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# Pharmacoeconomic management of patient with severe asthma in the Emergency Department: retrospective multicentric and cost of illness study

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**Abstract. – OBJECTIVE: The aim of the study was to develop a cost-of-illness model that would investigate the costs associated with the management of patients suffering from asthma and severe asthma in the context of acute episodes managed in the emergency room.**

**PATIENTS AND METHODS: A total of 795 records were collected between adults and paediatric patients. The data collection form reported an identification code for each patient included, gender, age, main discharge diagnosis, medical examinations carried out in the emergency room, the hospitalizations, and, if required by the patient condition, an outpatient visit performed by a pneumologist after the acute event that led the patient to the emergency room. In addition, the data collection form included information related to the pharmacological therapy taken by the patient.**

**RESULTS: Among adult patients who had an admission with an asthma diagnosis, the average cost for the management of an adult patient in a green code in the emergency room is €330.39. As for the yellow code and the red code, the cost rises respectively to €444.04 and €808.25. The paediatric population has a slightly higher cost. As for the green code, the average cost stands at €355.87, for the yellow code €562.34 and €1,041.96 for the red code.**

**CONCLUSIONS: Asthma and severe asthma impose a high burden on patients and society due to its chronicity, losses of productivity, and an increase in use of healthcare resources. We carried out the present observational retrospective analysis on asthma and severe asthma patients with the aim of assessing the economic impact from the Italian NHS perspective focusing also on the prescribed pharmacological therapies in the target conditions.**

*Key Words:*
Severe asthma, Pharmacoeconomic, Emergency department.

## Introduction

Asthma is a common and chronic respiratory and inflammatory disease affecting about 8% of the Western population. It is clinically characterized by alternating episodes of chest tightness, shortness of breath, wheezing and coughing as a consequence of bronchoconstriction[1]. Asthma exacerbation is defined as an imbalance in the asthmatic disorder and is provoked, acutely or

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sub-acutely, by an external agent or by poor compliance with treatment[2]. Surely, asthma requires an appropriate treatment; latest GINA 2019 Guidelines recommend that adults and adolescents with mild asthma should be treated with low-dose inhaled corticosteroids (ICS)-formoterol or, if not available, low-dose ICS and short acting beta agonists (SABA) or regular ICS or ICS in combination with long acting beta agonists (LABA) every day plus SABA if needed or maintenance treatment with ICS-formoterol[3]. On the other hand, a reduced but still significant number of patient report severe asthma, defined as a condition requiring a high dose inhaled ICS treatment together with a second drug (and/or systemic corticosteroids) to prevent the disease either to grow or remain uncontrolled despite the recourse to the above-mentioned therapies[4]. In this situation, treatment is different from mild asthma and consists of standard medications, including bronchodilators/ICS and biological drugs, such as the monoclonal antibodies benralizumab, omalizumab, mepolizumab, dupilumab and reslizumab[5]. Ali et al[6] have demonstrated that asthma education programs significantly reduce asthma attacks and, therefore, recurrence to the emergency department (ED) and global costs. At the same time, increasing knowledge on emergency medicine physicians about the clinical and therapeutic management of severe asthma may possibly improve patient compliance and reduce its clinical manifestations. However, no studies focusing clinical management, compliance with the latest GINA Guidelines and cost of illness of severe asthma in the ED setting are currently available. The aim of the study was to develop a cost-of-illness model that would investigate the costs associated with the management of patients suffering from asthma and severe asthma in the context of acute episodes managed in the ED. For this purpose, an Advisory Board has defined the criteria for defining the data collection form used during the study. These data were collected retrospectively in eight hospitals of the Lazio Region. Data on access to the emergency room on a total of 795 patients were collected retrospectively.

## Patients and Methods

Data on 795 among paediatric (< 14 years old) and adult patients from the San Camillo Forlanini Hospital, G.B Grassi, Viterbo Belcolle Hospital, Pertini Hospital, Sant'Eugenio Hospital, Casilino Hospital, Gemelli Hospital and Tor Vergata Polyclinic ED were collected. All the ED accesses considered in the study refer to 2019. The collection form contained the following information: patients' identification code, gender, age, main discharge diagnosis (ICD9 code) and results of medical examinations. Moreover, the collection form contained information regarding the hospitalization or whether patients were recommended a medical examination from a pneumologist after the acute event that led the patient to the ED. In addition, data collection form included information related to the prescribed pharmacological therapy before the occurrence of the acute event, during the ED visit and in the post-discharge phase. Compliance with GINA 2019 (Global Initiative for Asthma) guidelines[7] was also assessed. Finally, the triage code and the presence of comorbidities were reported. In order to define the economic burden of the disease the following drivers were considered:

- Cost of the admission in the ED
- Medical examinations in the ED
- Hospitalizations
- Pharmacological treatments (at home, in the ED and after the discharge)
- Specialist examinations.

The following article has been approved by local Ethics Committee of the institutions involved.

### Descriptive Analysis of the Sample

The sample consisted of 488 adults (61%) and 307 paediatric patients (39%). Mean age was 31.59 and 5.14 years for adult and paediatric patients respectively. As regards to the main discharge diagnosis, 88% of the patients reported a diagnosis of "asthma" (88%), in 10% as "other kind of asthma" (e.g., chronic obstructive pulmonary disease, acute asthmatic bronchitis, etc.) while in only 2% of them a specific diagnosis of "severe asthma", consistently diagnosed to GINA 2019 Guidelines, was reported.

Most of the patients were admitted to the ED with a green colour code (73%). Patients with a higher access priority represent 23% and 4% of the sample (yellow and red code respectively). Approximately 9% of the patients were hospitalized following the acute episode, while among non-hospitalized patients, 71% were referred to

an outpatient visit with a pneumologist. The recourse to biological drugs was reported in only 0.25% of the patients.

### Data

In order to define the economic burden of the medical examinations and accesses to the ED, national tariffs were considered (Table I). The cost of the admission in the ED (Commissioner Decree No. U00265 of 1 September 2014) equals to € 261.35 regardless of the assigned "triage" color code. Pulmonologist visit in the ambulatory care setting was valued € 20.66. Concerning the economic valorization of hospitalization, reference was made to the Diagnosis Related Groups (DRGs) shown in Table II. The chosen DRGs were dependent to the comorbidities reported in the data collection form.

Regarding pharmacological treatments, no information concerning adherence, or the date of therapy initiation were collected. For this reason, although we had provided a cost estimate of the pharmacological therapies, we are reporting below only a descriptive analysis of the pharmaceutical classes used by the patients included in the study in three specific phases:

– at home, before the occurrence of the acute event;
– during the medical investigations in the ED;
– in the post-discharge phase.

As shown in Figure 1, most of the patients had a home therapy based on steroids and/or SABA, 402 records indicated "other", meaning a therapy which does not correspond to any of those indicated for the conditions under analysis. Moreover, about 90% of patients did not take any medication to manage their condition, highlighting the fact that there are high percentages of non-controlled asthmatic patients or poorly adhering to therapies. In the emergency department setting (Figure 2), the most prescribed therapies are represented by steroids and/or SABA followed by beta-agonists in association with steroids. None substantial differences were described between therapies prescribed in the ED and in the discharge phase (Figure 3). Furthermore, the analysis focused on patients with more than one ED access during the time horizon considered (one year), consisting of 99 patients (12% of the sample). This focus was made in order to understand whether there are considerable differences in terms of pharmacological therapies prescribed between the first ED accesses and following accesses. However, no significant differences were found regarding prescribed treatments in this subgroup.

## Results

Results of the cost-of-illness analysis are reported in Table III. Data were stratified by principal discharge diagnosis and by triage colour code. Results are then further differentiated between adults and pediatric patients.

Table III reports the total and the average costs for each category considered in the analysis. Among adult patients who were admitted in the ED with a diagnosis of asthma, the average cost is €330.39, €444.04 and €808.25 for

**Table I.** Medical examinations in ED: This table show the national tariffs for the medical examinations.

| Blood count | € 3.17 |
|---|---|
| C-reactive protein | € 3.87 |
| crEATInInE | € 1.13 |
| Urea [S/P/U/dU] | € 1.13 |
| Chloride, sodium and potassium | € 3.17 |
| Aspartate aminotransferase (AST) (GOT) [S] | € 1.04 |
| Alanine aminotransferase (ALT) (GPT) [S/U] | € 1.00 |
| Systemic arterial hemogasanalysis | € 12.32 |
| Electrocardiogram | € 11.62 |
| Protrombine time | € 2.85 |
| Partial thromboplastin time (PTT) | € 2.85 |
| D-dimer (Latex test) | € 4.99 |
| Fibrin/Fibrinogen: PROD. Degradation (FD/FSP) [S/U] | € 12.18 |
| Troponin I | € 11.46 |
| Radiography of the chest of routine, NAS | € 15.49 |

**Table II.** Diagnosis Related Groups (DRG) costs: this table show the DRG used for the economic valorisation of hospitalized patients.

| Description | Ordinary admissions rate hospitalization duration > 1 day and within threshold - (per episode of admission) | Ordinary admissions rate duration of stay 0-1 day, Transferred or Deceased (per day) | Ordinary admissions rate with a hospital stay of 0-1 days. Day shelters (by recurrence: DRG chir.co; per day/ access: DRG doctor) | Day Rate Over Threshold Value (per day) | DRG weight | Threshold value (days) |
|---|---|---|---|---|---|---|
| Bronchitis and asthma, age > 17 years with CC | € 2,537.00 | € 296.00 | € 198.00 | € 132.00 | 0.80328553 | 18 |
| Bronchitis and asthma, age > 17 years without CC | € 1,832.00 | € 274.00 | € 197.00 | € 132.00 | 0.55630058 | 17 |
| Bronchitis and asthma, age < 18 years | € 1,538.00 | € 256.00 | € 185.00 | € 123.00 | 0.38158314 | 10 |
| Respiratory signs and symptoms with CC | € 2,782.00 | € 337.00 | € 206.00 | € 134.00 | 0.88761214 | 27 |

CC: complications or comorbidities.

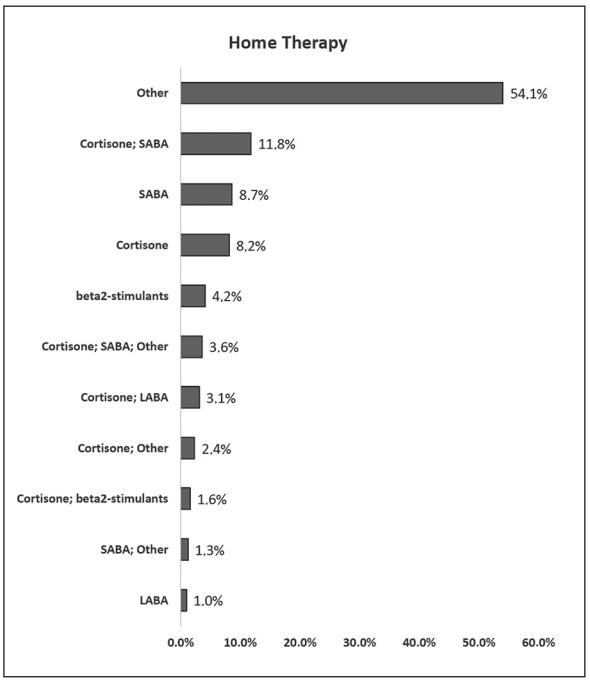


**Figure 1.** Home Therapy. This Figure describes the pharmacological treatment associated to the patients in the home setting (SABA: Short-acting β-agonist; LABA: Long-acting β-agonist).

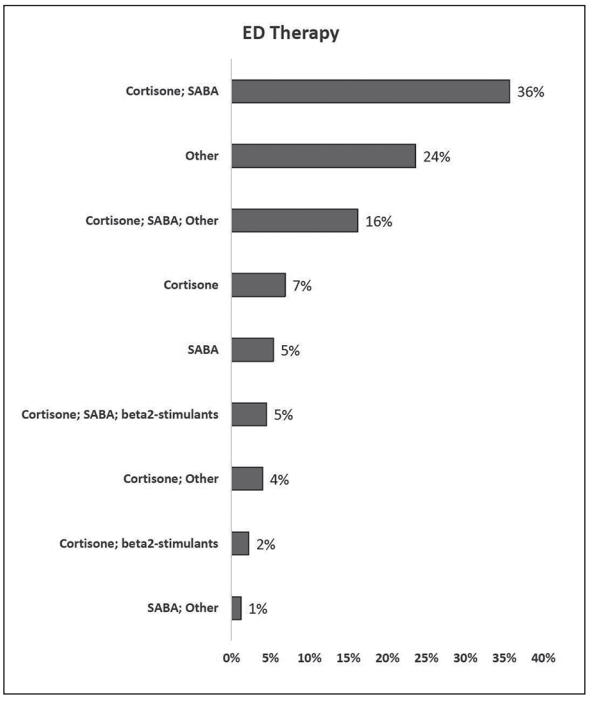


**Figure 2.** Emergency department therapy: This figure shows the pharmacological treatments prescribed during the acute event in the emergency room (SABA: Short-acting β-agonist; LABA: Long-acting β-agonist).

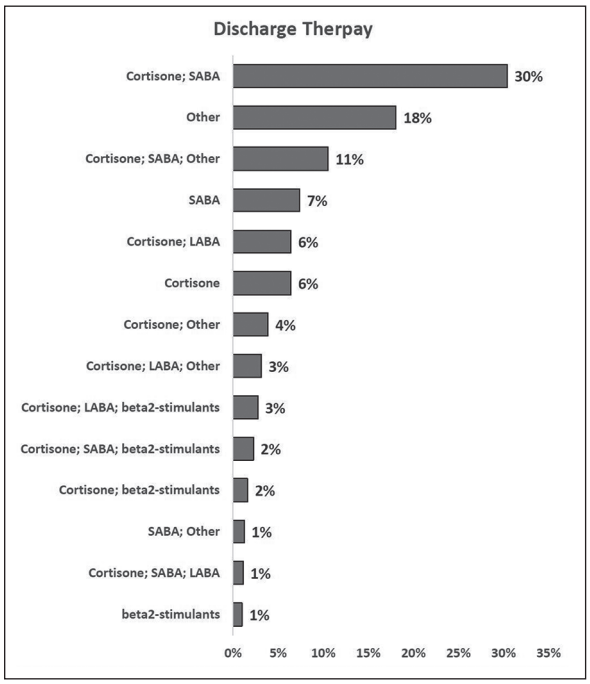


**Figure 3.** Discharge therapy: this figure shows the pharmacological treatments prescribed during the discharge phase (SABA: Short-acting β-agonist; LABA: Long-acting β-agonist).

green, yellow and red codes respectively. In the paediatric population we have observed a slightly higher average costs equal to €355.87, €562.34 and €1,041.96 for green, yellow and red codes respectively. Moreover, patients with a diagnosis of severe asthma are associated with higher costs. In fact, in adults the average cost ranges from a minimum of €929.08 for a green code to €1,495.13 for a red code. Regarding the paediatric population even though only data for green (€294.10) and yellow code (€1,064.18) are available, we observed a higher cost in the yellow code respect to paediatric patient diagnosed with asthma (Figure 4).

Table IV shows the results of patients accessing the ED for "other causes", which include the following diagnosis: bronchial asthma, bronchospasm, acute bronchospasm, acute asthmatic bronchitis, asthmatic bronchitis, exacerbated asthma, and bronchopneumonia in the course of asthma, respiratory difficulty in asthmatic bronchitis, tonsillitis, perforated otitis and pneumonia.

Table V shows the total costs of the analysis, considering all the patients included in our dataset. On 795 accesses, the total burden related to direct medical costs in the ED for asthma patients

**Table III.** Cost of illness results: this table shows the results of the cost-of-illness model stratified for patients (adults and pediatrics) and for diagnosis.

| Triage code | Diagnosis | N. patients | ED Tariff | Medical examinations | Hospitalization | Pharmacological therapy | | | Pulmonologist visit | Total | Per patient |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Home | ED | Discharge | | | |
| **Cost of illness – asthma (adults)** | | | | | | | | | | | |
| Green | Asthma - Code Icd9-Cm 493.Xx | 302 | € 78,927 | € 10,334.60 | € 7,328.00 | € 65.04 | € 78.65 | €110.05 | € 2,933.72 | € 99,777 | € 330.39 |
| Yellow | | 103 | € 26,919 | € 4,680.41 | € 13,107.00 | € 21.33 | € 32.12 | € 25.92 | € 950.36 | € 45,736 | € 444.04 |
| Red | | 23 | € 6,011 | € 1,109.68 | € 11,276.00 | € 13.93 | € 19.01 | € 15.37 | € 144.62 | € 18,589 | € 808.25 |
| **Cost of illness - asthma (pediatric population)** | | | | | | | | | | | |
| Green | Asthma - Code Icd9-Cm 493.Xx | 209 | € 19,212 | € 2,320.14 | € 16,918.00 | € 49.79 | € 77.12 | € 100.35 | € 289.24 | € 74,376 | € 355.87 |
| Yellow | | 60 | € 29,954 | € 666.07 | € 17,212.00 | € 24.21 | € 26.18 | € 27.63 | € 103.30 | € 33,740 | € 562.34 |
| Red | | 4 | € 1,045 | € 44.40 | € 3,076.00 | € 0.02 | € 1.01 | € 0.99 | € - | € 4,167 | € 1,041.9 |
| **Cost of illness – severe asthma (adults)** | | | | | | | | | | | |
| Green | Severe asthma - definition severe asthma according to gina guidelines | 3 | € 522.70 | € 167.74 | € 1.832.00 | € 1.60 | € 1.32 | € 0.52 | € - | € 2,787.2 | € 929.08 |
| Yellow | | 4 | € 1,045.4 | € 150.36 | € 2,537.00 | € 2.26 | € 5.01 | € 3.37 | € 41.32 | € 3,784.7 | € 946.18 |
| Red | | 6 | € 1,568.1 | € 377.24 | € 6,906.00 | € 3.88 | € 8.41 | € 3.85 | € 103.30 | € 8,970.7 | € 1,495 |
| **Cost of illness – severe asthma (pediatric populations)** | | | | | | | | | | | |
| Green | Severe asthma - definition severe asthma according to gina guidelines | 1 | € 261.35 | € 11.10 | € - | € 0.49 | € 0.47 | € 0.02 | € 20.66 | € 294.10 | € 294.10 |
| Yellow | | 2 | € 522.70 | € 22.20 | € 1,538.00 | € 0.50 | € 1.98 | € 1.66 | € 41.32 | € 2,128.3 | € 1,064 |
| Red | | 0 | € - | € - | € - | € - | € - | € - | € - | € - | € - |

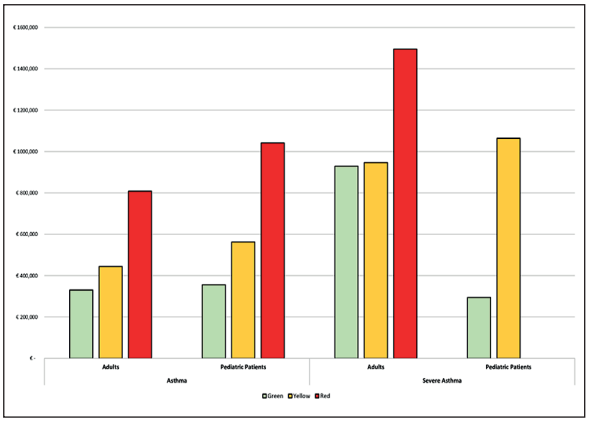


**Figure 4.** Result of the cost of illness: this graph shows the tendency of costs related to the triage color code for each category of patients included in the analysis. Results are based on the available data.

is € 337,935.5, for an average cost associated with each patient of € 425.08. About 63.1% of total costs are related to ED rate, while 31.2% is due to management costs in the emergency setting. Other costs, such as medical examinations in the ED, pneumological evaluation, and pharmacological therapies had a significantly lower economic impact on total costs (4%, 1.5% and 0.2% respectively).

An estimate of the total cost associated to the management of asthmatic patients in the ED setting was carried out based on the results of the cost-of-illness analysis on our dataset considering all the patients of the Lazio Region. For this purpose, epidemiological indices were used to estimate the target population affected by asthma in the Lazio region. We used a prevalence of 0.045. In order to assess the annual incidence rate of asthma[7] (0.00256), data from Pesce et al[8] (2015) were extrapolated. Since the resident population of the Lazio region is around 5898,000[9], we considered 280,509 asthmatic patients in order to develop the analysis. Moreover, in order to be more consistent, patients were divided into four categories considering the following types of asthma severities: intermittent, mild, moderate and severe. Additionally, the accesses to the ED and resource utilization for each category have been projected according to the study by Antonicelli et al[10] (2004) and Accordini et al[11] (2006). An estimate on the burden of asthmatic patients in the Lazio region is shown in Table VI. For the purposes of the analysis, different average cost was associated depending on the severity of the asthmatic condition. For intermittent and mild type, the average cost considered was equal to those patients who have been admitted to the ED with a green code without being hospitalized. Regarding moderate and severe asthma, the average cost refers to patients who have been admitted to the ED with a yellow or red code. Part of the hospitalization costs were also weighed on this average cost assuming that these categories of patients have a greater probability of being hospitalized following the acute event. Thus, considering the prevalence and the incidence of the condition and the assumptions made on costs through the collection of real-world data, the absorption of resources for the Regional Health System associated with the management of asthmatic patients in the emergency departments resulted equal to € 43,029,983.65 on one-year time horizon.

We also investigated on the potential correlation between the assumed prolonged use of cortisone and the following comorbidities: diabetes, hypertension, obesity, heart failure and other forms of cardiac ischemia. In fact, the presence of comorbidities associated to each patient admitted to the ED was reported in the data collection form by healthcare professionals. Thus, we stratified the sample considering patients with a prescription of cortisone in one of the three phases assessed in the study. In this case, paediatric patients are not considered. The results of this analysis are shown in Figure 5.

153 patients were included in this analysis. We are presenting the results in term of comorbidities which are potentially correlated with this therapy. In the analysed sample, patients affected by hypertension represent the highest percentage (28.76%) while 12.42% were suffering from diabetes. Regarding the obesity, we found a percentage equal to 1.96%. Heart failure and other forms of cardiac ischemia reached a percentage of 1.96% and 4.58%, respectively.

## Conclusions

Asthma and severe asthma are chronic conditions contributing to the high economic burden not only for National Health Care Systems but also for patients and society, producing loss of productivity, and increasing the recourse to healthcare services. This study pres-

**Table IV.** Cost of illness results: this table shows the results of the cost-of-illness model stratified for patients (adults and pediatrics) and for diagnosis.

| Triage code | Diagnosis | N. patients | ED Tariff | Medical examinations | Hospitalization | Pharmacological therapy | | | Pulmonologist visit | Total | Per patient |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Home | ED | Discharge | | | |
| **Cost of illness – "other" diagnosis (adults** | | | | | | | | | | | |
| Green | Other | 36 | € 9,408.60 | € 1,228.41 | € - | € 5.26 | € 15.95 | € 20.31 | € 123.96 | € 10,802.5 | € 300.07 |
| Yellow | | 10 | € 2,613.50 | € 514.06 | € 6,906.00 | € 6.74 | € 4.06 | € 3.19 | € 20.66 | € 10,068.2 | € 1,006.8 |
| Red | | 1 | € 261.35 | € 64.58 | € 1,832.00 | € 0.01 | € 0.51 | € 0.01 | € - | € 2,158.45 | € 2,158.4 |
| **Cost of illness – "other" diagnosis (pediatric patients)** | | | | | | | | | | | |
| Green | Other | 27 | € 7,056.4 | € 299.73 | € 10,766.00 | € 3.54 | € 4.52 | € 7.42 | € - | € 18,137.6 | € 671.77 |
| Yellow | | 4 | € 1,045.4 | € 44.40 | € 1,538.00 | € 0.50 | € 1.49 | € 0.53 | € - | € 2,630.34 | € 657.58 |
| Red | | 0 | € - | € - | € - | € - | € - | € - | € - | € - | € - |

**Table V.** Aggregate result of the COI model (Cost-Of-Illness): this table shows the aggregate results of the COI model based on the 795 records on our dataset.

| ED Tariff | Medical examinations | Hospitalization | Pharmacological therapy | | | Pulmonologist visit | Total | Per Patient |
|---|---|---|---|---|---|---|---|---|
| | | | Home | ED | Discharge | | | |
| € 207,773.25 | € 22,035.15 | € 102,772.00 | € 147.22 | € 200.46 | € 234.97 | € 4,772.46 | € 337,935.51 | € 425.08 |
| € 261.35 | € 16.62 | € 129.27 | € 0.19 | € 0.26 | € 0.30 | € 6.03 | | |

ents an observational retrospective analysis on asthma and severe asthma patients estimating the annual costs from the Italian NHS perspective, focusing on the resources needed in the ED setting. This is one of the few studies measuring asthma costs in such care setting. Expenditure data include both medical examination costs, admission and hospitalization. The analysis demonstrates that the average cost for treating a patient suffering from asthma in the ED setting is related with the severity of the condition. Further investigation would be needed in order to estimate the social burden of the disease in terms of indirect costs. Severe asthma is a highly debilitating disease that often remains undiagnosed for a long time. In Italy, asthma affects approximately 4.5% of the population, 2.8 million people, while severe asthma ranges from 5% to 10% of the total asthmatic population. Furthermore, severe asthma is characterized by a higher risk of asthma-related symptoms, morbidities, and exacerbations. Systemic corticosteroids (SCS) are usually prescribed as add-on therapy to treat asthma and others inflammatory conditions, such as rheumatologic and autoimmune diseases, and inflammatory bowel disease. Commonly these drugs are added in order to solve or reduce the risk of flare-ups or to achieve a better control of the disease. However, the concern with maintenance SCS use is related to the increased risk of infections and cardiovascular events, chronic conditions such as type 2 diabetes mellitus, osteoporosis, and cataracts, metabolic effects (for instance: weight gain), and neuropsychiatric effects (i.e., insomnia, depression, and behavioural disturbances). A dose-response relationship with SCS exposure has been documented for many of these events. Even short-term use of oral corticosteroids (OCS) was associated, in a large population-based study, with increased rates of sepsis, thromboembolism, and fractures within 30 days of OCS initiation. Recently, a revision of six phase III trials was launched, evaluating a total of 3068 patients with severe asthma undergoing biologic therapy in 798 sites across 26 countries. These researches demonstrated a significant steroid-sparing effect (reduction of 75% of prednisone dose)[12]. Our study shows a great variability in the pharmacological management of patient with asthma and severe asthma. Data collected show that ED is one of the most important setting for the management of asthmatic patients; in fact, this is the setting where an acute episode may be treated, formulating a first appropriate diagnosis and prescribing the most coherent treatment. It is also important to underline that a significant proportion of asthma accesses in the ED are due to poorly controlled asthma or to poor adherence to treatment. Thus, in this context, it is needed a precise strategy designed to create a specific care pathway for severe asthma patients, aiming to avoid a frequent recourse to the ED. This may be realized by providing a multidisciplinary approach that is necessary for an effective and efficient management of these patients. It is also crucial a stratification of patients on the basis of some specific parameters, such as the medical history, the number of acute episodes and the effectiveness of the therapies administered in the ED setting. Based on the patient's condition, ED doctors can then outline a personalized post-discharge clinical pathway for each case. This will likely result in the improvement of patients' compliance to the therapy and, at the same time, in the reduction of the direct and indirect costs associated with the asthmatic condition.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

**Table VI.** Forecast of the regional impact (Lazio Region): this table shows an estimate of the economic impact of the management of asthmatic patients in the ED, considering the incidence and the prevalence of the asthmatic condition in the Lazio region. Assumptions were made in order to estimate an average cost associated to the patients with different severity of asthma.

| ***Population of Lazio Region***<br>***Italy asthma prevalence***<br>***Average annual incidence rate of asthma***<br>***Asthma patients in Lazio, Italy*** | **5898,000**<br>**0.045**<br>**0.00256**<br>**280,509** | ***Istat***<br>***Ginasthma***<br>***Pesce et al[8]***<br><br>**No. of patients for severity** | **ED access rate** | **No. access to emergency department** | **Average emergency health care cost** | **Total** | |
|---|---|---|---|---|---|---|---|
| Intermittent | 0.348 | 97,617 | 0.1 | 9.762 | € 285.00 | € 2,782,087 | Antonicelli et al[10] |
| Mild | 0.268 | 75.176 | 0.44 | 33.078 | € 285.00 | € 9,427,118 | Antonicelli et al[10] |
| Moderate | 0.306 | 85.836 | 0.51 | 43.776 | € 413.00 | € 18,079,577 | Antonicelli et al[10] |
| Severe | 0.078 | 21.880 | 1.41 | 30.850 | € 413.00 | € 12,741,201 | Antonicelli et al[10] |
| Totale | | | | | | € 43,029,983.65 | |

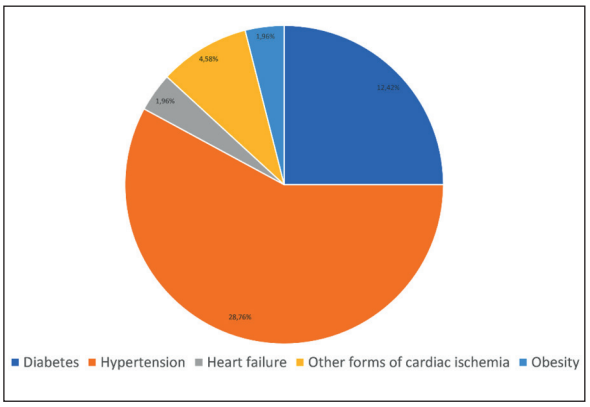


**Figure 5.** Comorbidities in patients with cortisone prescribed in home, ED and discharge therapy.

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