Asthma exacerbations in a tertiary hospital: clinical features, triggers, and risk factors for hospitalization

Running title: Asthma exacerbations profile in Madrid

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Abstract

Background: Risk factors for asthma exacerbations are not fully understood. The aim of this study was to determine the epidemiological and clinical characteristics of patients with an asthma exacerbation, potential triggers, and possible predictors of hospitalization.

Methods: A retrospective, non-interventional cohort study was conducted in adult patients who attended the Emergency Department of a tertiary hospital with an asthma exacerbation during 2014.

Results: 831 patients (888 events) were included. The highest number of episodes occurred in January and May. Respiratory infection was considered the trigger in 523 events. 34.21% had ≥260 eosinophils/mm^3 (20.7%≥400 eosinophils/mm^3), significantly associated with allergic asthma (p<0.0001). Risk factors for hospitalization were: older age [OR:1.58 (95% CI 1.46-1.71)]; no previous diagnosis of asthma [OR:1.40(95% CI 1.06-1.86)]; poorly controlled asthma[OR:1.78 (95% CI 1.10-2.88)]; respiratory infection [OR:2.65 (95% CI 1.95-3.62)]; and severe crisis with more treatment requirements. Of those asthmatics with ≥400 eosinophils/mm^3, the rate of hospitalization was lower (p<0.001).

Conclusion: Older age, absence of a previous asthma diagnosis, uncontrolled disease or concomitant COPD are frequent among patients presenting to the ED with asthma exacerbations. There were some features associated with higher risk of admission. Blood eosinophilia should be considered as a marker of asthma, but not as a predictor of hospitalization.

Key words: asthma, exacerbation, risk of hospital admission, eosinophilia.

Resumen

Objetivo: Los factores de riesgo de las exacerbaciones de asma no se conocen por completo. El objetivo de este estudio fue determinar las características epidemiológicas y clínicas de los pacientes con exacerbaciones de asma, los potenciales factores desencadenantes y los posibles predictores de hospitalización.

Métodos: Se llevó a cabo un estudio de cohorte retrospectivo, no intervencionista, en pacientes adultos que acudieron al Servicio de Urgencias de un hospital terciario con una exacerbación de asma durante el año 2014.

Resultados: Se incluyeron 831 pacientes (888 eventos). El mayor número de episodios ocurrió en Enero y Mayo. La infección respiratoria se consideró como desencadenante en 523 eventos. 34.21% tenían ≥260 eosinófilos/mm3 (20,7% ≥ 400 eosinófilos/mm3), estando lo cual asociado significativamente con el asma alérgica (p<0,0001). Los factores de riesgo para la hospitalización fueron: edad avanzada [OR: 1,58 (IC 95%: 1,46 a 1,71)]; ausencia de diagnóstico previo de asma [OR: 1,40 (IC 95%: 1.06-1.86)]; mal control del asma [OR: 1,78 (IC 95%: 1.10-2.88)]; infección respiratoria [OR: 2,65 (IC 95%: 1.95-3.62)]; y crisis graves con mayor necesidad de tratamiento. En los asmáticos con ≥ 400 eosinófilos/mm3, la tasa de hospitalización fue menor (p <0,001).

Conclusión: La edad avanzada, la ausencia de un diagnóstico de asma previo, el mal control de la enfermedad o el padecer EPOC de forma concomitante son frecuentes entre los pacientes que acuden al Servicio de Urgencias con exacerbaciones de asma. Se detectaron algunas características asociadas con un mayor riesgo de ingreso. La eosinofilia periférica debe ser considerada como un marcador de asma, pero no como un predictor de la hospitalización.

Palabras clave: asma, exacerbación, riesgo de hospitalización, eosinofilia.

Introduction

Most patients with asthma, despite maintenance treatment, remain symptomatic and experience exacerbations, indicating poor asthma control [1]. An asthma exacerbation is considered an increase in asthma symptoms with worsening of lung function that requires an increase in medication (including systemic corticosteroid therapy), an emergency department visit, or hospitalization [2]. Although some countries have seen a decline in asthma-related hospitalizations and deaths [3], the global burden of exacerbations and day-to-day symptoms has increased by almost 30% in the past 20 years [4]. In fact, exacerbations constitute the major cause of morbidity and mortality in asthma [5], increasing the annual cost of treatment threefold [6]. Patients who have frequent exacerbations usually experience an accelerated loss of lung function [7].

Asthma exacerbations are commonly triggered by upper respiratory tract infections and/or exposure to environmental allergens, and less frequently due to other factors [8]. Certain features and conditions have been associated with an increased risk of exacerbations in adults, including obesity, smoking, severe sinus conditions, allergy, gastroesophageal reflux (GER), repeated respiratory infections, psychiatric disorders, obstructive sleep apnea syndrome, vitamin D deficiency, non-white race, low socioeconomic status, or female sex [9]. Indicators of poor asthma control, such as having suffered an exacerbation in the previous year or having received three or more cycles of oral corticosteroids, as well as poor treatment adherence [10] and eosinophilia in sputum [11] or blood [12], have been described as risk factors for exacerbation.

Knowing which risk factors could lead to an exacerbation, recognizing indicators of potential severity, and establishing the most appropriate treatment and more effective preventive measures are not only necessary, but could prove indispensable to improving control of asthma. In Spain, a few studies on the profile of asthma exacerbations have been conducted. In 2009, a study was published including 262 episodes of asthma exacerbations treated in hospital Emergency Department (ED) and home-care services in Barcelona [13]. The most frequent etiology was possible viral infection of the respiratory tract, but the period of observation was only October and November. Retrospective studies have been published on quality of care [14] and epidemiology [15]. However, there are still many aspects that remain unknown and more information could be useful to prevent the onset of asthma exacerbations.

The present study was designed to assess epidemiological and clinical characteristics, potential triggering factors, and possible predictors of hospitalization in patients (with or without a prior diagnosis of asthma) who had experienced at least one asthma exacerbation and were treated in the ED of a tertiary hospital in Spain.

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Methods

We conducted a retrospective and observational (non-interventional) cohort study using data collected from medical records or charts at the ED of La Paz University Hospital (HULP), Madrid, Spain. This hospital is the tertiary referral center for a population of 500,000 in Northern Madrid. The total number of ED visits was 211,031 in 2014 [16]. This study was approved by the institutional Ethics Committee, and permission was obtained from the hospital for the use and treatment of confidential data.

A specific search was performed for any of the International Statistical Classification of Diseases and Related Health Problems 9th Revision, (ICD-9-CM) codes for asthma(493; 493.0; 493.1; 493.2; 493.8; 493.9)[17], and a supplementary search was later performed following other possible and no-codified diagnoses: bronchial asthma; asthmatic bronchitis; asthmatic crisis; acute asthmatic attack; and asthma exacerbation. Every event in which COPD or COPD exacerbation was mentioned as a possible cause for the ED visit was excluded. Isolated pneumonia diagnosis was also excluded. All patients aged >14 years who attended the ED with one of the aforementioned "labels" suggestive of an asthma exacerbation, from January 1stto December 31st, 2014, were enrolled. Data were collected by the same four investigators during the inclusion period. Each episode was defined as an event. After ED or hospital discharge and a period of 7 days of stability after resolution of an exacerbation [18, 19] cases in which the same patient visited the ED less than 15 days after the previous event were classified as relapses, while visits after this 15-day period were considered new events.

For each event, 84 variables were identified for data collection, grouped under the following five headings: patient demographics, epidemiology, comorbid conditions (including asthma diagnosis and previous level of control according to then current consensus criteria of the 2009 Spanish guideline on asthma management GEMA) [21], and regular treatments; evaluation of asthma exacerbation (trigger factors if they were explicitly recorded in the chart (ICD-9-CM codes: 465, 466 for respiratory infections; 477 for allergic rhinitis; 372 or 995 for allergy; 935.8 for non-steroidal anti-inflammatory drugs)[17] ; clinical features, such as cough, wheezing, fever, etc.); severity of the exacerbation (defined by GEMA 2009) [20];and laboratory tests, with particular attention to eosinophilia, defined as ≥260 eosinophils/mm^3 in blood)[21]; treatment administered at the ED; patients' response to treatment and subsequent outcome (discharge, observation, hospital admission, intensive care admission, or death); and, finally, referral to an asthma specialist (allergist or pulmonologist) at discharge. As elevated blood eosinophil counts have been proposed as a risk factor for asthma exacerbations, we also considered a cutoff of 400 eosinophils/mm^3, as previously reported [12].

Statistical analysis

Quantitative data are expressed as mean ± standard deviation (SD), maximum, and minimum. Discrete variables were presented as frequency distribution, percentages, and, when necessary, 95% confidence intervals. For univariate exploratory analysis of discrete variables, the Pearson chi-square test or Fisher's exact test were used as appropriate. Correlated data were analyzed using a generalized linear mixed model (GLMM) with the restricted maximum pseudo-likelihood Method (RMPL). Regarding the first objective, to estimate "probability of the event" (for each event separately: asthma event, admission, and relapse), a random intercept and unstructured covariance matrix was added to the GLMM with binomial distribution and logit link function, to test the need for a random effect. If a random effect was not necessary, a logistic regression was used to estimate the probability of the event. Then, "specific epidemiological and clinical variables" were added into the model and their relationships with binary outcome in terms of the odds ratio (OR) were estimated. The Mann–Whitney test was used to assess the role of eosinophil level (<260) and patient age. The relationship between age and the month of the event was estimated using Spearman correlations. All tests were two-tailed, and the significance level was set as $p<0.05$. Exploratory univariate analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY, IBM Corp., USA), while GLMM analysis was carried out in SAS Enterprise Guide 5.1 software (Cary, NC, SAS Institute Inc., USA). The procedures used were "*proc glimmix"* and *"proc logistic*".

Results

831 patients (563 women) experiencing 888 episodes were included; 54 patients had more than one episode. Mean age was 57.3 years (range, 14 to 102 years). Data on patient characteristics and comorbidities are shown in Table 1. When information on variables such as obesity, GER, or confirmed nasal polyps could not be collected from a sufficient number of patients, the outcome was excluded from final analysis. The average likelihood of relapse was 6%, and that of hospitalization, 32% (Table 2).

In this population, 45.7% of patients (n=380) had no known previous recorded diagnosis of asthma. Among those already diagnosed with asthma (n=451), 81 were not receiving any regular treatment, 108 (23.94%) used only a short-acting beta-agonist (SABA) as needed, and 255 (more than half of the known asthmatic population) were on regular treatment with inhaled corticosteroids (ICS) with or without long-acting beta-agonists (LABA). Of the total population, 102 patients (12.27%) had experienced at least one exacerbation requiring emergency care in the previous year. Only 15 patients had ever been admitted to an intensive care unit (ICU).

A blood eosinophil count was obtained from 681 patients. Overall, 233 patients (34.21% of those tested) had an eosinophil level ≥260 cells/mm^3, whereas 141 (20.7% of the tested

population) had >400 cells/mm^3. Eosinophilia was weakly associated with younger age, and weakly but significantly associated with a known diagnosis of respiratory allergy ($p< 0.0001$). The OR for this association increased by 1.16 (95% CI. 1.1-1.22) for every additional 100 cells/mm^3.

The distribution of the total 888 events per month is shown in Figure 1. The frequency of episodes was highest in January and May, [142 (16%) and 158 (17.8%) respectively], and lowest in July and August. However, April and November were the months when the highest rates of hospitalization (43.4% and 38.3%, respectively). The suspected etiologies of the exacerbations and their clinical characteristics are reported in Table 3.Respiratory infection was the most common trigger for exacerbation (523/888 episodes), followed by direct exposure to aeroallergens (in 70 episodes). In 29% of episodes, the triggering agents or factors were not identified.

Regarding severity, 319 of the 888 episodes (35%) were considered moderate-to-severe exacerbations, with risk of imminent respiratory arrest in 5 cases. The most common symptoms were dyspnea (90%) and cough (78%), mostly without expectoration (54%). Ten patients arrived with an altered level of consciousness. On physical examination, 77% had wheezing, and only 25 patients had absent breath sounds. A baseline oxygen saturation <92% was observed in31% of patients. Overall, 51% of the episodes required systemic corticosteroids, and 25% were treated with antibiotics. After treatment, approximately 68% of patients were discharged (8.3% after staying in an observation bay), and 285 events (32.1%), corresponding to 259 patients, were admitted (six to the ICU). No fatal events were registered due to asthma attacks.

Associations between the variables of interest and hospitalization are shown in Table 4. In general, older age (Figure 2), absence of a previous diagnosis of asthma or uncontrolled disease, suspected respiratory infection, severe crisis, and increased need for ED treatment were associated with a higher risk of admission. However, only 25.5% of patients with a blood eosinophil count >400 cells/ml required hospitalization, versus 44.2% of those with <400 eosinophils/ml ($p<0.001$)

DISCUSSION

The incidence of asthma exacerbations in real-life surveys is much higher than that seen in clinical trial settings [4]. Moreover, exacerbations occur among patients with poorly controlled asthma across the spectrum of severity, even in subjects treated with inhaled corticosteroid [23]. Loss of asthma control usually leads to unscheduled clinical visits; in one study, 70% of

uncontrolled asthmatics had an unscheduled visit to a physician, 36% had an ED visit, and 14% were hospitalized in the last year [24]. Indeed, history of an asthma exacerbation in the previous year is the strongest predictor of future exacerbations in adults [25]. In our population, there were a large number of asthmatics on SABA monotherapy. Despite the important role of inflammation in asthma, 15 years after the AIRE study, in which more patients had used rescue medication (63%) than inhaled corticosteroids (23%) in the past 4 weeks [26], we still find that many patients diagnosed with asthma are not on regular maintenance treatment. This might be a consequence of an overestimation of asthma control that does not match symptom severity. However, the rate of patients with a previous ED visit during the preceding year was lower in our sample than in other published observational studies [23], and, interestingly, did not significantly predict a new exacerbation during the analyzed period.

One potential weakness of this study was the unavailability of data for all the outcomes, due to the retrospective design. Therefore, a prospective cohort is warranted to assess the actual influence of this specific variable (i.e., previous exacerbation).One of the major strengths, however, is the inclusion of patients seen in the same hospital and by the same ED medical team throughout the year, thus decreasing the risk of bias, including seasonal patterns. Thus, we believe our sample is representative of real-life practice in our geographic area, which could reflect that a substantial number of asthmatic patients might not be correctly diagnosed and, possibly, could be receiving substandard care or even untreated. It is remarkable that 45% of the patients who experienced an asthma exacerbation in this study had no previous diagnosis of asthma or, alternatively, this disease had not been adequately registered in the medical record at the ED. We believe that the retrospective character of this study may have influenced the data collection, especially since we have considered only data recorded in the charts, according to real-world conditions and trying to avoid any interpretation bias by the investigators. In the ASMAB II study [13], only 31% of the patients attending the ED used regularly inhaled steroids. Dominguez-Ortega *et al*. analyzed 83 bronchospasm episodes seen at urgent care during a storm in spring, and21% of the patients had no previous recorded diagnosis of asthma, 93 % had no regular medical visits and 61.45 % did not receive any treatment for asthma [27]. Serrano-Pariente *et al*. defined three different phenotypes of patients with near-fatal asthma. Particularly, in cluster 3, characterized by an insufficient anti-inflammatory treatment and frequent sensitization to *Alternaria alternata* and soybean, only 4% of patients showed a periodic medical monitoring of their asthma; only 30% of them received ICS treatment; and none of patients followed a written action plan for asthma during the NFA attack [28]. Misdiagnosis of asthma has been reported in stable disease, leading to inappropriate treatment and suboptimal patient outcomes [29], and could affect up to 26% of frequent exacerbators (requiring ≥ 2 ED visits or hospitalization) [30]. It is also remarkable that more than 40% of patients were not referred to a specialist on discharge despite having required urgent attention,

providing an opportunity for collaboration between the ED physicians and allergists and pulmonologists.

Although it has been published that women [31] and current smokers [32] are at higher risk of asthma exacerbations, surprisingly, there were not found high prevalence associated with either parameter in our study. In contrast, older age and previously uncontrolled disease were more prevalent in this population. We did not analyze these outcomes independently; since older patients are usually at risk for future poorer asthma control [33].We also found that, in our population, age was associated with a higher rate of hospitalization. Moreover, in the studied sample, 13.7% of patients had been previously diagnosed with chronic obstructive pulmonary disease (COPD). The prevalence of asthma and COPD overlap syndrome(ACOS)among adult patients with COPD or asthma ranges from 13 to 30%, and patients with ACOS usually have severe disease, with increased rates of exacerbation and hospitalization [34].Accordingly, we found a frequent association between asthma and comorbid COPD in this population. These results are in agreement with a recent Italian multicenter observational study conducted in patients older than 65 years with documented physician-diagnosed asthma. This study highlighted the negative impact of COPD on asthma control [35]. We also found frequent associations in this population with several comorbidities that are also more prevalent among the elderly, such as arterial hypertension, diabetes, and psychiatric disorders. It has been previously described that dyspnea perception decreases with worsening asthma, with advancing age, and with depression status. Subjects with major depression had 3.4-fold higher odds of asthma than did those with minimal or no depressive symptoms [36].Other comorbidities are being explored, with GER, atherosclerosis, hypertension, ischemic heart disease, lipid disorders, and neoplastic disease possibly playing a role, as all have been shown to worsen the degree of asthma control significantly [37]. However, further research is needed to assess whether these comorbidities might influence the risk of asthma exacerbation.

Although at present there are no biomarkers that can accurately predict asthma exacerbations, an elevated eosinophil count in sputum or blood has been found to be associated with a higher risk of asthma exacerbation and hospitalization [12]. Eosinophilic asthma is a common asthma phenotype, and blood eosinophil count may be useful, as it is easy to assess in clinical practice [38]. However, there is some controversy about the eosinophils count in blood to determine whether a patient has an eosinophilic phenotype, and which would be the optimal cut-off point to denote an increased risk of exacerbation. We had selected a cutoff of 260 eosinophils/mm^3 according to previous recommendations [22]. In addition, 300 eosinophils/mm^3has been reported as a potential biomarker associated with a successful response to omalizumab treatment [39], and in the PREDUNA study [40] (a retrospective cohort study that examined the

relationship between blood eosinophil count at baseline and asthma exacerbations in the following 12 months), suggested that a blood eosinophil cutoff of ≥400/mm^{3}was strongly associated with future uncontrolled asthma (exacerbations and excessive SABA use). However, we found no association between blood eosinophil count and presence of exacerbation. This is in agreement with work by Tran *et al*, who did not find a clear association in adults over a 10-year survey, although they found a clearer trend toward increased asthma attacks when an additional adjustment for levels of exhaled FeNO and treatment for asthma in the prior 3 months was included [41]. Moreover, neutrophilic inflammation has been consistently observed in acute asthma associated with viral respiratory tract infections [42], in contrast to non-infective causes of asthma, which are characterized by increased IL-5 and eosinophil activation; this suggests differential patterns of inflammation depending on the etiology of the exacerbation. It is interesting that, in children, eosinophil levels were significantly higher in those who reported more asthma attacks (median blood eosinophil count = 300 cells/mm^3), suggesting that higher blood eosinophil counts might play a different role in children with asthma than in adults with the disease. A higher rate of allergic asthma could influence these results. In allergic asthma, inflammation is clearly associated with the presence of eosinophils in the airway and characteristic Th2 cytokine expression [43].As expected, in our study, allergic asthma was significantly associated with a higher blood eosinophil cutoff point. Nevertheless, we found a significant inverse association between eosinophil count and risk of admission. This finding is in disagreement with the data published by Hasegawa *et al*[44], who found, in a pilot study of 80 patients hospitalized for asthma exacerbation, that 40% of patients had blood eosinophilia (300 cells/mm^3). However, there were several potential limitations, specifically the inclusion of patients with severe acute asthma in the analytic cohort population, which may suggest that their study population was sicker than overall patients hospitalized for asthma exacerbation. We also consider that, in our population, the rate of infection as a cause of exacerbation was exceedingly high, which might have influenced eosinophil counts [45]. Moreover, the low rate of hospitalizations due to acute allergic exposure in this population might also have influenced the results, decreasing the impact of eosinophilia in the whole population.

In conclusion, asthma exacerbations represent a significant burden on patients with asthma and in the healthcare system. In this large, population-based, study of asthma exacerbations treated at a tertiary hospital over a 1-year period, we found several factors that are relatively common in exacerbated asthmatics and could be related to risk of hospitalization. Older age, absence of a previous asthma diagnosis, uncontrolled disease, and concomitant COPD were frequent among these patients with exacerbated asthma. These factors were also associated with a higher risk of admission, as were respiratory infections, severity of the crisis, and need for intense treatment in

the ED. Blood eosinophil counts should be considered as a specific marker of asthma phenotype, but not as a predictor of hospital admission. Nevertheless, further studies are warranted to better elucidate the role of each specific variable in predicting asthma exacerbations and risk of hospitalization *per se*.

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Table 1. Demographic and clinical features of the study population. n=831

	n (%)
Gender	563 female (67.7%) /268 male (32.3%)
Smokers	150 (18.1%)
Ex-smokers	102 (12.3%)
Previous diagnosis of Asthma	451 (54.3%)
Previous diagnosis of respiratory allergy	117 (14.1%)
Previous diagnosis of COPD	114 (13.7%)
Previous diagnosis of psychiatric disorders	166 (20%)
Previous diagnosis of drug allergies	135 (16.2%)
Previous diagnosis of high blood pressure	296 (35.6%)
Previous diagnosis of Diabetes mellitus	116 (14%)
Previous diagnosis of dyslipidemia	131 (15.8%)
Regular treatment with Statins	150 (18%)
Regular treatment with ACE inhibitors	138 (16.6%)
Regular treatment with Betablockers	72 (8.7%)
Regular treatment with NSAIDs	27 (3.3%)

Table 2. Average probability of hospitalization, more than one event and relapse in the studied population estimated by a Generalized Linear Mixed Model.

Effect	Estimate	Standard Error	p	Mean	Standard Error Mean
Admission	-0.7496	0.0721	<.0001	0.3209	0.01569
≥1 event	-0.0420	0.1052	<.0001	0.1149	0.01070
Relapse	-2.7372	0.1404	<.0001	0.06081	0.008020

Table 3. Clinical characteristics of the exacerbations. n=888.

Severity	%
Mild	60
Moderate/Severe	35
Imminent respiratory arrest	0.5
Suspected Triggers	
Respiratory infection	60
Respiratory allergy	9
Physical exercise	0.8
Drug intake	0.6
Psychological factors	0.6
Food allergy	0.1
Others and unknown	28
Symptoms	
Dyspnoea	90.5
Cough	78
Expectoration	46
Wheezing	43
Low level consciousness	1.1
Chest tightness	15
Nasal symptoms	13
Ocular symptoms	4
Physical examination	
Auscultation: normal	19.5
Auscultation: wheezing	78
Auscultation: abolished sounds	2.5
Tachycardia > 99 lpm	33.5
Tachypnea>19 rpm	26.8
High temperature (>37.7ºC)	3.6
Basal oxygen saturation <92%	31

Table 4. Estimation of the relationship between hospitalization and the analyzed outcomes

	OR	**CI 95% OR**
Older age	1.58	1.46-1.71
Male gender	0.981	0.724-1.328
No previous diagnosis of asthma	1.403	1.056-1.863
Uncontrolled asthma	1.786	1.105-2.879
Mild exacerbation (VS moderate/severe)	0.091	0.065-0.128
Ex-smokers VS smokers	1.746	1.073-2.843
Previous diagnosis of DM	3.247	2.205-4.781
Previous diagnosis of DL	2.020	1.401-2.912
Previous diagnosis of respiratory allergy	0.324	0.194-0.539
Previous diagnosis of drug allergies	2.130	1.489-3.048
Previous diagnosis of high blood pressure	3.778	2.805-5.089
Respiratory infection as a trigger	2.655	1.948-3.618
Respiratory allergy as a trigger	0.159	0.068-0.369
Blood eosinophilia (>260/mm^3)	0.459	0.327-0.644
Arterial blood gases in the ED	8.314	5.783-11.954
Treatment with Oxygen	7.082	5.142-9.753
Treatment with short acting inhaled B-2 agonists	1.825	1.290-2.581
Treatment with corticosteroids	2.374	1.741-3.238
Treatment with inhaled ipratropium bromide	1.935	1.372-2.729
Treatment with antibiotics	10.379	7.286-14.787

Figure 1. Monthly distribution of exacerbations.

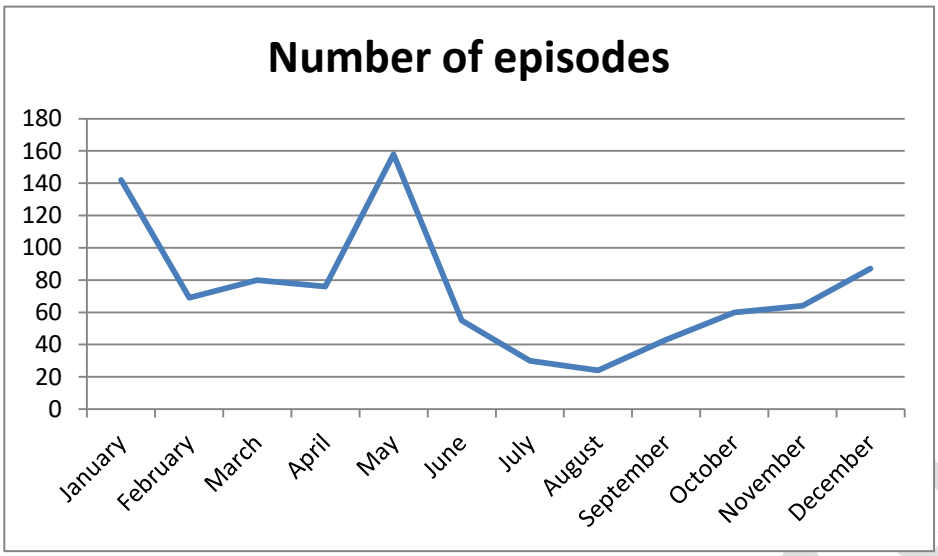

Figure 2. Relation between age and hospitalization.