Protein C after asthma exacerbation was 90 (range: 44-124) compared to 101 (range: 85-140), p0.0001. This was in agreement with the findings of Manuyakorn et al. (6), who studied children's blood coagulation during an asthma exacerbation and a stable condition to identify differences in coagulation patterns. They found that plasma levels of activated protein C were lower in individuals with asthma who were experiencing an exacerbation. In addition to boosting fibrinolysis, the anticoagulant properties of activated protein C contribute to a healthy coagulation balance. Subsequently, individuals with acute asthma exacerbation would have increased clot formation and reduced fibrinolysis due to the lack of protein C.

We found no statistically significant difference (P>0.05) between median D-dimer levels during an asthma exacerbation and those during a stable condition. This agreed with the findings of Manuyakorn et al. (6), who found no statistically significant variation in D-dimer levels between the acute phase and the resting phase. Sneeboer et al. (12) found an enhanced prothrombin production, plasminogen activator inhibitor-1 (PAI-1), and D-dimer in asthmatics, documenting a prothrombotic condition in this disease.

The current investigation demonstrated that the median CRP during asthma exacerbation was considerably greater than that of the steady state: median 6 mg/l (range: 6– 24) vs median 4 mg/l (range: 3–6), p =0.0001. This was consistent with the findings of Manuyakorn et al. (6), who found that CRP levels were higher during an asthma exacerbation than in the stable period. At exacerbation, CRP rose, although not considerably, in the population studied by Owen et al. (11).

When compared to asthma attacks triggered by other variables, those triggered by an upper respiratory tract infection had a considerably higher median Protein C (p=0.015). Both the D-dimer and C-reactive protein median values were not substantially different amongst asthma triggers (P>0.05). In a subgroup analysis on the causes of asthma exacerbation, Manuyakorn et al. (6) reported that they did not find significant differences in the levels of CRP, protein C, and coagulation markers between children who had asthma exacerbation due to respiratory tract infection and those who had asthma exacerbation due to poor compliance.

Longer periods of asthma exacerbation were associated with higher median levels of Protein C during the exacerbation (p0.0001). Median values of D-dimer and C-reactive protein did not change significantly across asthma exacerbation duration groups (P>0.05). This agreed with the findings of Manuyakorn et al. (6), who discovered a disparity in protein C concentrations between individuals whose asthma exacerbations lasted for shorter or longer periods of time. Protein C levels were observed to be significantly lower in those who had had an asthma exacerbation for 7 hours. It has been hypothesised that protein C was utilised in the coagulation pathway to help control early asthma exacerbations. Once asthma symptoms had worsened for 7 hours, the body's coagulation system was able to restore balance by producing more protein C.

Therapy with inhaled corticosteroid (ICS) was able to manage airway inflammation, resulting in low levels or no activation of coagulation, in mild asthma; but, in severe asthma, ICS treatment was not merely able to control this airway inflammation, resulting in higher coagulation activation (12).

In a large sample of asthmatics, Mohamed et al. (13) reported a statistically significant rise in d-dimer levels after treatment with ICS. In addition, we showed that d-dimers were elevated in asthmatic groups receiving moderate to high dosages of ICS. Therefore, variations in ICS dosage may account for observed shifts in hemostatic parameters and add to the already-present hemostatic system imbalance in patients with chronic airway inflammation (12). There was no correlation between changes in inflammatory markers including eosinophils, neutrophils, and CRP and hemostatic measures in asthmatic patients, according to the research by Mohamed et al. (13).

Corticosteroids have been implicated as a potential mechanism of the prothrombotic condition in asthma. Severe asthma requires high-dose ICS usage on a constant basis and, in certain cases, systemic corticosteroid treatment to prevent and treat asthma episodes. Although it has been recognised for some time that corticosteroids may cause hypercoagulability, the extent to which the steroids themselves or the underlying severe illness may contribute to this hypercoagulable condition is still up for discussion (14).

Oral corticosteroids have been demonstrated to increase coagulant factors and decrease fibrinolytic factors, potentially affecting the hemostatic system and significantly impacting the risk of venous thromboembolism in a number of investigations. Past research has shown that airway inflammation from eosinophils and neutrophils may be a risk factor for pulmonary eosinophilia (15, 16).

According to the results of the current research, there is a statistically significant inverse relationship between asthma severity and protein C, but a statistically significant direct relationship between asthma severity and CRP. Although Manuyakorn et al. (6) found no correlation between asthma exacerbation severity and protein C, coagulation markers, or CRP levels. Patients with severe asthma showed higher values of the prothrombotic condition found by Sneeboer et al. (12) compared to those with moderate asthma.

The results of this investigation found no correlation between asthma severity and D dimer levels. In contrast, Manuyakorn et al. (6) revealed the positive connection of D -dimer, the smallest component of fibrin breakdown products from clot formation and fibrinolysis, with the severity of asthma exacerbation indicated by the clinical asthma exacerbation score.

**Conclusion**

Our investigation indicated that Protein C during asthma exacerbation was much lower than that of the steady condition. There was no statistically significant difference between the exacerbation and stability groups for D-dimer levels. Exacerbations of asthma were associated with elevated CRP compared to periods of normal lung function.

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**Table 1: Demographic and clinical characters of the studied group**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | | **The studied group (30)** | | |
| **Age (years)** | | 5.5±2.1 | | |
| **Gender** | Females | 18  12 | 60.0  40.0 | |
| Males |
| Clinical characters of asthmatic children | | | frequency | % |
| **Exacerbation duration** | * < 7 hours | | 5 | 16.7 |
|  | * 7-12 hours | | 22 | 73.3 |
|  | * >12 hours | | 3 | 10.0 |
| **Severity** | * Mild | | 20 | 66.7 |
|  | * Moderate | | 10 | 33.3 |
| **asthma score**  Mean ± SD  median(range) | 3.9±1.6  4(1-7) | | |  |
| **Precipitating factor** | * Upper respiratory tract infection | | 19 | 63.3 |
|  | * Others | | 11 | 36.7 |
| **Inhaled corticosteroid** | * Yes | | 17 | 56.7 |
|  | * No | | 13 | 43.3 |
| **Control** | * Well | | 19 | 63.3 |
|  | * Partial | | 6 | 20.0 |
|  | * Uncontrolled | | 5 | 16.7 |

**Table 2: Comparison of Protein C, D-dimer and CRP during asthma exacerbation and the stable state**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable Coagulation parameters in asthma children | State of asthmatic children | | Paired t/w | p-value |
| At exacerbation state | At stable  state |
| Protein C | 90.7±20.9 | 107.9±18.2 | 9.1 | 0.0001 |
| D dimer | 153.4±94.4 | 152.4±46.5 | 1.26 | 0.206 |
| CRP mg/l | 8.2±4 | 4.1±1.13 | 4.83 | 0.0001 |

**Table 3: Comparison of Protein C, D-dimer and CRP in asthma exacerbation according to its precipitating factor**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Coagulation parameters in children | precipitating factor for asthma attack | | t/u | p-value |
| Upper respiratory tract infection  n.19 | others  n.11 |
| Protein C | 97.6±18.4 | 78.7±20.4 | 2.6 | 0.015 |
| D dimer | 141.3±81.7 | 174.2±114.3 | 1.53 | 0.125 |
| CRP mg/l | 7.3±2.5 | 9.8±5.5 | 1.48 | 0.139 |

**Table 4: Comparison of Protein C, D-dimer and CRP in asthma exacerbation according to its duration per hours**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Coagulation parameters in asthma children | Exacerbation duration | | | f/KW | p-value |
| < 7 hours | 7-12 hours | >12 hours |
| Protein C | 60.4±15.1 | 96±15.6 | 101.7±23.1 | 10.58 | 0.0001 |
| D dimer | 174.8±150.4 | 154.4±87.2 | 110±1.7 | 0.414 | 0.81 |
| CRP mg/l | 12±7.3 | 7.4±2.6 | 8±3.5 | 3.28 | 0.19 |

**Table 5: Comparison of Protein C, D-dimer and CRP in asthma exacerbation according to asthma severity**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variables | | Coagulation parameters in children according asthma severity | | | t/u | p-value |
| Mild  n.20 | Moderate  n.10 | |
| Protein C | 100.1±16.1 | | | 71.9±16.6 | 4.5 | 0.0001 |
| D dimer | 116.3±29.2 | | | 227.4±133.2 | 1.46 | 0.145 |
| CRP mg/l | 6.3±1.34 | | | 12±4.9 | 4.15 | 0.0001 |

**Table 6: Comparison of Protein C, D-dimer and CRP in asthma according to use of inhaled corticosteroid**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Coagulation parameters in asthmatic children | | Uses of inhaled corticosteroid | |  | p-value |
| yes  n.17 | no  n.13 |
| Protein C | 83.8±20.8 | | 99.7±18 | 2.2 | 0.036 |
| D dimer | 179.3±116.3 | | 119.5±36.1 | 0.73 | 0.46 |
| CRP mg/l | 9.5±4.8 | | 6.5±1.7 | 2.3 | 0.021 |

**Table 7: Comparison of Protein C, D-dimer and CRP in asthma according to asthma control**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Coagulation parameters in asthma children | Control level of asthma in children | | | f/KW | p-value |
| Well  n.19 | Partial  n.6 | Uncontrolled  n.5 |
| Protein C | 98.63±17.5 | 87.6±14.3 | 64±18.4 | 8.24 | 0.002 |
| D dimer | 115.6±30.1 | 171.7±91 | 274.8±156.4 | 5.6 | 0.061 |
| CRP mg/l | 6.6±1.9 | 8±3.1 | 14.4±5.4 | 15.4 | 0.0001 |

**Table 8: Correlation matrix between asthma score, Protein C, D dimer, CRP mg/l (n.30):**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variables | asthma score | | Protein C | | D-dimer | |
| **R** | **p** | **R** | **p** | **r** | **p** |
| Protein C | -0.591 \*\* | 0.001 | 1 | . |  |  |
| D dimer | 0.237 | 0.208 | -0.093 | 0.624 | 1 | . |
| CRP mg/l | 0.730\*\* | 0.0001 | -0.548 \*\* | 0.002 | 0.478\*\* | 0.008 |

(r) correlation coefficient \*\* Correlation is significant at the 0.01 level, \* Correlation is significant at the 0.05 level.