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# A cost-of-illness study estimating the direct cost per asthma exacerbation in Turkey

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| KEYWORDS           | Summary  |
|--------------------|--|
| Asthma attack;     | Objective: To calculate direct cost per asthma exacerbation at tertiary healthcare centers   |
| Attack severity;   | across Turkey.   |
| Direct cost items; | Methods: A total of 294 persistent asthma patients (mean age: $50.4 \pm 15.1$ years) were  |
| Health economics;  | included in this retrospective study upon admission with an acute asthma attack. Direct costs  |
| Asthma control;    | including drug treatment, non-drug treatment, healthcare resource utilization, emergency   |
| Asthma cost        | care, tests and consultations were calculated per asthma attack in relation to asthma attack severity.<br><i>Results</i> : The asthma attack was moderate in 57.5% of the patients. Direct cost was $\in$ 214.9 (95% CI: 183.9; 245.8) per attack. The cost of severe attack $\in$ 308.2 (95% CI: 258.2; 358.2)] was significantly higher than moderate [ $\in$ 172.6 (95% CI: 155.1; 190.2)] and mild [ $\in$ 128.6 (95% CI: 102.6; 154.7) attacks. It was also significantly higher for inpatient follow-up [ $\in$ 257.7 (95% CI: 220.4; 295)] vs. outpatient follow-up [ $\in$ 54.5 (95% CI: 47; 62; $p < 0.001$ )] and uncontrolled asthma [ $\in$ 288.2 (95% CI: 216.7; 359.6)] vs. controlled [ $\in$ 128.9 (95% CI: 92.1; 165.8); $p < 0.01$ ] asthma.<br><i>Conclusion</i> : Health policies targeting achievement of better asthma control and lower disease severity during the stable periods of the disease as well as appropriate hospitalization of patients and rational prescribing of drugs will play crucial role in the reduction of economic burden of asthma for the patient and the society.<br>$\otimes$ 2010 Elsevier Ltd. All rights reserved. |

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### Introduction

Economic burden of asthma has been a current topic of interest across several countries due to worldwide increase in the prevalence of the disease comparable to the burden of diabetes and hypertension.<sup>1,2</sup> Although recommendations for asthma control are included in the international guidelines, many patients continue to suffer sub-optimal control of symptoms and experience exacerbations<sup>1</sup> requiring medical intervention that affect the quality of life for the patient and the family<sup>3</sup> imposing a considerable strain on the healthcare budget.<sup>4</sup> Therefore, having 300 million sufferers worldwide with additional 100 million people estimated to be affected by 2025,<sup>5</sup> asthma also deserves to be included in investigations concerning economic implications of diseases with a high prevalence.<sup>6</sup> Accordingly, several cost-of-illness (studies examining the economic impact of asthma in the society) have been performed in many countries leading to annual cost of asthma ranging from \$10.7 billion to  $\in$  74 billion per year in total and \$300 to 1300 per patient.7-9

Almost all indirect costs and 1/3 of direct costs of asthma were documented to be related to exacerbations and poor control of the disease<sup>10</sup> with more than threefold increase in average cost of managing a patient documented in case of asthma exacerbation.<sup>2</sup>

Direct healthcare costs such as medication, medical bills, clinical visits and hospitalization(s), and indirect costs such as loss of productivity have been shown to rise dramatically for more persistent and severe disease.<sup>11,12</sup>

Lacking sufficient data based on health system records, the number of patients diagnosed with asthma in Turkey was estimated to be 3-4 million<sup>13</sup> and the prevalence of asthma in Turkey was documented to be 7.4% according to Global Initiative for Asthma (GINA) - Global Burden of Asthma Report.<sup>14</sup> Furthermore, a low level of asthma control in urban Turkish population was reported by the recently published AIRET survey despite the use of the national asthma management guideline in the clinical practice since 1995.<sup>15</sup> Likewise, asthma control was also documented to be inadequate at the tertiary level while overall control was better than past reports.<sup>16</sup> Patients with severe asthma account for a substantial portion of healthcare costs despite well documented low prevalence of severe form in overall asthmatic population.<sup>17-19</sup> The direct cost of these patients was reported to be two and four times higher than that of moderate and mild asthma patients, respectively<sup>20</sup> resulting from high risk of exacerbations, hospitalizations, and death associated with poor control of the disease despite the use of high dose inhaled or oral steroids.<sup>18</sup>

While mean annual direct medical costs of asthma were reported as \$1465.7  $\pm$  111.8 per capita with the medication cost being the major element (81%) of the total direct cost in a recent study conducted in a single tertiary center in Turkey,<sup>20</sup> national data concerning cost per asthma attack across Turkey is lacking. Therefore, the present study was designed to estimate the direct medical cost per asthma exacerbation to provide country specific data in relation to attack severity and level of disease control in Turkey.

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### Methods

### Study population

This national, multi-center study involving 294 patients with persistent asthma admitted to healthcare service upon symptoms of acute exacerbation was conducted retrospectively, concerning past 24 months at 15 different tertiary healthcare centers across Turkey. Tertiary healthcare centers for chest diseases were selected by the Project Advisory Board of the study according to the geographical distribution of specialists and family physicians in Turkey. In accordance with the real life setting of the study based on routine clinical practice, inclusion criteria were kept at minimum. Being >18 years of age, having diagnosis of persistent asthma and being admitted to the hospital with symptoms of acute asthma attack within the past 24 months were the inclusion criteria of the study. In fact, regardless of the attack count/year, the last attack of patient with an interval of at least 3 months from the prior one within 24 months was evaluated in the present study. Hence data on just one single asthma attack per patient were collected to calculate the cost per the most recent attack in each patient. Therefore, while it is possible to encounter more than one attack in the same patient within the 24-month window, the last and the most recent one was selected for the cost analysis.

Exclusion criteria were composed of diagnosis of asthma attack during patient's routine visit and determination of less than 3 months interval between subsequent admissions of the same patient related to acute asthma exacerbation within the screening period. The selected time interval of at least 3 months between consecutive attacks was based on to be able to calculate the cost per the most recent attack excluding the likelihood of certain complications related to prior attack that may interfere with the cost calculations such as carry over effects.

The study was conducted in accordance with International Conference on Harmonisation (ICH) – Good Clinical Practice (GCP) guideline and local regulations. Data were collected via a standardized form including items on patient demographics and clinical data concerning severity of the attack, medications and tests applied for the acute attack. Direct cost of acute asthma attack including treatment, healthcare resources utilization, and test and consultation items was evaluated in relation to attack severity, type of follow-up (outpatient vs. inpatient) and level of disease control.

# Classification according to attack severity and asthma control level

Participating clinicians were responsible for assessing the severity of attack based on Global Initiative for Asthma (GINA) guideline.<sup>14</sup> Asthma control level was classified as controlled, partly controlled and uncontrolled based on the time prior to the attack and asthma attack severity was categorized into four groups as mild, moderate, severe and life-threatening according to the same guideline.<sup>14</sup> In this regard, patients in the study population are amongst the follow-up patients of the study clinics. Most of them were

hospitalized patients having detailed records of data concerning pre-attack asthma control and severity.

### **Cost calculations**

Direct medical costs were calculated including the associated cost items composed of treatment, healthcare resources utilization, and diagnostic test and consultation costs. For drugs, retail prices from the updated price list and updated institution discount list of Social Security Institution (SSI) for 2008 were taken into account in calculation of the unit costs. Costs related to non-pharmacological treatments and tests were calculated considering the Health Implementation Notification by SSI. Hospitalization and consultation costs were calculated using unit prices also based on the same SSI notification. Salaries and labor force of healthcare staff giving service to patients with asthma was provided from the Healthcare Organization Questionnaire composed of Staff Inventory Form and Information Form on the Labor Force Spent during an Asthma Attack filled for each study center.

Neither direct non-medical costs of different origin (e.g. transfers of patient and caregivers for examinations and/or hospitalization, home care, etc.) nor indirect costs (loss of productivity occurring as a result of a patient's inability to work) were included. The costs in Turkish Lira (TL) are converted to  $\in$  o ( $\in$ ) by using the average exchange rate of the years 2008 and 2009 which is  $\in 1 = 2.02315$  TL.

### Statistical analysis

Statistical analysis was made using computer software (SPSS version 13.0, SPSS Inc. Chicago, IL, USA). Student's-test, ANOVA and post hoc Tukey test were used in comparison of clinical parameters in terms of average direct cost items. Medical expenses related to diagnosis, treatment, follow-up and management of acute asthma attack was the main parameter of the study. Cost model was based on the following equation: "Cost =  $\sum$  (Frequency; %)  $\times$  (Unit price; TL)". As central tendency measurement, both mean and median were calculated for all cost items. Although it is known that cost figures show non-normal distribution, mean cost was used for the whole group as it represents the disease burden better. Standard deviation and IOR values were calculated as dispersion measure, and 95% confidence intervals (CI) were also calculated. Data were expressed as "mean  $\pm$  standard deviation (SD)", percent (%) and median (min-max) where appropriate. p < 0.05 was considered statistically significant.

Since life-threatening asthma episodes were represented by only 4 cases, analysis for this group was confined to descriptive statistics. Therefore, all of the comparisons considering severity of the attack included mild, moderate and severe attacks.

### Results

### Demographic and clinical data

Demographic and basic clinical features of the study population are presented in Table 1. Majority of the patients were females (80.3%) and the overall mean age was  $50.4 \pm 15.1$  (18–90) years. Only 13.9% of them had controlled asthma prior to the attack. First admission was determined to be to the emergency department only by 32% of the patients. The asthma attack was moderate in more than half (57.5%), mild in 18.7%, severe in 22.4% and life-threatening in 1.4% of the patients. Hospitalization ratio was determined to be 78.9%.

## Medications and tests applied for the acute attack treatment and follow-up

Parenteral steroids in 72% of the patients and oral steroids in 29% were the anti-inflammatory drugs used in the treatment of asthma attack. Bronchodilators were determined to be SABAs in 53% and short acting anti-cholinergic plus salbutamol combination in 42% of the patients. Reflecting the way of bronchodilator application, nebulizer was the most commonly used treatment tool (91.8%).

Spirometry and chest X-ray were the most frequent tests (85.4% for both) used during attack followed by oxygen saturation measurement (62.6%). The other tests used during the attack were as follows: ECG (60.7%), arterial blood gas sampling (55.5%), complete blood count (36.9%), blood biochemistry (25.2%), peak expiratory flow (PEF; 5.5%), and others (microbiological tests, thorax CT, echocardiography).

### Cost analysis

### Total direct cost items in relation to severity of the asthma attack

Average total direct cost per asthma exacerbation was  $\in$ 214.9 (95% CI: 183.9; 245.8). Treatment cost (55.6%) was the most predominant direct cost item followed by healthcare resources utilization (24.7%), diagnostic tests (19.2%) and consultation (0.5%) costs (Table 2). Total direct cost per attack was significantly higher in patients with severe asthma attacks when compared to moderate and mild attacks (p < 0.001 for each; Fig. 1).

#### Treatment cost item in subgroups of attack severity

Treatment cost item per attack was significantly higher in the severe attack group when compared to moderate and mild attacks (p < 0.001 for each; Fig. 1). Among treatment cost items, drug treatment cost, asthma medication cost and non-drug treatment cost were significantly higher in the severe attack group when compared to moderate and mild attack groups (p < 0.01 for each). Average cost of asthma medication was €23.9 (95% CI: 18.53; 29.30) in mild attacks; €32.1 (95% CI: 27.55; 36.55) in moderate attacks and €43.3 (95% CI: 35.78; 50.89) in severe attacks. Nondrug treatment costs were €32.6 (95% CI: 25.21; 39.92); €42.6 (95% CI: 36.31; 48.88) and €101.1 (95% CI: 80.95; 121.26) in mild, moderate and severe attacks, respectively. As expected, other drug treatment (drugs other than asthma medication) cost was not significantly different between groups with different attack severity.

### Healthcare resources utilization and cost of diagnostic tests in subgroups of attack severity

Overall healthcare resources utilization cost was significantly higher in the severe attack group when compared to

|                     |                    | Mean ± SD                         |  |
|---------------------|--------------------|-----------------------------------|--|
| Age (years)         | Overall            | 50.4 ± 15.1                       |  |
|                     | Female             | $\textbf{52.0} \pm \textbf{14.8}$ |  |
|                     | Male               | $\textbf{43.7} \pm \textbf{14.4}$ |  |
|                     |                    | n (%)                             |  |
| Gender              | Female/Male        | 236/58 (80.3/19.7)                |  |
| Pre-attack          | Controlled         | 41 (13.9)                         |  |
| asthma control      | Partly controlled  | 138 (46.9)                        |  |
|                     | Uncontrolled       | 115 (39.1)                        |  |
| Admission to        | Emergency          | 94 (32.0)                         |  |
|                     | department         |                                   |  |
|                     | Outpatient clinics | 200 (68.0)                        |  |
| Attack severity     | Mild               | 55 (18.7)                         |  |
|                     | Moderate           | 169 (57.5)                        |  |
|                     | Severe             | 66 (22.4)                         |  |
|                     | Life threatening   | 4 (1.4)                           |  |
| Outpatient follow-  | 62 (21.0)          |                                   |  |
| Inpatient follow-up |                    | 232 (78.9)                        |  |

Table 1 Demographic and basic clinical features of patients with asthma attack.

moderate and mild attack groups (p < 0.05 for each; Fig. 1). Inpatient follow-up cost, diagnostic test cost and consultation cost were significantly higher in the severe attack group when compared to moderate and mild attack groups (p < 0.05 for each). Average cost of inpatient follow-up was €26.5 (95% CI: 18.44; 34.46) in mild attacks; €43.02 (95% CI:36.76; 49.28) in moderate attacks; and  $\in$  67.3 (95% CI: 55.65; 78.84) in severe attacks. Diagnostic test costs were €26.5 (95% CI: 21.37; 31.71) in mild attack while it was €34.5 (95% CI: 30.55; 38.51) in moderate and €59.7 (95% CI: 48.5; 70.6) in severe attacks. Consultation costs were €0.22 (95% CI: 0.00; 0.43); €0.8 (95% CI:0.46; 1.12) and  $\in$ 1.8 (95% CI:1.13; 2.46) in mild, moderate and severe attacks, respectively. On the other hand, outpatient follow-up cost in the mild attack [ $\in 2.78$  (95% CI:1.78; 3.79); p < 0.05] was significantly higher when compared to severe attack [€1.03(95% CI:1.78; 3.79) and emergency department cost in the moderate attack [€1.5 (95% CI:0.98; 1.95)] was lower than severe attack [ $\in 2.75$  (95% CI:1.59; 39); *p* < 0.05].

### Direct cost of outpatient vs. inpatient follow-up

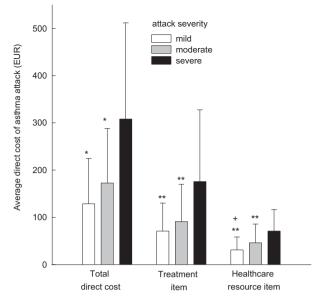
When outpatient and inpatient follow-up costs were compared in terms of total direct cost and its items including treatment, healthcare resources utilization, diagnostic test and consultation costs, it was found that all were significantly higher in case of inpatient follow-up (p < 0.001 for each; Table 3).

### Direct cost with respect to prior asthma control level and use of inhaled steroids

Overall direct cost and healthcare resource utilization cost were found to be higher in patients with uncontrolled asthma compared to those with partly controlled and controlled disease (p < 0.05; for each; Fig. 2). When analyzed separately, inpatient follow-up cost was found to be higher in patients with uncontrolled asthma [ $\in$ 65.0 (95% CI: 49.7; 80.3)] compared to patients with partly controlled [ $\in$ 42.9 (95% CI:35.7; 50.2); p < 0.05] and controlled disease [ $\in$ 28.0 (95% CI: 18.0; 38.0); *p* < 0.01]. On the contrary, outpatient follow-up cost [€3.3 (95% CI: 2.1; 4.5)] was found to be higher in patients with controlled asthma compared with partial [€1.8 (95% CI: 1.2; 2.3); *p* < 0.05] and poor [€1.0 (95% CI: 0.5; 1.5); *p* < 0.001] asthma control.

Table 2 Average direct costs of asthma exacerbation ( $\in$ /attack) with respect to treatment, healthcare resources utilization, tests and consultation items (n = 294).

|                                       | Average direct cost (€/attack)        |                 |                |  |
|---------------------------------------|---------------------------------------|-----------------|----------------|--|
|                                       | Mean $\pm$ SD                         | Median (IQR)    | 95% CI         |  |
| Total                                 | $\textbf{214.85} \pm \textbf{268.38}$ | 159.46 (175.74) | 183.93; 245.77 |  |
| Treatment item                        |                                       |                 |                |  |
| Overall                               | $\textbf{119.54} \pm \textbf{183.80}$ | 78.12 (106.71)  | 98.44; 140.63  |  |
| Drug treatment                        |                                       |                 |                |  |
| Overall                               | $\textbf{62.99} \pm \textbf{144.36}$  | 38.73 (54.60)   | 46.43; 79.57   |  |
| Asthma medication                     | $\textbf{34.47} \pm \textbf{31.94}$   | 26.05 (37.71)   | 30.81; 38.14   |  |
| Other                                 | $\textbf{28.52} \pm \textbf{127.02}$  | 1.62 (19.14)    | 13.94; 43.10   |  |
| Non-drug treatment                    | $\textbf{56.54} \pm \textbf{62.41}$   | 34.45 (55.04)   | 49.38; 63.70   |  |
| Healthcare resources utilization iter | n                                     |                 |                |  |
| Overall                               | $\textbf{53.01} \pm \textbf{61.1}$    | 44.49 (59.22)   | 45.99; 60.02   |  |
| Outpatient follow-up                  | $\textbf{1.69} \pm \textbf{3.17}$     | 0.00 (0.00)     | 1.32; 2.05     |  |
| In patient follow-up                  | $\textbf{49.47} \pm \textbf{62.18}$   | 37.7 (59.32)    | 42.33; 56.61   |  |
| Emergency department                  | $\textbf{1.85} \pm \textbf{3.62}$     | 0.00 (0.00)     | 1.43; 2.26     |  |
| Tests item                            |                                       |                 |                |  |
| Overall                               | $\textbf{41.33} \pm \textbf{44.53}$   | 31.09 (28.8)    | 36.22; 46.44   |  |
| Consultation item                     |                                       |                 |                |  |
| Overall                               | $\textbf{0.98} \pm \textbf{2.28}$     | 0.00 (0.00)     | 0.72; 1.24     |  |



**Figure 1** Average direct cost (mean  $\pm$  SD;  $\in$ ) of asthma exacerbation including treatment and healthcare resource utilization items with respect to severity of asthma attack. \*p < 0.05 and \*\*p < 0.001 compared to cost in severe asthma attack.  $^+p < 0.05$  compared to cost in moderate asthma attack.

Similar to overall healthcare resource utilization, overall treatment cost was found to be higher in patients with uncontrolled asthma compared to patients with partly controlled (p < 0.05) and controlled (p < 0.01) disease (Fig. 2). In detail, asthma medication cost was higher in the uncontrolled asthma group [ $\in$ 39.4 (95% CI: 32.8; 46.0)] vs. controlled [ $\in$ 24.5 (95% CI: 16.8; 32.2); p < 0.05]; and non-drug treatment cost was higher in the uncontrolled asthma [ $\in$ 85.1 (95% CI: 69.9; 100.2)] compared with partly controlled [ $\in$ 41.6 (95% CI: 35.3; 47.9)] and controlled [ $\in$ 26.8 (95% CI: 20.0; 33.6)] asthma (p < 0.001 for each).

Costs related to diagnostic tests and consultations were also higher in the uncontrolled asthma compared with partly controlled and controlled forms of the disease (p < 0.001; for each; Fig. 2).

Interestingly, when analyzed according to ICS use prior to the attack, cost of emergency care was detected to be higher in ICS positive patients [ $\in$ 2.04 (95% Cl:1.5; 2.5)] when compared to lack of steroid administration [ $\in$ 1.02 (95% Cl:0.2; 1.8); p < 0.05]. Similarly, significantly higher costs were found regarding diagnostic tests [ $\in$ 44.6 (95% Cl:38.0; 51.2) vs.  $\in$  31.24 (95% Cl:26.2; 39.3); p < 0.05] and consultations [ $\in$ 1.14 (95% Cl:0.8; 1.4) vs.  $\in$ 0.52 (95% Cl:0.2; 0.9); p < 0.05] in patients received ICS.

### Discussion

In this study, average direct cost of asthma an attack was found to be  $\in$ 214.9 per asthma attack across Turkey. Indicating the burden of severe attack on health economics, direct cost was calculated to be  $\in$ 128.6 for mild attack,  $\in$ 172.6 for moderate attack,  $\in$ 308.2 for severe attack and  $\in$ 1645 for life-threatening asthma attack. There are a limited number of multi-center studies concerning cost of asthma attack in the literature. Representing one of them, COAX study was conducted with more than 2000 subjects from fifteen countries and reported the cost of asthma attack to be  $\in$ 445 in primary and  $\in$ 1349 in secondary care centers with the cost of  $\in$ 737 for mild attack, while  $\in$ 881 and  $\in$ 1074 for moderate and severe attacks.<sup>10</sup> Notably, there are no studies concerning cost per asthma attack in primary and secondary care in our country. Therefore, while cost per asthma attack in primary and secondary care in other countries seems immensely higher when compared to cost per attack in tertiary care across Turkey, the data from different countries may not be comparable due to significant differences between countries in terms of health policies as well as the disease management.

According to our findings, as the major item of direct cost per attack, treatment cost (55.6%) was calculated to be  $\in$ 70.7 for mild attack,  $\in$ 90.9 for moderate attack, €175.5 for severe asthma attack. Our data concerning the relation of higher asthma medication cost to the severe asthma attack are in line with the past studies from Sweden, the Netherlands, the United States and France signifying the drugs as the key cost driver among the direct costs both in the different age groups and also among the different severity grades of asthma.<sup>6,8,21,22</sup> Besides drug costs, non-drug treatment costs were also significantly higher in the severe attack group when compared to moderate and mild attack groups in the present study. Moreover, significant proportion of overall treatment cost in our study was composed of non-drug treatment item which was determined to exceed drug cost in moderate and severe attack patients. Drug cost and hospitalization were also documented to be main items responsible for the burden of asthma on health economics in a past study in Turkish asthmatic patients in which significant difference in the annual cost of outpatient (139.76 TL) and inpatient follow-up (506.91 TL) of asthma was emphasized.<sup>20</sup>

Asthma attacks that were associated with hospitalization were reported to account for 90% of the total costs of attacks.<sup>23</sup> Accordingly, all direct cost items were significantly higher among inpatient population when compared to outpatient follow-up for asthma in our study. Based on major contribution of inpatient follow-up to healthcare resource utilization cost, appropriate hospitalization seems to have a significant role in the direct cost of asthma attack. Unfortunately, detection of hospitalization in almost 80% of our patients is highly suggestive of unnecessary and inappropriate hospitalization since asthma attack was mild to moderate in more than 75% of them. As a matter of fact, since asthma prior to acute attack was determined to be controlled and partially controlled in as much as 75% of patients in the outpatient follow-up group, higher outpatient costs associated with good asthma control compared with partial or poor control seem to reflect how patients are managed rather than a real difference in healthcare costs.

According to our findings, higher attack severity was significantly associated with increase in direct medical cost including drug and non-drug treatment, healthcare resources utilization and tests cost items. In fact, similarity between mild to moderate attacks in terms of cost item seems to indicate the inevitable burden of severe asthma attacks on health economics which may be reduced by

|                                 | Average direct cost (€/attack)                    |                                       |                |  |
|---------------------------------|---|---------------------------------------|----------------|--|
|                                 | Mean $\pm$ SD                                     | Median (IQR)                          | 95% CI         |  |
| Total direct cost               |   |                                       |                |  |
| Outpatient                      | $\textbf{54.47} \pm \textbf{29.46}^{\textbf{**}}$ | 44.60(25.18)                          | 46.99; 61.95   |  |
| Inpatient                       | $\textbf{257.71} \pm \textbf{288.21}$             | 193.10(166.17)                        | 220.43; 294.99 |  |
| Treatment cost                  |   |                                       |                |  |
| Overall                         |   |                                       |                |  |
| Outpatient                      | $31.98 \pm 24.39^{**}$                            | 22.71(23.95)                          | 25.79; 38.18   |  |
| Inpatient                       | $\textbf{142.94} \pm \textbf{200.20}$             | 96.01(109.57)                         | 117.04; 168.83 |  |
| Drug treatment                  |   |                                       |                |  |
| Overall                         |   |                                       |                |  |
| Outpatient                      | 18.79 $\pm$ 24.35**                               | 8.57(18.04)                           | 12.61; 24.97   |  |
| Inpatient                       | $\textbf{74.81} \pm \textbf{160.04}$              | 43.43(57.42)                          | 54.11; 95.51   |  |
| Asthma medication               |   |                                       |                |  |
| Outpatient                      | 12.51 $\pm$ 15.43**                               | 7.09(10.30)                           | 8.59; 16.43    |  |
| Inpatient                       | $\textbf{40.35} \pm \textbf{32.67}$               | 34.09(35.07)                          | 36.12; 44.57   |  |
| Other                           |   | · · ·                                 | ,              |  |
| Outpatient                      | $6.28 \pm 17.18^{*}$                              | 0.07(0.68)                            | 1.92; 10.65    |  |
| Inpatient                       | $\textbf{34.47} \pm \textbf{142.19}$              | 3.35(22.42)                           | 16.08; 52.86   |  |
| Non-drug treatment              |   | , , , , , , , , , , , , , , , , , , , | ,              |  |
| Outpatient                      | $13.19\pm6.74^{*}$                                | 12.36(5.33)                           | 11.48; 14.90   |  |
| Inpatient                       | $\textbf{68.13} \pm \textbf{65.49}$               | 43.01(58.38)                          | 59.65; 76.59   |  |
| Heathcare resources utilization | 1   |                                       |                |  |
| Overall                         |   |                                       |                |  |
| Outpatient                      | $\textbf{7.60} \pm \textbf{0.09*}$                | 7.66(0.08)                            | 7.58; 7.63     |  |
| Inpatient                       | $\textbf{65.14} \pm \textbf{63.52}$               | 51.90 (43.02)                         | 56.92; 73.36   |  |
| Outpatient follow-up            |   | . ,                                   |                |  |
| Outpatient                      | $\textbf{5.03} \pm \textbf{3.63}^{\star}$         | 7.54 (7.66)                           | 4.11; 5.95     |  |
| Inpatient                       | $\textbf{0.79} \pm \textbf{2.33}$                 | 0.00 (0.00)                           | 0.49; 1.09     |  |
| Inpatient follow-up             |   | · · ·                                 |                |  |
| Outpatient                      | _   | _                                     | _              |  |
| Inpatient                       | $\textbf{62.69} \pm \textbf{63.82}$               | 48.81 (43.10)                         | 54.44; 70.95   |  |
| Emergency department            |   |                                       | ,              |  |
| Outpatient                      | $\textbf{2.58} \pm \textbf{3.63}$                 | 0.00 (7.58)                           | 1.66; 3.50     |  |
| Inpatient                       | $\textbf{1.65} \pm \textbf{3.61}$                 | 0.00 (0.00)                           | 1.19; 2.12     |  |
| Diagnostic tests                |   |                                       |                |  |
| Outpatient                      | $\textbf{14.79} \pm \textbf{7.95}^{*}$            | 15.89(4.24)                           | 12.77; 16.81   |  |
| Inpatient                       | $\textbf{48.42} \pm \textbf{47.53}$               | 35.99(31.00)                          | 42.27; 54.57   |  |
| Consultation                    |   |                                       |                |  |
| Outpatient                      | $0.09\pm0.53^{*}$                                 | 0.00 (0.00)                           | -0.04; 0.23    |  |
| Inpatient                       | $\textbf{1.22} \pm \textbf{2.50}$                 | 0.00 (2.97)                           | 0.89; 1.54     |  |

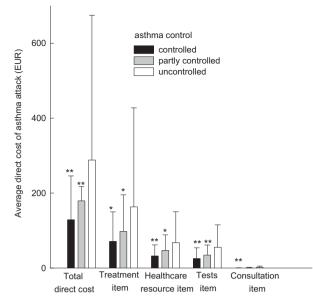
**Table 3** Comparison of outpatient (n = 62) vs. inpatient (n = 232) follow-up in terms of total direct cost ( $\in$ /attack), treatment, healthcare resources utilization, diagnostic tests and consultation cost items.

SD: Standard deviation; IQR: Interquartile range; CI: Confidence interval. \*p < 0.05; \*p < 0.01 and \*\*p < 0.001 compared to inpatient cost.

earlier identification of patients at highest risk for adverse outcomes<sup>24</sup> which is potentially a cost-effective measure.<sup>25</sup> In this context, while represented by only 4 patients limiting to draw exact conclusions about, life-threatening asthma attack was associated with at least 10 times increase in cost items. In a similar fashion, 4–9 times increase in cost items were also evident for hospitalization compared with outpatient therapy according to our findings. Higher cost related to severe attacks in our study conducted at tertiary healthcare centers seems to be relevant with respect to documented linear relation

between cost and the severity of attack managed in the secondary care.<sup>1,2</sup> Likewise, in a recent local study evaluating cost of asthma attack in a university hospital in Turkey, severe attack was documented to be related to increased cost.<sup>26</sup>

Despite universal agreement on beneficial effects of steroids in the management of acute asthma exacerbations, there appears to be little consensus regarding the route and dose for initial emergency department administration, outpatient regimen, and duration of outpatient steroid therapy.<sup>14</sup> Accordingly, despite suggested to reduce the



**Figure 2** Average direct cost (mean  $\pm$  SD;  $\in$ ) of asthma attack in patients with controlled (n = 41), partly controlled (n = 138) and uncontrolled (115) asthma. \*p < 0.05 and \*\*p < 0.01; compared to uncontrolled asthma.

likelihood of hospitalization for asthma attacks, and accident and emergency visits especially if combined with long-acting inhaled bronchodilators, 1,27 use of inhaled corticosteroids (ICS) was shown to be associated with higher costs related to emergency care, tests and consultations in our patients in relation to associated disease severity. Based on the higher severity of the attack among our ICS positive patients leading higher emergency costs than those without ICS who were determined to have much milder attacks, ICS positivity seems to be an indicator of more severe disease. In this regard, use of inhaled corticosteroid was reported to be 20-30% among asthma patients in the AIRET study with predominance of severe asthma, as well as in other AIR survey populations.<sup>28</sup> Moreover, it was shown that patients with achievement of good control with inhaled corticosteroids were still vulnerable to asthma exacerbations, usually in association with clinical respiratory infections.<sup>29</sup> Indeed, currently available medications have been considered to fail to achieve complete control of asthma in all patients even in the context of clinical trials.<sup>30</sup> Consistent with our findings, past studies conducted in Turkey have also pointed out the inadequate treatment of asthma as a common problem.<sup>15,31,32</sup>

Justifying recommendation of continuous preventive care rather than symptom-driven and crisis oriented care in several national and international 'asthma management' guidelines which place greater emphasis on the assessment of asthma control versus asthma severity, <sup>11,33</sup> our findings related to higher costs including total direct cost, health-care resource utilization, inpatient follow-up, asthma medication, non-drug treatment, tests and consultations in poor control of the disease are in line with the suggestion concerning reduction in overall burden of the illness for patients, healthcare systems, and society via achievement of the optimal control of asthma.<sup>34</sup>

To assist with decisions on priorities and budgets for healthcare, the present study presents national data on economic burden of asthma attacks in relation to clinical presumptions regarding real-life management of asthma disorder as well as acute asthma attack, retrospectively from a Turkish perspective. This may provide a baseline scale for future national studies concerning identification of components of asthma cost across our country with a special emphasis on "preventable" items which were stated important for the development of successful cost reduction strategies.<sup>35</sup>

In conclusion, since severe attack is associated with increase in direct costs, health policies targeting achievement of better and stricter asthma control and lower disease severity during the stable periods of the disease will play a crucial role in the reduction of economic burden of asthma for society and the patient. As drugs and hospitalization are the principal components of the direct cost, appropriate hospitalization of patients as well as rationale prescribing of drugs seem to have a crucial role in the reduction of the burden of asthma attacks on health economics.

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### **Conflict of interest**

The authors declare they have no conflict of interest.

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