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Risk of exacerbation and mortality in asthma: a 10-year retrospective financial database analysis of the Hungarian Health Insurance Fund

Gábor Tomisa,[1] Balázs Sánta ,[2,3] Alpár Horváth,[3,4] László Németh,[5] Balázs Tamás,[5] Gabriella Gálffy,[6] Lilla Tamási,[1] Noémi Eszes[1]

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LT and NE contributed equally.

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[1]Department of Pulmonology, Semmelweis University, Budapest, Hungary
[2]Department of Pulmonology, Szent Borbala Korhaz, Tatabanya, Hungary
[3]Chiesi Hungary Ltd, Budapest, Hungary
[4]Pulmonology Institute of Törökbálint, Törökbálint, Hungary
[5]Healthware Consulting Ltd, Budapest, Hungary
[6]Pulmonology Hospital of Törökbálint, Törökbálint, Hungary

Correspondence to
Dr Lilla Tamási;
tamasi.lilla@med.semmelweis-univ.hu

ABSTRACT

Introduction Asthma is the most prevalent obstructive pulmonary disease, with drastically improved treatment options over the past decades. However, there is still a proportion of patients with suboptimal level of asthma control, leading to multiple hospitalisation due to severe acute exacerbation (SAE) and earlier death. In our study, we aimed to assess the risk of SAEs and mortality in patients who suffered an SAE.

Methods The database of the National Health Insurance Fund was used to retrospectively analyse the data of all asthmatic patients who had been hospitalised for an SAE between 2009 and 2019. We used a competing risk model to analyse the effect of each exacerbation on the risk of further SAEs with age, sex, Charlson index and the number of severe and moderate exacerbations included as covariates.

Result Altogether, 9257 asthmatic patients suffered at least one exacerbation leading to hospitalisation during the study time. The majority (75.8%) were women, and the average age was 58.24 years. Most patients had at least one comorbidity. 3492 patients suffered at least one further exacerbation and 1193 patients died of any cause. In the competing risk model, each SAE increased the risk of further exacerbations (HR=2.078–7.026; p<0.0001 for each case) but not death. The risk of SAEs was also increased by age (HR=1.008) female sex (HR=1.102) and with the number of days of the first SAE (HR=1.007).

Conclusions Even though asthma is generally a well-manageable disease, there still are many patients who suffer SAEs that significantly increase the risk of further similar SAEs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is ample knowledge on the natural course of chronic obstructive pulmonary disease exacerbations and their effect on mortality; however, there is scarcity of data on risk factors of exacerbations and mortality of asthmatic patients, especially in Central-Eastern-Europe.

WHAT THIS STUDY ADDS

⇒ With the inclusion of more than 9000 patients, we assessed the effect of asthma exacerbations on subsequent hospitalisation due to flare-ups and mortality. We found that in asthma each exacerbation significantly increased the risk of further exacerbations but not mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study highlights the importance of the prevention of asthma exacerbations and the fact that despite the advancements in asthma treatment over the past decades, there is still need for further improvements in asthma management.

INTRODUCTION

Asthma is among the most common non-communicable diseases, affecting more than 250 million patients worldwide, including approximately 300 000 registered cases in Hungary.[1] The diagnosis and treatment of asthma has significantly improved over the past decades, resulting in a marked decrease in mortality. Currently, asthma is considered a manageable disease; however, there is a sizeable proportion of patients whose asthma control is difficult to achieve. About 17% of all asthma cases fall in the category of difficult-to-treat asthma, with 3.7% of them considered as severe, according to the Global Initiative for Asthma (GINA) guidelines.[2] The main difference between the aforementioned groups is the optimisation of treatment—to consider someone a severe asthmatic patient, their adherence, inhaler training and other contributing factors have to be managed properly. Even though severe patients make up less than 5% of all asthmatics, their care is estimated to account for more than 60% of all costs associated with asthma care.[3] Uncontrolled asthma is much more common in the difficult-to-treat and severe asthma populations, and this results in a higher risk for exacerbations and mortality in these patient groups[3–6]; however, up to 30% of asthma

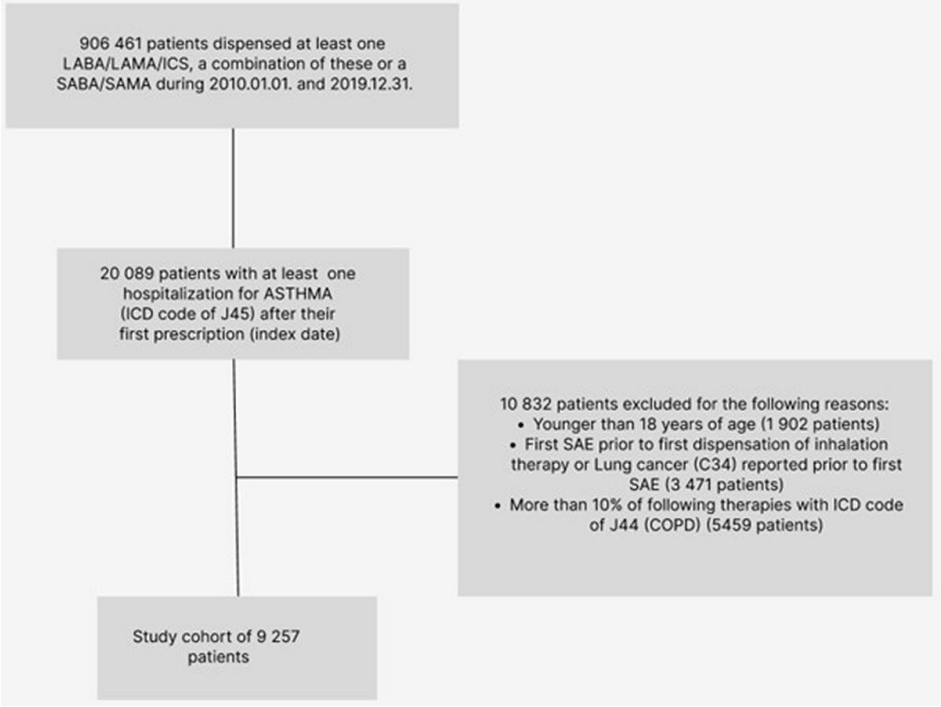

Figure 1 Flow chart of cohort formation. COPD, chronic obstructive pulmonary disease; ICD-10, 10th edition of International Classification of Diseases; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta agonist; SAE, severe acute exacerbation; SAMA, short-acting muscarinic antagonist.

exacerbations and deaths affect patients with mild, infrequent symptoms.[7] Exacerbations and mortality, as worst asthma outcomes, have been associated with several risk factors. Most available studies list gender, older age, the number and severity of comorbidities, severity of asthma and earlier exacerbations as the main risk factors for death.[8–10] According to the latest results the risk of severe acute exacerbation (SAEs) and mortality also increases incrementally with higher short-acting beta agonist (SABA) use, and with multiple important biomarkers, such as fractional exhaled nitric oxide and blood eosinophils.[2 11] At the same time, recent data on prevalence of frequent exacerbating phenotype and mortality rates in asthma is scarce.

Chronic obstructive pulmonary disease (COPD) and asthma share multiple similarities, resulting in the difficulty of differential diagnosis.[12] The main risk factors for mortality also seem to be similar in the two diseases. In our earlier publication, whose methodology was based on the well-known study by Suissa *et al*,[13] we assessed the effect of severe COPD exacerbations on future exacerbation and mortality risk and found that despite the therapeutic advances in the past decade, the natural course of the disease remained the same.[14] However, no studies assessed the same questions in general asthmatic population—in the current database analysis, we present the results of the same investigational model in asthma.[14] Finally, as many comorbid conditions are among the main risk factors for uncontrolled asthma, we also examined the prevalence and co-occurrence of comorbidities in this patient population.[8 15]

METHODS

Data source

A longitudinal, retrospective analysis using the National Health Insurance Fund's (NHIF) database (DB) was performed. This is a complex database that encompasses the entire population of Hungary, collecting certain healthcare data, including all reimbursement drug prescriptions, inpatient and outpatient visits, laboratory and imaging examinations, and the 10th edition of International Classification of Diseases (ICD-10) codes for all these events. Further details on the DB had been reported in our previous publication.[14] The analysis was performed under the same regulatory approval. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Patients

First, all patients who received at least one inhalation drug (inhaled corticosteroid (ICS), long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA) or any fixed combination of these or SABA or short-acting muscarinic antagonist (SAMA)) with the ICD-10 code of asthma (J45), between 1 January 2010 and 31 December 2019. A total of 906 461 patients were identified. After the first respiratory medication, at least one SAE was required for enrolment. A severe asthma exacerbation was defined as a hospital admission (inpatient hospital or ambulatory emergency care) with the ICD-10 code of asthma as the primary discharge diagnosis. This event was referred to as the index hospitalisation for exacerbation

Table 1 Baseline parameters of the study cohort characteristics of the entire patient population, patients who had suffered at least one subsequent SAE and patients who died during follow-up

		Entire cohort	At least one subsequent exacerbation	Death
At the time of the index date	No. of patients	9257	3492	1193
	Age at cohort entry (years; mean (SD))	58.24 (15.74)	60.28 (12.71)	70.95 (11.66)
	Charlson Comorbidity Index; mean (SD)	2.25 (1.60)	2.34 (1.61)	3.13 (1.93)
	Female (%)	7013 (75.8)	2774 (79.4)	815 (68.3)
One year prior to the index date	ICS therapy (%)	7201 (77.8)	2775 (79.5)	986 (82.6)
	SABA therapy (%)	6366 (68.8)	2380 (68.2)	865 (72.5)
	LABA therapy (%)	6878 (74.3)	2684 (76.9)	961 (80.6)
	LAMA therapy (%)	531 (5.7)	214 (6.1)	133 (11.1)
	SABA therapy without ICS therapy (%)	917 (9.9)	267 (7.6)	91 (7.6)
	More than 3 SABA therapy (%)	2836 (30.6)	1054 (30.2)	522 (43.8)
	Any therapy but ICS therapy (%)	1106 (11.9)	337 (9.7)	125 (10.5)
	Any therapy AND ICS therapy (%)	8151 (88.1)	3155 (90.3)	1068 (89.5)
Comorbidity in year prior to the index date (%)	Cardiovascular diseases (%)	3949 (42.7)	1646 (47.1)	798 (66.9)
	Heart failure (%)	1051 (11.4)	395 (11.3)	334 (28.0)
	Myocardial infarction (%)	200 (2.2)	71 (2.0)	58 (4.9)
	Anxiety (%)	2375 (25.7)	983 (28.2)	308 (25.8)
	Depressive episode (%)	1788 (19.3)	779 (22.3)	204 (17.1)
	Cerebrovascular disease (%)	1689 (18.2)	715 (20.5)	318 (26.7)
	Diabetes (%)	1486 (16.1)	583 (16.7)	292 (24.5)
	Peripheral vascular disease (%)	793 (8.6)	319 (9.1)	175 (14.7)
	Cancer (not lung) (%)	572 (6.2)	238 (6.8)	129 (10.8)
	Liver disease (%)	289 (3.1)	121 (3.5)	41 (3.4)
	Schizophrenia (%)	237 (2.6)	91 (2.6)	44 (3.7)
	Renal disease (%)	198 (2.1)	68 (1.9)	62 (5.2)
	Rheumatoid arthritis (%)	191 (2.1)	81 (2.3)	32 (2.7)
	Dementia (%)	88 (1.0)	32 (0.9)	29 (2.4)
	Metastatic cancer (%)	38 (0.4)	16 (0.5)	24 (2.0)
	Peptic ulcer (%)	34 (0.4)	17 (0.5)	NA
	Hemiplegia or paraplegia (%)	27 (0.3)	10 (0.3)	NA
	At least one moderate exacerbation (%)	3134 (33.9)	1309 (37.5)	420 (35.2)

For age, data on the Charlson index are shown as mean and SD. For all other variables, data are shown as the number of patients and percentages.
ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta agonist; SAE, severe acute exacerbation; SAMA, short-acting muscarinic antagonist.

event in the following sections (20 089 patients—100%). The baseline period was defined as 1 year before the index hospitalisation event. Patients who were under 18 years of age (1902 patients—9.47%) or had been hospitalised with the J45 ICD-10 code 1 year prior to the first dispensation of asthma treatment or had lung cancer (C34 ICD-10 code) in the baseline period were excluded from the study (3471 patients—17.28%). To ensure exclusion of misdiagnosed patients with COPD, we excluded all patients who had more than 10% of all their prescribed inhalation medications with the ICD-10 code of COPD (J44), resulting in the exclusion of further 5459 (27.17%).

Follow-up of all patients continued until the end of the study (31 December 2019.), the date of death or 1 year before the occurrence of lung cancer. During the follow-up time, all SAEs were recorded.

The steps of cohort formation are shown in figure 1.

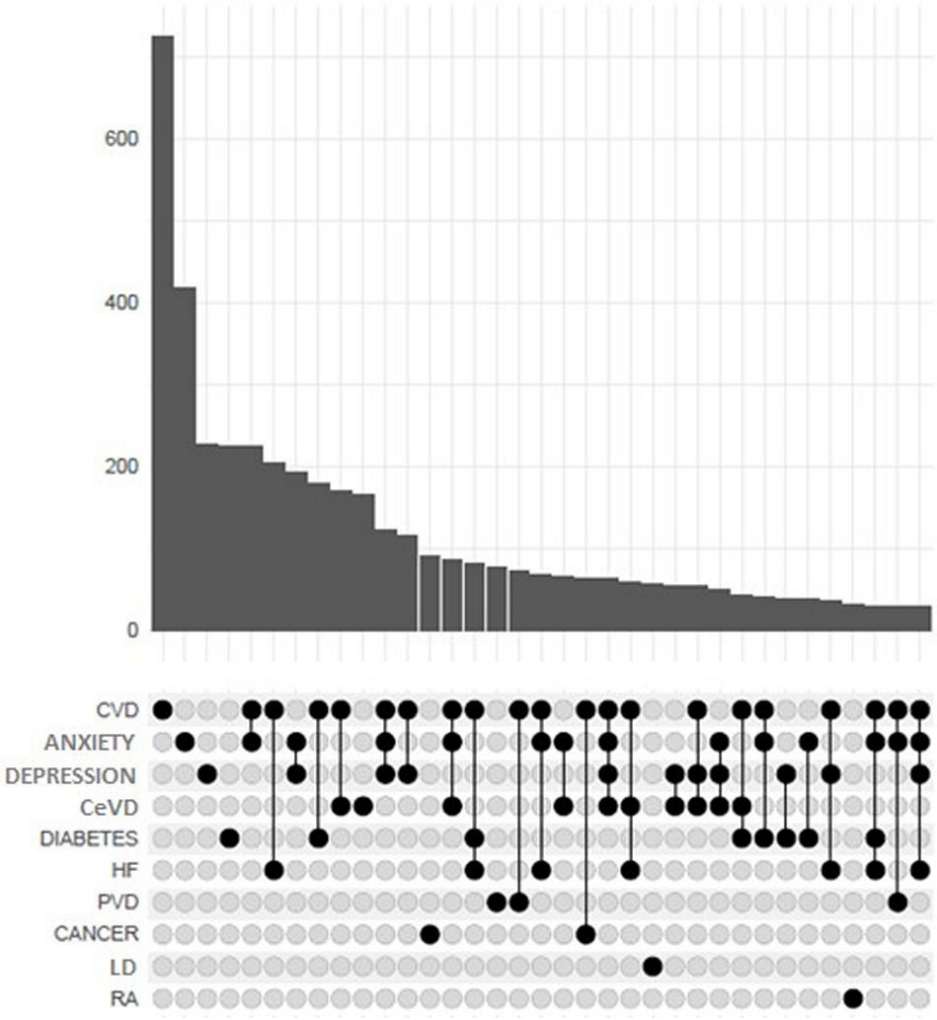

Figure 2 Most common single and co-occurring comorbidities in the study population. CVD, cardiovascular diseases; CeVD, cerebrovascular diseases; HF, heart failure; LD, liver disease; PVD, peripheral vascular disease; RA, rheumatoid arthritis.

Data analysis

Descriptive parameters such as gender, age (calculated at the first event of exacerbation) and length and type (acute inpatient care/rehabilitation) of the first hospitalisation were collected on the index date. One year before the first SAE, a baseline period was applied, which was used to collect information on comorbidities and dispensed treatments. Data on comorbidities were collected to form the Charlson index based on the ICD-10 codes definition by Sundararajan *et al*.[16] We also collected data on several psychological disorders to explore their prevalence in the asthmatic population. Collective cardiovascular disease (CVD) umbrella term was formed, encompassing ischaemic heart disease, heart failure (HF), arrhythmias, previous myocardial infarcts and cardiogenic shock. The prevalence and co-occurrence of comorbid conditions at baseline were analysed based on the reported ICD-10 codes of prescriptions, inpatient and outpatient events. Finally, moderate exacerbation was also investigated. It was defined as prescription dispensation for oral corticosteroids with the ICD-10 of asthma. If a moderate event was followed by a severe event within 7 days, both events were considered as a single SAE.

The main outcomes of the study were subsequent exacerbations and death of any cause. The start of follow-up was defined as the date of live discharge from hospital. The overall hazard function of successive severe asthma exacerbations was estimated using two approaches. In the first approach a competing risk model was used, where the event was defined as the next severe asthma exacerbation or death, whichever occurred first, while in the second approach Kaplan-Meier method was used, where beside the lost to follow-up the occurrence of death was also censor event.[13] For graphically representation of the hazard function of successive SAE over time, the hazard functions of each successive SAE were combined with the median interexacerbation time. Competing risk model was also used to estimate the relative risk of each successive SAE on the subsequent one and on mortality. The number of previous severe and moderate exacerbations was included in the model as a time-dependent covariate, maximised at a value of 9, with sex, age, duration of the

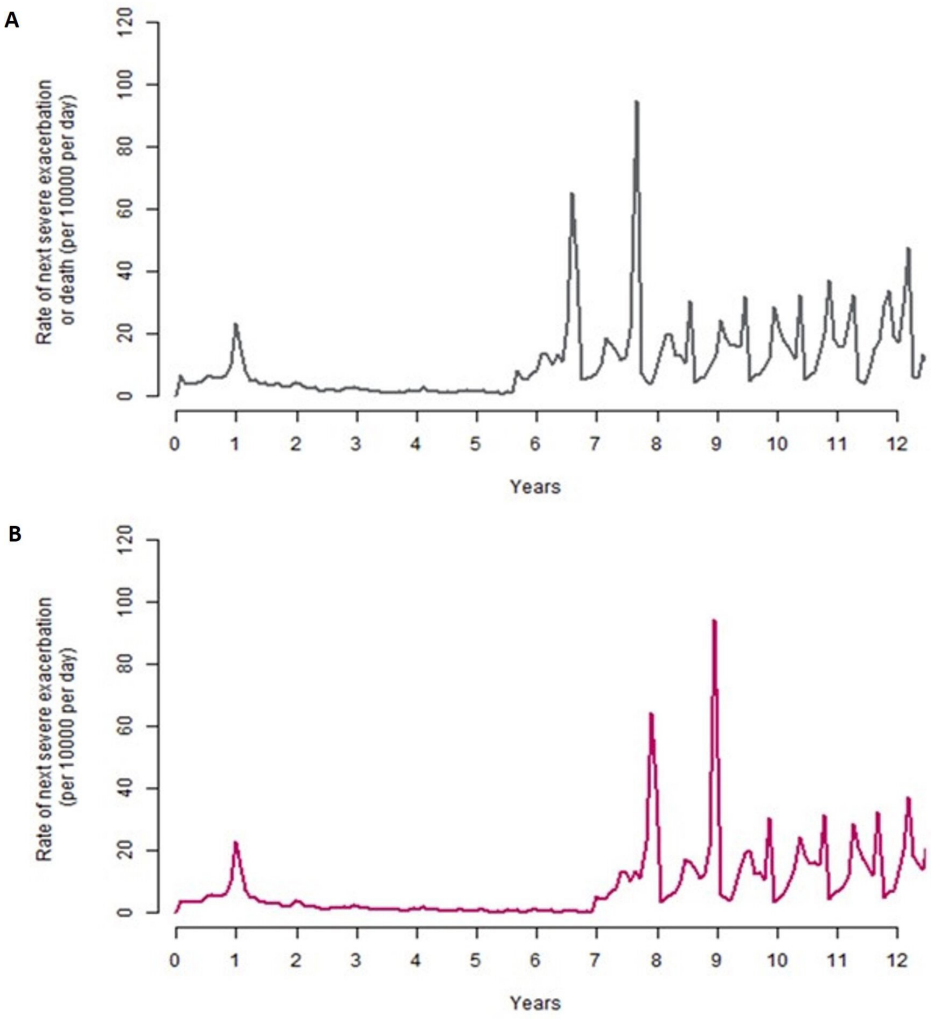

Figure 3 Hazard function of all subsequent SAEs (per 10 000 per day) from the time of the first SAE over the follow-up period, with the time between successive exacerbations estimated using: (A) the median interexacerbation times as time to the next exacerbation or death, whichever occurs first and (B); the median interexacerbation times to the next exacerbation, conditional on survival with death as a censor event. Survival was assessed by the Kaplan-Meier method, median survival time was not reached during the follow-up. SAE, severe acute exacerbation.

index hospitalisation and Charlson Comorbidity Index as time-independent covariates. The values of the Charlson index were classified in the model as mild (values of 1–2), moderate (3–4) or severe (5).[17] Finally, as a sensitivity analyses the effect of subsequent SAEs on mortality was also analysed using a simple Cox proportional hazards model.

RESULTS

Descriptive results

After the application of all exclusion criteria, a final cohort of 9257 patients was formed. Their average age was 58.24 years. 75.8% of all patients were women. All patients were prescribed at least one inhaled medication prior to their first SAE including agents such as ICS, β agonists and muscarinic antagonists. Most patients (88.1%) received ICS-containing treatment, with 74.3% of them receiving a LABA treatment as well 1 year prior to their index hospitalisation. 11.9% of patients did not receive any ICS-containing medications, and 9.9% used only SABA treatment in the baseline period. 68.8% of all patients were prescribed at least one SABA medication, while 30.6% of them used at least three canisters of SABA as reliever therapy. The average Charlson index score was 2.25 with CVDs (42.7%), anxiety (25.7%), depression (19.3%) and cerebrovascular diseases (18.2%) being the most common comorbidities. Details on all descriptive statistics are shown in table 1.

Data on prevalence and co-occurrence of comorbidities are shown in figure 2. The majority of patients suffered from at least one comorbidity. As seen on the figure, the most common comorbidities were CVDs, anxiety, depression and diabetes, while the most common co-occurring comorbidities were CVD and anxiety, CVD and HF and anxiety depression.

A total of 3492 patients (37.7%) experienced at least one subsequent SAE and 1193 patients (12.9%) died during follow-up. There were important differences in

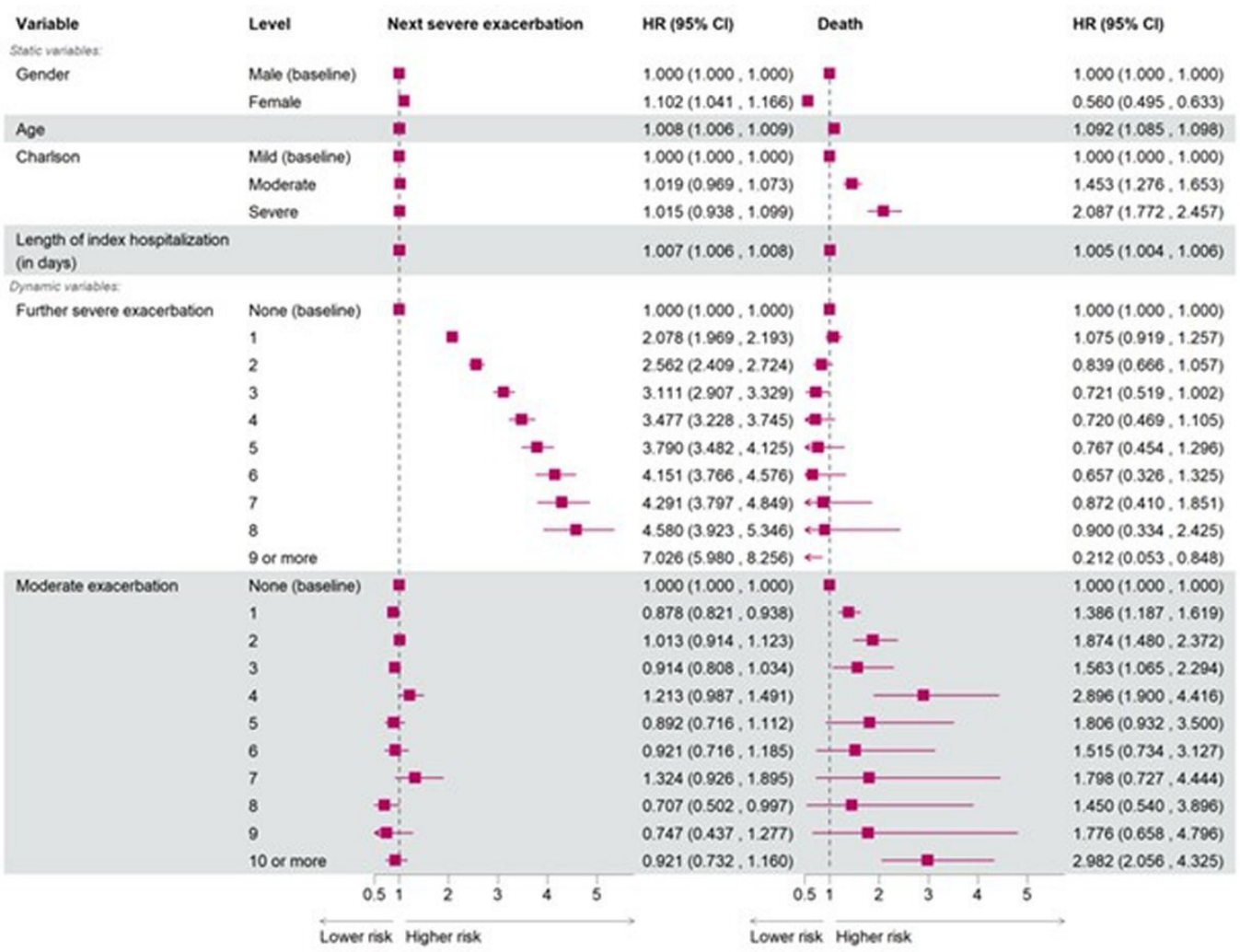

Figure 4 Model-estimated HRs and respective 95% CIs for risk of next severe exacerbation and death.

baseline parameters among the overall population and those who suffered at least one subsequent SAE and those who died during the follow-up period. The latter were the oldest (average age of 70.95 years) but with the smallest proportion of female patients, but still greater than that of men. Their average Charlson index score was 3.13, with most diseases being much more prevalent, except for anxiety (25.8%) and depression (17.1%), which showed a similar prevalence. The proportion of each prescribed inhaled respiratory medication was similar in all groups, although among those who died, the percentage of SABA overusers (prescribed ≥3 canisters annually) was higher compared with the others (table 1). All included patients had dispensed at least one reliever or maintenance therapy in the baseline period.

During the index hospitalisation, 16% of our patients were treated for a single day (most likely at an emergency ward), while the second most frequent time of hospitalisation was 4 days (12% of all patients were treated for 4 days exactly).

Figure 3A displays the hazard function of the time between SAEs and the next SAE or death, whichever occurred first. The average time between exacerbations decreased markedly between later exacerbations. Figure 3B shows a similar pattern regarding the time to the next SAE after the first severe asthma exacerbation leading to hospitalisation, however, the median time to first event was much longer.

Model results

In the competing risk model for next exacerbation, a relevant and statistically significant increase was seen in the risk for next SAE event, after each SAE (HR 2.078, 95% CI 1.969 to 2.193 after the second SAE and HR 7.026 95% CI 5.980 to 8.256 after the ninth SAE). In the model Charlson Comorbidity Index did not have a significant effect on next SAE risk. The risk, however, was slightly increased with age (HR 1.008 95% CI 1.006 to 1.009) in female patients (HR 1.102 95% CI 1.041 to 1.166) and with the number of days of the index hospitalisation (HR 1.007 95% CI 1.006 to 1.008).

In the competing risk model for mortality, there was no significant effect of successive SAEs on mortality.

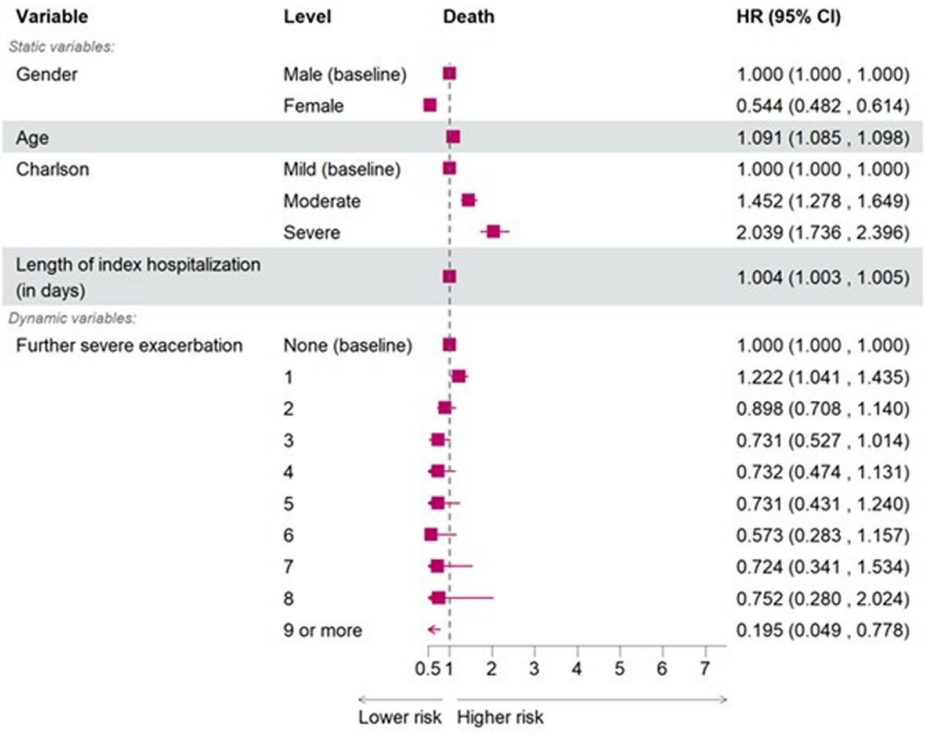

Figure 5 Model-estimated HRs and respective 95% CIs for risk of death.

Charlson Comorbidity Index (HR 2.087, 95% CI 1.772 to 2.457 for severe Charlson scores) and older age (HR 1.092 95% CI 1.085 to 1.098) caused significant increase in risk of mortality. Length of index hospitalisation also had a minor increasing effect on mortality (HR 1.005, 95% CI 1.004 to 1.006). Female patients had a significantly lower risk for death than their male counterparts (HR 0.560 95% CI 0.495 to 0.633).

Moderate exacerbations did not have a consistent significant effect on either outcomes. HR values and CIs can be seen in figure 4.

There was a possibility that within the competing risk model, a higher risk for exacerbations might diminish the increased risk for mortality after multiple SAEs, so we created a separate Cox regression model where the event was death without competing risk for next SAE.

In the Cox regression model for mortality, after the second SAE (HR 1.222; 95% CI 1.041 to 1.435), we did not see a significant effect of subsequent SAEs on the risk of death. Similarly, to the competing risk model older age, male gender, longer index hospitalisation and more severe Charlson score were risk factors for death. All HR values and CIs are shown in figure 5.

DISCUSSION

In our retrospective financial database analysis, we could prove that SAEs significantly increase the risk for future SAEs in asthma patients. These results, based on the long-term follow-up of more than 9000 asthma patients, are in line with our previous work assessing the same endpoints in COPD, during the same time frame.[14] Similarly, to that study, the risk for subsequent SAEs increased markedly after each SAE event, resulting in an HR of >7 after the ninth event. However, the risk for mortality did not increase with the number of SAEs in the competing risk model and only increased after the second SAE in the Cox regression model. This result might be due to the low number of deaths and the relatively short time of follow-up.

Interestingly, there were some differences in the results of this asthma population and the patients with COPD reported in our earlier publication.[14] While in both studies and both populations, a risk for next SAE increased significantly after each successive SAE, the increase in risk differed after certain events. In our previous study in patients with COPD, the risk for next event showed a steady increase after each SAE, while in current study in asthmatics, the risk peaked after the second and third events. At the same time, the median time to next event was much longer after the first SAE in asthma patients than with COPD, but with the events stacking up, median times decreased as well. These data might suggest that the first few SAEs focus the clinicians' attention to asthmatics much more than to patients with COPD that might result in higher level of care and thus longer median time between events. Also in contrast to patients with COPD, in the case of frequent exacerbator asthmatic patients, the changes in treatment (dose increase of corticosteroids and in a certain patient populations, usage of biological therapies) could have a higher effect on disease management. Patients with asthma may also have higher medication adherence after the first

SAE than those of COPD thus achieving higher disease control. Interestingly moderate exacerbations did not have any significant effect on SAE and mortality risk in asthma.

It is also important to stress the effect of hospitalisation length of the first SAE. Both in the exacerbation and death models longer hospital stays resulted in a higher risk for both outcomes. Even though the numerical effect was little, it was conveyed by even a single day of further hospital stay. This result highlights the importance of optimal patient management to minimise the need for hospital admission duration. In this research, we did not assess the effect of the length of further hospitalisations due to SAEs but uncovering the possible additional risks of the days spent in hospitals, further analysis is warranted.

Uncontrolled comorbidities can worsen asthma control, decrease therapeutic effect of and adherence to asthma treatment and can also mimic asthma symptoms resulting in needless treatment escalation.[15 18] In our study, the prevalence of most measured comorbidities was higher than reported in the work of Tomisa *et al* from Hungary[8] and was about the upper limit of prevalence reported in international studies.[15 19 20] This might be among the causes for worse disease control and higher risk for exacerbations than the general asthma population. The most common co-occurring comorbidities were CVDs and their complications, with psychiatric disorders being present at the same time. The occurrence of psychiatric disorders was frequent, even the prevalence of schizophrenia far exceeded that of the general population.[21]

The overuse of short-acting bronchodilators is an important risk factor for exacerbations and death. Overuse is defined as the use of 3 or more canisters of reliever therapy in 12 months.[2] In our study, among the patients who died, the prevalence of SABA overusers was much higher than in the general study population. The risk associated with high SABA use had recently been investigated in the SABINA nationwide cohort study, which found that even 3–5 dispensation of SABA canisters a year was associated with a significant increase in mortality risk.[22] It is paramount to check medication usage and to reassess patients' treatments and inhalation technique if their control is not achieved despite proper adherence. Increasing the ICS dose or adding additional medications (tiotropium or leukotriene receptor antagonist) might be necessary to decrease the need for rescue medications.

The main strength of our study is the possibility for long-term follow-up of a huge number of patients. Furthermore, due to a single health insurance fund in our country, presumably nearly all treated asthmatic patients could be identified. With the use of the NHIF's DB it is possible to include a much larger number of patients than what would be feasible in clinical settings. Also, as a financial database, the collected data are very accurate making the overall analysis very reliable. Finally, through this database the examination of comorbidities is much easier and more accurate than what could be achieved in clinical setting.

The key limitation of our study is the missing clinical parameters from the financial database. Also, we have no way of acquiring spirometry results, so the selection of patients has to be based solely on their prescription history. To ensure the exclusion of patients with COPD, we had to apply very strict criteria which might have also excluded some asthmatic patients. Another limitation of our study stems from its retrospective nature. Also it is not appropriate to equate prescription of a drug with the actual use; hence, it is not possible to attribute any of our results as therapeutic effect. Finally, the NHIF database does not include the cause of death for patients who did not die in a hospital, so we could not determine the exact cause for all patients.

To summarise, we have performed a long-term retrospective study to assess future exacerbation and mortality risk in more than 9000 asthma patients, who had been hospitalised due to an asthma exacerbation. Our results suggest that each SAE event significantly increases the risk for further asthma exacerbation, showing a similar pattern to that of patients with COPD. Even though asthma is generally a well-manageable disease a smaller proportion of patients still suffer from very serious symptoms, resulting in multiple hospitalisations, probably leading to earlier death.

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Contributors All authors made a significant contribution to the work reported. GT and BS in the conception, study design, execution, acquisition of data, analysis and interpretation, took part in the drafting of the manuscript; AH, GG, NE and LT took part in the conception, study design, execution, acquisition of data and in revising, or critically reviewing the article; LN and BT took part in the conception, study design, execution, acquisition of data, analysis and interpretation, revising or critically reviewing the article; all authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work. LT was responsible for the overall publication.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Permission was provided by the National Institution of Pharmacy and Nutrition of Hungary, based on the beneficial assessment by the National Scientific and Research Ethics Committee of Hungary (docket number: IV/8716-3/2021/EKU).

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Data availability statement Data may be obtained from a third party and are not publicly available.

ORCID iD
Balázs Sánta http://orcid.org/0009-0003-2547-7972

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