Acute Severe Asthma: Changes in Patient Characteristics, Management, and Outcomes over a Period of 20 Years (1997 to 2017), Insights from Cub-Réa Network.

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Acute Severe Asthma: Changes in Patient Characteristics, Management, and Outcomes over a Period of 20 Years (1997 to 2017), insights from Cub-Réa network.

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ABSTRACT

Background: While acute severe asthma (ASA) is the leading cause of emergency department visits and the third cause of hospitalization in children younger than 18 years old, there is a lack of data regarding adult patients admitted in intensive care units (ICU) for ASA. We aimed to describe the evolutions in epidemiology, management, and outcomes of ASA in adult patients, over a period of twenty years in the Greater Paris area ICUs (CUB-Réa Database).

Methods: Demographics, severity and supportive treatments were collected from the CUB-Réa Database. The primary endpoint was the prevalence of ASA by periods of 5 years. The secondary endpoints were in-ICU survival, in-hospital survival, use of mechanical ventilation including non-invasive and invasive and catecholamine. Multivariate analysis was performed to assess correlating factors of ICU Mortality.

Results: Of the 475 357 ICU admissions from January 1997 to January 2016, 7049 were admitted for ASA with a decreasing prevalence over time, respectively 2.8%, 1.7%, 1.1%, and 1.1% of total ICU admissions ($p < 0.001$). The median age was 46 years old [IQR: 25%-75%: 32-59], 3906 (55%) were female, the median SAPS II was 20 [IQR: 13-28], and 1501 (21%) had mechanical ventilation. Over time, age, the SAPSII and the Charlson Comorbidity Index tended to increase. The use of invasive and non-invasive mechanical ventilation increased ($p < 0.001$), whereas the use of catecholamine decreased ($p < 0.001$). The in-ICU survival rate improved from 97% to 99% ($p = 0.008$). In the multivariate analysis, factors associated with in-ICU mortality were SAPSII ($p < 0.001$), renal replacement therapy ($p < 0.001$), catecholamine ($p < 0.001$), cardiac arrest ($p < 0.001$), pneumothorax ($p < 0.001$), ARDS ($p < 0.001$), sepsis ($p < 0.001$) and IMV ($p < 0.001$).

Conclusion: ICU admission for ASA remains uncommon and decreases over time. Despite an increasing severity of patients and the use of mechanical ventilation, the use of catecholamine decreases with high in-ICU survival rate which could be related to a better management of mechanical ventilation.

Key Words: Acute severe asthma, intensive care unit, epidemiology, mechanical ventilation

BACKGROUND

Worldwide, asthma prevalence and severity have been increasing over the last decades. Asthma tends to be a lifelong condition with a high morbidity and economic burden to patients, their families and the society[1]. The natural history of asthma can be punctuated by acute exacerbations leading to acute respiratory failure and requiring admission to an intensive care unit (ICU) for monitoring and/or mechanical ventilation. While asthma is the leading cause of emergency department visits and the third cause of hospitalization in children younger than 18 years old[2], evidence is sparse concerning acute severe asthma (ASA) management and outcomes in adults, whereas it may account for up to 1% of mechanically ventilated patients[3].

Latest studies from England and Wales examined the patients' demographics, outcomes and trends of admissions with ASA in critical care units between 2002 and 2011 and demonstrated that it represents a modest burden of work with a high survival rate in ICUs[4]. Another cohort in Australia, spanning from 1996 to 2003, showed a reduction in the incidence and mortality of patients with ASA in critical care units[5,6]. Despite the lack of data regarding changes in epidemiology and outcome of patients admitted in ICU, noninvasive mechanical ventilation (NIV) use for ASA increased over the past two decades[3,7]. Similarly, few data exist regarding the use of invasive mechanical ventilation (IMV) and extracorporeal life support (ECLS).

Therefore, the aim of this 20-year retrospective study is to describe the epidemiology, the in-ICU management and the outcome of ASA patients hospitalized in the Greater Paris area ICUs (Collège des Utilisateurs de Bases de données en Réanimation (Intensive Care Database User Group) CUB-REA[8].

MATERIAL AND METHODS

Study and patients

We used the prospectively collected database of the Greater Paris area ICUs (CUB-Réa Database), which has been described previously[9]. Participating centers are listed in the Supplementary material online, Appendix S1.

All adult patients admitted from the first of January 1997 to the first of January 2017 with ASA were included. Only patients with primary or secondary diagnosis of ASA were included. Patients identified as having an associated COPD diagnosis were excluded.

Definitions

The Acute Severe Asthma exacerbation group was defined as all hospital stays with a primary diagnosis of ASA (ICD-10 code J459) or Status Asthmaticus (ICD-10 code J46), or with ASA as secondary diagnosis associated with a cardiac arrest (I460 or I469), an acute respiratory failure (J960), an acute respiratory distress syndrome (ARDS) (J80), a pulmonary infection; whether viral or bacterial (J121, J122, J129, J13, J14, J152, J154, J156, J157, J159, J180, J181, J188, J189), a bronchitis (J206, J208), a flu (J90, J10.0, J10.1) or a pleural effusion (J90, J91, J86.0), a sepsis (A403, A412- A419, B349, B59), a systemic inflammatory response syndrome (SIRS) (R651), a hemoptysis (R042) or a pneumothorax (J930 or J939).

The exclusion criterion was defined as any diagnosis of COPD (J44, J440, J448, and J449).

Data collection

Usual demographic characteristics (age, sex, Charlson Comorbidity Index) were collected. Severity was assessed by using the Simplified Acute Physiology Score II (SAPS II). Supportive treatments (catecholamine, NIV, IMV, RRT and ECLS) were collected.

Outcome

The primary endpoint was the prevalence of ASA in critical care units.

The secondary endpoints were in-ICU and in-hospital mortality, use of NIV and IMV, associated diagnosis to ASA, catecholamine use, RRT and ECLS.

Statistical analysis

Quantitative data were expressed as medians (25th–75th percentiles) and compared by analyses of variance. Categorical variables, expressed as numbers and percentages, were compared using the $\chi 2$ test.

The primary outcome was the prevalence of ASA divided into 5-year time periods (1997- 2001, 2002- 2007, 2007- 2011, 2012- 2016).

Multivariable analyses of in-ICU mortality were performed using a generalized linear model analysis including all variables with a p-value below 10% in univariate analysis. We then performed a model selection based on a backward-stepwise procedure, in order to retain the best model, corresponding to the model according to AIC criterion.

All analyses were two-sided and p-values lower than 5% were considered statistically significant. Statistical analysis was performed using R studio software (R© Development Core Team, 2019).

In line with the French regulations for ethical use of personal data, the CUB-Réa project was approved by the *Commission Nationale Informatique et Liberté* (French Data-protection Watchdog agreement #564407). The present study was also approved by the ethics committee of the *Société de Réanimation de Langue Française* (French Society of Intensive Care Medicine) with a waiver of informed consent. CUB-Réa was initially funded by the Paris public hospital system, *Assistance Publique-Hôpitaux de Paris*.

RESULTS

Population characteristics

During this period, 465 357 consecutive ICU admissions were recorded in the 40 participating ICUs of Cub-Réa. A total of 13 270 admissions with an ASA code were reviewed (2.9%). Among them, 7049 admissions for ASA or status asthmaticus without associated diagnosis of COPD were included for the analysis (See Figure 1, flow chart). The median age was 46 years old (IQR: 25%-75%: 32-59), 3906 (55%) were women, median SAPS II was 20 (13-28) and the median Charlson comorbidity index was 0 (0-1). Among the 7049 admissions, 1071 admissions (15%) had invasive, 430 (6%) had noninvasive mechanical ventilation, and 108 (1.5%) had both NIV and IMV. Catecholamines were used in 1247 patients (18%) and RRT in 42 patients (1%).

The in-ICU mortality was 2.4% (170 admissions) and hospital mortality was 2.8% (197 admissions).

Incidence of ASA

There was a significant trend for lower admission incidence for ASA over time ($p<0.001$), 2.8% of total ICU admissions (n= 2 841) between 1997 and 2001, 1.7% (n= 1 717) between 2002 and 2006, 1.1% (n= 965) between 2007 and 2011, and 1.1% (n= 1 526) between 2012 and 2016 (See Figure 2).

Evolution over time

Mean age increased over the study period with more comorbidities (Charlson comorbidity index) and higher severity (SAPS II).

The use of IMV alone and NIV alone increased, as well as the use of NIV and IMV starting 2007, whereas the use of catecholamine decreased (See Table 1).

Among the whole asthma critically ill patients, one patient had an extracorporeal CO_2 removal ($ECCO_2R$) and 8 had an ECLS, of which 6 between 2012 and 2016.

Outcome

The median ICU length of stay was 3 [IQR: 1-5] days until 2011, and 6 [3-11] days starting 2012 (p <0.001). The median in-hospital stay remained unchanged from 1997 to 2016 (6 days). However, the survival rate in the ICU remained high during the different time periods, respectively 98%, 97%, 97% and 99% (p=0.002) (See Table 1).

ASA and associated diagnosis

Among the 7 049 admissions for ASA collected between 1997 and 2016, 3260 had at least one associated diagnosis. A total of 2 689 admissions (82%) were registered with an acute respiratory failure, and 132 admissions (4%) with an associated cardiorespiratory arrest (See table 2).

ASA and respiratory infections

Pulmonary infections associated with acute severe asthma were reported in 231 out of the 7 049 patients (3.3%). There was a significant trend for increased pulmonary infections over the different time periods and for more viral and notably influenza related pneumonia (p < 0.001) (See Table 2).

Factors associated with mortality

In a multivariate analysis, factors associated with mortality were SAPSII (OR per point 1.06 [IQR: 1.05, 1.07]), RRT (OR 6.78 [IQR: 2.79, 16.49]), and catecholamine OR 2.6 [IQR: 1.52, 4.47]). Among the associated secondary diagnosis, cardiac arrest was associated to a more than thirteen-fold increased risk of mortality (OR 13.8 [IQR: 7.28, 26.14]), pneumothorax and ARDS to a more than two-fold increased risk (OR 2.55 [IQR: 0.19, 33.73], OR 2.56 [IQR: 0.73, 8.98] respectively), and sepsis to a five-fold increased risk (OR 5.15 [IQR: 1.57, 16.86]). Invasive mechanical ventilation implied an almost four-fold increase in mortality risk (OR 3.86 [IQR: 2.18, 6.84]) (See Table 3). Neither age nor comorbidities impacted the mortality.

DISCUSSION

In this study, we noticed a decrease in the prevalence of ASA admissions in the ICU from 1997 to 2016. However, it tended to increase between 2012 and 2016. The mortality remained stable despite more severe patients, a higher use of NIV, and an almost four-fold increase in mortality risk with IMV. The high female prevalence reflected the previously well-documented sex variation in asthma[10–12].

The first report of the Global Initiative for Asthma (GINA) published in 1995 provided the foundation for asthma guidelines and has undergone a major paradigm shift; the change in the late 1990s from an opinion- to an evidence-based approach for the management of asthma severity[13]. And so, the notable decrease of ASA admissions during the study period may imply a better control and a clearer understanding of this inflammatory disease over the years[14] and a possible decrease in ambient air pollution. Thereby, for the same reasons, only older and more severely ill patients required ICU for ASA.

ASA is characterized by a major increase in airway resistance and expiratory flow is dramatically reduced with a resultant major dynamic hyperinflation[15]. Studies have shown that patients with severe airflow obstruction receiving mechanical ventilation are at risk of inadvertent pulmonary hyperinflation with morbidity and mortality caused by pneumothorax and circulatory depression. Given the high mortality risk in severe intubated patients, prevention of intubation is an essential goal[16–21].

The evidence regarding the role of NIV in asthma is weak and no recommendation is offered in the latest guidelines[22]. Despite the lack of supporting evidence to guide practice, NIV is increasingly used throughout the study period for the management of ASA. In several observational studies, NIV improved ventilation/perfusion mismatch, decreased work of breathing and had a bronchodilator effect[20,21], and was used in patients with severe asthma exacerbation as a mean to obviate the need for intubation and

invasive mechanical ventilation and its detrimental effects[23–25]**.** A review of the effect of NIV in ASA pointed out the possible benefits of its use in order to avoid and to prevent endotracheal intubation (ETI), by unloading the respiratory muscles, diminishing airway resistances and improving gas-exchanges[26]**.** Nonetheless, its use should not delay intubation when needed[27]. In the time-period between 2007 and 2011, we noticed an increased use of mechanical ventilation, whether it is IMV, NIV or both. However, starting 2012, the use of IMV tended to decrease, whereas the use of NIV alone remained stable and more patients with IMV used NIV as well. However, the CUB-réa database doesn't mention the sequence of NIV and IMV.

In addition, we speculate that the management of mechanically ventilated patients has improved over the last decade because of strategies aiming at preventing or reducing ventilator-induced lung injury and mortality[28,29]. Even if the need for invasive mechanical ventilation was associated with mortality, the need for catecholamine decreased and almost disappeared starting 2007, which implies that improvement in mechanical ventilation of ASA may have reduced heart-lung interaction with lowest dynamic hyperinflation[30]. If the mortality associated with ASA remained stable despite more severe patients, then it is imperative that clinicians treating such patients have a clear understanding of how gas trapping can occur and of how it may be recognized, measured and limited.

Considering the reversibility of the pathophysiology of asthma[31], several retrospective studies and case reports have emphasized the interesting use of $ECCO_2R$ for asthmatic patients with life-threatening barotrauma[32–35], or even in awake spontaneous breathing patients[36]. However, the benefits and potential complications of this therapy have yet to be fully investigated. The use of extracorporeal life support such as ECMO was low, and even though ASA is associated with respiratory acidosis requiring mechanical ventilation, the ECCO2R was used once, and the outcome of this intervention was not recorded in the database. That said, it might require a more detailed evaluation.

While the environmental causes of asthma exacerbation are heterogeneous, common upper respiratory tract viruses are one of the most common and important causes of exacerbation in both children and adults[37,38]. Indeed, the prevalence of viral infection associated with asthma exacerbation in ICU tended to increase with the years. This could be explained by the increased detections with the development of more sensitive diagnostic techniques.

The major strength of our study is the accuracy of the CUB-réa database and the large size of the population that allow us to closely evaluate changes over two decades. However, the retrospective design of this study and the restraints of the database generate some limitations.

The parameters of the mechanical ventilation are not recorded, neither the timing nor the sequence of modalities of ventilation. Throughout the two decades, the need for catecholamine decreases and almost disappears starting 2007 and outcomes of severe asthma improve with fewer in-hospital deaths, suggesting a better management of hyperinflation. However, the lack of tracking doesn't allow us to clearly identify the possible correlation between the progress in mechanical ventilation techniques and this hypothesis. Besides, the mortality rate related to other interventions, such as ECLS, is not recorded. Very few ECLS were used during the last two decades; and the type of ECMO, whether it was veno-venous or veno-arterial was not specified.

In addition, there might be possible bias in the coding of the associated diagnosis. The infections were not specified whether they were nosocomial or viral in the database. During the last period, there has been an increase in health-system strengthening and an improvement in influenza testing capacities. Therefore, increased prevalence of associated viral infections might be related to increased detection.

CONCLUSION

The prevalence of acute severe asthma among patients admitted in the ICU decreases over time with a change in patients' profile, which are older, more severely ill and with a higher Charlson comorbidity index, which could be explained by a better management of asthma and environmental changes. Although the use of mechanical ventilation, and specifically noninvasive ventilation, increases with time, the survival rate remains stable and the catecholamine use decreases. This could likely result from a better management of mechanical ventilation in this population.

LIST OF ABBREVIATIONS

ASA: Acute severe asthma

ARDS: Acute respiratory distress syndrome

Cub-Réa: Collège des Utilisateurs des Bases de données en Réanimation

COPD: Chronic obstructive pulmonary disease

$ECCO_2R$: Extracorporeal CO_2 removal

ECMO: Extracorporeal membrane oxygenation

ECLS: Extracorporeal life support

ICU: Intensive care unit

IMV: Invasive mechanical ventilation

NIV: Noninvasive mechanical ventilation

SAPS 2: Simplified acute physiology score II

SIRS: Systemic inflammatory response syndrome

DECLARATIONS

Ethical approval and consent to participate

In the line with the French regulations for ethical use of personal data, the CUB-Réa project was approved by the Commission National Informatique et Liberté (French Data-protection Watchdog agreement #564407).

Consent for publication

The present study was also approved by the ethics committee of the Société de Réanimation de Langue Française (French Society of Intensive Care Medicine) with a waiver of informed consent.

Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Competing interests

The authors declared no conflict of interest.

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Authors' contributions

Conceptualization: RY, JLA and NA. Acquisition, analysis, or interpretation of the data: RY, JLA, AN. Statistical analysis: JLA and BH. Drafting of the manuscript and editing: RY, JLA, BH, BG, PA, NP, EG, AN, CHB, AH, CB, FS, JLD, NA.

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All the authors involved read and approved the final manuscript.

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Figures

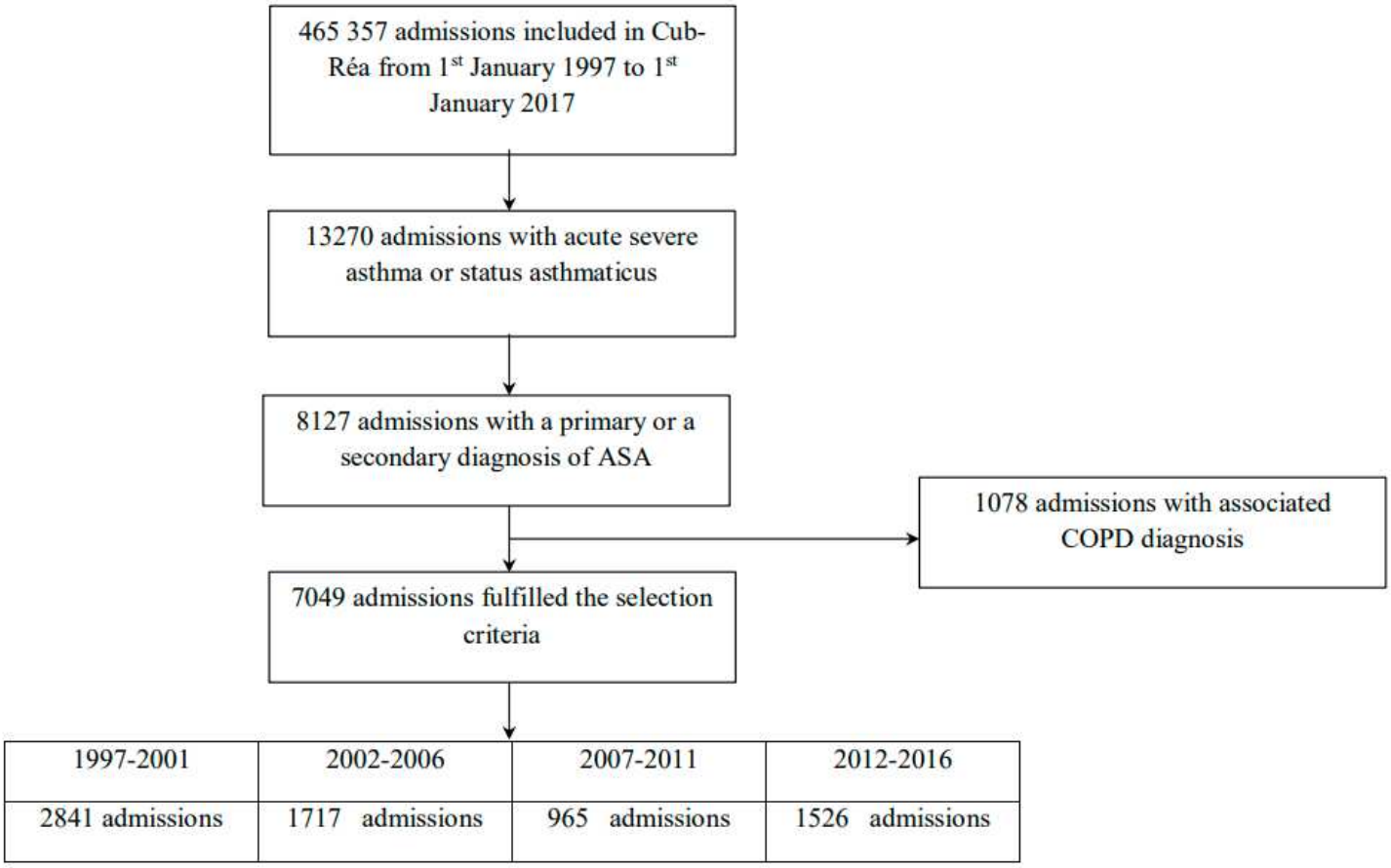

Figure 1

Flow chart

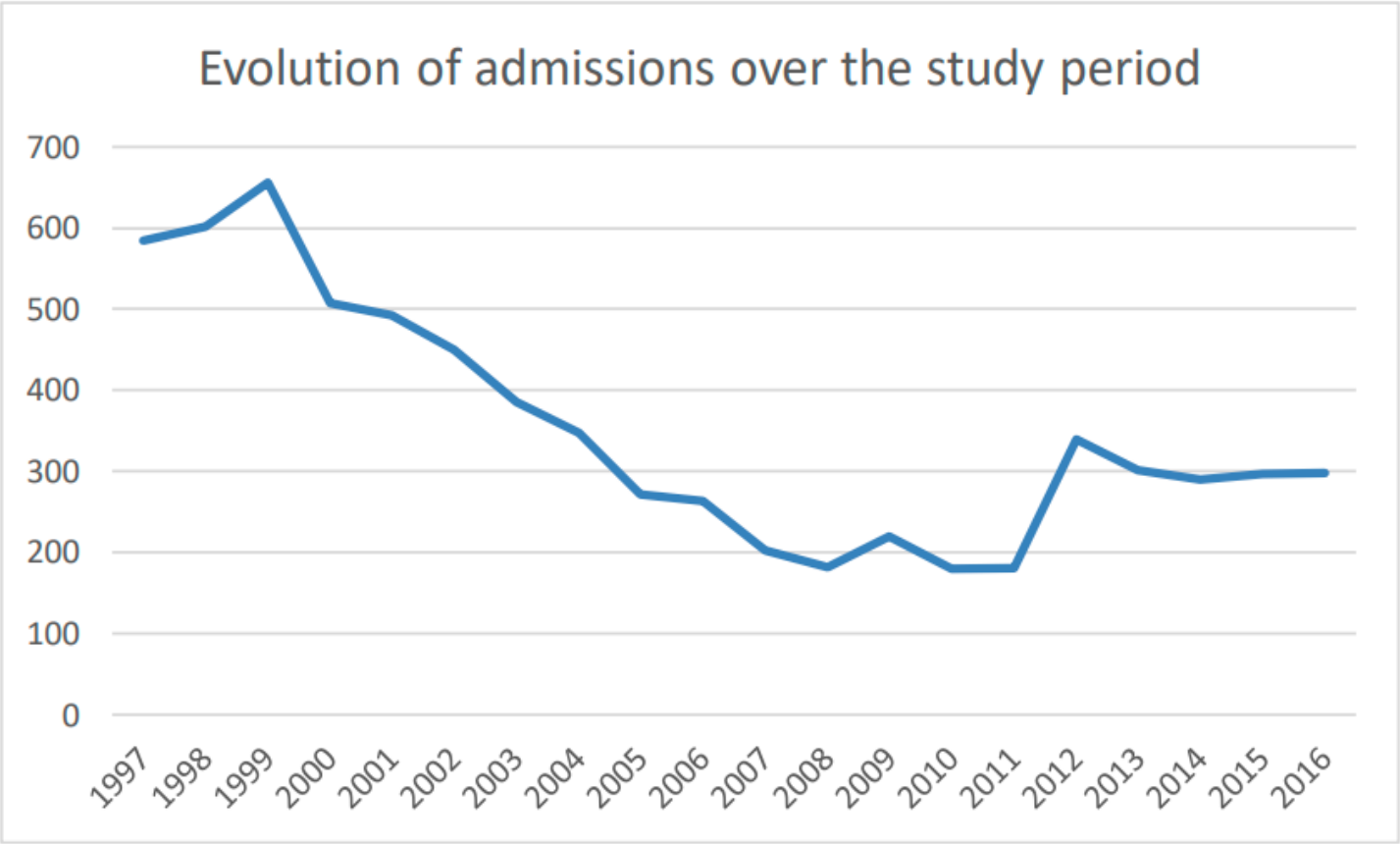

Figure 2

Evolution of admissions for acute severe asthma over the study period

Supplementary Files

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- APPENDIXS1.pdf